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ESTIMATION OF THE PROBABILITY OF PASSING THE USP DISSOLUTION TEST

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To ensure that a drug product will meet standards for identity, strength and stability as specified in the United States Pharmacopedia and National Formulary (USP/NF), it needs to pass a number of tests such as the content uniformity test and dissolution test at various stages of the manufacturing process. The sponsors usually have in-house specification limits based on some lower bounds of the probabilities of passing USP/NF tests to make sure that there is a high probability of passing the tests. Several probability lower bounds for dissolution test have been provided in the literature. In this paper, a method of calculating the probabilities of passing the dissolution tests is proposed. For the population mean and variance in some specified range, the probability derived from the methodology is very close to the exact probability. Therefore, the proposed method can provide an easy and accurate way to calculate the probability.

Key Words: Dissolution test.

1. INTRODUCTION

To ensure that a drug product will meet standards for identity, strength, and stability as specified in the United States Pharmacopedia and National Formulary (USP/NF), it needs to pass a number of tests such as the content uniformity test and dissolution test at various stages of the manufacturing process (see Chow and Shao, 2002). A manufacturing process is considered to pass the USP/NF tests if the test results conform to the respective acceptance criteria.

The sponsors usually establish in-house specification limits to make sure that there is a high probability of passing the USP/NF tests. In establishing in-house specification limits, it is necessary to calculate the probability of passing a given USP/NF test. The probability is a function of the population mean and variance under some parameter model assumption, and it does not have an explicit form. Bergum (1990), Chow and Liu (1995), and Chow et al. (2002) provided several lower bounds for the probabilities. Although the probabilities of these USP/NF tests can be derived by computer simulation methods, it is too time consuming to compute when establishing in-house specification limits. Therefore, the lower bounds probability provided in the literature can be of more practical use.

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In this article, we propose a methodology to calculate the probabilities of passing the dissolution test. Numerical analysis in Section 4 shows that the methodology can provide good approximations for the probability. When the population mean and variance are in some range, the derived probability is very close to the exact probability.

2. DISSOLUTION TEST

The USP dissolution test is provided as a standard to determine compliance with the dissolution specifications stated in the individual monograph for a dosage form. It is a three-stage test. Let Q be the amount of dissolved active ingredient specified in the individual monograph of USP/NF. For the first stage, six units are randomly selected. The drug product passes the dissolution test if each unit is not less than $Q + 5\%$. If the product fails to pass at the first stage, an additional six units are randomly selected. The drug product passes the second stage if each unit of the 12 units is not less than $Q - 15\%$ and the average of the 12 units is not less than Q. If the drug product fails to pass the second stage, an additional 12 units are sampled. The drug product passes the third stage if each of the 24 units is not less than $Q - 25\%$, no more than two units are less than $Q - 15\%$ and the average of the 24 units is not less than Q. A product passes the dissolution test if it passes one of the three stages.

Let y_i, $i = 1, \ldots, 24$ denote the sample dissolution testing results and $\bar{y}_k$ denote the average of $y_1, \ldots, y_k$. The event of passing the USF dissolution test can be expressed as follows.

$$
\begin{aligned}
T_1 &= \{y_i \geq Q + 5, i = 1, \ldots, 6\} \\
D_{21} &= \{y_i \geq Q - 15, i = 1, \ldots, 12\} \\
D_{22} &= \{\bar{y}_{12} \geq Q\} \\
D_{31} &= \{y_i \geq Q - 25, i = 1, \ldots, 24\} \\
D_{32} &= \{\text{no more than two } y_i'\text{s} < Q - 15\} \\
D_{33} &= \{\bar{y}_{24} \geq Q\} \\
T_2 &= D_{21} \cap D_{22} \\
T_3 &= D_{31} \cap D_{32} \cap D_{33}
\end{aligned}
$$

The events T_1, T_2, and T_3 are the events which meet the requirements of the first, second and third stages, respectively. The event of passing the dissolution test is $T_1 \cup T_2 \cup T_3$.

3. COVERAGE PROBABILITY

For establishing in-house specification limits, the sponsors need to be aware of the probabilities of passing USP/NF tests. The probabilities of passing the dissolution test is $P(T_1 \cup T_2 \cup T_3)$, respectively. These probabilities can be obtained by computer simulation. The simulation method is to generate N sets of data

and perform the test based on each data set. Let N^* denote the number of times the dissolution test is passed. By the law of large number, $P(T_1 \cup T_2 \cup T_3)$ can be approximated by N^*/N if N is large enough. Since the computer simulation is time consuming, Bergum (1990), Chow and Liu (1995), and Chow et al. (2002) provide several lower bounds for these probabilities for in-house decision making. The lower bounds of Chow et al. (2002) are close to the true probabilities when the population mean and variance are in a reasonably broad range.

In this section, we will derive estimated probabilities of passing the test. These estimated probabilities are very close to the true probabilities when the population mean and variance are in a reasonably broad range.

Assume that y_i, $i = 1, \ldots, 24$, which is the sample dissolution testing results, is normally distributed with known mean μ and variance σ^2. The probability $P(T_1 \cup T_2 \cup T_3)$ can be rewritten as

$$P(T_1) + P(T_2 \cap T_1^c) + P(T_3 \cap T_1^c) - P(T_2 \cap T_3) + P(T_1 \cap T_2 \cap T_3). \tag{1}$$

When σ is small and μ lies in a range $(Q - l, Q + l)$, where l is a constant that is not large, we expect that the probability of $P(y_i < Q - 15)$ and $P(y_i > Q + 5)$ is small. $P(T_1)$ is small and $P(T_1 \cap T_2 \cap T_3)$ is also small compared with the other three probabilities in (1). Therefore, $P(T_1 \cup T_2 \cup T_3)$ can be approximated by $P(T_2 \cap T_1^c) + P(T_3 \cap T_1^c) - P(T_2 \cap T_3)$. The probability $P(T_2 \cap T_1^c)$ can be approximated by the probability $P(D_{22})$ and the probability $P(T_3 \cap T_1^c)$ can be approximated by the probability $P(D_{33})$. Let

$$a = P(D_{22}) = 1 - \Phi((Q - \mu)/(\sigma/\sqrt{12}))$$

and

$$b = P(D_{33}) = 1 - \Phi((Q - \mu)/(\sigma/\sqrt{24})) \tag{2}$$

The probability $P(T_2 \cap T_3)$ can be approximated by $P(D_{22} \cap D_{33})$. Let $x_1 = \bar{y}_{12} = (y_1 + \cdots + y_{12})/12$, $x_2 = (y_{13} + \cdots + y_{24})/12$. Since y_i are i.i.d. from $N(\mu, \sigma^2)$, x_1 and x_2 are independent and identically random variables following $N(\mu, \sigma^2/12)$. The event $D_{22} \cap D_{33}$ can be rewritten as $D' = \{(x_1, x_2) : x_1 \geq Q, (x_1 + x_2)/2 \geq Q\}$.

From Fig. 1, the event D' is the shaded area. The probability of this area is

$$c = \int_{12Q-12\mu}^{\infty} \int_{24Q-24\mu-t_2}^{\infty} \left(\frac{1}{\sqrt{2\pi 12\sigma^2}}\right)^2 e^{-\frac{t_1^2+t_2^2}{24\sigma^2}} dt_1 dt_2. \tag{3}$$

Combining the above result, for μ in a range $(Q - l, Q + l)$ and where σ is not large, we have

$$P(T_1 \cup T_2 \cup T_3) = a + b - c. \tag{4}$$

The probability of passing the dissolution test is (4) when $\mu \in (Q - l, Q + l)$ and σ is not large.

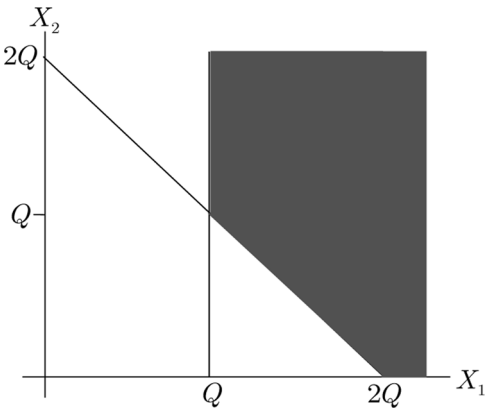

Figure 1 The shaded area is the event D'

4. NUMERICAL COMPARISONS

In this section, the proposed methodology is compared with the true probabilities calculated by simulation. We include some specific cases in the paper. Many other scenarios have been investigated and show results similar to those presented in the paper. Based on the numerical analysis, the proposed methods have good performance in these ranges.

Figure 2 shows the estimated probability and the probability derived from simulation of passing the dissolution test for fixed μ cases with $\mu = 75, 75.5, 76$, and 76.5, and for fixed σ cases with $\sigma = 3, 4, 5$ and 6 when Q is 75%.

Since it is hard to visualize how far off they are from the figures, Tables 1–2 list the probabilities derived from the proposed method and the probability from the simulations for some cases.

Table 1: The table lists the probabilities of passing the dissolution test derived from the proposed method (4) and from the simulation when the population mean is at 75% and $Q = 75\%$.

Table 2: The table lists the probabilities of passing the dissolution test derived from the proposed method (4) and from the simulation when the population mean is at 80% and $Q = 75\%$.

Table 1 Probability when the mean is at 75%

σ	Estimated probability of the proposed method (4)	Probability from simulation
3	0.625	0.6240
4	0.625	0.6267
5	0.625	0.6195
6	0.625	0.6165
7	0.625	0.6170
8	0.625	0.5914
9	0.625	0.5662
10	0.625	0.5173

Table 2 Probability when the mean is at 80%

σ	Estimated probability of the proposed method (4)	Probability from simulation
3	1.000	1.000
4	1.000	1.000
5	1.000	1.000
6	1.000	1.000
7	1.000	1.000
8	0.999	0.997
9	0.998	0.988
10	0.995	0.966

We can see that the estimated probability of passing the dissolution test is very close to the simulation result over a very broad range. From Fig. 2, the estimated probability of passing the dissolution test is different from the simulation result when the σ is greater than 7. However, the estimated probability of passing the dissolution test is still closer to the true probability than the methods in the literature. The estimated probability for the dissolution test is calculated by the software Mathematica.

5. EXAMPLE AND CONCLUSION

An example is given in the following to illustrate an application of the proposed methodology.

Example 1. In establishing in-house specification limits, a sponsor needs to calculate the probabilities of a manufacturing process passing the dissolution test. For applying the proposed methodology as in Eq. (4), the mean and the variance of the quantity of active ingredient dissolved need to be estimated first. We can randomly select n units, and calculate the quantity of active ingredient dissolved in each of the n units. Let $\hat{\mu}$ and $\hat{\sigma}$ denote the sample mean and standard deviation of the sample. Assume $n = 30$ and $\hat{\mu}$ and $\hat{\sigma}$ of the 30 units are 76 and 5. Then use 76 and 5 as estimators of μ and σ. For computing the estimated probability of passing the dissolution test as in Eq. (4), the three integrations in Eqs. (2) and (3) have to be calculated first, which can be computed by software, like Mathematica. When $\mu = 76$ and $\sigma = 5$, the three values of a, b and c are 0.75789, 0.836407, and 0.703812, respectively. Then we have Eq. (4) $= 0.75789 + 0.836407 - 0.703812 = 0.890485$, which is the estimated probability of passing the dissolution test.

In conclusion, the aim of this paper is to provide estimators of probabilities of passing the USP dissolution test. From the numerical analysis, the proposed probability as in Eq. (4) of passing the dissolution test can provide a better estimator compared to the methodologies in the literature. Therefore, the proposed method can provide an easy and accurate way to calculate the probability.

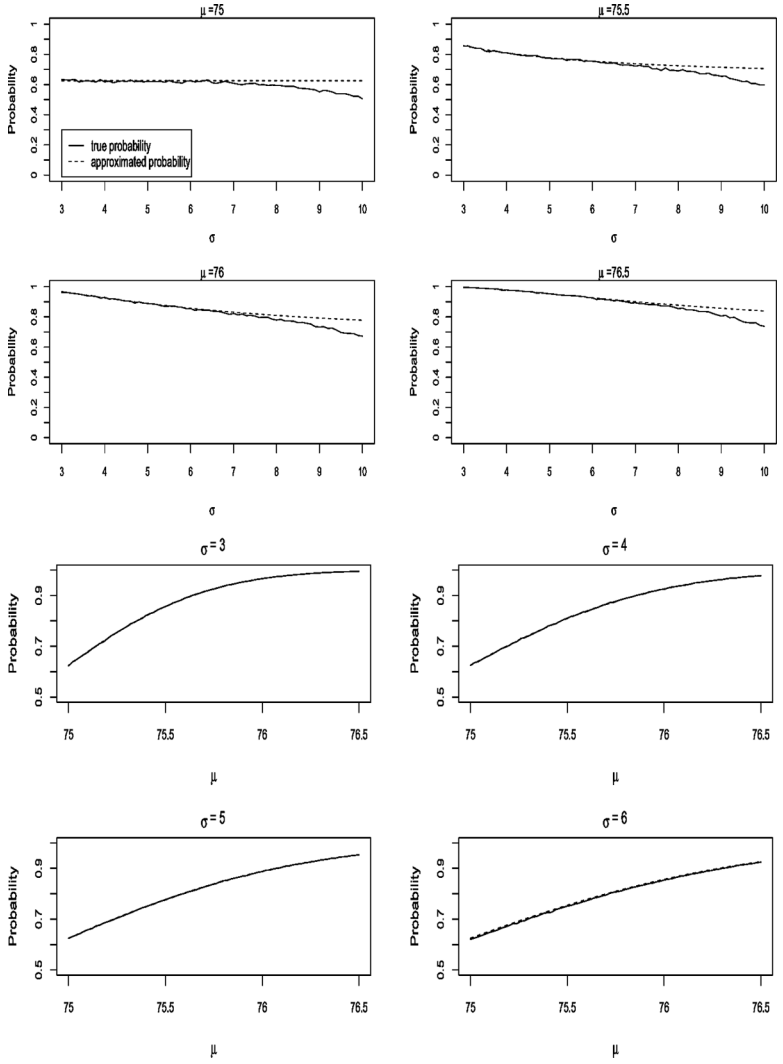

Figure 2 True probability and the estimated probability of passing the dissolution test.

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REFERENCES

USP/NF (2000). *The United States Pharmacopedia XXIII and the National Formulary XVIII*. Rockville, MD: The United States Pharmacopedial Convention.

Bergum, J. S. (1990). Constructing acceptance limits for multiple stage tests. *Drug Dev. Ind. Pharm.* 16:2153–2166.

Chow, S. C., Liu, J. P. (1995). *Statistical Design and Analysis in Pharmaceutical Science*. New York: Marcel Dekker.

Chow, S. C., Shao, J. (2002). *Statistics in Drug Research: Methodologies and Recent Developments*. New York: Marcel Dekker.

Chow, S. C., Shao, J., Wang, H. (2002). Probability lower bounds for USP/NF tests. *J. Biopharm. Stat.* 1:79–92.