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PROBABILITY LOWER BOUNDS FOR USP/NF TESTS

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ABSTRACT

In the pharmaceutical industry, a number of tests such as content uniformity and dissolution testing are usually performed at various stages of drug manufacturing process to ensure that the drug product meets standards for identity, strength, quality, purity, and stability of the drug product as specified in the United States Pharmacopedia and National Formulary (USP/NF). The USP/NF provides requirements for sampling plans, testing procedures, and acceptance criteria for these tests. To ensure that there is a high probability of passing the USP/NF tests, the sponsors usually establish in-house specification limits based on some lower bounds of the probabilities of passing USP/NF tests for future samples. In this article, we derive some probability lower bounds for USP/NF tests. It is shown that the proposed probability lower bounds are better than the existing ones and are very close to the true probabilities in a broad range of the population mean and variance of the test sample.

Key Words: USP/NF test; Content uniformity; Dissolution; In-house specification limit

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INTRODUCTION

To ensure that a drug product will meet the standards for the identity, strength, quality, and purity of the drug product as specified in the United States Pharmacopedia and National Formulary (USP/NF), a number of tests, such as potency testing, weight variation testing, content uniformity testing, dissolution testing, and disintegration testing, are usually performed at various stages of the manufacturing process of the drug product.[1] We will refer to these tests as the USP/NF tests. The USP/NF provides requirements of sampling plans, testing procedures, and acceptance criteria for these tests. For example, requirements for disintegration testing, weight variation and content uniformity testing, and dissolution testing can be found in Sections [701], [705], and [711] of general chapters of the USP/NF, respectively. The requirements are met if the test results conform to the respective acceptance criteria.

For a given USP/NF test, under the specific sampling plan and acceptance criteria, the probability of passing the USP/NF test for test results of a given sample is a function of the population mean and variance (under some parametric model such as the normal model). When the acceptance criteria are complex (e.g., criteria in a multistage test), however, this function does not have an explicit form. Although computer simulation (Monte Carlo) methods can be used to evaluate this function for a given set of population mean and variance, it may be too time consuming to compute this function in establishing in-house specification limits for critical decision making.[2,3] Thus, it is useful to find a lower bound for the probability of passing the USF/NF test that can be easily and quickly evaluated when the population mean and variance are known (or estimated). Lower bounds are considered in the interest of conservative decision for quality assurance.

Bergum[2] and Chow and Liu[3] provided some lower bounds for the probability of passing USP/NF tests such as the dissolution test. These lower bounds, however, are sometimes too low to be of practical use.

The purpose of this article is to derive better lower bounds for the probability of passing USP/NF tests. In particular, we consider weight variation, content uniformity, and dissolution testing for which the probabilities of passing are complex functions of the population mean and variance. The criteria for USP/NF tests are described in the next section. Improved probability lower bounds are derived in the section “Probability Lower Bounds.” In “Numerical Comparisons,” we numerically evaluate the proposed lower bounds and compare them with the true probabilities that are obtained by computer simulation. The results show that the proposed lower bounds are very close to the true probabilities when the population mean and variance are in a reasonably board range.

USP/NF TESTS

A multiple stage sampling is usually employed for a USP/NF test, where each stage involves a number of criteria that must be simultaneously satisfied in order to pass the test. Let S_i denote the event that the ith stage of a k-stage USP/NF test is passed. Also, let C_{ij} be the event that the jth criterion at the ith stage is met, where $j = 1, \ldots, m_i$ and $i = 1, \ldots, k$. Then

$$S_i = C_{i1} \cap C_{i2} \cap \cdots \cap C_{im_i}, \quad i = 1, \ldots, k$$

and the event of passing the USP/NF test is

$$S_1 \cup S_2 \cup \cdots \cup S_k. \tag{1}$$

In what follows, we focus on two USP/NF tests, namely, content uniformity (or weight variation) testing and dissolution testing.

The uniformity of dosage units is usually demonstrated either by weight variation testing or content uniformity testing (see the general chapter [905] of the USP/NF). Content uniformity testing is a two-stage test. In the first stage, 10 dosage units are randomly sampled and assayed individually. From the result of the assay, as described in the individual monograph, the content of the active ingredient in each of the 10 units is calculated. Homogeneous distribution of the active ingredient is assumed. The requirements for dosage uniformity are met if the amount of active ingredient in each of the 10 dosage units lies within the range 85–115% of label claim and the coefficient of variation is less than 6%. If one unit is outside the range 85–115% of label claim and none is outside the range 75–125% of label claim, or if the coefficient of variation is greater than 6%, or if both conditions prevail, then 20 additional units are sampled and tested in the second stage. The requirements are met if not more than one unit of the 30 units is outside the range 85–115% of label claim and no unit is outside the range 75–125% of label claim and the coefficient of variation of the 30 units does not exceed 7.8%.

A mathematical expression of the previously stated test rule can be obtained as follows. Let y_i be the active ingredient of the ith sampled unit and CV_n be the sample coefficient of variation based on $y_1, \ldots, y_n$, $n = 10$ or 30. Define

$$C_{11} = \{85 \le y_i \le 115, i = 1, \ldots, 10\},$$

$$C_{12} = \{\mathrm{CV}_{10} < 6\},$$

$$C_{21} = 75 \le y_i \le 125, i = 1, \ldots, 30\},$$

$$C_{22} = \{\text{no more than one of } y_i\text{'s} < 85 \text{ or } > 115, \quad 1 \le i \le 30\},$$

$$C_{23} = \{\mathrm{CV}_{30} < 7.8\},$$

$$S_1 = C_{11} \cap C_{12},$$

$$S_2 = C_{21} \cap C_{22} \cap C_{23}.$$

Then, the event of passing the USP/NF content uniformity test is $S_1 \cup S_2$.

The general chapter for dissolution testing of USP/NF contains an explanation of the test for acceptability of dissolution rates. The requirements are met if the quantities of active ingredient dissolved from the units conform to the USP/NF acceptance criteria. Let Q be the amount of dissolved active ingredient specified in the individual monograph of USP/NF. The USP/NF dissolution test comprises a three-stage testing procedure. For the first stage, six units are sampled and tested. The product passes the USF/NF dissolution test if each unit is not less than $Q + 5\%$. If the product fails to pass at stage one, an additional six units are sampled and tested at the second stage. The product passes the USF/NF dissolution test if the average of the 12 units from two stages is no smaller than Q and if no unit is less than $Q - 15\%$. If the product fails to pass at stage two, an additional 12 units are sampled and tested at the third stage. If the average of all 24 units from three stages is no smaller than Q, no more than two units are less than $Q - 15\%$, and no unit is less than $Q - 25\%$, the product has passed the USP/NF dissolution test; otherwise the product fails to pass the test.

A mathematical expression of the USP/NF dissolution test can be obtained as follows. Let y_i, $i = 1, \ldots, 6$, be the dissolution testing results from the first stage, y_i, $i = 7, \ldots, 12$, be the dissolution testing results from the second stage, y_i, $i = 13, \ldots, 24$, be the dissolution testing results from the third stage, and $\bar{y}_k$ be the average of $y_1, \ldots, y_k$. Define the following events:

$$S_1 = \{y_i \geq Q + 5, \;\; i = 1, \ldots, 6\},$$

$$C_{21} = \{y_i \geq Q - 15, \;\; i = 1, \ldots, 12\},$$

$$C_{22} = \{\bar{y}_{12} \geq Q\},$$

$$C_{31} = \{y_i \geq Q - 25, i = 1, \ldots, 24\},$$

$$C_{32} = \{\text{no more than two } y_i\text{'s} < Q - 15\},$$

$$C_{33} = \{\bar{y}_{24} \geq Q\},$$

$$S_2 = C_{21} \cap C_{22},$$

$$S_3 = C_{31} \cap C_{32} \cap C_{33}.$$

Then, the event of passing the USP/NF dissolution test is $S_1 \cup S_2 \cup S_3$.

PROBABILITY LOWER BOUNDS

When the event given in Eq. (1) is the event of passing a given USP/NF test, the probability of passing the test,

$$P = P(S_1 \cup S_2 \cup \cdots \cup S_k), \tag{2}$$

can be evaluated by simulation. That is, we generate N sets of data from the distribution of y_i and perform the USP/NF test based on each generated data set. Then

$$P \approx \frac{\text{The number of times the USP/NF test is passed}}{N}. \tag{3}$$

For in-house decision making, it may be more effective to consider a lower bound of P in terms of some probabilities (such as $P(C_{ij})$'s) that can be easily and quickly evaluated or estimated. A simple but rough lower bound for P in Eq. (2) is

$$\begin{aligned} P &\geq \max\{P(S_i), \quad i = 1, \ldots, k\} \\ &\geq \max\left\{0, \sum_{j=1}^{m_i} P(C_{ij}) - (m_i - 1), \quad i = 1, \ldots, k\right\}, \end{aligned}$$

which is used in Refs. [2,3]. For a particular test, however, an improved lower bound may be obtained.

Content Uniformity Testing

Let y_i, CV_n, S_i, and C_{ij} be those defined in section "USP/NF tests." A lower bound for P derived in Appendix A is

$$\underline{P} = \max(0, P_1^{10} + 10P_1^{29}P_2 - P_3 - P_4, P_1^{10} - P_3, P_1^{30} + 30P_1^{29}P_2 - P_4), \tag{4}$$

where

$$P_1 = P(85 \leq y_i \leq 115),$$

$$P_2 = P(75 \leq y_i \leq 85) + P(115 \leq y_i \leq 125),$$

$$P_3 = P(\mathrm{CV}_{10} \geq 6),$$

$$P_4 = P(\mathrm{CV}_{30} \geq 7.8).$$

This lower bound can be easily evaluated if P_j's are known or estimated. If y_i is normally distributed with known mean μ and variance σ^2, then

$$P_1 = \Phi\left(\frac{115-\mu}{\sigma}\right) - \Phi\left(\frac{85-\mu}{\sigma}\right),$$

$$P_2 = \Phi\left(\frac{125-\mu}{\sigma}\right) - \Phi\left(\frac{75-\mu}{\sigma}\right) - P_1,$$

$$P_3 = \mathcal{T}_9\left(\frac{\sqrt{10}}{6}\middle|\frac{\sqrt{10}\mu}{\sigma}\right) - \Phi\left(-\frac{\sqrt{10}\mu}{\sigma}\right)$$

and

$$P_4 = \mathcal{T}_{29}\left(\frac{\sqrt{30}}{7.8}\middle|\frac{\sqrt{30}\mu}{\sigma}\right) - \Phi\left(-\frac{\sqrt{30}\mu}{\sigma}\right),$$

where Φ is the standard normal distribution function and $\mathcal{T}_n(\cdot|\theta)$ is the noncentral t-distribution function with n degrees of freedom and the noncentrality parameter θ. If μ and σ^2 are estimated by $\hat{\mu}$ and $\hat{\sigma}^2$, respectively, then P_j's can be estimated with μ and σ^2 replaced by $\hat{\mu}$ and $\hat{\sigma}^2$, respectively.

Dissolution Testing

Bergum[2] provided the following lower bound for the probability of passing the USP/NF dissolution test:

$$P_B = P_{Q-15}^{24} + 24P_{Q-15}^{23}(P_{Q-25} - P_{Q-15}) + 276P_{Q-15}^{22}(P_{Q-25} - P_{Q-15})^2 - P(\bar{y}_{24} \leq Q) \quad (5)$$

(P_B is replaced by 0 if it is negative), where

$$P_x = P(y_i \geq x).$$

This lower bound is obtained by using the inequalities

$$P(S_1 \cup S_2 \cup S_3) \geq P(S_3)$$

and

$$P(C_{31} \cap C_{32} \cap C_{33}) \geq P(C_{31} \cap C_{32}) - P(C_{33}^{c}),$$

where A^c denotes the complement of the event A, and the fact that $S_3 = C_{31} \cap C_{32} \cap C_{33}$ and y_i's are independent and identically distributed. When the probability $P(C_{33}^{c})$ is not small, these inequalities are not sharp enough.

The following lower bound for the probability of passing the UPS/NF dissolution test is derived in Appendix A:

$$\underline{P} = \max(0, P_B) + \max(0, P_C, P_D) + P_E, \quad (6)$$

where P_B is given by Eq. (5),

$$P_C = P_{Q-15}^{12} - P_{Q-15}^{24} - 12P_{Q-15}^{23}(P_{Q-25} - P_{Q-15}) - 66P_{Q-15}^{22}(P_{Q-25} - P_{Q-15})^2 - P(\bar{y}_{12} < Q)$$

$$P_D = P(\bar{y}_{12} \geq Q, \bar{y}_{24} < Q) - (1 - P_{Q-15}^{12}),$$

and

$$P_E = P_{Q+5}^6 - P_{Q+5}^6 P_{Q-15}^6 - 6P_{Q+5}^6 P_{Q-15}^{17}(P_{Q-25} - P_{Q-15}) - 87P_{Q+5}^6 P_{Q-15}^{16}(P_{Q-25} - P_{Q-15})^2.$$

This lower bound is given in terms of six probabilities P_{Q+5}, P_{Q-15}, P_{Q-25}, $P(\bar{y}_{12} < Q)$, $P(\bar{y}_{24} < Q)$, and $P(\bar{y}_{12} \geq Q, \bar{y}_{24} < Q)$. If y_i is normally distributed with mean μ and variance σ^2, then

$$P_x = 1 - \Phi\left(\frac{x - \mu}{\sigma}\right),$$

$$P(\bar{y}_k < Q) = \Phi\left(\frac{\sqrt{k}(Q - \mu)}{\sigma}\right),$$

and

$$P(\bar{y}_{12} \geq Q, \bar{y}_{24} < Q) = P(\bar{y}_{24} < Q) - P(\bar{y}_{12} < Q, \bar{y}_{24} < Q) = \Phi\left(\frac{\sqrt{24}(Q - \mu)}{\sigma}\right) - \Psi(Q - \mu, Q - \mu),$$

where $x = Q + 5$, $Q - 15$, or $Q - 25$, $k = 12$ or 24, Φ is the standard normal distribution function, and Ψ is the bivariate normal distribution with mean 0 and covariance matrix

$$\frac{\sigma^2}{24}\begin{pmatrix} 2 & 1 \\ 1 & 1 \end{pmatrix}.$$

If μ and σ^2 are unknown, they can be estimated using data from previously sampled test results.

Tsong et al.[4] found that the three-stage dissolution test procedure is rather liberal and is incapable of rejecting a lot with a high fraction of units dissolved less than Q and with an average amount dissolved just slightly larger than Q. One of their suggestion is to change $Q - 15\%$ at stages 2 and 3 of the USP/NF dissolution test to a more stringent limit of $Q - 5\%$, which was proposed by Givand.[5] The corresponding lower bound is still given by Eq. (6) except that P_{Q-15} should be replaced by P_{Q-5}. In fact, the lower bound given by Eq. (6) can be easily modified to investigate properties of the dissolution test that replaces $Q+5\%$, $Q-15\%$, and $Q-25\%$ in the three-stage test by $Q+a\%$, $Q-b\%$, and $Q-c\%$, respectively.

NUMERICAL COMPARISONS

A numerical comparison is made for the true probability of passing the USP/NF content uniformity and dissolution tests, the lower bounds proposed in "Probability

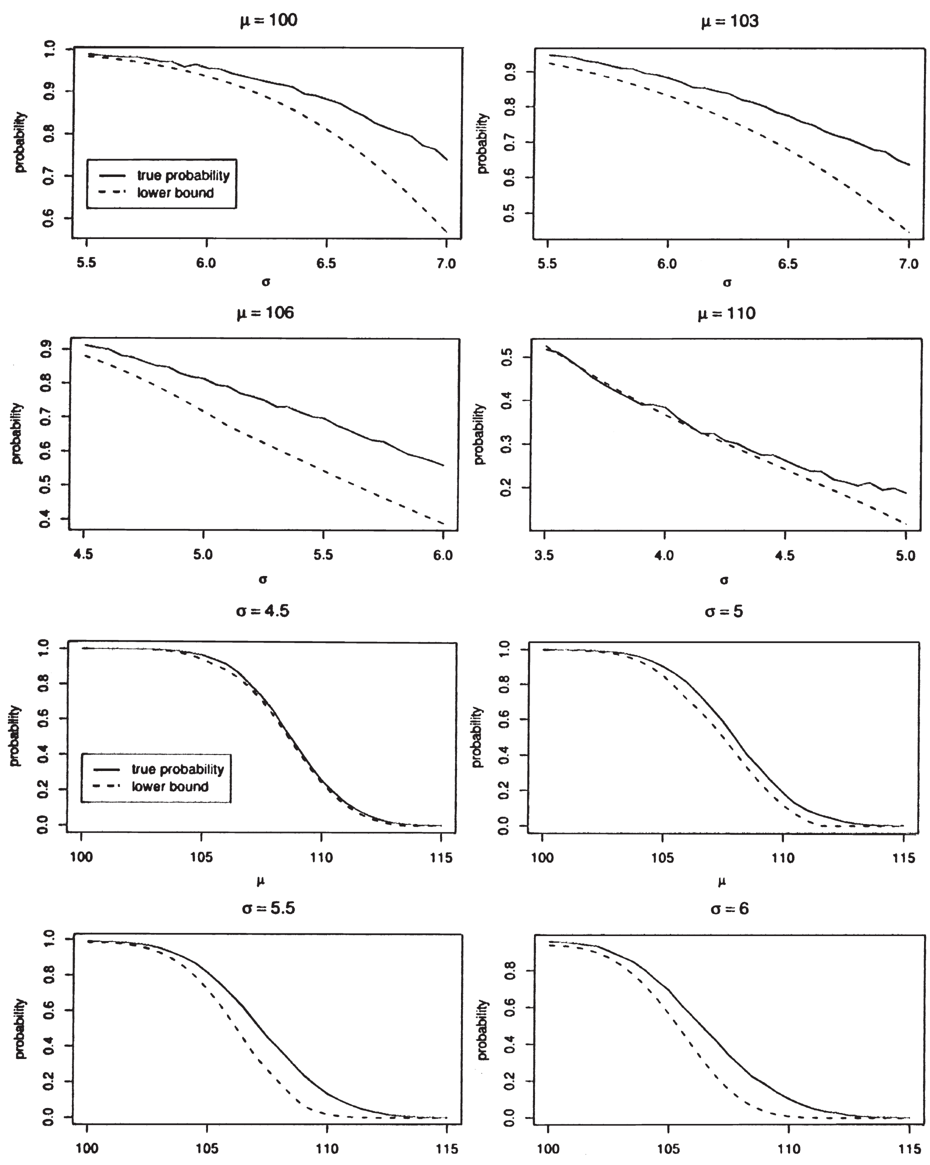

Figure 1. Probability of passing the content uniformity test and its lower bound.

Lower Bounds," and Bergum's lower bound in the case of dissolution testing. It is assumed that y_i's are independently distributed as $N(\mu,\sigma^2)$. The true probabilities for given μ and σ are approximated by Monte Carlo with size $N = 10{,}000$ [see formula (3)]. The lower bounds can be calculated exactly when μ and σ are given.

The results for content uniformity testing are plotted in Fig. 1. It can be seen that the lower bound proposed in "Probability Lower Bounds" is close to the true probability when $\sigma \leq 5$ or $95 \leq \mu \leq 105$.

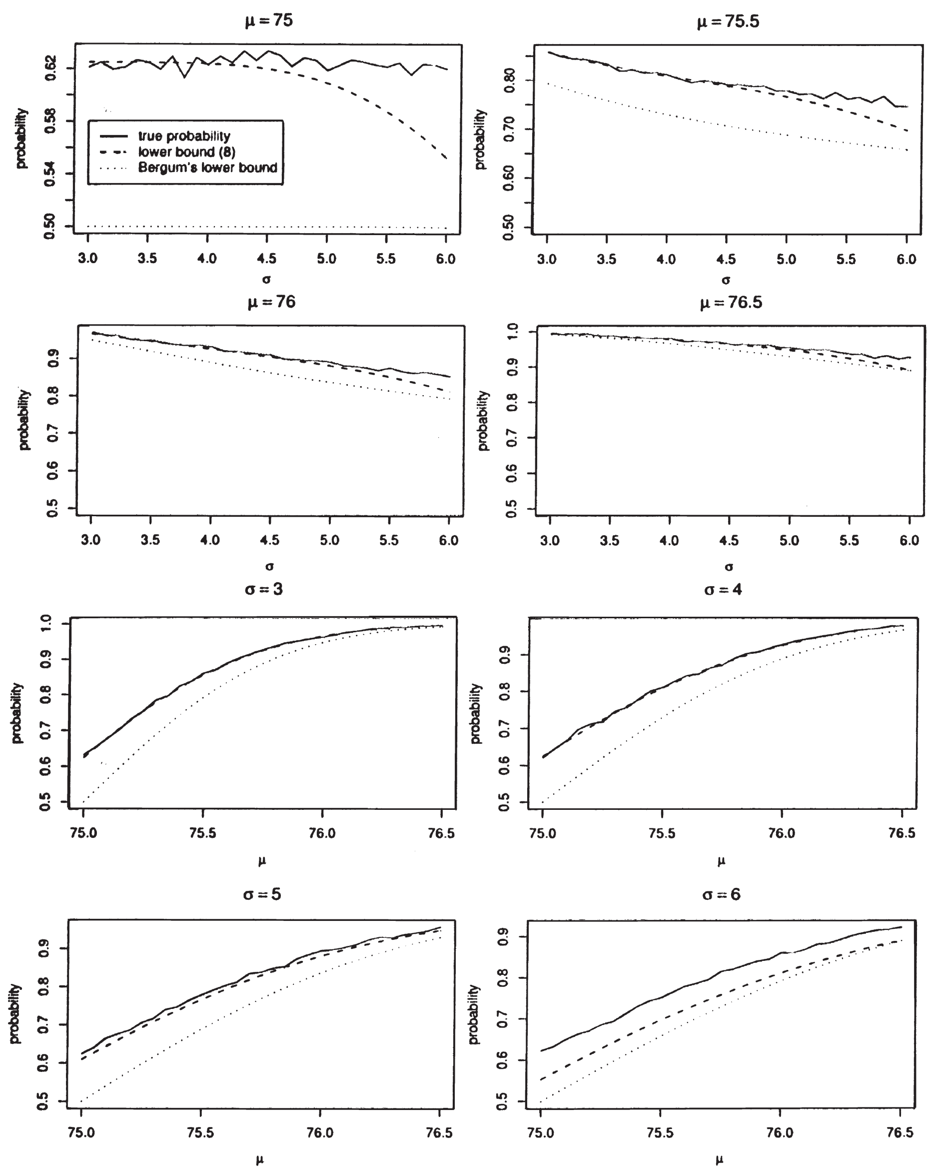

Figure 2. Probability of passing the dissolution test and its lower bounds.

The results for dissolution testing with $Q = 75$ are given in Fig. 2. It is clear that the lower bound given in Eq. (6) is better than Bergum's lower bound and, in fact, it is a very accurate approximation to the true probability when $\sigma \leq 5$.

CONCLUDING REMARKS

In the pharmaceutical industry, it is of interest to ensure that there is a high probability of passing USP/NF tests for future samples. As a result, a set of in-house specification limits for the mean and variance of the test result is usually established based on the probability lower bound of the test. If the test results meet the in-house specification limits, then there is a high probability of passing the USP/NF test. Thus, the improved probability lower bounds not only help in establishing efficient in-house specification limits, but also provide a more accurate and reliable assessment of the passage of USP/NF tests.

APPENDIX A

The Derivation of Bound (4)

Let A^c denote the complement of the event A. Then, the probability of passing the USP/NF content uniformity test is

$$
\begin{aligned}
P &= P(S_1 \cup S_2) = P(S_1) + P(S_1^c \cap S_2) \\
&= P(C_{11} \cap C_{12}) + P(S_1^c \cap C_{21} \cap C_{22} \cap C_{23}) \\
&\geq P(C_{11}) - P(C_{12}^c) + P(C_{11}^c \cap C_{21} \cap C_{22}) - P(C_{23}^c) \\
&= P_1^{10} + 10P_1^{29}P_2 - P_3 - P_4,
\end{aligned}
$$

where the last equality follows from the fact that y_i's are independent and identically distributed and

$$
P(C_{11}^c \cap C_{21} \cap C_{22}) = 10P\begin{pmatrix} 75 \leq y_1 < 85 \text{ or } 115 < y_1 \leq 125 \\ 85 \leq y_i \leq 115,\ i = 2, \ldots, 30 \end{pmatrix}.
$$

On the other hand,

$$
P = P(S_1 \cup S_2) \geq P(S_1) \geq P(C_{11}) - P(C_{12}^c) = P_1^{10} - P_3
$$

and

$$
P = P(S_1 \cup S_2) \geq P(S_2) \geq P(C_{21} \cap C_{22}) - P(C_{23}^c) = P_1^{30} + 30P_1^{29}P_2 - P_4.
$$

Combining these results, we obtain the lower bound (4).

The Derivation of Bound (6)

Since the probability of passing the USP/NF dissolution test is

$$P = P(S_3) + P(S_2 \cap S_3^c) + P(S_1 \cap S_2^c \cap S_3^c),$$

a lower bound for P can be obtained by deriving a lower bound for each of $P(S_3)$, $P(S_2 \cap S_3^c)$, and $P(S_1 \cap S_2^c \cap S_3^c)$. We take Bergum's bound P_B in Eq. (5) as the lower bound for $P(S_3)$. For $P(S_2 \cap S_3^c)$, consider the fact that

$$\begin{aligned} P(S_2 \cap S_3^c) &= P(C_{21} \cap C_{22} \cap S_3^c) \\ &\geq P(C_{21} \cap S_3^c) - P(C_{22}^c) \\ &= P(C_{21} \cap C_{31}^c) + P(C_{21} \cap C_{31} \cap C_{32}^c) \\ &\quad + P(C_{21} \cap C_{31} \cap C_{32} \cap C_{33}^c) - P(\bar{y}_{12} < Q) \\ &\geq P(C_{21} \cap C_{31}^c) + P(C_{21} \cap C_{31} \cap C_{32}^c) - P(\bar{y}_{12} < Q). \end{aligned}$$

Since y_i's are independent and identically distributed,

$$P(C_{21} \cap C_{31}^c) = P(C_{21}) - P(C_{21} \cap C_{31}) = P_{Q-15}^{12} - P_{Q-15}^{12} P_{Q-25}^{12}.$$

Note that

$$\begin{aligned} P(C_{21} \cap C_{31} \cap C_{32}) &= P(y_i \geq Q - 15,\ i = 1, \ldots, 24) \\ &\quad + 12P\begin{pmatrix} y_i \geq Q - 15,\ i = 1, \ldots, 23 \\ Q - 25 \leq y_{24} < Q - 15 \end{pmatrix} \\ &\quad + \binom{12}{2} P\begin{pmatrix} y_i \geq Q - 15,\ i = 1, \ldots, 22 \\ Q - 25 \leq y_i < Q - 15,\ \ i = 23, 24 \end{pmatrix} \\ &= P_{Q-15}^{24} + 12P_{Q-15}^{23}(P_{Q-25} - P_{Q-15}) \\ &\quad + 66P_{Q-15}^{22}(P_{Q-25} - P_{Q-15})^2. \end{aligned}$$

Hence,

$$P(C_{21} \cap C_{31} \cap C_{32}^{c}) = P(C_{21} \cap C_{31}) - P(C_{21} \cap C_{31} \cap C_{32})$$
$$= P_{Q-15}^{12} P_{Q-25}^{12} - P_{Q-15}^{24} - 12 P_{Q-15}^{23} (P_{Q-25} - P_{Q-15})$$
$$- 66 P_{Q-15}^{22} (P_{Q-25} - P_{Q-15})^2.$$

Thus, a lower bound for $P(S_2 \cap S_3^c)$ is

$$P_C = P_{Q-15}^{12} - P_{Q-15}^{24} - 12 P_{Q-15}^{23} (P_{Q-25} - P_{Q-15})$$
$$- 66 P_{Q-15}^{22} (P_{Q-25} - P_{Q-15})^2 - P(\bar{y}_{12} < Q), \tag{7}$$

This lower bound is good when $P(\bar{y}_{12} < Q)$ is small. On the other hand,

$$P(S_2 \cap S_3^c) = P(C_{21} \cap C_{22} \cap (C_{31} \cap C_{32} \cap C_{33})^c)$$
$$\geq P(C_{21} \cap C_{22} \cap C_{33}^c) \geq P(C_{22} \cap C_{33}^c) - P(C_{21}^c)$$
$$= P(\bar{y}_{12} \geq Q, \bar{y}_{24} < Q) - (1 - P_{Q-15}^{12}).$$

The previous two inequalities provide an accurate lower bound if $P(C_{21}^c)$ and $P(C_{21} \cap C_{31}^c \cup C_{32}^c)$ are small. Thus, a better lower bound for $P(S_2 \cap S_3^c)$ is the larger of P_C in Eq. (7) and

$$P_D = P(\bar{y}_{12} \geq Q, \bar{y}_{24} < Q) - (1 - P_{Q-15}^{12}).$$

For $P(S_1 \cap S_2^c \cap S_3^c)$, consider the fact that

$$P(S_1 \cap S_2^c \cap S_3^c) = P(S_1 \cap C_{21}^c \cap S_3^c) + P(S_1 \cap C_{21} \cap C_{22}^c \cap S_3^c)$$
$$\geq P(S_1 \cap C_{21}^c \cap S_3^c)$$
$$= P(S_1 \cap C_{21}^c \cap C_{31}^c) + P(S_1 \cap C_{21}^c \cap C_{31} \cap C_{32}^c)$$
$$+ P(S_1 \cap C_{21}^c \cap C_{31} \cap C_{32} \cap C_{33}^c)$$
$$\geq P(S_1 \cap C_{21}^c \cap C_{31}^c) + P(S_1 \cap C_{21}^c \cap C_{31} \cap C_{32}^c)$$
$$= P(S_1 \cap C_{21}^c \cap C_{31}^c) + P(S_1 \cap C_{21}^c \cap C_{31})$$
$$- P(S_1 \cap C_{21}^c \cap C_{31} \cap C_{32})$$
$$= P(S_1 \cap C_{21}^c) - P(S_1 \cap C_{31} \cap C_{32})$$
$$+ P(S_1 \cap C_{21} \cap C_{31} \cap C_{32}).$$

Since

$$P(S_1 \cap C_{21}^{c}) = P(S_1) - P(S_1 \cap C_{21}) = P_{Q+5}^{6} - P_{Q+5}^{6} P_{Q-15}^{6},$$

$$\begin{aligned}
P(S_1 \cap C_{31} \cap C_{32}) = {} & P\begin{pmatrix} y_i \geq Q+5,\ i = 1, \ldots, 6 \\ y_i \geq Q-15,\ i = 7, \ldots, 24 \end{pmatrix} \\
& + 18P\begin{pmatrix} y_i \geq Q+5,\ i = 1, \ldots, 6 \\ y_i \geq Q-15,\ i = 7, \ldots, 23 \\ Q-25 \leq y_{24} < Q-15 \end{pmatrix} \\
& + \binom{18}{2} P\begin{pmatrix} y_i \geq Q+5,\ i = 1, \ldots, 6 \\ y_i \geq Q-15,\ i = 7, \ldots, 22 \\ Q-25 \leq y_i < Q-15,\ i = 23, 24 \end{pmatrix} \\
= {} & P_{Q+5}^{6} P_{Q-25}^{18} + 18 P_{Q+5}^{6} P_{Q-15}^{17} (P_{Q-25} - P_{Q-15}) \\
& + 153 P_{Q+5}^{6} P_{Q-15}^{16} (P_{Q-25} - P_{Q-15})^2
\end{aligned}$$

and

$$\begin{aligned}
P(S_1 \cap C_{21} \cap C_{31} \cap C_{32}) = {} & P\begin{pmatrix} y_i \geq Q+5,\ i = 1, \ldots, 6 \\ y_i \geq Q-15,\ i = 7, \ldots, 24 \end{pmatrix} \\
& + 12P\begin{pmatrix} y_i \geq Q+5,\ i = 1, \ldots, 6 \\ y_i \geq Q-15,\ i = 7, \ldots, 23 \\ Q-25 \leq y_{24} < Q-15 \end{pmatrix} \\
& + \binom{12}{2} P\begin{pmatrix} y_i \geq Q+5,\ i = 1, \ldots, 6 \\ y_i \geq Q-15,\ i = 7, \ldots, 22 \\ Q-25 \leq y_i < Q-15,\ i = 23, 24 \end{pmatrix} \\
= {} & P_{Q+5}^{6} P_{Q-15}^{18} + 12 P_{Q+5}^{6} P_{Q-15}^{17} (P_{Q-25} - P_{Q-15}) \\
& + 66 P_{Q+5}^{6} P_{Q-15}^{16} (P_{Q-25} - P_{Q-15})^2,
\end{aligned}$$

a lower bound for $P(S_1 \cap S_2^c \cap S_3^c)$ is

$$P_E = P_{Q+5}^6 - P_{Q+5}^6 P_{Q-15}^6 - 6P_{Q+5}^6 P_{Q-15}^{17}(P_{Q-25} - P_{Q-15}) - 87P_{Q+5}^6 P_{Q-15}^{16}(P_{Q-25} - P_{Q-15})^2.$$

Combining these results, we obtain the lower bound (6) for the probability of passing the UPS/NF dissolution test.

REFERENCES

1. USP/NF, *The United States Pharmacopedia XXIII and the National Formulary XVIII*; The United States Pharmacopedial Convention: Rockville, MD, 2000.
2. Bergum, J.S. Constructing Acceptance Limits for Multiple Stage Tests. Drug Dev. Ind. Pharm. **1990**, *16*, 2153–2166.
3. Chow, S.C.; Liu, J.P. *Statistical Design and Analysis in Pharmaceutical Science*; Marcel Dekker: New York, 1995.
4. Tsong, Y.; Hammerstorm, T.; Lin, K.K.; Ong, T.E. The Dissolution Testing Sampling Acceptance Rules. J. Biopharm. Stat. **1995**, *5*, 171–184.
5. Givand, T.E. An Evaluation of the Dissolution Test Acceptance Sampling Plan of USP XX. Pharmacopeial Forum **1980**, *March–April*, 186–190.