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A strategy for population pharmaceutical quality assessment based on quality by design

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ABSTRACT

From a regulatory perspective, drug quality consistency evaluation must concern different processes used for the same drug. In this study, an assessment strategy based on quality by design (QbD) was developed for population pharmaceutical quality evaluation. A descriptive analysis method based on QbD concept was first established to characterize the process by critical evaluation attributes (CEAs). Then quantitative analysis method based on an improved statistical process control (SPC) method was established to investigate the process indicators (PIs) in the process population, such as mean distribution, batch-to-batch difference and abnormal quality probability. After that rules for risk assessment were established based on the SPC limitations and parameters. Both the SPC parameters of the CEAs and the risk of PIs were visualized according to the interaction test results to obtain a better understanding of the population pharmaceutical quality. Finally, an assessment strategy was built and applied to generic drug consistency assessment, process risk assessment and quality trend tracking. The strategy demonstrated in this study could help reveal quality consistency from the perspective of process control and process risk, and further show the recent development status of domestic pharmaceutical production processes. In addition, a process risk assessment and population quality trend tracking provide data-based information for approval. Not only can this information serve as a further basis for decision-making by the regulatory authority regarding early warnings, but it can also reduce some avoidable adverse reactions. With continuous addition of data, dynamic population pharmaceutical quality is meaningful for emergencies and decision-making regarding drug regulation.

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1. Introduction

Due to the cost and time investment necessary for new drug research and development, a large gap is always present between the demand for brand-name drugs and the purchasing power of patients, which gives generic drugs an enormous an market potential [1]. Furthermore, the economic benefits of generic drugs, such as reducing national medical expenditures, have attracted government attention. Therefore, countries and regions worldwide, including the US, the European Union (EU) and Japan, are generally promoting the use of generic drugs [2]. China is a large generic drug market that primarily relies on domestic generic pharmaceutical products. In addition, the volume and potential of generic drug exports should not be underestimated [3]. Undoubtedly, the rapid development of generic drugs has created new challenges for regulation, particularly for the drug review and evaluation system.

Since China joined the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) in June 2017, the pharmaceutical industry in China has been required to conform with international standards. Thus, both the drug regulatory authorities and research and development institutions in the pharmaceutical industry must gradually transform their processes and implement the highest international technical standards and guidelines. Since 2016, the Chinese government has issued a series of regulations and drafts concerning generic drug

consistency evaluation that aim to effectively enhance the innovation capability and international competitiveness of the domestic pharmaceutical industry [4].

In the past 10 years, the Chinese government has invested millions of RMB each year in sampling and evaluating listed drugs according to the current quality standards; this effort is known as the National Evaluation Sampling and Test Project (NESTP). The purpose of NESTP is to evaluate the quality status of domestic medicines, analyze the main product quality problems, identify the relevant process problems and improve the current quality standard, such as monographs in the Chinese Pharmacopeia (ChP). NESTP can be said to be the most comprehensive and timely drug quality information source currently available in China. According to its annual report, although the pass rate for chemical drugs was high (above 98%), many types of problems were found during the project studies, particularly in production processes and process control. This indicates that the gaps between domestic generic drugs and drugs imported from the EU and the US stem from the process control level, which is reflected in differences between batches and sometimes even within a batch [5]. Therefore, a focus on process when assessing quality consistency is necessary and crucial.

Both the EU and the US have implemented process analytical technology (PAT)-based process validation and real-time release (RTR) testing in continuous manufacturing process, which allow production of better-quality final products [6,7]. However, in China, batch mode is the mainstream, and PAT is not widely used in the pharmaceutical industry, and currently there is no RTR testing protocol that is supported by policy. From a regulatory perspective, quality consistency evaluation must characterize different processes for the same product. How should we assess products that are produced both with and without PAT? Fortunately, since the current Good Manufacturing Practice (cGMP) standards were launched, the current quality standards are based on the quality by design (QbD) concept instead of quality by test (QbT). QbD requires manufacturers to fully understand their own processes and ensure continuous improvement in the quality of final products [8,9]. There is a wealth of information related to the processes in the readily measurable attributes (e.g., assay, impurities and dissolution) of final products. From the regulation point of view, the evolution is a process of seeking common ground while reserving differences, where the quality attributes are the common ground and process parameters are the differences. Thus, we need to find universal indicators and methods to characterize different processes used for the same product.

Recently, the U.S. Food and Drug Administration (USFDA) proposed the knowledge-aided assessment and structured application (KASA) system to improve the consistency and objectivity of regulatory assessments [10]. Statistical methods, such as six sigma theory and statistical process control (SPC), have been more and more applied to process monitoring in the pharmaceutical industry [11,12]. In addition to process monitoring, statistics are also widely applied in annual review of drug quality. Tôrres et al. [13] used multivariate statistical process control (MSPC) method to analyze the historical quality data of hydrochlorothiazide tablets in 2009 and 2013, and evaluated the process correction in the past 11 years. Kharbach et al. [14] used six process indicators from the annual product review data to perform principal component analysis (PCA) based MSPC analysis, found the interaction of process indicators, and detected abnormal products by Hotelling T^2. Different from process monitoring and annual review, population quality evaluation is to find out the distribution of process levels. Although PCA based MSPC can well characterize the population process level, the evaluation is not directional, poor in interpretability, and cannot be traced back to individual process indictors [15].

Furthermore, unlike the original drugs pharmaceutical research and manufacturing [16], generic drug evaluation has the advantage that most safety and efficiency information is known. When evaluating the generic drug, attention should also be paid to the quality controllability related to process amplification as well as safety and efficiency. This kind of indirect evaluation could facilitate obtainment of certain forward-looking trends based on retrospective data, which make up for the lack of direct evaluation of clinical practice such as expensive, hindsight and individualized difference. Our study was created to fill the gap.

In this study, an assessment strategy focusing on evaluating the quality controllability based on population pharmaceutical quality data was established to explore commonality of generic drugs process evaluation. Critical evaluation attribute (CEA) was defined and an improved SPC method for population quality based on CEAs was developed to determine the limitations and parameters closely related to the process performance. Ceftriaxone sodium for injection and aztreonam for injection were taken as examples to demonstrate the strategy application for quality consistency evaluation.

2. Materials and methods

2.1. Data and programs

All data and information were collected from NESTP and relevent literature. The data on ceftriaxone sodium for injection included 551 batches from 48 manufacturers for process assessment, and the data on aztreonam for injection included 233 batches from 27 manufacturers; all the data were collected over two nonconsecutive years for an annual review assessment of process consistency.

The programs for computation were developed using the MATLAB platform (Version 2018a).

2.2. Descriptive analysis method

In our study, the objects were population pharmaceutical quality of a certain drug instead of individual quality of a certain product. The drug quality standard was the regulation of various inspection items, indicators, limits and ranges, etc. to ensure the quality of drugs, which comprehensively reflect the purity, impurities, hydrogen, sterility and even physicochemical properties of the drug. In traditional pharmaceutical analysis and evaluation system, all the items are evaluated with the fixed limitation in quality standard one by one, where the variation and links are always neglected. It is precisely these variation and links that reflect the quality of the production processes. Therefore, to describe a population quality, the main point is to describe the quality of production process.

From a QbD regulation perspective, although the production processes are complex and diverse, our concept is to describe final products of different process parameters by common quality elements-quality target, quality variation and risks (Fig. 1), where the variation is controllable, and risk is uncontrollable. For a population of production processes used for the same product, the mean distribution, batch-to-batch difference and abnormal quality probability well represented the elements of QbD and were defined as process indicators (PIs) in our study.

2.3. Quantitative analysis method

SPC technology is the most efficient method for process analysis and control, which continues to be an important and indispensable tool for quality management, research and healthcare
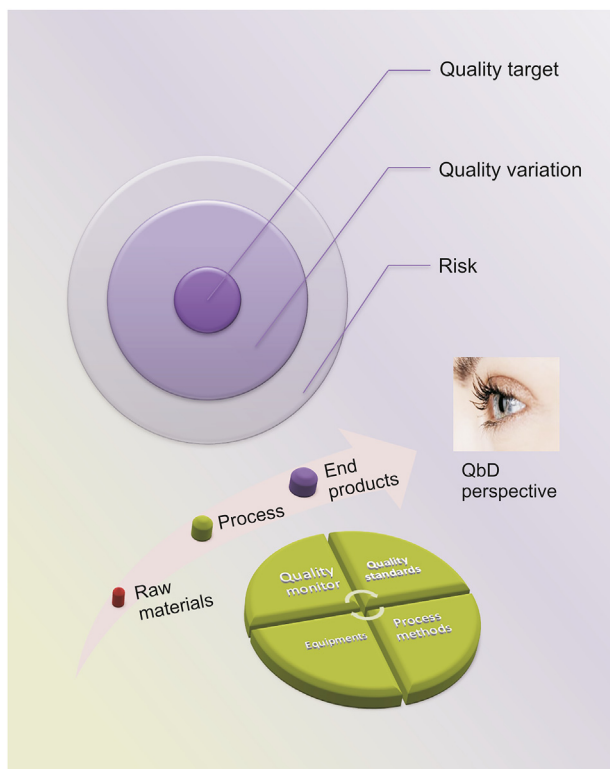
Fig. 1. The quality of pharmaceutical processes from the QbD regulation perspective based on end product characteristics.

improvement [17]. The principle [18] is to preplan the sampling interval and sample capacity to obtain real-time process data under the premise that the sample population follows a normal distribution with an upper control limit (UCL), lower control limit (LCL), centerline (CL) and a sequence of sample statistic values. In industry, the $\overline{X}$ control chart and the R control chart are commonly used to detect abnormal points in the process, and they are also the most widely used methods in process monitoring and quality annual review. However, the population data collected from NESTP are retrospective data rather than real-time process data, and the sampling interval and sample capacity are random and uncontrollable. Furthermore, the range R in the R control chart, which reflects the degree of data dispersion, has the disadvantage of fatal dependence on the sample size, reliance on a tiny amount of information and susceptibility to individual outliers and thus cannot completely characterize batch-to-batch differences. Therefore, the classic SPC method commonly used in process monitoring and quality annual review is not applicable for the quantitative analysis of population quality and thus an improved SPC method was developed for the quantitative analysis of the population process distribution and the individual processes relative to the population distribution (mean distribution), the batch-to-batch difference distribution (difference distribution) and the abnormal product probability (abnormal probability).

2.3.1. Mean distribution

Generally, for a specific drug product, domestic production processes are at a similar level, and the process characteristics of the population, despite its variety, are in line with the normality assumption. If the number of NESTP samples (processes) is sufficiently representative, the population processes can be considered to follow a normal distribution with an unknown μ and σ. Due to

the severe heterogeneity in sample size (the number of batches of each product), in the present study, the median of the process samples was used to characterize the individual process levels and estimate the μ and σ of the normal population process distribution. The average median of each process sample was used to estimate the μ of the population process, and the median deviation of each process was used to estimate the σ of the population process.

Suppose there are m process samples with sample sizes of n_i ($i = 1, 2, ..., m$), and the median of each process sample can be calculated using Formula (1):

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

Then, the mean value μ of the population process can be estimated using Formula (2):

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

The population process standard deviation σ is estimated using the median of the average absolute deviation (MAAD) [19] according to Formula (3):

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

Thus, the median X_i^{med} of each process falls within interval A with a probability of 100 $(1-\alpha)$ % (Formula (4)):

$$\left[\dot{\mu} - t_{\alpha/2}\dot{\sigma} \ , \ \dot{\mu} + t_{\alpha/2}\dot{\sigma}\right] \tag{4}$$

and when $t_{\alpha/2} = 3$, the 3σ level is defined as the good quality process control limit A_0 [LCL_0, UCL_0], and when $t_{\alpha/2} = 6$, the 6σ level is defined as the population quality process control limit A_1 [LCL_1, UCL_1]. The pharmacopeia control limit [LCL_p, UCL_p] is defined as U. If the attribute is one-sided, such as with impurity content, LCL_0 and LCL_1 should be forced to equal LCL_p. In addition, the relationship between A_1 and U provides information on the suitability of the actual current quality standard to the current process control level.

2.3.2. Difference distribution

We used the semi-interquartile range (R^q), which is half of the difference between the third quartile and the first quartile or the 75th percentile and the 25th percentile (Formula (5)), to describe the batch-to-batch difference for each process sample. Here, we did not use the range ($R = x_{max} - x_{min}$) as the normal control chart because R^q is not susceptible to interference by individual anomalous data and is superior in characterizing variation in the population process.

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

The mean and standard deviation of R^q can be calculated with Formulas (6) and (7):

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

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

Then, the 100 $(1-\alpha)$ % confidence interval B of R_i^q can be

calculated using Formula (8):

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

and when $t_{\alpha/2} = 3$, the 3σ level is defined as the good quality inter-batch difference B_0 [RqLCL$_0$, RqUCL$_0$], and when $t_{\alpha/2} = 6$, the 6σ level is defined as the population batch-to-batch difference control limit B_1 [RqLCL$_1$, RqUCL$_1$].

2.3.3. Abnormal probability

The distribution of products within each process is expressed by the probability of being within the control limit of A_1. We define the probability of exceeding A_0 as the abnormal quality probability, and it includes two cases: those that exceed A_0 but still fall below A_1 are around-corner products, whose probability is recorded as P^{ac} (Formula (9)); those that are outside A_1 are substandard products, whose probability is recorded as P^{ss} (Formula (10)). Obviously, the abnormal quality probability has a negative relationship with the quality of the process.

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

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

The abnormal product probability of binary indicators is the percentage of the number of substandard products (n^s) in the total number of samples (n_i) of the process, recorded as P_i^s (Formula (11)).

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

2.4. Interaction test

An interaction test is developed to find representative of the chosen CEAs. The more orthogonal they are, the more representative of the population quality it is. Singular value decomposition (SVD) algorithm based PCA was applied to calculate orthonormal principal component coefficient of each quality attribute (QA). SVD has a less rounding error and effectively reduces the error of PCA information reconstruction. The principal component variances are the eigenvalues of the covariance matrix of CEAs. When variables are represented in the principal component space by a vector, the direction and length of the vector indicate the interaction of CEAs, which is a very important basis of visualization of both population parameters and risk distribution space.

2.5. Risk assessment method

Based on the SPC results, the process risk scoring was performed under the rules shown in Table 1. Grades 0, 0.5 and 1 were set to score the risk based on the distribution in the 3σ level, between the 3σ and 6σ level or outside the 6σ level, respectively. Finally, the risk scores of each item were summed to obtain the risk assessment for each process. The smaller the risk score is, the better the process is.

2.6. Assessment strategy

The strategy for assessing population quality of pharmaceutical processes [20] is shown in Fig. 2. First of all, CEAs were selected. Generally, data from each manufacturer were considered valid when at least three batches were included. CEAs can be either the known critical quality attributes (CQAs) obtained from PAT or selected from attributes in the quality standard [21], such as identification, active pharmaceutical ingredient (API) content, impurities and specific formulation-related test items, according to experience. Secondly, CEAs were classified. CEAs might be measured on different scales, such as continuous or binary responses. Binary attributes, such as traits, identification, pyrogen and sterility, were added as additional attributes in the characterization only if positive attributes (FR≠0) appeared in the overall data. Of note, for the binary CEAs, the abnormal probability was calculated only when necessary. Thirdly, PIs were investigated by the descriptive and quantitative methods developed above. Then, data visualization can aid in obtaining a better understanding of both the process space and abnormal distribution and the synthesis process risk grade. When there were fewer than three CEAs representative PIs, a spatial vector was used for visualization in 2- or 3-dimensional space. When there were four or more chosen representative processes, either a dimension-reduction algorithm or a glyph plot was available.

3. Results and discussion

Two examples of an antibiotic injection were utilized to demonstrate the application of the strategy in two cases. As an example of a case in which a reference listed drug (RLD) was available, we performed a quality consistency assessment on generic ceftriaxone sodium injections, while to present a case in which an RLD was not available, we performed a process risk assessment and population quality trend tracking on generic aztreonam injections.

3.1. Application of quality consistency assessment

Ceftriaxone is a broad-spectrum cephalosporin launched by Roche under the brand name Rocephin in 1982 [22]. In China, dozens of manufacturers produce generic ceftriaxone. Rocephin, as well as the generic drugs, is a sterile powder injection containing ceftriaxone sodium (API). Therefore, Rocephin is the listed RLD. A clinical survey showed that the gaps between generic ceftriaxone and Rocephin are directly reflected in a slow clinical effect and the clarity of the solution [23,24]. The former is due to the low salt formation rate, and the latter is primarily related to the crystallinity [25]. Ceftriaxone sodium (Fig. 3) is a crystalline powder with a molecular formula that contains two sodium ions and 3.5 water molecules. The theoretical value of ceftriaxone and water in wet products should be 83.8% and 9.5%, respectively, and the theoretical ceftriaxone content in anhydrous ceftriaxone sodium can be calculated as 92.7%. Theoretically, an anhydrous ceftriaxone content of more than 92.7% indicates insufficient salt formation, while a water content less than 9.5% indicates insufficient crystallinity. Thus, the anhydrous ceftriaxone content and water content are closely related to the quality of ceftriaxone sodium for injection production process.

In our study, we took these two attributes as the CEAs to perform the process assessment strategy. According to ChP, the anhydrous ceftriaxone content should not be less than 84.0%. We set an upper limit according to both theoretical value and the upper limit of European Pharmacopeia. Thus, the U$_{API}$ of the anhydrous ceftriaxone content [^{API}LCL$_P$, ^{API}UCL$_P$] is [84.0%, 94.6%]. While the water content should be in the range of 8.0%–11.0% according to ChP, and thus, the U$_{water}$ of the water content [^{Water}LCL$_P$, ^{Water}UCL$_P$] is [8.0%, 11.0%]. Population parameters of domestic generic ceftriaxone sodium for injection were calculated using the quality data of 551 batches from 48 manufacturers, as shown in Table 2. The mean distribution of the water content was 8.75% (CL^{water}), with a 6σ level moving a little beyond the ^{Water}LCL$_P$, which indicates that the

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
		$X_i^{med} \in A_1 \big| X_i^{med} \notin A_0$	0.5
		$X_i^{med} \notin A_1$	1
	Difference distribution	$R_i^q \in B_0$	0
		$R_i^q \in B_1 \big| R_i^q \notin B_0$	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	$P_i^s = 0$	0
		$P_i^s \neq 0$	3
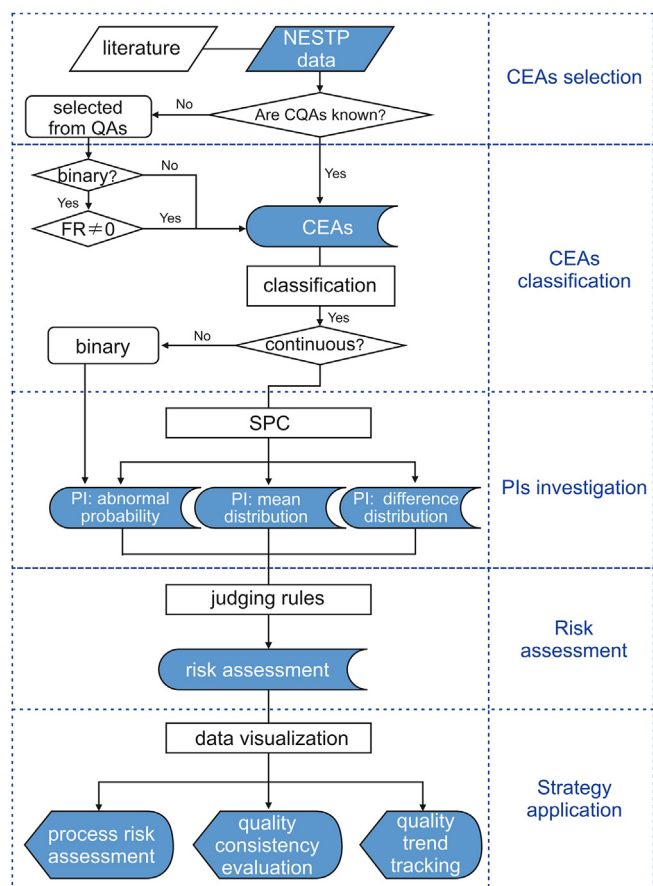
Fig. 2. Flow chart showing the population quality assessment strategy.

Fig. 3. Molecular structure of ceftriaxone sodium.

process control levels compared with Rocephin. For some manufacturers such as M13, M26, M28, M35 and M42, the salt formation rates are seriously insufficient. Individual outliers appeared in M10, M11, M27 and M28, which indicates the risk of product failure.

The process risk assessment was performed based on the PI values and risk scores, where the risk scores of the anhydrous ceftriaxone content captured the risk of salt formation and the risk scores of water content showed the risk of crystallinity (Table S1). As Fig. 5 shows, the ceftriaxone production process distribution space is divided into three risk grades: low-risk for a risk score below 1, mid-risk for a risk score between 1 and 2, and high-risk for a risk score greater than 2. And each process is described by vectors with coordinates of the assessment parameters. Most domestic processes are at risk grades 1 and 2, and those at risk grade 1 have a better process control level than those at risk grade 2. In addition, the risk assessment can also indicate the shortest plank requiring improvement for an individual process. For instance, the risk assessment of M24 is zero for the salt formation process but 1.0 for the crystallinity process, which indicates that this manufacturer should pay close attention to the crystallinity when raw materials are produced or purchased; the risk assessment of M26 is less than 0.5 for the crystallinity process but 2 for the salt formation process, suggesting that M26 should pay more attention to the latter
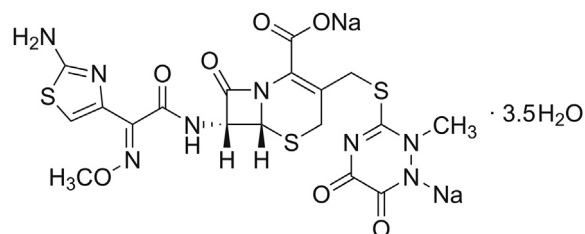
crystallinity process needs to be improved. The mean distribution of the anhydrous ceftriaxone content was 91.25%, with a 6σ level moving far beyond the $^{API}UCL_P$, which indicates that there are universal problems in salt formation process of domestic products. Moreover, the batch-to-batch differences were appropriate and abnormal product probability (P^{ab}) was around 10% of both CEAs.

Fig. 4A shows a weak interaction of CEAs; therefore, both population parameter and risk distribution can be visualized in an orthogonal space (Fig. 4B). As shown in Fig. 4B, a 2D boxplot of the Rocephin process is also included in the space for comparison. The population parameter A_0 (green dash rectangle) covered the Rocephin process distribution (pink 2D boxplot), which proves that A_0 is consistent with RLD, although there is an obvious gap in

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

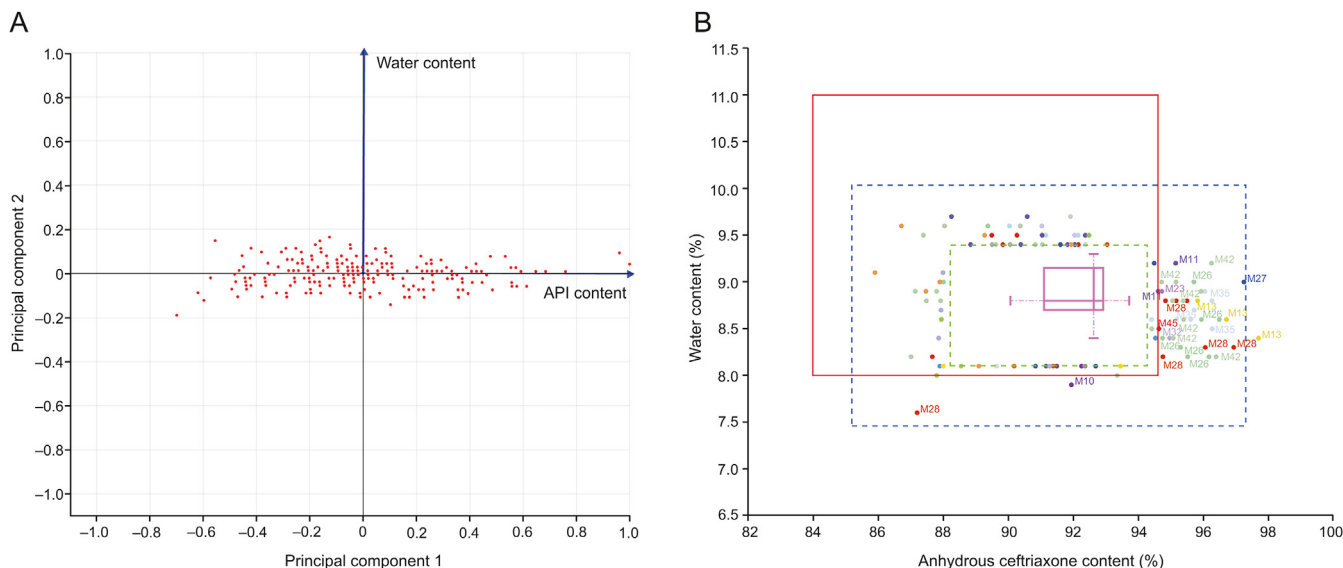| Population parameters	Crystallinity (water content (%))	Salt formation (anhydrous ceftriaxone content (%))
CL (%)	8.75	91.25
A_0 (%)	[8.10, 9.39]	[88.22, 94.27]
A_1 (%)	[7.46, 10.04]	[85.20, 97.30]
U (%)	[8,11]	[84, 94.6]
Rq	0.2135	1.014
B_0 (%)	[0.173, 0.254]	[0.773, 1.26]
P^{ab} (%)	10.34	11.80

Fig. 4. Interaction of CEAs and SPC graph of API and water content in generic ceftriaxone sodium injections. (A) The blue arrow lines are the CEA variable vectors and red points are the raw data distributing in the principal component space; (B) the red rectangle is U, the blue dashed rectangle is A_1, the green dashed rectangle is A_0, the pink 2D boxplot presents the data for Rocephin, the colored markers are the abnormal batches from different manufacturers, and those varied beyond U are marked.

process. Furthermore, for those close to the high-risk line, such as M28, the risk assessment calls attention to both processes.

3.2. Process risk assessment and population quality trend tracking

Aztreonam is a β-lactam antibiotic against gram-negative bacteria that was marketed by Squibb in 1986 under the brand name Azactam; it is a 25% (m/V) aqueous solution. Due to polymerization in water, the current formulation of aztreonam is a sterile powder injection containing aztreonam and arginine. Therefore, there is no RLD available for consistency evaluation. There are two types of production processes used for domestic generic aztreonam injection: a mixed powder process and a freeze-drying process. According to the NESTP report, although all the samples were qualified, the quality of the raw materials, the arginine feeding process control, and the freeze-drying and filling processes are the main factors affecting product quality. Thus, a production process assessment seems necessary and important.

We used the anhydrous and arginine-free aztreonam content, average loading of the aztreonam content and total impurity content as CEAs to evaluate the process consistency. First, the anhydrous and arginine-free aztreonam content was calculated based on the aztreonam content, water content, and arginine content in the product, which could characterize the consistency of the mixed materials (MC). Second, the labeled amount of aztreonam content was calculated from the aztreonam content and the average loading, which reflects the stability of preparation production process (PS). Finally, according to previous research, impurities and degradants are the main quality factors that cause adverse reactions, and thus, the total impurity content was used to characterize the consistency of the API raw material (RC).

According to ChP, both the API content and the impurities can be measured by HPLC, which stipulates that the anhydrous and arginine-free aztreonam content should be 91.0%−103.0%, the labeled amount content should be 90.0%−105%, and the impurity content should not be greater than 5%. Therefore, the ^{MC}U of anhydrous and arginine-free aztreonam content [$^{MC}LCL_P$, $^{MC}UCL_P$] is [91.0%, 103%], the ^{PS}U of the labeled amount content [$^{PS}LCL_P$, $^{PS}UCL_P$]

is [90.0%, 105.0%] and the ^{RC}U of the total impurity content [$^{RC}LCL_P$, $^{RC}UCL_P$] is [0%, 5.0%].

PIs were calculated from the processes of the 27 manufacturers of generic aztreonam for injection for the two years (Table 3). The mean distribution of anhydrous and arginine-free aztreonam content indicates that there were some issues with the MC process between 2012 and 2018 due to the formula change. The mean distribution of the labeled amount content indicates that although the PS process had been extensively improved by 2018, certain problems remained for future improvement. The mean distribution of the total impurity content indicates that the RC process had been improved from 2012 to 2018. The most recent PIs of batch-to-batch difference and
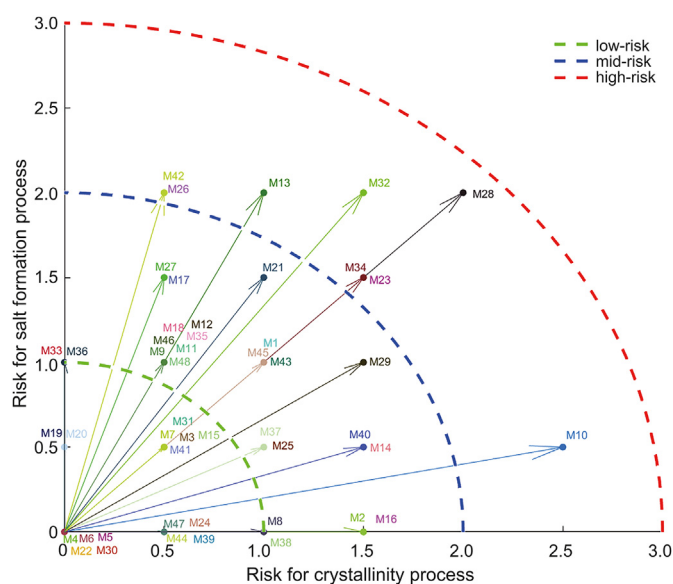

Fig. 5. Risk assessment for processes and the process vector distribution of generic ceftriaxone sodium injections. (The colored vectors distributed in the space represent each process of 48 manufacturers.)

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
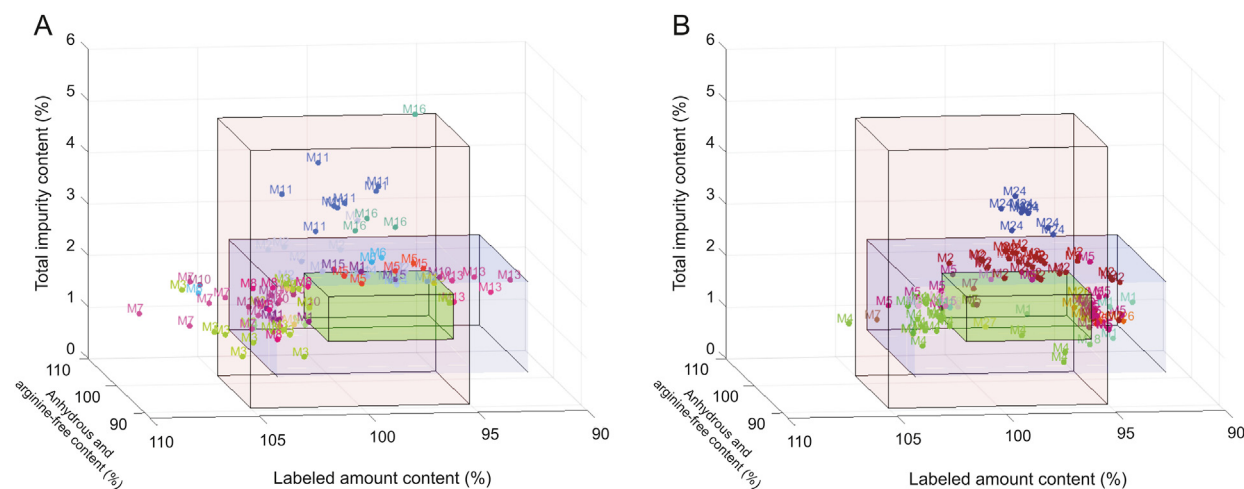
Fig. 6. SPC cube and abnormal batches distribution in the process space for generic aztreonam injections. (A) Abnormal batches distribution of 2012 NESTP, and (B) abnormal batches distribution of 2018 NESTP. The red cube is U, the blue cube is A_1, the green cube is A_0, and the colored markers are the batches out of A_0.
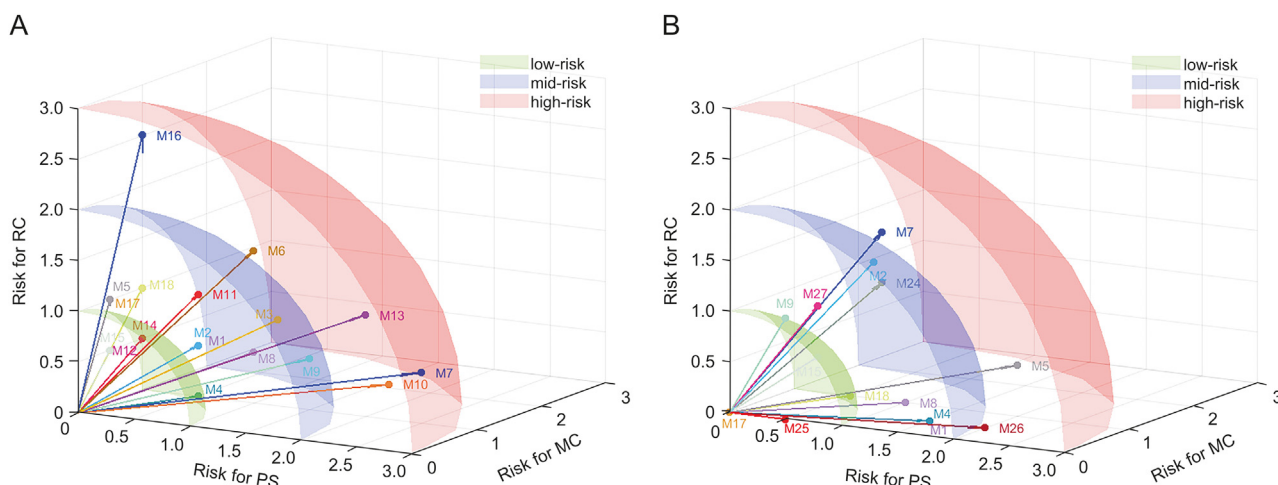

Fig. 7. Annual comparison of process vector distribution of generic aztreonam injections. (A) 2012, and (B) 2018. (The colored vectors distributed in the space represent the comprehensive process control levels for each manufacturer.)

abnormal probability showed the current status of a quality variation problem for the MC process and a high out-of-control risk for the PS process.

CEAs are orthogonal in the interaction test, and the SPC

parameter A_0 in the latest year was used as a reference (green cube in Fig. 6). In Fig. 6, the current ChP and latest SPC limitations were put into a 3D process space of CEAs. The abnormal batches distribution showed an obvious optimization of all CEAs. However,

significant process problems were also observed, such as RC of M2 and M24, PS of M4, and both RC and PS of M5.

The process risk assessments for the years 2012 and 2018 are illustrated in Fig. 7, where the PIs of risk for MC, PS and RC were used to construct a 3D quarter-spherical risk distribution space. We found that the risk distribution moved toward the lower risk direction from 2012 to 2018, which indicates an improvement in the overall process control trend. Although the overall process control trend is optimistic, the trend in individual processes varies. Some products, such as those from M2 and M17, showed an obvious increase in process control. M7 greatly improved the PS process but had a negative trend for RC. For M5, the risk for RC was slightly decreased, while that for both PS and MC increased. Thus, these manufacturers should focus on the relevant process problems and determine which factors lead to the risk increase in process control. Furthermore, it is worth noting that risk distribution assessment is useful for both process changes and process improvements with relative data supplementation for approval.

4. Conclusions

The advantages of the strategy we established for population pharmaceutical quality assessment are 1) a kind of process-evaluation mechanism based on the QbD was established using structured drug quality data; 2) it offers a universal approach for assessing different industrial production processes for the same drug; 3) it can be applied to generic drugs consistency evaluation, process risk assessment and quality trend tracking, which can provide data-based information for approval.

The established assessment strategy, which mines the process information related to population quality and investigates intrinsic links between QbD elements, provides a scientific tool for objectively and comprehensively evaluating quality consistency and promoting the regulation status of domestic generic drugs. Not only does this approach reflect the commonality in the different processes, but it also shows the development status of domestic pharmaceutical production processes over the past few years. From the regulatory perspective, it also reveals the gap between the quality target and the current process level. With continuous addition of information and data, dynamic trends of the population pharmaceutical quality could be observed for emergencies and for decision-making related to drug regulation based on the QbD concept.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpha.2020.11.001.

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