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Distributions of results of cetirizine dihydrochloride assay in bulk material

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Abstract

The distribution of the cetirizine dihydrochloride assay results in correlation with the pharmacopoeia limits is analyzed. The data for analysis were obtained at Chemagis Ltd., Israel, for 13 batches during a year in two laboratories by five analysts using three different titroprocessors (total 114 results of the determination). The hypothesis on the normal distribution of the data was tested using ω^2-criterion and accepted at the level of confidence 0.90. A control chart is designed for indication of warning and action limits of the determination results and for diagnoses of outliers in the further titrations. The distribution of the analyte content in different batches and the distributions of the titration results at the pharmacopoeia limits were plotted. The probabilities of the erroneous decisions of Type 1 and Type 2 on the batch quality were calculated from these distributions.

Keywords: Certirizine dihydrochloride; Assay; Distribution; Pharmacopoeia limits; Batch quality

1. Introduction

The cetirizine dihydrochloride assay in a bulk material is provided according to the European Pharmacopoeia (1999) by the acid-base potentiometric titration of acetone-water solution of the analyte against sodium hydroxide. By the pharmacopoeia definition cetirizine dihydrochloride contains not less than 99.0% and not more than the equivalent of 100.5% of (*RS*)-2-[2-[4-[(4-chlorophenyl)phenilmethyl]piperazin-1-yl]ethoxy]-acetic acid dihydrochloride, calculated with reference to the dried substance. True content of cetirizine dihydrochloride in a bulk material depends on the content of such impurities as (*RS*)-1-[(4-chlorophenyl)phenilmethyl]piperazin, (*RS*)-2-[4-[(4-chlorophenyl)phenilmethyl]piperazin-1-yl]-acetic acid and (*RS*)-2-[2-[4-[(2- chlorophenyl)-phenilmethyl]piperazin-1-yl]ethoxy]acetic acid.

Since cetirizine dihydrochloride has three titratable hydrogen ions, the end point of the titration is the last point of inflexion. Besides known sources of the measurement uncertainty inherent

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for the acid–base potentiometric titration in such cases, traces of the hydrochloric acid, which is used for the material processing, and acidity of the solvent used can also vary results of the assay. Therefore, the decision on the quality of the bulk material (batch of cetirizine dihydrochloride) may be erroneous. Type 1 error (Miller and Miller, 1993) in this case consists of the rejection of the batch when the true value of the cetirizine dihydrochloride content is into the pharmacopoeia limits. The error of Type 2 arises at acceptance of the batch which true content of the cetirizine dihydrochloride is out of the pharmacopoeia limits. Note, that both kinds of the errors are possible both at the EUP lower (99.0%) and at the upper (100.5%) limits.

To study the error probabilities, the information is necessary on the distribution of the true analyte content in batches, and on the distribution of the assay (titration) results. The data for the study were obtained during a year at Chemagis Ltd., Israel, for 13 batches by five analysts using three different titroprocessors: total 114 results of the cetirizine dihydrochloride determination. Evaluation of these data and corresponding decisions on the quality of the bulk material is the subject of the present paper.

2. Preliminary statistical analysis

The rolled up data are presented in Table 1, where N is the number of batches, assays and others; S_C is the standard deviation of an average for batch result from their total average value (the same for other parameters); S_r is the average replicate standard deviation in the corresponding group of the data, for example, for replicates obtained for batches; the $f_1 = N - 1$ is the number of degrees of freedom of S_C; f_2 is the number of degrees of freedom of S_r; $F\{f_1, f_2\} = S_C^2 n_{av}/S_r^2$ is the empirical Fisher ratio, where n_{av} is introduced to equalize the 'weights' of the variances S_C^2 and S_r^2; $F_{0.05}\{f_1, f_2\}$ is the critical one-tailed F-value for the level of confidence 0.95 (Miller and Miller, 1993). Since an assay result C is the average of two or sometimes three replicate determinations ($n_r = 2$ or 3), the average numbers of replicates per batch, day, analyst or per instrument n_{av} are fractional. The numbers of analysts participated in the analysis of a batch, instruments used by them, assays and days of the analysis were also variable. Therefore, total average cetirizine dihydrochloride concentrations C_{av} obtained for batches, analysts, days and other parameters differ from the overall value.

From comparison of the empiric and critical values of the Fisher ratio for batches one can see a significant difference between them: $F\{f_1, f_2\} > F_{0.05}\{f_1, f_2\}$. The same results of the test for days of the analysis, analysts and instruments may be caused by correlation of the corresponding groups

Table 1
Rolled up data on the cetirizine dihydrochloride determinations

Parameter	Batch	Day	Analyst	Instrument	Overall	
					Assay	Replicate
N	13	14	5	3	56	114
C_{av}, %	99.731	99.685	99.711	99.811	99.681	99.687
S_C, %	0.400	0.504	0.244	0.324	0.487	–
n_{av}	8.77	8.14	22.8	38.0	2.04	–
S_r, %	0.464	0.298	0.505	0.491	0.202	0.536
f_1	12	13	4	2	55	–
f_2	101	100	109	111	58	–
$F\{f_1, f_2\}$	6.52	23.3	5.31	16.5	11.9	–
$F_{0.05}\{f_1, f_2\}$	1.86	1.85	2.47	3.08	1.53	–

of the data (for example, practically every batch was analysed in the specific day, each analyst used only one or two instruments and so on). So, the difference between days of the analysis, analysts and instruments requires an additional study.

3. Distribution of the determination results

The hypothesis on the normal distribution of the data (114 results of the analyte determination) was tested using Kramer-Mizes ω^2-criterion (Owen, 1962):

$$\omega_n^2 = -n - 2\sum_{j=1}^{n} \{[(2j-1)/2n] \ln F(x_j) + [1-(2j-1)/2n] \ln [1-F(x_j)]\}, \quad (1)$$

where $j = 1, 2, \ldots, n$ is the number of the determination result C_j in the statistical sample ranked by increasing C value ($C_1 \le C_2 \le \ldots \le C_n$); $x_j = (C_j - C_{av})/S_r$ is the normalized value of the j-th determination result which is distributed with the mean 0 and the standard deviation 1; $F(x_j)$ is the function of the theoretical (normalized normal) distribution. The advantage of this criterion in comparison to the Kolmogorov or other tests for an statistical sample big enough (more than 100 values) consists of the possibility to not divide the data on ranges according their values, and therefore, to use the maximum of the information contained in these data.

The probability that $\omega_n^2 = 1.70$ calculated by us will exceed the corresponding critical value Ω_n^2 (tabulated in the handbook by Owen, 1962) is α. For example, for $\alpha = 0.10$ the value $\Omega_n^2 = 1.94$. The hypothesis on the normal distribution is not rejected at the level of confidence $1-\alpha$, if $\omega_n^2 \le \Omega_n^2$. So, in our case the hypothesis is not rejected as minimum at the level of confidence $1 - 0.10 = 0.90$ ($\Omega_n^2 = 1.70$ at $\alpha = 0.14$).

Corresponding empirical histogram and theoretical distribution one can see in Fig. 1.

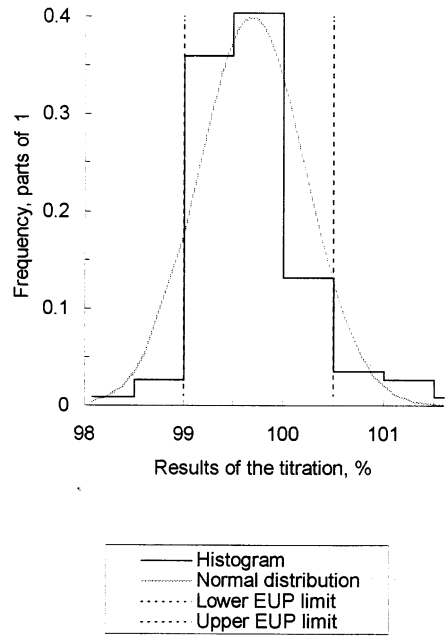

Fig. 1. Empirical histogram and theoretical (normal) distribution of the titration results.

3.1. Control chart

A control chart based on the normal distribution is designed for indication of warning and action limits of the determination results (2 and 3 standard deviations from the average value, correspondingly) and for diagnoses of outliers in the further titrations (Fig. 2). By the normal distribution, the probability that a titration result falls outside the warning lines (98.6–100.8%), when the analysis is under control, is 0.025, i.e. 1 in 40. For example, one can see such results at 6th month in the chart. In this case the analysis should be repeated. The probability to fall randomly outside the action lines (98.1–101.3%) for the analysis under control is only 0.003, i.e. 3 in 1000 (Miller and Miller, 1993). Results of this kind one can see at the beginning of the chart. All the titration conditions, materials and instruments used in the analysis are checked, when it happened.

The warning and action limits of the chart are wider than the EUP limits. So, less than 95% of the results can be accepted as satisfactory.

3.2. Type I and type II errors

The normal distribution of the analyte content in different batches and the normal distributions

of the titration results (assays) at the pharmacopoeia limits are plotted in Fig. 3. The batch distribution has the mean $C_{av} = 99.731\%$ and the standard deviation $S_C = 0.400\%$ (see Table 1). The titration results distributions were constructed for an average of $n_r = 2.04$ replicates, as far as in 98% of the database the assays were calculated from two replicates and only in 2% — from three replicates. Using average standard deviation $S_r = 0.202\%$ of the replicates in an assay (Table 1) one can obtain for the average of n_r replicates the following standard deviation: $S_a = S_r/\sqrt{n_r} = 0.141\%$. So, the left distribution of assays in Fig. 3 has the lower EUP limit $C_{EUP\text{-}ll} = 99.0\%$, as the mean, and the standard deviation $S_a = 0.141\%$. Simultaneously, the right distribution has the upper EUP limit $C_{EUP\text{-}ul} = 100.5\%$, as the mean, and the same standard deviation S_a.

The probabilities of the erroneous decisions on the batch quality can be calculated from these distributions. For example, the probability P_{ll} to obtain a batch with the true content of the cetirizine dihydrochloride less then the lower EUP limit ($C < C_{EUP\text{-}ll}$) is

$$P_{ll} = [1/(S_C\sqrt{2\pi})] \times \int_{-\infty}^{C_{EUP\text{-}11}} \exp\{-(C - C_{av})^2/2S_C^2\}\, dC = 0.034. \quad (2)$$

The probability P_{ul} to obtain a batch with the true content of the cetirizine dihydrochloride more then the upper EUP limit ($C > C_{EUP\text{-}ul}$) is

$$P_{ul} = [1/(S_C\sqrt{2\pi}] \int_{C_{EUP\text{-}ul}}^{+\infty} \exp\{-(C - C_{av})^2/2S_C^2\} \times dC = 0.027. \quad (3)$$

The probabilities P_a to obtain an assay result less then corresponding EUP limit or more then this limit, when the true analyte content equals to the limit, are 0.5 (see Fig. 3). Therefore, the probability $P_{1\text{-}ll}$ of the error of Type 1 (to reject a batch corresponding to the pharmacopoeia requirements) at the lower EUP limit is $P_{1\text{-}ll} = 0.5(1 - P_{ll})$ and equals 0.483. The probability of the error of Type 2 at this limit (to accept a bad batch) is $P_{2\text{-}ll} = 0.5P_{ll}$ and equals 0.017. These probabilities for the upper EUP limit are $P_{1\text{-}ul} = 0.5(1 - P_{ul}) = 0.486$ and $P_{2\text{-}ul} = 0.5\ P_{ul}$ and equals 0.013, correspondingly.

Naturally, for $C > C_{EUP\text{-}ll}$ and $C < C_{EUP\text{-}ul}$ the probabilities $P_{1\text{-}ll}$ and $P_{1\text{-}ul}$ of the error of Type 1 are decreased, while the probabilities $P_{2\text{-}ll}$ and $P_{2\text{-}ul}$ of the error of Type 2 are reduced when C falls out of the the EUP range. It should be noted, that even at the EUP limits the probabilities to accept a bad batch ($P_{2\text{-}ll} = 0.017$ and $P_{2\text{-}ul} = 0.013$) seem not high. However, more detailed analysis 'what is high and what not' can be done only

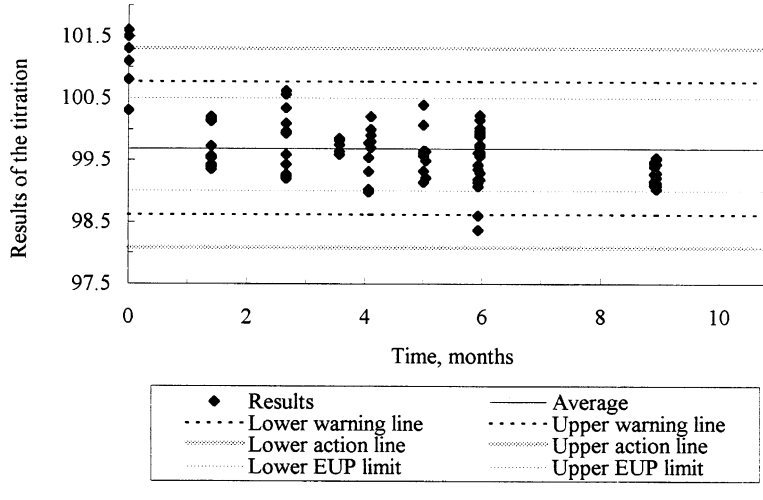

Fig. 2. Control chart of the titration results vs time.

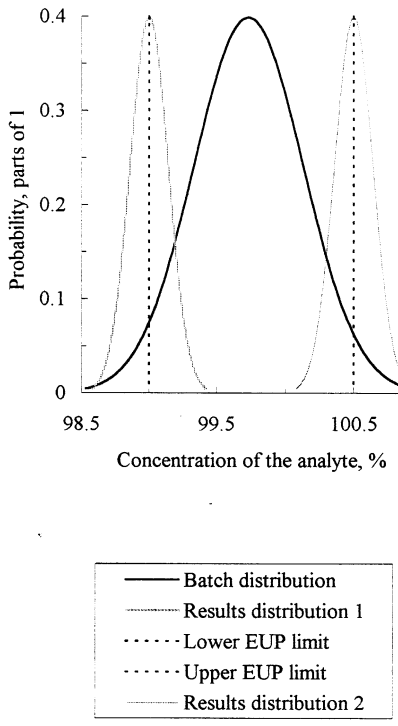

Fig. 3. The normal distribution of the analyte content in different batches and the normal distributions of the titration results at the pharmacopoeia limits.

using economic information on expenses of a cetirizine dihydrochloride producer from the errors in decisions on the material quality and possible their results for the material users.

4. Conclusions

Results of cetirizine dihydrochloride determination during a year are distributed normally. The distribution allows to plot a control chart for diagnosis of outlier results and to analyze the probabilities of errors in decisions on a batch quality.

There are possibilities to improve the quality control of the product by analysis of statistically essential differences between analysts, instruments and other factors. The requirements to the system should be based on the cost of the risks of the erroneous decisions on the batch quality.

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