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溶離率試驗機率之統計評估

A Statistical Evaluation on the Probability of USP Dissolution Test

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中文摘要

溶離率指的是藥錠或膠囊類藥物在人體內溶解的百分率，此一特性會直接影響到藥物中的有效成分釋出及人體吸收率。故在每一批藥品出廠時，都必須檢驗其溶離率是否符合在藥典中所註冊之溶離率。USP/NF(United States Pharmacopeia and National Formulary)提供了一個三階段式的溶離率試驗流程，用以檢驗一批藥物的溶離率是否符合要求。藥物生產者在將藥物產品送檢之前，可先抽一份樣本，用以估計該批藥物通過溶離檢驗。但由於在USP/NF的溶離率試驗流程中，其三階段皆不獨立，且各階段中也同時要求平均值要保持在標準值之上以及淘汰劣質品的條件。這些彼此不獨立的檢驗條件，造成了通過機率的估算式難以用明確的式子表達。在過去的文獻中，除了對於通過機率給予一個下界估計值，也有在限定條件下，直接對通過機率給於一個近似的估計方法。在本論文中，借由蒙地卡羅的大量模擬法，將需要討論之參數範圍做適當的切割，把所有的通過機率精確的估算出來。並將模擬結果製成表格，提供使用者一個明確容易的方法來得 到藥品通過溶離率檢驗機率之估計值。

關鍵字: USP/NF溶離率檢驗、通過檢驗之機率 、 三階段不獨立之試驗流程、蒙地卡羅模擬法

Abstract

Dissolution is the rate that drug dissolves in human body from a solid dosage form(tablet, capsule) after oral administration. It directly influences the quantity of chemical compound releasing from drug. So dissolution is important to the strength of drugs. The dissolution rate of each drug product is then needed to be examined before it release to consumers. For testing whether a drug product has an enough dissolution rate, the United States Pharmacopeia and National Formulary (USP/NF) provides a three-stage dissolution testing procedure. The sponsors usually wants to establish in-house passing probability. The USP/NF dissolution testing procedure is a three-stages test and these stages are dependent. In addition, the criteria at each stage consists of the characteristic of individual units (individual requirements) and the distribution of the sample means (average requirements). It follows that the average requirement and individual requirement are not only dependent within the stage but also correlated between stages. As a result, approximated methods may provide over-estimation or under-estimation of the true passing probability. In this thesis, we use Monte Carlo simulation to provide accurate estimations. Tables of the passing probabilities are provided for practical use. An example is given to illustrate the application of

the proposed methods.

Keyword: USP/NF dissolution test, passing probability, dependent three-stage procedure, Monte Carlo simulation

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Chapter 1

Introduction

The United States Pharmacopeia and National Formulary (USP/NF) is an official public standards-setting authority for all prescription and over-the-counter medicines and other health care products manufactured or sold in the United States(USP/NF, 2000). Pharmacopeia is a book containing a compilation of pharmaceutical products with their formulas and methods of preparation. When a new drug was discovered and developed, all its properties and specifications must be registered in the pharmacopeia. These standards help to ensure the identity, quality, purity, strength, and consistency of pharmaceutical products made for public consumption. For examining whether each drug product satisfies the standards or not, the USP/NF defined sampling plans, testing procedure, and acceptance criteria for each property of the drug. These tests are content uniformity testing, disintegration testing, dissolution testing, potency testing, weight variation testing, and others (USP/NF, 2000). All above-mentioned tests are called USP/NF tests. These standards of USP/NF are recognized and used in more than 130 countries around the globe. Before a drug product is released to consumers, it must pass USP/NF tests.

In this thesis, we will focus on the USP/NF dissolution testing. Dissolution is the rate that drug dissolves in human body from a solid dosage form (tablet or capsule) after oral administration. It directly influences on the quantity of the chemical compound releasing from drug. So dissolution is important to the strength of drugs. It needs a sufficient dissolution rate of drug to ensure that sufficiently pharmaceutical active ingredients will permeate across the gastrointestinal tract. Therefore, the dissolution rate is equal to absorbability of a drug. The USP/NF dissolution test measures the dissolution rate of a drug with the *in-vitro* condition.

The USP/NF dissolution test is a three-stage testing procedure. Let Q be the amount of dissolved active ingredient specified in the individual monograph of USP/NF. The first stage, 6 units are randomly selected from the batch of drugs. The drug product passes the dissolution test if each unit is not less than Q + 5%. If the drug product fails to pass the first stage, it needs to sample additional 6 units randomly. The criteria for the second stage are based on these 12 dosage units. For the second stage, the batch of drugs passes this stage if each unit of the 12 units is not less than Q − 15% and if the average of the 12 units is not less than Q. If the drug product fails to pass the second stage, additional 12 dosage units are randomly sampled. Based on the 24 dosage units from all three stages 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, the batch of drugs passes the USP/NF dissolution test. If the batch of drugs fails at the third stage, it fails to pass the USP/NF dissolution test. Table 1.1 provides a summary of the USP/NF three-stage dissolution test.

We could express each condition at these three stages with events. Let $y_i, i = 1, \ldots, 6$, be the 6 randomly selected units at the first stage, $y_i, i = 7, \ldots, 12$, be the 6 randomly selected units at the second stage, $y_i, i = 13, \ldots, 24$, be the 12 randomly selected units at the third stage. And $\bar{y}_6$ be the average of 6 units at the first stage, $\bar{y}_{12}$ be the average of 12 units at the second stage, $\bar{y}_{24}$ be the average of 24 units at the third stage. These stages are expressed by the events as follows:

Define:

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

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

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

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

$C_{32} = \{$no more than two y_i's$<$ Q $-15, i = 1, \ldots, 24\}$, and

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

The event of the passing probability for the second stage is the intersection of C_{21} and C_{22} as

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

Similarly, the event of the passing probability for the third stage is the intersection of C_{31}, C_{32}, and C_{33} as

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

The event of passing the USP/NF dissolution test is then the union of S_1, S_2, and S_3 as $S_1 \cup S_2 \cup S_3$.

A graphical presentation of the USP/NF dissolution test by event is provided in Figure 1.1. Besides, S_1, S_2, and S_3 are dependent; C_{21} and C_{22} are dependent; C_{31}, C_{32}, and C_{33} are dependent. These dependences results in that the explicit form of the passing probability is difficult to derive.

The sponsors usually try to estimate the probability of passing the USP/NF tests for each batch of drug.

Since the USP/NF dissolution test is not developed by statistician, the passing probability has not an explicit form. The true passing probability is too complicated to derive and unknown even the true population mean and variance are known. The main interest is to find a method that unbiasedly estimates the passing probability of USP/NF tests of certain drug products with high accuracy. This way can help sponsors understand the quality of each batch of drug products, and could effectively make in-house decision.

Bergem(1990) suggests a lower bond of the passing probability that constructs the acceptance limit for multiple stage test. But the lower bound is not established especially for the USP/NF dissolution test. Consequently, it is a very crude estimate,which severely under-estimates the passing probability. Chow(2002) provides probability lower bounds for USP/NF content uniformity testing and dissolution testing respectively. But the lower bound for USP/NF is conservative when the variation of population is large. Wang(2007) gives an approximate formula for estimating the probability of passing the USP/NF dissolution test. This approximation is based on the assumption that population average and variation lie in the pre-defined region. If this assumption is violated, it could result in an over-estimation of the true passing probability.

All the above methods should be compared to the true passing probability. How could we getting the true probability? In the fact, the true probability of passing the USP/NF tests could be estimated precisely by the Monte Carlo algorithm if the number of replicates of simulation is large. Under certain randomness assumption, we can set all the random units in program, then to simulate the procedure of USP/NF tests for N times. Let N* be the numbers of times for which the USP/NF test is passed. If the N large enough, the passing probability could be estimated by N*/N with high accuracy . We construct tables for estimated passing probability by the simulation method. In addition, the passing probability at each stage will also be estimated and discussed. Furthermore, within each stage, the passing probability the individual characteristics and the mean characteristics are also estimated. On the other hand, the estimated passing probability by the simulation method are compared with those proposed by Bergum(1990) and Wang(2007). We also provide the table of passing probability for practical use. A numerical example is provided in Chapter 4 to illustrate the application of the proposed method. Discussion and conclusion are given in Chapter 5.

Table 1.1: Acceptance Criteria for Dissolution

Stage	Added units	Pass if:
S_1	6	Each unit is not less than Q+5 %
S_2	6	Average of 12 units is equal to or greater than Q, and no unit is less than Q−15%
S_3	12	Average of 24 units is equal to or greater than Q no more than two units are less than Q−15% , and no unit is less than Q−25%

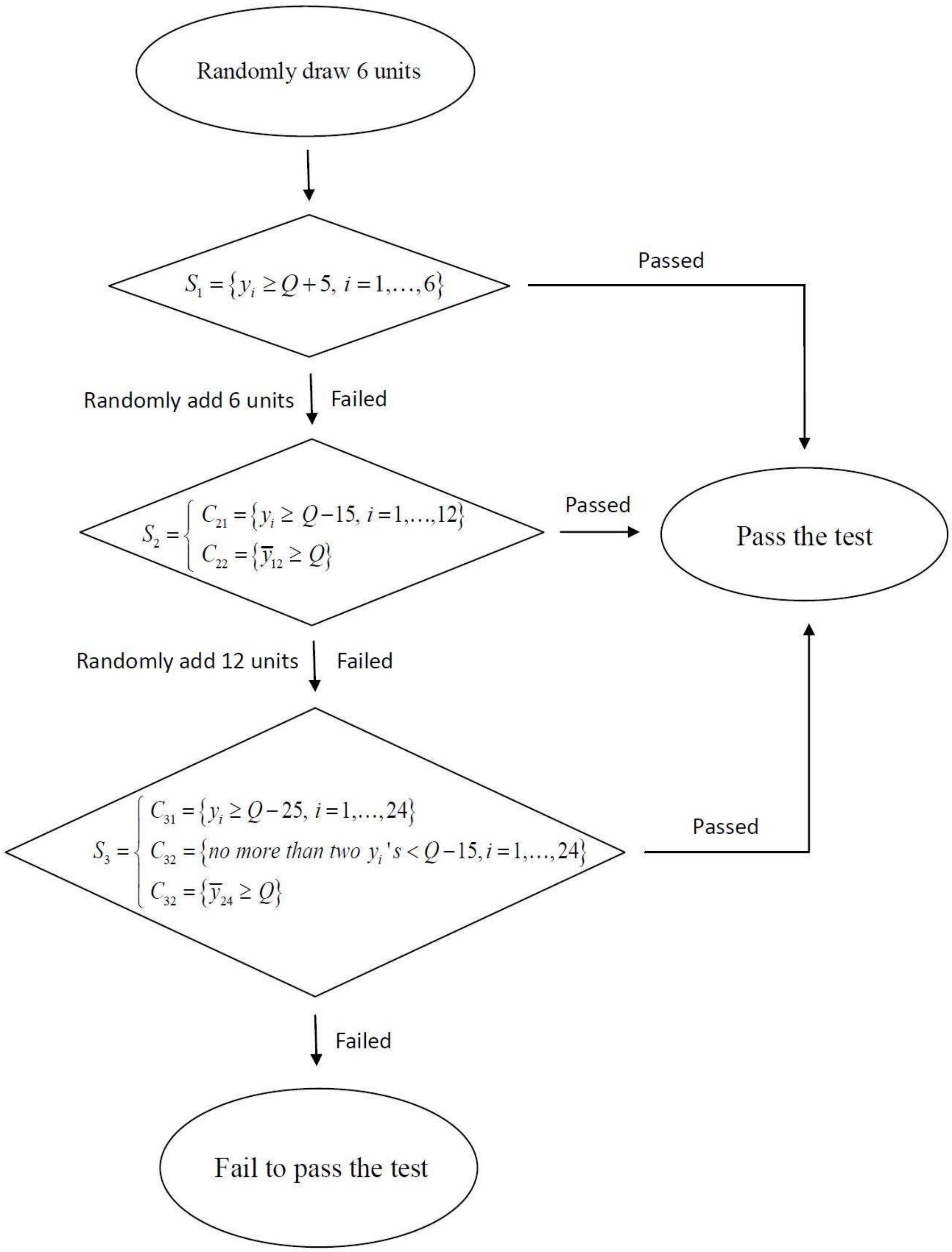

Figure 1.1: Graphical presentation of USP/NF dissolution test

Chapter 2

Literatures review

2.1 Assumptions

The dissolution rates of all units are assumed to be identically independently distributed(i.i.d) as a normal distribution with unknown mean (μ)and unknown variance (σ^2). The passing probability can be expressed by a function of Q , μ ,and σ. Since μ and σ are unknown,we can estimate them by the sample mean($\bar{x}$) and sample standard deviation(s), respectively. Then the probability of passing USP/NF dissolution test can be established.

2.2 Bergum's method

Bergum(1990) provided a lower bound for multiple stages tests. For USP/NF dissolution test, it is derived by following formula:

Since

$P(S_2) = P(C_{21} \cap C_{22}) = P(C_{21}) + P(C_{22}) - P(C_{21} \cup C_{22})$

$\geq P(C_{21}) + P(C_{22}) - 1$,and

$P(S_3) = P(C_{31} \cap C_{32} \cap C_{33}) = P(C_{31} \cap C_{32}) + P(C_{33}) - P[(C_{31} \cup C_{32}) \cup C_{33}]$

$\geq P(C_{31} \cap C_{32}) + P(C_{33}) - 1,$

it follows that

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

$\geq \text{Max } (P(S_1), P(S_2), P(S_3))$

$\geq \text{Max } (P(S_1), P(C_{21}) + P(C_{22}) - 1, P(C_{31} \cap C_{32}) + P(C_{33}) - 1).$

Furthermore

$P(S_1) = [P(Q + 5 \leq Y_i)]^6,$

$P(C_{21}) + P(C_{22}) = [P(Q - 15 \leq Y_i)]^{12} + P(Q \leq \bar{Y}_{12}),$

$P(C_{31} \cap C_{32}) = \binom{24}{2}[P(Q - 25 \leq Y_i \leq Q - 15)]^2[P(Q - 15 \leq Y_i)]^{22}$

$+\binom{24}{1}P(Q-25 \leq Y_i \leq Q-15)[P(Q-15 \leq Y_i)]^{23} + [P(Q-15 \leq Y_i)]^{24}$,and

$P(C_{33}) = P(Q \leq \bar{Y}_{24}).$

The probabilities of above-mentioned events all can be calculated. Therefore the lower bound can be estimated by substituting population mean and standard deviation by the sampling mean and standard deviation.

2.3 Wang's Method

Wang(2007) gives an approximation of the passing probability of USP/NF dissolution test. It assumes that μ lies in the interval $(Q-l, Q+l)$ and σ is small. And l is a constant that is not large. The passing probability can be reexpressed as follows:

Since

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

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

the passing probability can then be factorized as

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

$= P(S_1) + P(S_2) + P(S_3) - P(S_1 \cap S_2) - P(S_1 \cap S_3) - P(S_2 \cap S_3)$

$+P(S_1 \cap S_2 \cap S_3)$

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

Further assume that all tailed probability involving the unit characteristics are assumed zero, i.e., $P(Y_i > Q+5) = 0$, $P(Y_i < Q-15) = 0$, and $P(Y_i < Q-25) = 0$. In other words, all tailed probability are ignored. So the terms involving S_1 are deleted. These events S_1^c, C_{21} , C_{31} ,and C_{32} are bounded to occur with probability 1. It follows that approximation formula is given as

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

$\approx P(S_1^c \cap S_2) + P(S_1^c \cap S_3) - P(S_2 \cap S_3)$.

Because

$\bar{Y}_{12} \sim N(\mu, \sigma^2/12)$, and

$\bar{Y}_{24} \sim N(\mu, \sigma^2/24)$,

these terms are approximated by

$P(S_1^c \cap S_2) \approx P(S_2) = P(C_{21} \cap C_{22}) \approx P(C_{22}) = 1 - \Phi(\frac{Q-\mu}{\sigma/\sqrt{12}})$,

$P(S_1^c \cap S_3) \approx P(S_3) = P(C_{31} \cap C_{32} \cap C_{33}) \approx P(C_{33}) = 1 - \Phi(\frac{Q-\mu}{\sigma/\sqrt{24}})$, and

$P(S_2 \cap S_3) = P(C_{21} \cap C_{22} \cap C_{31} \cap C_{32} \cap C_{33}) \approx P(C_{22} \cap C_{33})$

Let

$X_1 = \bar{Y}_{12} = (Y_1 + \cdots + Y_{12})/12$, and

$X_2 = 2\bar{Y}_{24} - \bar{Y}_{12} = (Y_{13} + \cdots + Y_{24})/12$.

The event $C_{22} \cap C_{33}$ is equal to $D' = \{(x_1, x_2) : x_1 \geq Q, \frac{x_1+x_2}{2} \geq Q\}$.

Furthermore

$X_1 \sim N(\mu, \sigma^2/12)$,

$X_2 \sim N(\mu, \sigma^2/12)$,and

X_1 and X_2 are independent

Let W_1 and W_2 be the standardized variables of X_1 and X_2 as

$W_1 = (X_1 - \mu)/(\sigma/\sqrt{12})$, and

$W_2 = (X_2 - \mu)/(\sigma/\sqrt{12})$.

W_1, W_2 are independent standard normal variables.

Now the probability $P(C_{22} \cap C_{33})$ can be derived by integration from the joint distribution of W_1 and W_2. The approximation of the passing probability can be obtained by following formula:

$$P(S_1 \cup S_2 \cup S_3) \approx P(C_{22}) + P(C_{33}) - P(C_{22} \cap C_{33})$$

$$= [1 - \Phi(\frac{Q-\mu}{\sigma/\sqrt{12}})] + [1 - \Phi(\frac{Q-\mu}{\sigma/\sqrt{24}})]$$

$$- \int_{12Q-12\mu}^{\infty} \int_{24Q-24\mu-w_2}^{\infty} (\frac{1}{\sqrt{2\pi 12\sigma^2}})^2 exp[-\frac{w_1^2 + w_2^2}{24\sigma^2}] dw_1 dw_2$$

The integration can be calculated by numerical method.

Chapter 3

Proposed Method - Monte Carlo Simulation

The simulation method is to randomly generate N sets of samples and perform the testing procedure based on each data set. Let N* denote the number of sets of samples that the USP/NF dissolution test is passed. The passing probability $P(S_1 \cup S_2 \cup S_3)$ can be approximated by the proportion N*/N if N is large enough. Since the passing probability is a function of Q , μ ,and σ. More precisely, it is a function of $\mu-$Q and σ. The range of σ is from 0.5 to 10, dividing by 0.1 . Compaq Visual Fortran 6.5 and IMSL's STAT/LIBRARY FORTRAN subroutines RNNOA were used to generate the normal variables with specified means and standard deviations.

All the simulations follow the procedure of the USP/NF dissolution test.

In the beginning, we set a combination of parameters(μ, σ and Q) and randomly generate 6 units. At first stage,if these 6 units satisfy the S_1 event, then it passes the test; if not, we randomly add other 6 units and begin next stage. At second stage, we combine these 12 units. If these 12 units satisfy the S_2 event, it passes the test; if not, we randomly add other 12 units and begin next stage. At third stage, we combine these 24 units. If these 24 units satisfy the S_3 event, it passes the test; if not, it fails the test. Each combination of parameters is simulated 100,000 times. Then we can use the times of passing the test to estimate the passing probability on each combination of parameters. The program code is applied in Appendix A.

According to the simulation results, when μ−Q = 0, the passing probability over all possible value of σ is only up to 0.6. When μ−Q = 5 and $\sigma < 9$, the passing probabilities exceeds over 0.99 . The passing probability is increases as $\mu - Q$ increases. When $\mu - Q < 0$ has a low passing probability. On the other hand, when $\mu - Q > 5$ has a high passing probability. Therefore for our simulation study the range of μ−Q is chosen from 0 to 5, dividing by 0.1. There are 96×51 = 4876 combinations. For each combination, we conducted Monte Carlo simulation with N =1,000,000(10^6) for estimation of the passing probability. The 95% maximum error bound for each estimation is 1.96 $\sqrt{[0.5 \times 0.5 \times 10^{-6}]} \approx 0.001(0.1\%)$. Since most of the passing probabilities are expressed as the percentage, therefore, for practical application, a maximum error bound of 0.001 is sufficient to provide an accurate estimate of the passing probability.

The estimated passing probabilities for all 4876 combinations are presented from Tables B.1 to B.15 of Appendix B. Figure 3.1 and 3.2 provide response surfaces of the estimated probability as function of the means and standard deviations. For the purpose of illustration, an abbreviate table of the estimated passing probabilities is given in Table 3.1 for $\mu-$ Q from 0 to 5 by 0.5; for σ from 0.5 to 10 by 0.5.

From Figure 3.1 , 3.2 and Table 3.1, the passing probability increases as $\mu-$Q increases and as σ decreases. When $\mu-$Q $= 0$, all estimated passing probabilities are below 0.65. This indicates that when the population is equal to the amount of the dissolved active ingredient specified in the USP/NF monographs. The drug product will fail the dissolution test with more than 35%. On the other hand, when the standard deviation is less than 2, except for $\mu-$Q $= 0$, the estimated passing probabilities are greater than 90%. In addition when $\mu-$Q ≥ 2, the estimated passing probabilities exceed 95% even when the standard deviation is as large as 6.5 . The above relationships clearly depicted in Figure 3.1 and 3.2.

Comparisons of the estimated passing probabilities between three methods are provided in Figures 3.3, 3.4, 3.5, and 3.6 for $\mu-$Q $= 0$, 1, 2, and 3, respectively. It shows that lower bound of Bergum's method under-estimates the passing probability. On the other hand, the approximation of Wang's approach over-estimates the passing probability when σ is large. From Figures 3.3 to 3.6, the probability curve of our proposed simulation method always lies between those of Bergum's method and Wang's method. However the difference in estimated passing probabilities between the Bergum's method and our proposed simulation are layer that between the Wang's approach and our proposed simulation. On the other hand, when $\mu-$Q increases and σ decrease, the difference among the three methods diminish.

Additional simulations were conducted to investigate the passing probabilities for each individual stage and for the criteria based on the characteristic of individual units and based on the mean characteristic. The results are provided from Table 3.2 to Table 3.7 for $\mu-$Q $= 0$ to 5 by 1. The passing probability at first stage can be directly derived by $P(S_1) = [1 - \Phi(\frac{Q+5-\mu}{\sigma})]^6$. The passing probability at first stage are less than 2% in the range for our simulation studies. At the second stage, $P(S_1^c \cap C_{21}^c)$ is the failed probability due to individual requirements. $P(S_1^c \cap C_{22}^c)$ is the failed probability due to average requirements. As a result, $P(S_1^c \cap C_{21}^c \cap C_{22}^c)$ is the failed probability due to both criteria. Similarly, define $A_1 = S_1^c \cap S_2^c \cap (C_{31} \cup C_{32})^c$, $A_2 = S_1^c \cap S_2^c \cap (C_{31} \cup C_{32})^c \cap C_{33}^c$, and $A_3 = S_1^c \cap S_2^c \cap C_{33}^c$. At the third stage, $P(A_1)$ is the failed probability due to individual requirements, $P(A_3)$ is the failed probability due to average requirements, and $P(A_2)$ is the failed probability due to both criteria. Through the simulations, we could compare the failed probabilities due to average and individual criteria.

From the results given in Tables 3.2 to 3.7, at the second stage, the failed probability due to average and individual requirements both decreases as μ increases. In addition, the failed probability due to individual requirements increases sharply when σ is large. On the contrary, the failed probability due to average requirements increases gradually when σ increases.

Similar pattern of the failed probability due to individual and average requirements can be observed at the third stage. Furthermore, the failed probability due to average requirements is a dominant term at the third stage. However, the dominance disappears when μ increases. Since failure at the third stage means that the the drug product fail the USP/NF dissolution test. As μ increases, the passing probability increases. Then the failed probability due to the average and individual requirements decreases. Therefore individual requirements are dominant terms when μ and σ are large. But the failed probability due to individual requirements are still small and its impact negligible.

Define $T_1 = S_1$, $T_2 = S_1^c \cap S_2$, and $T_3 = S_1^c \cap S_2^c \cap S_3$. The results given in Figures 3.7 to 3.11 demonstrate that the $P(T_1)$ is negligible for all conditions. On the other hand, $P(T_2)$ are greater than both $P(T_1)$ and $P(T_3)$. In addition, the passing probability at second stage is at least twice as that of the third stage. Therefore, the second stage is the dominant stage for determination of the passing probability for the USP/NF dissolution test. Besides, we can observe that $P(T_2)$ decreases as σ increases and $P(T_3)$ increases as σ increases. The third stage allows that the dissolution rate of two units is between Q−25% and Q−15% while at the second stage, the dissolution rate of all units should be at least Q−15%. Therefore, the above simulation results may be due to the fact that a more relaxed requirement of individual characteristic is used at the third stage than the second stage.

Table 3.1: Abbreviated list of the estimated passing probabilities by Monte Carlo Simulation

	$\mu - Q$	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
σ	0.5	0.625	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1	0.625	0.996	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.5	0.624	0.967	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2	0.625	0.926	0.996	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.5	0.626	0.889	0.984	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3	0.625	0.856	0.966	0.996	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3.5	0.625	0.831	0.947	0.989	0.998	1.000	1.000	1.000	1.000	1.000	1.000
	4	0.625	0.809	0.926	0.979	0.996	0.999	1.000	1.000	1.000	1.000	1.000
	4.5	0.625	0.792	0.906	0.967	0.991	0.998	1.000	1.000	1.000	1.000	1.000
	5	0.624	0.776	0.887	0.953	0.984	0.996	0.999	1.000	1.000	1.000	1.000
	5.5	0.623	0.764	0.871	0.939	0.976	0.992	0.998	0.999	1.000	1.000	1.000
	6	0.620	0.751	0.854	0.925	0.966	0.987	0.995	0.999	1.000	1.000	1.000
	6.5	0.616	0.738	0.838	0.910	0.955	0.980	0.992	0.997	0.999	1.000	1.000
	7	0.612	0.726	0.822	0.894	0.943	0.972	0.988	0.995	0.998	0.999	1.000
	7.5	0.602	0.711	0.805	0.878	0.929	0.962	0.981	0.991	0.996	0.998	0.999
	8	0.593	0.696	0.786	0.859	0.913	0.949	0.972	0.985	0.992	0.996	0.998
	8.5	0.579	0.677	0.764	0.836	0.892	0.932	0.959	0.976	0.986	0.992	0.995
	9	0.560	0.653	0.737	0.810	0.866	0.910	0.941	0.962	0.975	0.984	0.989
	9.5	0.539	0.626	0.705	0.777	0.836	0.881	0.916	0.942	0.959	0.971	0.980
	10	0.510	0.593	0.669	0.738	0.797	0.846	0.885	0.914	0.937	0.953	0.964

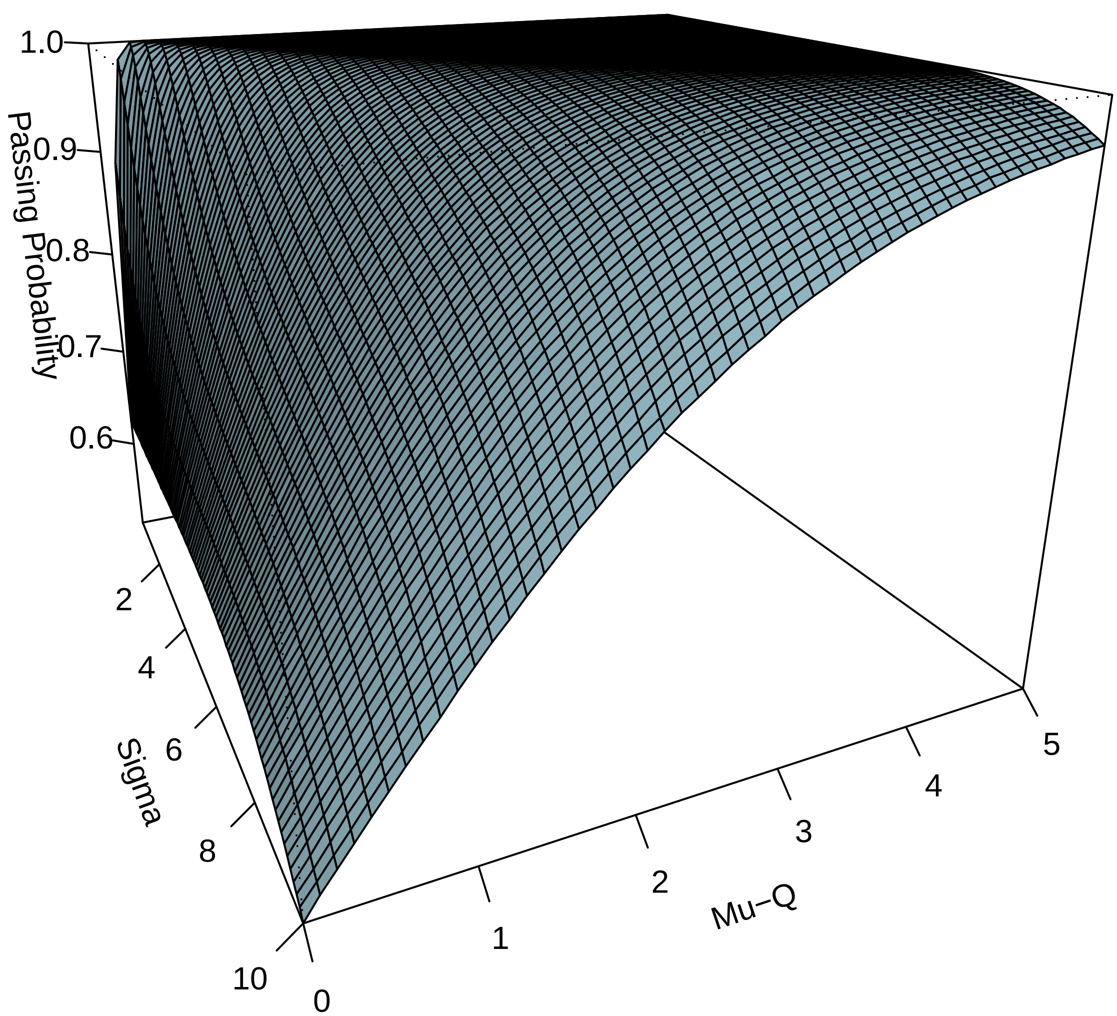

Figure 3.1: Response surface of passing probability

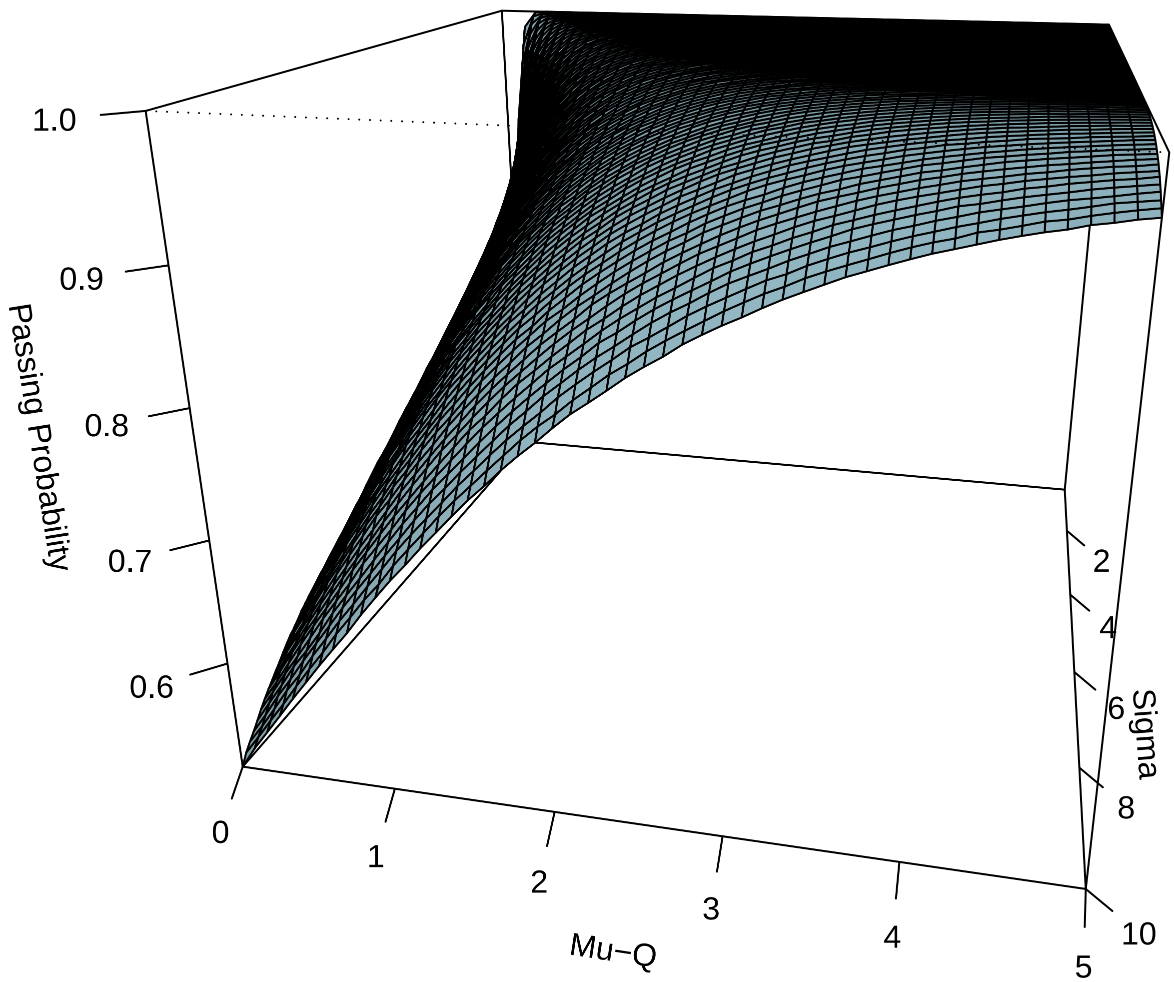

Figure 3.2: Response surface of passing probability

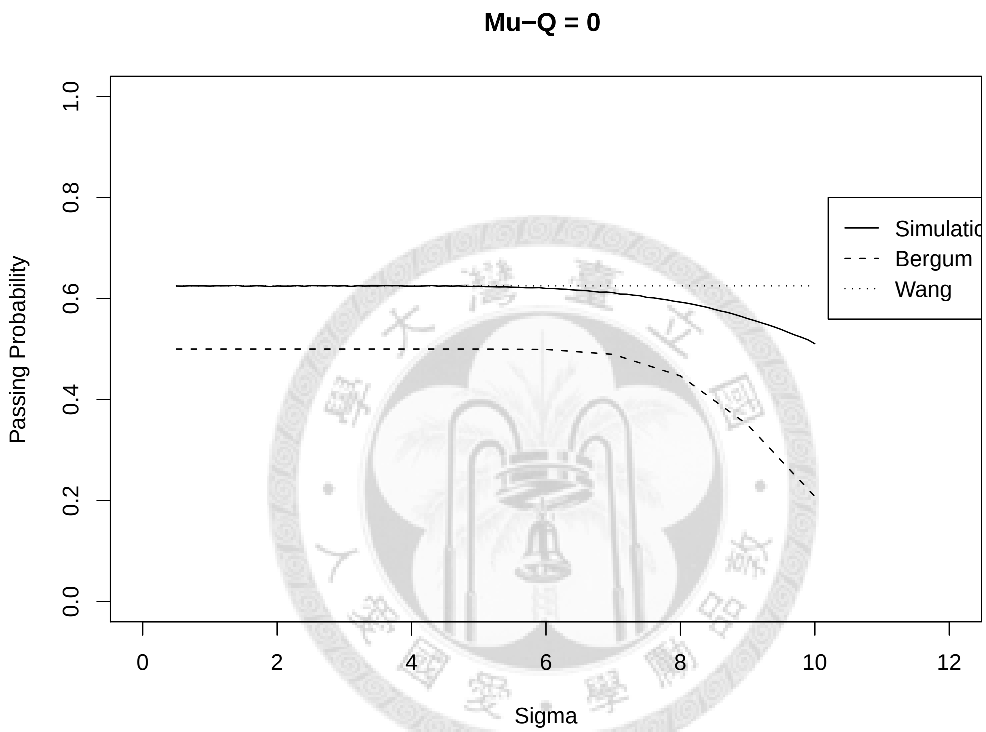

Figure 3.3: Comparison of estimated passing probabilities for $\mu-$ Q $= 0$

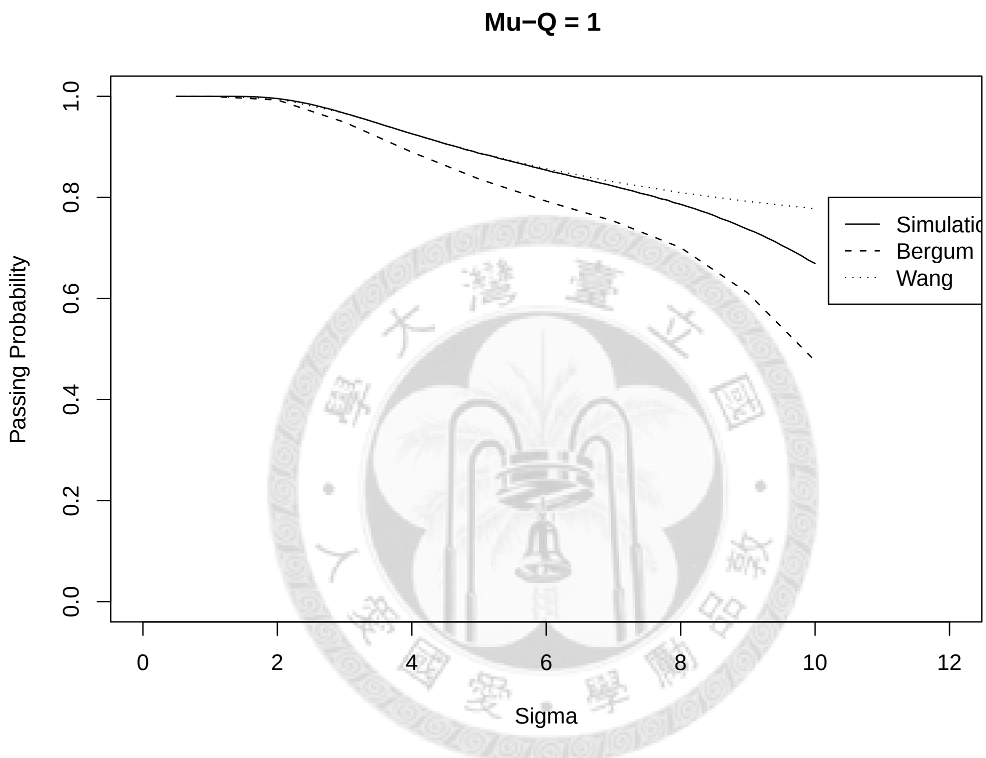

Figure 3.4: Comparison of estimated passing probabilities for $\mu-$ Q $= 1$

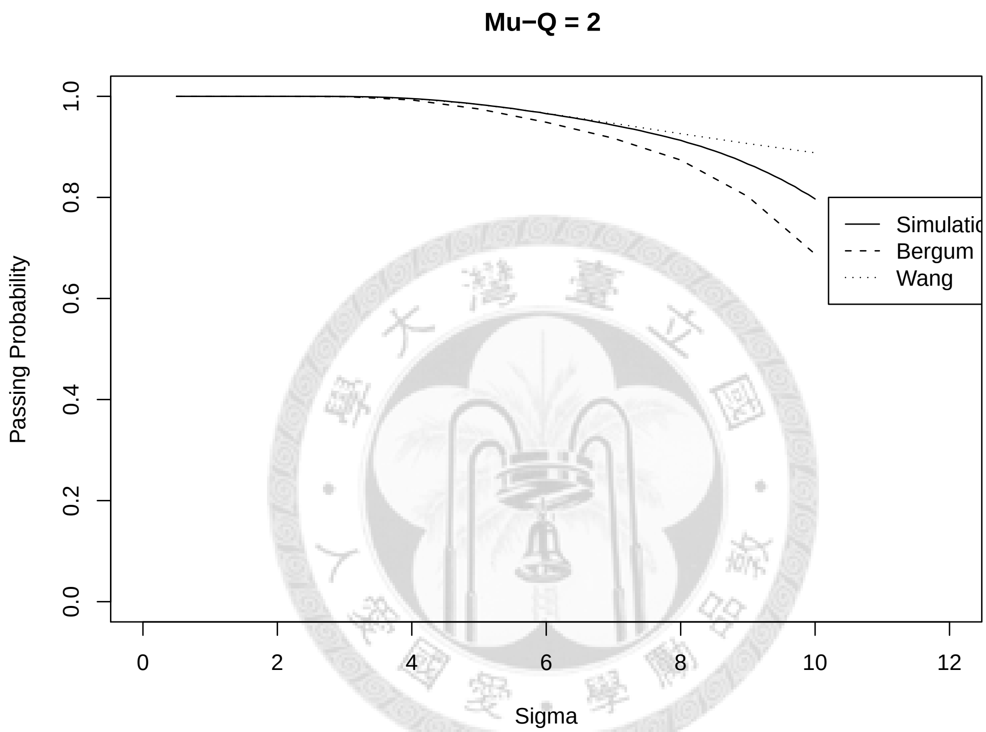

Figure 3.5: Comparison of estimated passing probabilities for $\mu-$ Q $= 2$

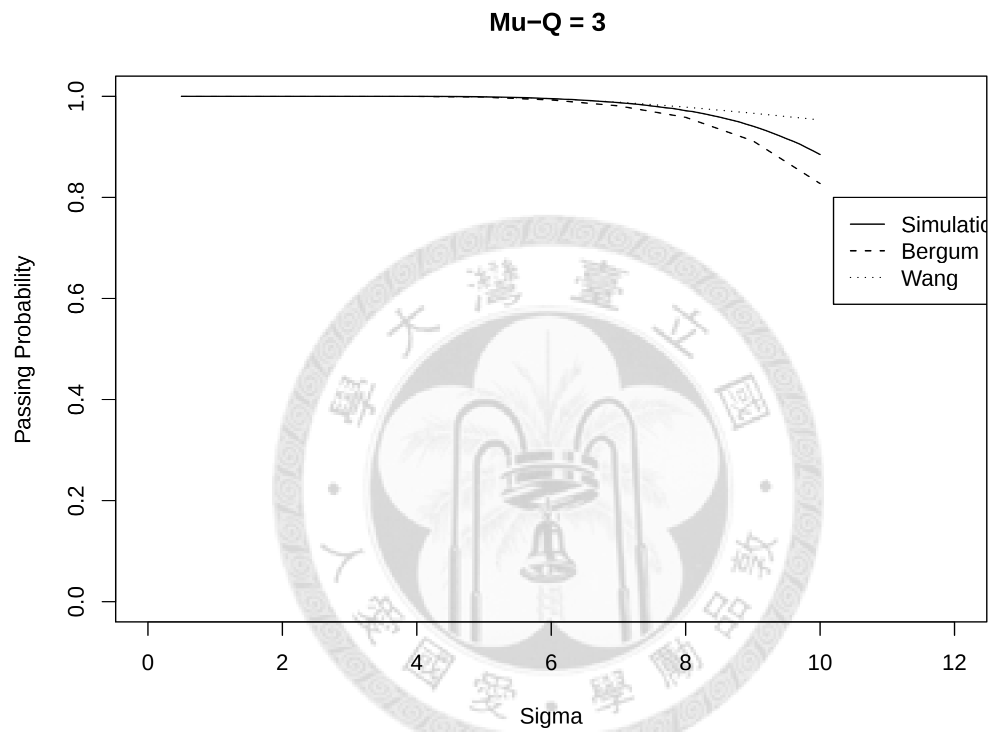

Figure 3.6: Comparison of estimated passing probabilities for $\mu-$ Q $= 3$

Table 3.2: The failed probability due to average and individual requirements for μ−Q = 0

μ−Q = 0						
σ	$P(S_1^c \cap C_{21}^c)$	$P(S_1^c \cap C_{21}^c \cap C_{22}^c)$	$P(S_1^c \cap C_{22}^c)$	$P(A_1)$	$P(A_2)$	$P(A_3)$
0.5	0.000	0.000	0.500	0.000	0.000	0.375
1.0	0.000	0.000	0.500	0.000	0.000	0.375
1.5	0.000	0.000	0.500	0.000	0.000	0.375
2.0	0.000	0.000	0.500	0.000	0.000	0.376
2.5	0.000	0.000	0.500	0.000	0.000	0.375
3.0	0.000	0.000	0.500	0.000	0.000	0.375
3.5	0.000	0.000	0.500	0.000	0.000	0.375
4.0	0.001	0.001	0.500	0.000	0.000	0.375
4.5	0.005	0.004	0.499	0.000	0.000	0.375
5.0	0.016	0.013	0.499	0.000	0.000	0.375
5.5	0.038	0.031	0.501	0.000	0.000	0.378
6.0	0.072	0.057	0.500	0.001	0.001	0.379
6.5	0.119	0.092	0.500	0.003	0.003	0.384
7.0	0.177	0.134	0.501	0.009	0.008	0.388
7.5	0.241	0.179	0.500	0.023	0.021	0.395
8.0	0.310	0.224	0.501	0.047	0.041	0.402
8.5	0.378	0.267	0.500	0.083	0.071	0.409
9.0	0.444	0.306	0.501	0.133	0.110	0.417
9.5	0.506	0.340	0.500	0.193	0.155	0.424
10.0	0.563	0.370	0.500	0.260	0.203	0.431

Table 3.3: The failed probability due to average and individual requirements for μ−Q = 1

μ−Q = 1

σ	$P(S_1^c \cap C_{21}^c)$	$P(S_1^c \cap C_{21}^c \cap C_{22}^c)$	$P(S_1^c \cap C_{22}^c)$	$P(A_1)$	$P(A_2)$	$P(A_3)$
0.5	0.000	0.000	0.000	0.000	0.000	0.000
1	0.000	0.000	0.000	0.000	0.000	0.000
1.5	0.000	0.000	0.010	0.000	0.000	0.000
2	0.000	0.000	0.042	0.000	0.000	0.004
2.5	0.000	0.000	0.083	0.000	0.000	0.016
3	0.000	0.000	0.124	0.000	0.000	0.033
3.5	0.000	0.000	0.161	0.000	0.000	0.054
4	0.000	0.000	0.193	0.000	0.000	0.074
4.5	0.002	0.001	0.221	0.000	0.000	0.094
5	0.008	0.005	0.244	0.000	0.000	0.112
5.5	0.022	0.013	0.264	0.000	0.000	0.129
6	0.045	0.027	0.282	0.000	0.000	0.145
6.5	0.080	0.048	0.298	0.001	0.001	0.162
7	0.126	0.075	0.310	0.004	0.003	0.177
7.5	0.180	0.105	0.322	0.010	0.008	0.191
8	0.241	0.138	0.332	0.024	0.017	0.207
8.5	0.305	0.172	0.342	0.047	0.032	0.221
9	0.370	0.204	0.351	0.081	0.054	0.237
9.5	0.432	0.234	0.357	0.126	0.082	0.249
10	0.491	0.262	0.365	0.182	0.114	0.264

Table 3.4: The failed probability due to average and individual requirements for μ−Q =2

μ−Q = 2

σ	$P(S_1^c \cap C_{21}^c)$	$P(S_1^c \cap C_{21}^c \cap C_{22}^c)$	$P(S_1^c \cap C_{22}^c)$	$P(A_1)$	$P(A_2)$	$P(A_3)$
0.5	0.000	0.000	0.000	0.000	0.000	0.000
1	0.000	0.000	0.000	0.000	0.000	0.000
1.5	0.000	0.000	0.000	0.000	0.000	0.000
2	0.000	0.000	0.000	0.000	0.000	0.000
2.5	0.000	0.000	0.003	0.000	0.000	0.000
3	0.000	0.000	0.010	0.000	0.000	0.000
3.5	0.000	0.000	0.024	0.000	0.000	0.002
4	0.000	0.000	0.042	0.000	0.000	0.005
4.5	0.001	0.000	0.062	0.000	0.000	0.009
5	0.004	0.001	0.083	0.000	0.000	0.016
5.5	0.012	0.004	0.104	0.000	0.000	0.024
6	0.027	0.011	0.124	0.000	0.000	0.034
6.5	0.052	0.021	0.143	0.000	0.000	0.044
7	0.087	0.036	0.161	0.002	0.001	0.056
7.5	0.131	0.054	0.177	0.005	0.002	0.068
8	0.185	0.076	0.194	0.012	0.006	0.082
8.5	0.240	0.099	0.207	0.026	0.012	0.094
9	0.301	0.124	0.221	0.048	0.023	0.108
9.5	0.361	0.148	0.233	0.080	0.037	0.122
10	0.421	0.171	0.244	0.122	0.055	0.134

Table 3.5: The failed probability due to average and individual requirements for μ−Q = 3

μ−Q = 3

σ	$P(S_1^c \cap C_{21}^c)$	$P(S_1^c \cap C_{21}^c \cap C_{22}^c)$	$P(S_1^c \cap C_{22}^c)$	$P(A_1)$	$P(A_2)$	$P(A_3)$
0.5	0.000	0.000	0.000	0.000	0.000	0.000
1	0.000	0.000	0.000	0.000	0.000	0.000
1.5	0.000	0.000	0.000	0.000	0.000	0.000
2	0.000	0.000	0.000	0.000	0.000	0.000
2.5	0.000	0.000	0.000	0.000	0.000	0.000
3	0.000	0.000	0.000	0.000	0.000	0.000
3.5	0.000	0.000	0.001	0.000	0.000	0.000
4	0.000	0.000	0.005	0.000	0.000	0.000
4.5	0.000	0.000	0.011	0.000	0.000	0.000
5	0.002	0.000	0.019	0.000	0.000	0.001
5.5	0.006	0.001	0.029	0.000	0.000	0.002
6	0.016	0.003	0.041	0.000	0.000	0.004
6.5	0.033	0.008	0.055	0.000	0.000	0.008
7	0.059	0.014	0.069	0.001	0.000	0.012
7.5	0.094	0.024	0.083	0.002	0.001	0.017
8	0.137	0.036	0.097	0.006	0.001	0.024
8.5	0.187	0.051	0.111	0.014	0.004	0.031
9	0.240	0.067	0.124	0.028	0.008	0.039
9.5	0.298	0.085	0.137	0.049	0.014	0.048
10	0.354	0.102	0.150	0.080	0.022	0.058

Table 3.6: The failed probability due to average and individual requirements for μ−Q = 4

μ−Q = 4

σ	$P(S_1^c \cap C_{21}^c)$	$P(S_1^c \cap C_{21}^c \cap C_{22}^c)$	$P(S_1^c \cap C_{22}^c)$	$P(A_1)$	$P(A_2)$	$P(A_3)$
0.5	0.000	0.000	0.000	0.000	0.000	0.000
1	0.000	0.000	0.000	0.000	0.000	0.000
1.5	0.000	0.000	0.000	0.000	0.000	0.000
2	0.000	0.000	0.000	0.000	0.000	0.000
2.5	0.000	0.000	0.000	0.000	0.000	0.000
3	0.000	0.000	0.000	0.000	0.000	0.000
3.5	0.000	0.000	0.000	0.000	0.000	0.000
4	0.000	0.000	0.000	0.000	0.000	0.000
4.5	0.000	0.000	0.001	0.000	0.000	0.000
5	0.001	0.000	0.003	0.000	0.000	0.000
5.5	0.003	0.000	0.006	0.000	0.000	0.000
6	0.009	0.001	0.010	0.000	0.000	0.000
6.5	0.020	0.002	0.016	0.000	0.000	0.001
7	0.039	0.005	0.024	0.000	0.000	0.002
7.5	0.065	0.009	0.032	0.001	0.000	0.003
8	0.100	0.015	0.042	0.003	0.000	0.005
8.5	0.142	0.023	0.052	0.007	0.001	0.008
9	0.189	0.033	0.062	0.016	0.002	0.011
9.5	0.240	0.044	0.072	0.030	0.004	0.015
10	0.293	0.056	0.083	0.051	0.007	0.020

Table 3.7: The failed probability due to average and individual requirements for μ−Q = 5

μ−Q = 5						
σ	$P(S_1^c \cap C_{21}^c)$	$P(S_1^c \cap C_{21}^c \cap C_{22}^c)$	$P(S_1^c \cap C_{22}^c)$	$P(A_1)$	$P(A_2)$	$P(A_3)$
0.5	0.000	0.000	0.000	0.000	0.000	0.000
1.0	0.000	0.000	0.000	0.000	0.000	0.000
1.5	0.000	0.000	0.000	0.000	0.000	0.000
2.0	0.000	0.000	0.000	0.000	0.000	0.000
2.5	0.000	0.000	0.000	0.000	0.000	0.000
3.0	0.000	0.000	0.000	0.000	0.000	0.000
3.5	0.000	0.000	0.000	0.000	0.000	0.000
4.0	0.000	0.000	0.000	0.000	0.000	0.000
4.5	0.000	0.000	0.000	0.000	0.000	0.000
5.0	0.000	0.000	0.000	0.000	0.000	0.000
5.5	0.002	0.000	0.001	0.000	0.000	0.000
6.0	0.005	0.000	0.002	0.000	0.000	0.000
6.5	0.012	0.000	0.004	0.000	0.000	0.000
7.0	0.025	0.001	0.007	0.000	0.000	0.000
7.5	0.045	0.003	0.010	0.001	0.000	0.000
8.0	0.071	0.005	0.015	0.002	0.000	0.001
8.5	0.105	0.009	0.021	0.004	0.000	0.001
9.0	0.146	0.014	0.027	0.009	0.000	0.002
9.5	0.191	0.020	0.034	0.018	0.001	0.004
10.0	0.239	0.028	0.042	0.032	0.002	0.006

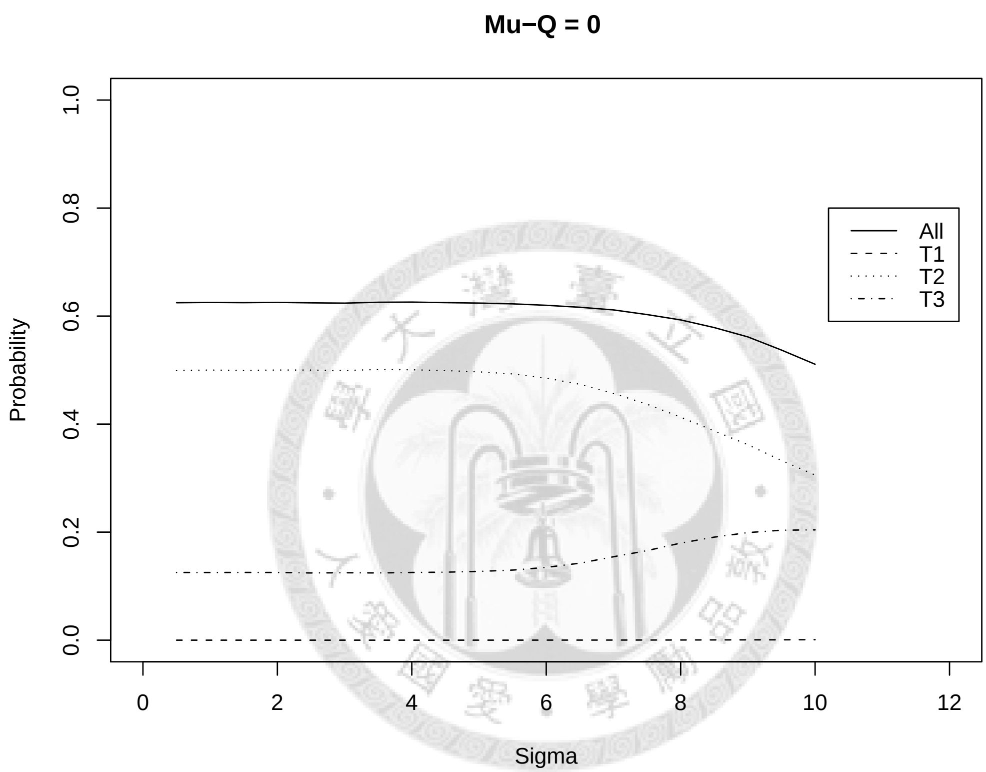

Figure 3.7: Estimated passing probability at each stage for μ−Q=0

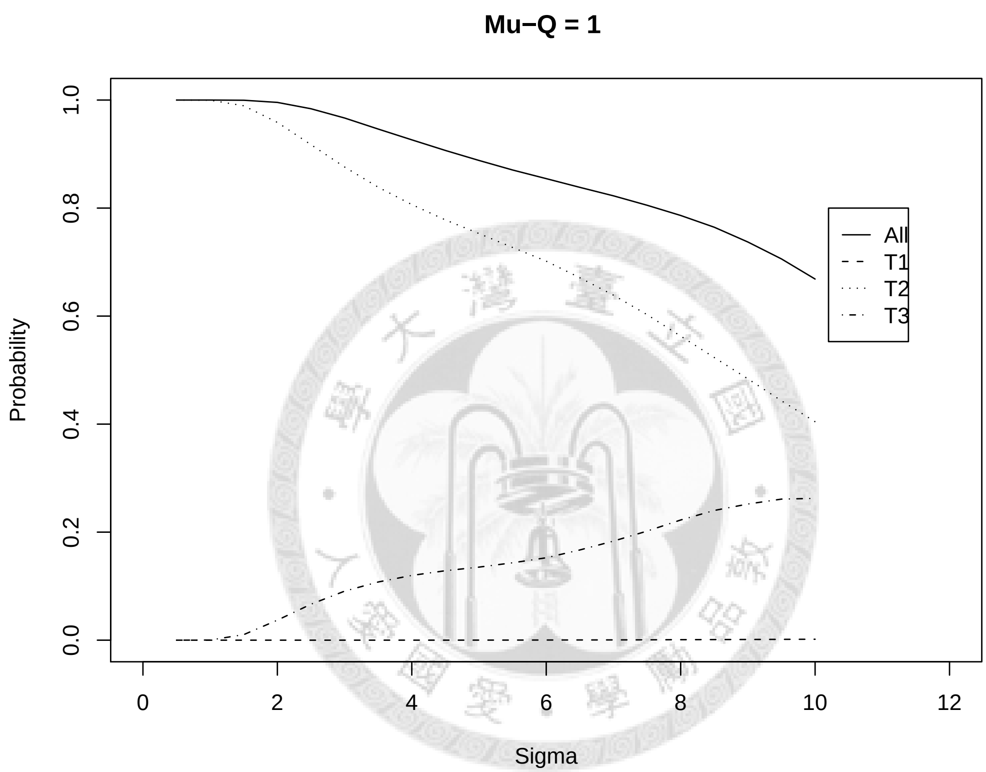

Figure 3.8: Estimated passing probability at each stage for $\mu-$Q=1

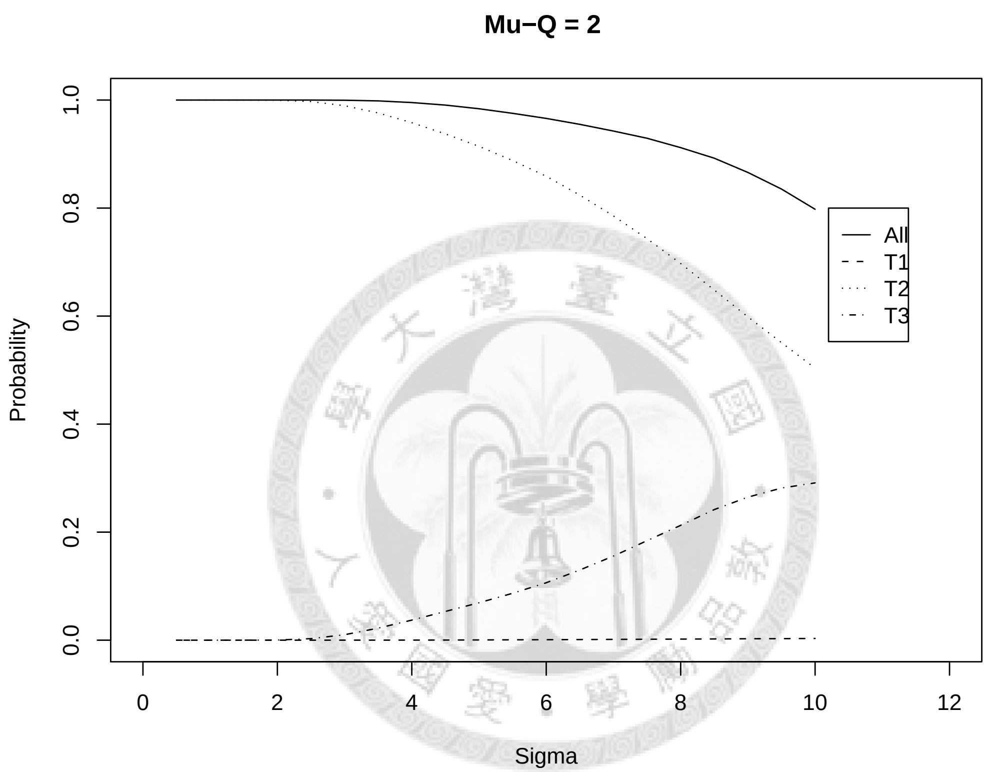

Figure 3.9: Estimated passing probability at each stage for μ−Q=2

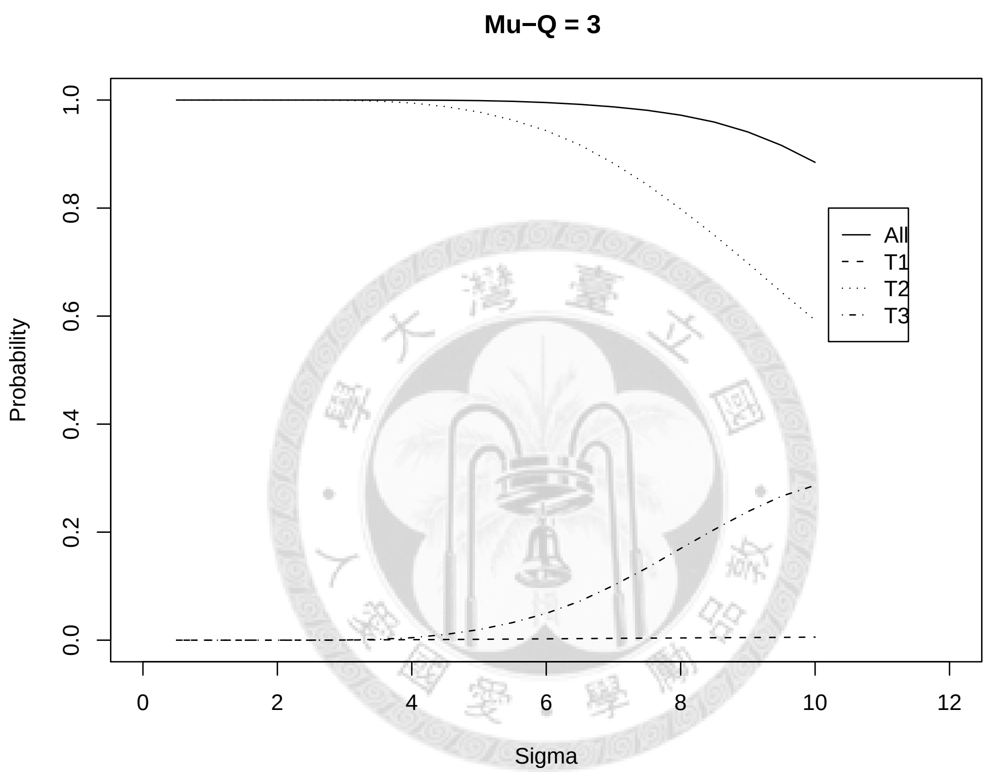

Figure 3.10: Estimated passing probability at each stage for μ−Q=3

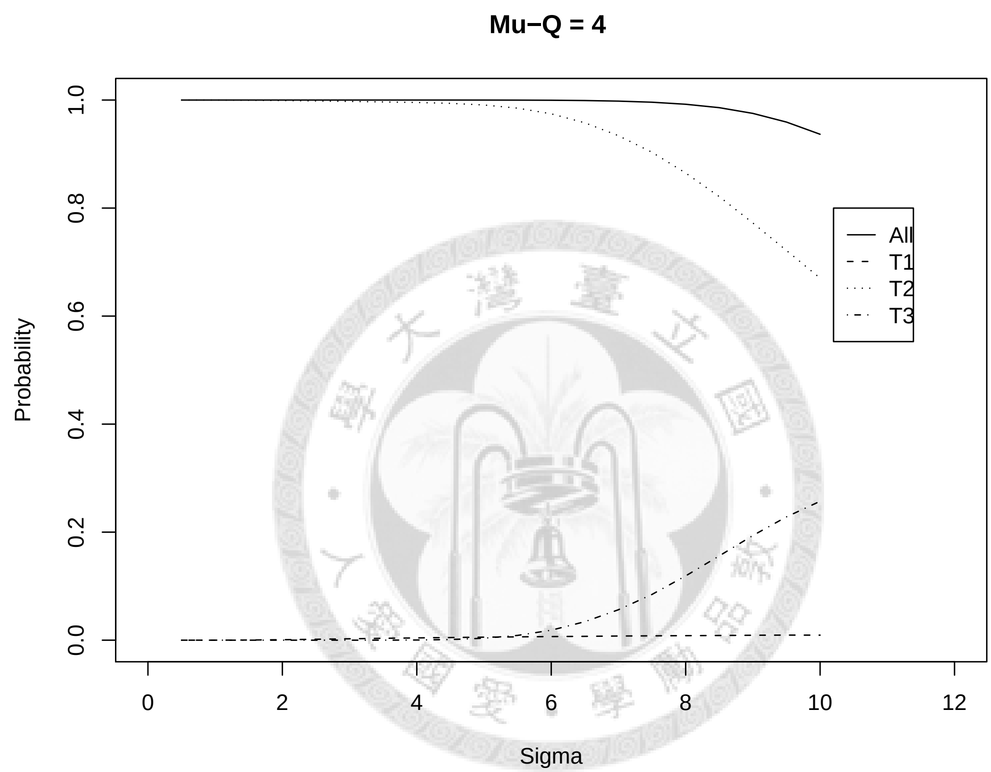

Figure 3.11: Estimated passing probability at each stage for μ−Q=4

Chapter 4

A Numerical Example

If a sponsor needs to establish in-house specification limits of passing USP/NF dissolution test for a batch of a drug product. The sponsor has to select randomly units as a sample with size n. The sample mean $\bar{x}$ and sample standard deviation s can be calculated. Then replaced μ and σ are by $\bar{x}$ and s, respectively. Finally, we can use the Tables in Appendix B to find the passing probability of the batch of drugs product.

For example, let $\bar{x}$=76.2765% , s = 4.1873% , and Q = 75%. It follows that $\bar{x}-$Q = 1.2765% . To be conservative, round off Q$-\mu$ as 1.2% , and σ as 4.2%. From the table given in B.5, we can find the passing probability is 0.946.

Chapter 5

Discussion and Conclusion

The USP/NF dissolution testing procedure is a multiple-stage test and the stages are dependent. At the same stage, the average and individual requirements are also dependent and are too complicate to separate. The true passing probability can not be found even when μ and σ are known. Therefore, we applied the Monte-Carlo Simulation approach to estimate the passing probabilities which are given from Table B.1 to B.15 in Appendix B. The Fortran codes for estimation of the passing probabilities are provided in Appendix A.

Although simulation is a reasonable method to derive the estimates of the passing probability. The estimation still depends on the sample statistics. In the other words, the sampling error is unavoidable. It is important to ensure the sample size is large enough for estimation.

The passing probability also can be estimated by confidence interval. Base on a sample, we can construct a (1-$\frac{\alpha}{2}$)100% lower confidence bound of μ and (1-$\frac{\alpha}{2}$)100% upper confidence bound of σ. We use these two value and tables in Appendix B to find the estimate of the passing probability. By the Bonferroni inequality, the estimate is an approximate (1-α)100% lower confidence bound of the passing probability.

In this thesis, we propose the Monte-Carlo simulation to estimate the passing probability. Since these is a normality assumption, the parametric bootstrap could be another method to estimate the passing probability.

So far the normality is assumed for all methods. But the dissolution rate is percentage with a range from 0 to 100%. When the population mean is near to 100%, the distribution of the population is skew. Therefore the normal assumption may be violated. Under this circumstance, the Beta distribution may provide an alternative distribution to generate the random sample for the proposed simulation procedure.

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Appendix A

Program code

Use the Fortran program. As an example of Monte Carlo Simulation, this code is written for estimating passing probabilities when μ−Q = 0 and $\sigma = 0.5$ to 10 by 0.1.

```
program main
use msimsl
implicit none
real :: s1(6) , s2(12), s3(24) , b2 ,b3
real :: Q , mu , sig , pi
real :: T(96,7)
integer :: i , j
character(5) head1
character(98) head2
pi = acos(-1.0)
head1 (1:5) = "Sigma"
head2(10:11) = "T1"
head2(24:25) = "T2"
head2(38:41) = "C21F"
head2(52:55) = "C22F"
```

```
head2(63:70) = "C21&C22F"

head2(80:81) = "T3"

head2(93:96) = "Pass"

open(10,file="75.0.txt")

! Setting the Combination of Parameters

Q = 75.0

mu = 75.0

do i=1, 96

sig = i*0.1+0.4

do j=1, 1000000

! First Stage

CALL RNNOA (6, s1)

CALL SSCAL (6, sig, s1, 1)

CALL SADD (6, mu, s1, 1)

if (all(s1>Q+5)) then

T(i,1) = T(i,1) + 1

else

! Second Stage

s2(1:6) = s1

CALL RNNOA (6, s2(7:12))

CALL SSCAL (6, sig, s2(7:12), 1)

CALL SADD (6, mu, s2(7:12), 1)

b2 = sum(s2)/12

if(b2>Q .and. all(s2>Q-15)) then

T(i,2) = T(i,2) + 1

else if(any(s2<Q-15)) then

T(i,3) = T(i,3) + 1

end if

if(b2<Q) then

T(i,4) = T(i,4) + 1
```

```
end if
if(b2<=Q .and. any(s2<=Q-15)) then
T(i,5) = T(i,5) + 1
end if
! Third Stage
s3(1:12) = s2
CALL RNNOA (12, s3(13:24))
CALL SSCAL (12, sig, s3(13:24), 1)
CALL SADD (12, mu, s3(13:24), 1)
b3 = sum(s3)/24
if(b3>Q .and. count(s3<Q-15)¡3 .and. all(s3>Q-25)) then
T(i,6) = T(i,6)+1
else
T(i,7) = T(i,7)+1
end if
end if
end if
end do ! j
end do ! i
write(10,”(A3,F4.1,A3,F4.1)”) ”mu=”,mu ,”Q=”,Q
write(10,”(A5,A98)”) head1, head2
do i = 1 , 96
T(i,1:7) = T(i,1:7)/1000000.0
write(10,”(F5.1,7F14.6)”) i*0.1+0.4 , T(i,1:6) , 1.0-T(i,7)
end do
write(10,*) ”–”
end program
```

Appendix B

Estimated Passing Probabilities by Monte Carlo Simulation

Table B.1: Estimated Passing Probabilities by Monte Carlo Simulation for μ−Q = 0 to 0.9 , σ = 0.5 to 3.9

	$\mu - Q$	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
σ	0.5	0.624	0.888	0.984	0.999	0.999	1.000	1.000	1.000	1.000	1.000
	0.6	0.624	0.856	0.966	0.995	0.999	0.999	1.000	1.000	1.000	1.000
	0.7	0.625	0.830	0.946	0.988	0.998	0.999	0.999	0.999	1.000	1.000
	0.8	0.625	0.809	0.926	0.978	0.995	0.999	0.999	0.999	0.999	1.000
	0.9	0.625	0.791	0.905	0.966	0.990	0.997	0.999	0.999	0.999	1.000
	1	0.624	0.777	0.888	0.953	0.984	0.995	0.999	0.999	0.999	0.999
	1.1	0.625	0.764	0.871	0.939	0.975	0.991	0.997	0.999	0.999	0.999
	1.2	0.625	0.754	0.856	0.926	0.966	0.986	0.995	0.998	0.999	0.999
	1.3	0.625	0.745	0.843	0.913	0.956	0.981	0.992	0.997	0.999	0.999
	1.4	0.626	0.737	0.830	0.900	0.946	0.974	0.988	0.995	0.998	0.999
	1.5	0.624	0.729	0.819	0.888	0.935	0.966	0.984	0.992	0.997	0.999
	1.6	0.624	0.723	0.809	0.876	0.926	0.958	0.978	0.989	0.995	0.998
	1.7	0.625	0.719	0.800	0.866	0.916	0.950	0.972	0.986	0.993	0.997
	1.8	0.624	0.713	0.791	0.857	0.906	0.942	0.966	0.981	0.990	0.995
	1.9	0.623	0.709	0.784	0.847	0.897	0.934	0.960	0.977	0.987	0.993
	2	0.624	0.705	0.777	0.839	0.888	0.926	0.953	0.972	0.984	0.991
	2.1	0.624	0.701	0.771	0.830	0.879	0.918	0.946	0.966	0.979	0.988
	2.2	0.624	0.697	0.765	0.823	0.871	0.910	0.939	0.960	0.975	0.985
	2.3	0.625	0.695	0.759	0.816	0.864	0.902	0.933	0.955	0.970	0.982
	2.4	0.624	0.692	0.754	0.808	0.856	0.895	0.925	0.949	0.966	0.978
	2.5	0.625	0.690	0.749	0.803	0.849	0.888	0.919	0.943	0.961	0.975
	2.6	0.625	0.687	0.745	0.797	0.842	0.881	0.913	0.937	0.956	0.971
	2.7	0.624	0.685	0.741	0.792	0.836	0.874	0.906	0.932	0.951	0.966
	2.8	0.625	0.683	0.737	0.787	0.830	0.868	0.900	0.925	0.946	0.962
	2.9	0.624	0.680	0.733	0.781	0.824	0.862	0.894	0.920	0.941	0.957
	3	0.625	0.679	0.730	0.777	0.819	0.856	0.888	0.914	0.936	0.953
	3.1	0.624	0.677	0.727	0.773	0.814	0.851	0.882	0.909	0.930	0.948
	3.2	0.625	0.675	0.724	0.769	0.809	0.845	0.876	0.904	0.925	0.944
	3.3	0.624	0.674	0.721	0.764	0.804	0.840	0.871	0.898	0.921	0.939
	3.4	0.624	0.673	0.718	0.761	0.800	0.835	0.866	0.893	0.916	0.935
	3.5	0.624	0.671	0.716	0.757	0.795	0.830	0.861	0.888	0.911	0.930
	3.6	0.625	0.669	0.712	0.754	0.792	0.826	0.857	0.883	0.906	0.926
	3.7	0.625	0.669	0.711	0.751	0.788	0.821	0.851	0.878	0.901	0.921
	3.8	0.625	0.667	0.709	0.748	0.784	0.817	0.847	0.874	0.897	0.917
	3.9	0.624	0.666	0.706	0.745	0.781	0.814	0.842	0.869	0.892	0.912

Table B.2: Estimated Passing Probabilities by Monte Carlo Simulation for $\mu-\mathrm{Q} = 0$ to 0.9 , $\sigma = 4$ to 6.9

	$\mu - Q$	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
σ	4	0.624	0.666	0.704	0.742	0.776	0.809	0.839	0.865	0.888	0.908
	4.1	0.624	0.665	0.703	0.739	0.774	0.806	0.835	0.860	0.883	0.904
	4.2	0.624	0.663	0.702	0.737	0.770	0.801	0.830	0.856	0.880	0.900
	4.3	0.625	0.663	0.700	0.735	0.768	0.798	0.825	0.852	0.875	0.896
	4.4	0.624	0.662	0.698	0.732	0.765	0.795	0.823	0.848	0.871	0.892
	4.5	0.625	0.660	0.696	0.730	0.761	0.791	0.819	0.845	0.867	0.888
	4.6	0.624	0.661	0.694	0.727	0.759	0.788	0.816	0.840	0.863	0.884
	4.7	0.625	0.659	0.693	0.725	0.757	0.785	0.812	0.837	0.859	0.880
	4.8	0.624	0.658	0.691	0.723	0.754	0.783	0.808	0.834	0.856	0.876
	4.9	0.623	0.657	0.690	0.721	0.751	0.779	0.805	0.830	0.852	0.872
	5	0.624	0.657	0.688	0.720	0.749	0.776	0.803	0.826	0.850	0.870
	5.1	0.623	0.656	0.687	0.718	0.746	0.773	0.800	0.823	0.845	0.866
	5.2	0.623	0.655	0.685	0.716	0.744	0.771	0.796	0.820	0.842	0.862
	5.3	0.622	0.654	0.685	0.713	0.741	0.768	0.794	0.817	0.839	0.858
	5.4	0.623	0.654	0.683	0.712	0.739	0.766	0.790	0.814	0.835	0.855
	5.5	0.622	0.652	0.682	0.710	0.738	0.764	0.788	0.811	0.832	0.852
	5.6	0.622	0.652	0.681	0.708	0.735	0.760	0.785	0.808	0.829	0.848
	5.7	0.621	0.651	0.679	0.707	0.732	0.758	0.781	0.804	0.826	0.845
	5.8	0.621	0.650	0.678	0.704	0.731	0.755	0.779	0.801	0.823	0.842
	5.9	0.621	0.648	0.677	0.702	0.728	0.753	0.776	0.799	0.819	0.839
	6	0.619	0.647	0.676	0.701	0.726	0.751	0.774	0.796	0.816	0.836
	6.1	0.619	0.647	0.673	0.699	0.724	0.748	0.771	0.793	0.813	0.833
	6.2	0.618	0.645	0.672	0.697	0.722	0.745	0.768	0.790	0.810	0.830
	6.3	0.618	0.643	0.670	0.696	0.720	0.743	0.765	0.787	0.807	0.826
	6.4	0.617	0.643	0.669	0.693	0.718	0.741	0.763	0.785	0.805	0.823
	6.5	0.616	0.642	0.666	0.691	0.716	0.738	0.759	0.782	0.802	0.820
	6.6	0.615	0.640	0.665	0.689	0.712	0.736	0.757	0.778	0.798	0.817
	6.7	0.614	0.639	0.663	0.687	0.711	0.733	0.755	0.775	0.796	0.814
	6.8	0.612	0.637	0.662	0.685	0.709	0.731	0.751	0.773	0.792	0.810
	6.9	0.612	0.636	0.660	0.683	0.705	0.728	0.750	0.769	0.788	0.808

Table B.3: Estimated Passing Probabilities by Monte Carlo Simulation for μ−Q = 0 to 0.9 , σ = 7 to 10

	$\mu - Q$	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
σ	7	0.611	0.634	0.657	0.682	0.704	0.726	0.746	0.766	0.787	0.804
	7.1	0.608	0.633	0.656	0.679	0.701	0.723	0.744	0.763	0.783	0.802
	7.2	0.608	0.631	0.653	0.677	0.699	0.721	0.741	0.760	0.780	0.798
	7.3	0.606	0.629	0.652	0.675	0.696	0.718	0.738	0.757	0.776	0.795
	7.4	0.605	0.627	0.650	0.672	0.694	0.714	0.735	0.754	0.772	0.791
	7.5	0.602	0.626	0.647	0.670	0.692	0.711	0.731	0.751	0.769	0.787
	7.6	0.601	0.623	0.645	0.667	0.688	0.708	0.728	0.747	0.766	0.784
	7.7	0.599	0.622	0.643	0.664	0.685	0.706	0.726	0.745	0.763	0.780
	7.8	0.597	0.618	0.640	0.662	0.681	0.702	0.723	0.740	0.759	0.777
	7.9	0.594	0.617	0.637	0.658	0.679	0.698	0.718	0.737	0.755	0.773
	8	0.592	0.614	0.635	0.655	0.676	0.696	0.715	0.733	0.751	0.769
	8.1	0.590	0.611	0.632	0.652	0.672	0.692	0.711	0.730	0.747	0.765
	8.2	0.588	0.609	0.629	0.649	0.668	0.688	0.708	0.725	0.743	0.760
	8.3	0.585	0.605	0.627	0.644	0.665	0.684	0.702	0.723	0.739	0.756
	8.4	0.582	0.601	0.622	0.641	0.661	0.680	0.699	0.717	0.734	0.752
	8.5	0.578	0.598	0.618	0.638	0.658	0.676	0.695	0.713	0.730	0.747
	8.6	0.575	0.596	0.615	0.634	0.653	0.672	0.690	0.707	0.726	0.743
	8.7	0.572	0.590	0.612	0.631	0.648	0.668	0.685	0.704	0.720	0.737
	8.8	0.568	0.587	0.606	0.626	0.644	0.663	0.681	0.698	0.716	0.731
	8.9	0.564	0.585	0.603	0.620	0.640	0.658	0.675	0.693	0.709	0.727
	9	0.560	0.579	0.598	0.617	0.636	0.653	0.671	0.688	0.704	0.721
	9.1	0.556	0.575	0.593	0.612	0.630	0.648	0.665	0.682	0.700	0.715
	9.2	0.552	0.570	0.588	0.607	0.625	0.642	0.659	0.676	0.692	0.709
	9.3	0.548	0.566	0.584	0.602	0.619	0.636	0.654	0.670	0.686	0.703
	9.4	0.543	0.560	0.578	0.597	0.614	0.630	0.647	0.665	0.681	0.697
	9.5	0.538	0.556	0.573	0.590	0.607	0.625	0.641	0.657	0.675	0.690
	9.6	0.533	0.550	0.567	0.586	0.601	0.617	0.635	0.651	0.667	0.683
	9.7	0.527	0.544	0.562	0.579	0.596	0.612	0.629	0.645	0.661	0.676
	9.8	0.523	0.538	0.556	0.573	0.589	0.606	0.622	0.638	0.653	0.669
	9.9	0.518	0.533	0.550	0.566	0.583	0.599	0.614	0.631	0.646	0.662
	10	0.510	0.528	0.544	0.560	0.576	0.592	0.608	0.623	0.638	0.654

Table B.4: Estimated Passing Probabilities by Monte Carlo Simulation for μ−Q = 1 to 1.9 , σ = 0.5 to 3.9

	$\mu - Q$	1	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9
σ	0.5	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.6	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.7	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.9	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.1	0.999	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.2	0.999	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.3	0.999	0.999	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.4	0.999	0.999	0.999	0.999	1.000	1.000	1.000	1.000	1.000	1.000
	1.5	0.999	0.999	0.999	0.999	0.999	0.999	1.000	1.000	1.000	1.000
	1.6	0.999	0.999	0.999	0.999	0.999	0.999	1.000	1.000	1.000	1.000
	1.7	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999	1.000	1.000
	1.8	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999	1.000	1.000
	1.9	0.996	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999	1.000
	2	0.995	0.997	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	2.1	0.993	0.996	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	2.2	0.991	0.995	0.997	0.998	0.999	0.999	0.999	0.999	0.999	0.999
	2.3	0.989	0.994	0.996	0.998	0.999	0.999	0.999	0.999	0.999	0.999
	2.4	0.986	0.992	0.995	0.997	0.998	0.999	0.999	0.999	0.999	0.999
	2.5	0.984	0.990	0.994	0.996	0.998	0.998	0.999	0.999	0.999	0.999
	2.6	0.980	0.988	0.992	0.995	0.997	0.998	0.999	0.999	0.999	0.999
	2.7	0.977	0.985	0.990	0.994	0.996	0.997	0.998	0.999	0.999	0.999
	2.8	0.974	0.982	0.988	0.993	0.995	0.997	0.998	0.999	0.999	0.999
	2.9	0.970	0.979	0.986	0.991	0.994	0.996	0.997	0.998	0.999	0.999
	3	0.966	0.976	0.984	0.989	0.993	0.995	0.997	0.998	0.998	0.999
	3.1	0.962	0.973	0.981	0.987	0.991	0.994	0.996	0.997	0.998	0.999
	3.2	0.958	0.970	0.978	0.985	0.989	0.993	0.995	0.997	0.998	0.998
	3.3	0.954	0.966	0.975	0.982	0.988	0.991	0.994	0.996	0.997	0.998
	3.4	0.950	0.963	0.973	0.980	0.985	0.990	0.993	0.995	0.997	0.998
	3.5	0.946	0.959	0.969	0.977	0.983	0.988	0.992	0.994	0.996	0.997
	3.6	0.942	0.956	0.966	0.975	0.981	0.986	0.990	0.993	0.995	0.997
	3.7	0.938	0.952	0.963	0.972	0.979	0.984	0.989	0.992	0.994	0.996
	3.8	0.934	0.948	0.959	0.969	0.977	0.983	0.987	0.991	0.993	0.995
	3.9	0.929	0.944	0.957	0.966	0.974	0.980	0.985	0.989	0.992	0.994

Table B.5: Estimated Passing Probabilities by Monte Carlo Simulation for μ−Q = 1 to 1.9 , σ = 4 to 6.9

	$\mu - Q$	1	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9
σ	4	0.925	0.940	0.953	0.963	0.972	0.978	0.983	0.988	0.991	0.993
	4.1	0.922	0.937	0.950	0.960	0.969	0.976	0.982	0.986	0.990	0.992
	4.2	0.918	0.933	0.946	0.957	0.966	0.974	0.980	0.985	0.988	0.991
	4.3	0.914	0.929	0.943	0.954	0.964	0.971	0.977	0.983	0.987	0.990
	4.4	0.910	0.926	0.939	0.951	0.960	0.968	0.975	0.981	0.985	0.989
	4.5	0.905	0.922	0.936	0.948	0.958	0.966	0.973	0.979	0.984	0.987
	4.6	0.902	0.918	0.932	0.945	0.955	0.964	0.971	0.977	0.982	0.986
	4.7	0.898	0.915	0.928	0.941	0.952	0.961	0.968	0.975	0.980	0.984
	4.8	0.894	0.911	0.926	0.938	0.949	0.958	0.966	0.973	0.978	0.983
	4.9	0.891	0.908	0.922	0.935	0.946	0.956	0.964	0.970	0.976	0.981
	5	0.887	0.904	0.918	0.932	0.943	0.953	0.961	0.969	0.974	0.979
	5.1	0.884	0.901	0.915	0.929	0.940	0.950	0.958	0.966	0.972	0.978
	5.2	0.881	0.897	0.912	0.925	0.937	0.948	0.956	0.964	0.970	0.976
	5.3	0.877	0.894	0.908	0.922	0.934	0.945	0.953	0.961	0.968	0.973
	5.4	0.874	0.890	0.905	0.919	0.931	0.942	0.951	0.959	0.966	0.972
	5.5	0.870	0.887	0.903	0.915	0.928	0.939	0.948	0.957	0.964	0.970
	5.6	0.867	0.884	0.899	0.913	0.925	0.936	0.945	0.954	0.961	0.968
	5.7	0.864	0.880	0.895	0.909	0.922	0.933	0.943	0.952	0.959	0.966
	5.8	0.860	0.877	0.892	0.906	0.919	0.930	0.940	0.949	0.957	0.963
	5.9	0.857	0.873	0.889	0.903	0.916	0.927	0.938	0.947	0.954	0.962
	6	0.854	0.871	0.885	0.900	0.913	0.924	0.935	0.944	0.952	0.959
	6.1	0.850	0.867	0.883	0.897	0.910	0.921	0.931	0.941	0.949	0.957
	6.2	0.847	0.864	0.879	0.893	0.907	0.919	0.929	0.939	0.947	0.954
	6.3	0.844	0.861	0.877	0.891	0.903	0.916	0.926	0.936	0.945	0.952
	6.4	0.841	0.858	0.873	0.888	0.900	0.913	0.923	0.934	0.942	0.950
	6.5	0.838	0.855	0.869	0.884	0.898	0.909	0.920	0.931	0.939	0.947
	6.6	0.835	0.851	0.867	0.881	0.895	0.906	0.918	0.928	0.937	0.945
	6.7	0.831	0.848	0.863	0.878	0.892	0.903	0.915	0.925	0.934	0.943
	6.8	0.828	0.845	0.860	0.874	0.888	0.900	0.912	0.922	0.931	0.940
	6.9	0.825	0.841	0.857	0.871	0.885	0.897	0.908	0.919	0.928	0.937

Table B.6: Estimated Passing Probabilities by Monte Carlo Simulation for $\mu - \mathrm{Q} = 1$ to 1.9 , $\sigma = 7$ to 10

	$\mu - Q$	1	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9
σ	7	0.822	0.838	0.853	0.867	0.881	0.894	0.905	0.916	0.926	0.934
	7.1	0.818	0.835	0.850	0.865	0.878	0.890	0.902	0.913	0.923	0.932
	7.2	0.815	0.831	0.847	0.861	0.875	0.887	0.899	0.910	0.920	0.929
	7.3	0.812	0.827	0.843	0.859	0.872	0.885	0.896	0.907	0.916	0.926
	7.4	0.808	0.825	0.840	0.854	0.868	0.881	0.893	0.903	0.913	0.923
	7.5	0.805	0.820	0.836	0.851	0.865	0.877	0.889	0.900	0.910	0.920
	7.6	0.801	0.818	0.832	0.847	0.861	0.873	0.886	0.897	0.907	0.916
	7.7	0.797	0.813	0.830	0.843	0.857	0.870	0.882	0.893	0.904	0.913
	7.8	0.794	0.809	0.824	0.839	0.854	0.866	0.878	0.890	0.900	0.910
	7.9	0.789	0.807	0.821	0.835	0.849	0.862	0.874	0.886	0.897	0.906
	8	0.786	0.802	0.816	0.832	0.845	0.858	0.870	0.882	0.892	0.903
	8.1	0.782	0.798	0.812	0.827	0.840	0.854	0.866	0.877	0.889	0.899
	8.2	0.778	0.793	0.808	0.823	0.836	0.849	0.862	0.874	0.884	0.895
	8.3	0.773	0.788	0.804	0.818	0.832	0.845	0.858	0.869	0.880	0.891
	8.4	0.769	0.783	0.799	0.813	0.827	0.840	0.853	0.865	0.876	0.886
	8.5	0.764	0.780	0.795	0.809	0.822	0.836	0.848	0.860	0.871	0.882
	8.6	0.758	0.774	0.790	0.803	0.817	0.831	0.844	0.855	0.866	0.877
	8.7	0.753	0.768	0.784	0.799	0.812	0.825	0.838	0.850	0.861	0.872
	8.8	0.748	0.763	0.778	0.793	0.807	0.820	0.833	0.845	0.855	0.867
	8.9	0.742	0.758	0.774	0.787	0.801	0.815	0.827	0.839	0.850	0.861
	9	0.736	0.753	0.768	0.781	0.795	0.809	0.822	0.834	0.845	0.856
	9.1	0.731	0.746	0.761	0.776	0.789	0.802	0.815	0.827	0.839	0.849
	9.2	0.725	0.740	0.755	0.769	0.783	0.796	0.809	0.821	0.832	0.844
	9.3	0.718	0.734	0.749	0.763	0.776	0.790	0.803	0.815	0.826	0.837
	9.4	0.712	0.727	0.742	0.756	0.770	0.784	0.795	0.808	0.820	0.831
	9.5	0.705	0.721	0.736	0.749	0.763	0.776	0.789	0.801	0.813	0.824
	9.6	0.698	0.714	0.728	0.742	0.755	0.768	0.781	0.794	0.806	0.817
	9.7	0.691	0.706	0.721	0.735	0.748	0.761	0.774	0.786	0.798	0.809
	9.8	0.684	0.699	0.714	0.727	0.740	0.754	0.766	0.779	0.791	0.802
	9.9	0.675	0.692	0.706	0.719	0.733	0.746	0.758	0.771	0.782	0.794
	10	0.669	0.684	0.697	0.711	0.724	0.738	0.751	0.762	0.775	0.786

Table B.7: Estimated Passing Probabilities by Monte Carlo Simulation for $\mu - \mathrm{Q} = 2$ to 2.9 , $\sigma = 0.5$ to 3.9

	$\mu - Q$	2	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9
σ	0.5	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.6	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.7	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.9	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.2	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.3	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.4	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.5	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.6	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.7	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.9	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.1	0.999	1.000	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.2	0.999	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.3	0.999	0.999	0.999	0.999	1.000	1.000	1.000	1.000	1.000	1.000
	2.4	0.999	0.999	0.999	0.999	0.999	1.000	1.000	1.000	1.000	1.000
	2.5	0.999	0.999	0.999	0.999	0.999	1.000	1.000	1.000	1.000	1.000
	2.6	0.999	0.999	0.999	0.999	0.999	1.000	0.999	1.000	1.000	1.000
	2.7	0.999	0.999	0.999	0.999	0.999	0.999	0.999	1.000	0.999	1.000
	2.8	0.999	0.999	0.999	0.999	0.999	0.999	0.999	1.000	0.999	1.000
	2.9	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	1.000	1.000
	3	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	1.000
	3.1	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	3.2	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	3.3	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	3.4	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	3.5	0.998	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	3.6	0.998	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	3.7	0.997	0.998	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	3.8	0.996	0.997	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	3.9	0.996	0.997	0.998	0.998	0.999	0.999	0.999	0.999	0.999	0.999

Table B.8: Estimated Passing Probabilities by Monte Carlo Simulation for μ−Q = 2 to 2.9 , σ = 4 to 6.9

	$\mu - Q$	2	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9
σ	4	0.995	0.996	0.997	0.998	0.998	0.999	0.999	0.999	0.999	0.999
	4.1	0.994	0.996	0.997	0.998	0.998	0.999	0.999	0.999	0.999	0.999
	4.2	0.993	0.995	0.996	0.997	0.998	0.998	0.999	0.999	0.999	0.999
	4.3	0.992	0.994	0.996	0.997	0.998	0.998	0.999	0.999	0.999	0.999
	4.4	0.991	0.993	0.995	0.996	0.997	0.998	0.998	0.999	0.999	0.999
	4.5	0.990	0.993	0.994	0.996	0.997	0.998	0.998	0.999	0.999	0.999
	4.6	0.989	0.992	0.993	0.995	0.996	0.997	0.998	0.998	0.999	0.999
	4.7	0.988	0.990	0.993	0.994	0.996	0.997	0.997	0.998	0.998	0.999
	4.8	0.986	0.989	0.992	0.994	0.995	0.996	0.997	0.998	0.998	0.999
	4.9	0.985	0.988	0.991	0.993	0.994	0.996	0.997	0.997	0.998	0.998
	5	0.983	0.987	0.990	0.992	0.994	0.995	0.996	0.997	0.998	0.998
	5.1	0.982	0.986	0.988	0.991	0.993	0.994	0.996	0.997	0.997	0.998
	5.2	0.980	0.984	0.987	0.990	0.992	0.994	0.995	0.996	0.997	0.998
	5.3	0.979	0.983	0.986	0.989	0.991	0.993	0.994	0.996	0.996	0.997
	5.4	0.977	0.981	0.985	0.988	0.990	0.992	0.994	0.995	0.996	0.997
	5.5	0.975	0.980	0.983	0.987	0.989	0.991	0.993	0.994	0.996	0.996
	5.6	0.973	0.978	0.982	0.985	0.988	0.990	0.992	0.994	0.995	0.996
	5.7	0.971	0.976	0.980	0.984	0.987	0.989	0.991	0.993	0.994	0.995
	5.8	0.969	0.974	0.979	0.983	0.986	0.988	0.990	0.992	0.994	0.995
	5.9	0.968	0.973	0.977	0.981	0.984	0.988	0.990	0.992	0.993	0.994
	6	0.965	0.971	0.976	0.980	0.983	0.986	0.988	0.991	0.992	0.994
	6.1	0.964	0.969	0.974	0.978	0.982	0.985	0.988	0.990	0.992	0.993
	6.2	0.961	0.967	0.972	0.977	0.981	0.984	0.987	0.989	0.991	0.992
	6.3	0.959	0.965	0.971	0.975	0.979	0.982	0.985	0.988	0.990	0.992
	6.4	0.957	0.963	0.969	0.973	0.977	0.981	0.984	0.987	0.989	0.991
	6.5	0.955	0.961	0.967	0.972	0.976	0.980	0.983	0.986	0.988	0.990
	6.6	0.953	0.959	0.964	0.970	0.974	0.978	0.981	0.984	0.987	0.989
	6.7	0.950	0.957	0.963	0.968	0.972	0.977	0.980	0.983	0.986	0.988
	6.8	0.948	0.954	0.961	0.966	0.971	0.975	0.978	0.982	0.985	0.987
	6.9	0.945	0.952	0.958	0.964	0.969	0.973	0.977	0.980	0.983	0.986

Table B.9: Estimated Passing Probabilities by Monte Carlo Simulation for $\mu{-}Q = 2$ to 2.9 , $\sigma = 7$ to 10

	$\mu - Q$	2	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9
σ	7	0.942	0.950	0.956	0.962	0.967	0.971	0.976	0.979	0.982	0.985
	7.1	0.940	0.948	0.954	0.959	0.965	0.969	0.974	0.978	0.981	0.984
	7.2	0.937	0.945	0.951	0.958	0.962	0.968	0.972	0.976	0.979	0.982
	7.3	0.935	0.942	0.949	0.955	0.961	0.965	0.970	0.974	0.978	0.981
	7.4	0.932	0.939	0.946	0.953	0.959	0.963	0.968	0.972	0.976	0.979
	7.5	0.928	0.937	0.944	0.950	0.956	0.962	0.966	0.970	0.974	0.978
	7.6	0.925	0.934	0.941	0.948	0.954	0.959	0.964	0.968	0.972	0.976
	7.7	0.922	0.930	0.938	0.945	0.951	0.957	0.962	0.966	0.970	0.974
	7.8	0.919	0.927	0.935	0.942	0.948	0.954	0.959	0.964	0.968	0.972
	7.9	0.916	0.924	0.932	0.939	0.945	0.951	0.956	0.962	0.966	0.970
	8	0.912	0.920	0.928	0.936	0.942	0.949	0.954	0.959	0.964	0.968
	8.1	0.908	0.917	0.925	0.933	0.939	0.945	0.951	0.956	0.961	0.965
	8.2	0.904	0.913	0.921	0.929	0.936	0.942	0.948	0.953	0.958	0.963
	8.3	0.901	0.909	0.918	0.926	0.932	0.939	0.945	0.950	0.956	0.960
	8.4	0.896	0.905	0.914	0.922	0.929	0.935	0.941	0.947	0.953	0.957
	8.5	0.892	0.901	0.910	0.917	0.925	0.931	0.938	0.943	0.949	0.954
	8.6	0.887	0.896	0.905	0.913	0.920	0.928	0.934	0.940	0.946	0.950
	8.7	0.882	0.891	0.900	0.909	0.916	0.923	0.930	0.936	0.942	0.947
	8.8	0.877	0.887	0.895	0.904	0.912	0.919	0.926	0.932	0.938	0.943
	8.9	0.871	0.882	0.891	0.899	0.907	0.914	0.921	0.928	0.934	0.940
	9	0.865	0.876	0.885	0.894	0.902	0.909	0.917	0.923	0.930	0.935
	9.1	0.860	0.870	0.879	0.888	0.896	0.904	0.912	0.918	0.925	0.931
	9.2	0.854	0.864	0.874	0.883	0.891	0.898	0.906	0.913	0.920	0.926
	9.3	0.848	0.858	0.867	0.877	0.885	0.893	0.900	0.908	0.915	0.921
	9.4	0.841	0.851	0.861	0.870	0.879	0.887	0.895	0.902	0.909	0.915
	9.5	0.835	0.844	0.854	0.864	0.873	0.881	0.889	0.896	0.903	0.910
	9.6	0.827	0.838	0.847	0.858	0.866	0.875	0.883	0.890	0.897	0.904
	9.7	0.821	0.831	0.841	0.850	0.859	0.868	0.876	0.884	0.891	0.898
	9.8	0.812	0.824	0.834	0.843	0.852	0.861	0.869	0.877	0.885	0.892
	9.9	0.805	0.815	0.825	0.835	0.845	0.853	0.862	0.870	0.877	0.884
	10	0.796	0.808	0.818	0.827	0.836	0.846	0.854	0.862	0.870	0.878

Table B.10: Estimated Passing Probabilities by Monte Carlo Simulation for μ−Q = 3 to 3.9 , σ = 0.5 to 3.9

	$\mu - Q$	3	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9
σ	0.5	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.6	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.7	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.9	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.2	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.3	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.4	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.5	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.6	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.7	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.9	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.2	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.3	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.4	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.5	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.6	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.7	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.9	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3.1	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3.2	1.000	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3.3	0.999	0.999	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3.4	0.999	0.999	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3.5	0.999	0.999	0.999	0.999	0.999	1.000	1.000	1.000	1.000	1.000
	3.6	0.999	0.999	0.999	0.999	0.999	1.000	1.000	1.000	1.000	1.000
	3.7	0.999	0.999	0.999	0.999	0.999	0.999	1.000	1.000	1.000	1.000
	3.8	0.999	0.999	0.999	0.999	0.999	0.999	1.000	0.999	1.000	1.000
	3.9	0.999	0.999	0.999	0.999	0.999	0.999	0.999	1.000	0.999	1.000

Table B.11: Estimated Passing Probabilities by Monte Carlo Simulation for $\mu{-}Q = 3$ to 3.9 , $\sigma = 4$ to 6.9

	$\mu - Q$	3	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9
σ	4	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	1.000	0.999
	4.1	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	1.000
	4.2	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	4.3	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	4.4	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	4.5	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	4.6	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	4.7	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	4.8	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	4.9	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	5	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	5.1	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	5.2	0.998	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	5.3	0.998	0.998	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	5.4	0.998	0.998	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	5.5	0.997	0.998	0.998	0.998	0.999	0.999	0.999	0.999	0.999	0.999
	5.6	0.997	0.997	0.998	0.998	0.999	0.999	0.999	0.999	0.999	0.999
	5.7	0.996	0.997	0.998	0.998	0.998	0.999	0.999	0.999	0.999	0.999
	5.8	0.996	0.997	0.997	0.998	0.998	0.998	0.999	0.999	0.999	0.999
	5.9	0.995	0.996	0.997	0.998	0.998	0.998	0.999	0.999	0.999	0.999
	6	0.995	0.996	0.997	0.997	0.998	0.998	0.998	0.999	0.999	0.999
	6.1	0.994	0.995	0.996	0.997	0.997	0.998	0.998	0.999	0.999	0.999
	6.2	0.994	0.995	0.996	0.997	0.997	0.998	0.998	0.998	0.999	0.999
	6.3	0.993	0.994	0.995	0.996	0.997	0.997	0.998	0.998	0.998	0.999
	6.4	0.992	0.994	0.995	0.996	0.996	0.997	0.998	0.998	0.998	0.999
	6.5	0.992	0.993	0.994	0.995	0.996	0.997	0.997	0.998	0.998	0.998
	6.6	0.991	0.992	0.994	0.995	0.996	0.996	0.997	0.998	0.998	0.998
	6.7	0.990	0.992	0.993	0.994	0.995	0.996	0.997	0.997	0.998	0.998
	6.8	0.989	0.991	0.992	0.994	0.995	0.996	0.996	0.997	0.997	0.998
	6.9	0.988	0.990	0.991	0.993	0.994	0.995	0.996	0.996	0.997	0.997

Table B.12: Estimated Passing Probabilities by Monte Carlo Simulation for μ−Q = 3 to 3.9 , σ = 7 to 10

	$\mu - Q$	3	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9
σ	7	0.987	0.989	0.991	0.992	0.993	0.994	0.995	0.996	0.997	0.997
	7.1	0.986	0.988	0.990	0.991	0.993	0.994	0.995	0.995	0.996	0.997
	7.2	0.985	0.987	0.989	0.990	0.992	0.993	0.994	0.995	0.996	0.996
	7.3	0.984	0.986	0.988	0.990	0.991	0.992	0.993	0.994	0.995	0.996
	7.4	0.982	0.984	0.987	0.988	0.990	0.992	0.993	0.994	0.995	0.995
	7.5	0.980	0.983	0.986	0.987	0.989	0.991	0.992	0.993	0.994	0.995
	7.6	0.979	0.982	0.984	0.986	0.988	0.990	0.991	0.992	0.993	0.994
	7.7	0.977	0.980	0.983	0.985	0.987	0.989	0.990	0.991	0.992	0.993
	7.8	0.976	0.978	0.981	0.983	0.986	0.987	0.989	0.990	0.991	0.993
	7.9	0.973	0.977	0.979	0.982	0.984	0.986	0.988	0.989	0.991	0.992
	8	0.971	0.975	0.978	0.980	0.983	0.984	0.987	0.988	0.989	0.991
	8.1	0.969	0.972	0.975	0.979	0.981	0.983	0.985	0.987	0.988	0.990
	8.2	0.967	0.970	0.974	0.977	0.979	0.981	0.984	0.985	0.987	0.988
	8.3	0.964	0.968	0.971	0.975	0.977	0.980	0.982	0.984	0.986	0.987
	8.4	0.961	0.965	0.969	0.972	0.975	0.978	0.980	0.982	0.984	0.985
	8.5	0.959	0.963	0.966	0.969	0.973	0.976	0.978	0.980	0.982	0.984
	8.6	0.955	0.959	0.964	0.967	0.970	0.973	0.976	0.978	0.980	0.982
	8.7	0.952	0.956	0.960	0.964	0.967	0.970	0.973	0.975	0.978	0.980
	8.8	0.949	0.953	0.957	0.961	0.964	0.968	0.970	0.973	0.976	0.978
	8.9	0.944	0.949	0.954	0.958	0.961	0.964	0.968	0.970	0.973	0.975
	9	0.941	0.945	0.950	0.954	0.958	0.962	0.964	0.967	0.970	0.973
	9.1	0.936	0.941	0.945	0.950	0.954	0.957	0.961	0.964	0.967	0.970
	9.2	0.931	0.937	0.941	0.946	0.951	0.954	0.957	0.961	0.964	0.967
	9.3	0.926	0.932	0.937	0.941	0.946	0.950	0.954	0.957	0.960	0.963
	9.4	0.921	0.927	0.932	0.937	0.942	0.945	0.949	0.953	0.957	0.960
	9.5	0.916	0.922	0.927	0.932	0.936	0.941	0.945	0.949	0.952	0.956
	9.6	0.911	0.916	0.922	0.927	0.932	0.936	0.941	0.945	0.948	0.952
	9.7	0.905	0.910	0.916	0.921	0.926	0.931	0.935	0.940	0.944	0.947
	9.8	0.898	0.904	0.910	0.915	0.921	0.926	0.930	0.934	0.939	0.942
	9.9	0.891	0.898	0.904	0.909	0.915	0.920	0.925	0.929	0.933	0.937
	10	0.884	0.890	0.897	0.903	0.909	0.914	0.919	0.924	0.928	0.932

Table B.13: Estimated Passing Probabilities by Monte Carlo Simulation for μ−Q = 4 to 5 , σ = 0.5 to 3.9

	$\mu - Q$	4	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5
σ	0.5	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.6	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.7	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.9	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.2	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.3	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.4	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.5	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.6	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.7	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	1.9	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.2	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.3	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.4	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.5	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.6	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.7	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	2.9	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3.1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3.2	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3.3	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3.4	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3.5	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3.6	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3.7	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	3.9	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Table B.14: Estimated Passing Probabilities by Monte Carlo Simulation for μ−Q = 4 to 5 , σ = 4 to 6.9

	$\mu - Q$	4	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5
σ	4	1.000	1.000	0.999	1.000	1.000	0.999	1.000	1.000	1.000	1.000	1.000
	4.1	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	4.2	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	4.3	0.999	1.000	1.000	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	4.4	0.999	1.000	1.000	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	4.5	0.999	0.999	0.999	0.999	1.000	1.000	1.000	1.000	1.000	1.000	0.999
	4.6	0.999	1.000	0.999	1.000	1.000	0.999	1.000	0.999	1.000	1.000	1.000
	4.7	0.999	0.999	0.999	0.999	0.999	0.999	1.000	1.000	1.000	1.000	1.000
	4.8	0.999	0.999	0.999	0.999	1.000	0.999	0.999	1.000	0.999	1.000	1.000
	4.9	0.999	0.999	0.999	0.999	0.999	0.999	0.999	1.000	1.000	1.000	1.000
	5	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	1.000	1.000	0.999
	5.1	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	1.000
	5.2	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	1.000	0.999	1.000
	5.3	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	5.4	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	1.000
	5.5	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	5.6	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	5.7	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	5.8	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	5.9	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	6	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	6.1	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	6.2	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	6.3	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	6.4	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	6.5	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	6.6	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	6.7	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	6.8	0.998	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	6.9	0.998	0.998	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999

Table B.15: Estimated Passing Probabilities by Monte Carlo Simulation for $\mu{-}Q = 4$ to 5 , $\sigma = 7$ to 10

	$\mu - Q$	4	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5
σ	7	0.998	0.998	0.998	0.998	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	7.1	0.997	0.998	0.998	0.998	0.998	0.999	0.999	0.999	0.999	0.999	0.999
	7.2	0.997	0.997	0.998	0.998	0.998	0.998	0.999	0.999	0.999	0.999	0.999
	7.3	0.997	0.997	0.997	0.998	0.998	0.998	0.998	0.999	0.999	0.999	0.999
	7.4	0.996	0.997	0.997	0.997	0.998	0.998	0.998	0.998	0.999	0.999	0.999
	7.5	0.995	0.996	0.997	0.997	0.997	0.998	0.998	0.998	0.998	0.999	0.999
	7.6	0.995	0.996	0.996	0.997	0.997	0.997	0.998	0.998	0.998	0.998	0.998
	7.7	0.994	0.995	0.996	0.996	0.997	0.997	0.997	0.998	0.998	0.998	0.998
	7.8	0.993	0.994	0.995	0.996	0.996	0.997	0.997	0.997	0.997	0.998	0.998
	7.9	0.993	0.994	0.994	0.995	0.995	0.996	0.996	0.997	0.997	0.997	0.998
	8	0.992	0.993	0.994	0.994	0.995	0.996	0.996	0.996	0.997	0.997	0.997
	8.1	0.991	0.992	0.993	0.993	0.994	0.995	0.995	0.996	0.996	0.997	0.997
	8.2	0.990	0.991	0.992	0.993	0.993	0.994	0.995	0.995	0.996	0.996	0.996
	8.3	0.988	0.990	0.991	0.992	0.992	0.993	0.994	0.994	0.995	0.995	0.996
	8.4	0.987	0.988	0.990	0.991	0.991	0.992	0.993	0.993	0.994	0.995	0.995
	8.5	0.985	0.987	0.988	0.989	0.990	0.991	0.992	0.993	0.993	0.994	0.994
	8.6	0.984	0.985	0.987	0.988	0.989	0.990	0.991	0.991	0.992	0.993	0.993
	8.7	0.982	0.983	0.985	0.986	0.988	0.988	0.989	0.990	0.991	0.992	0.992
	8.8	0.980	0.981	0.983	0.984	0.986	0.987	0.988	0.989	0.990	0.991	0.991
	8.9	0.977	0.979	0.981	0.982	0.984	0.985	0.986	0.987	0.988	0.989	0.990
	9	0.975	0.977	0.979	0.980	0.982	0.983	0.985	0.986	0.987	0.988	0.989
	9.1	0.972	0.974	0.976	0.978	0.980	0.981	0.983	0.984	0.985	0.986	0.987
	9.2	0.969	0.972	0.974	0.976	0.977	0.979	0.980	0.982	0.983	0.984	0.985
	9.3	0.966	0.969	0.971	0.972	0.975	0.976	0.978	0.980	0.981	0.982	0.984
	9.4	0.962	0.965	0.968	0.970	0.972	0.974	0.975	0.977	0.979	0.980	0.981
	9.5	0.959	0.962	0.964	0.966	0.969	0.971	0.973	0.975	0.976	0.977	0.979
	9.6	0.955	0.958	0.960	0.963	0.965	0.967	0.969	0.972	0.973	0.975	0.976
	9.7	0.951	0.954	0.957	0.959	0.962	0.964	0.966	0.968	0.970	0.972	0.974
	9.8	0.946	0.949	0.952	0.955	0.958	0.960	0.962	0.965	0.967	0.969	0.970
	9.9	0.941	0.944	0.948	0.951	0.954	0.957	0.958	0.961	0.964	0.966	0.967
	10	0.936	0.940	0.943	0.946	0.949	0.952	0.954	0.958	0.960	0.962	0.964