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Professional paper

Testing robustness in USP multistage testing using simulations

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Abstract

Content uniformity and dissolution are multistage tests which are specified by the United States Pharmacopeia (USP) to ensure that the drug product meets the specified standards. A manufacturing process is said to be in regulatory compliance, only if it meets the acceptance criteria for all the tests specified in USP. Estimating the probability of passing or failing these acceptance criteria is used by manufacturers to judge the quality of these products. The manuscript aims to use statistical simulations to create a new measure of probability to estimate the robustness of these multistage tests. Based on the results from simulations it was observed that multistage testing acceptance criteria for USP dissolution test was robust, whereas for USP content uniformity test robustness was related to mean and standard deviation values used in the simulation.

Key words: Content uniformity, dissolution, simulation, probability, robustness

Introduction

The USP <905> content uniformity test (USP<905>, 2011) is a two stage process, whereby if the samples pass in Stage 1, the batch passes the test and Stage 2 testing is only carried out if it fails in Stage 1. The USP <711> dissolution test (USP<711>, 2011) is a three stage process, wherein if the samples pass the first stage (S_1), then the batch is considered to pass. If the samples fail in the S_1 stage, then the second stage (S2) testing is performed. If the samples pass in S2 stage, then the batch is considered as pass, else third stage (S3) testing is performed. When the samples pass in S3 stage then the batch is considered as pass else the batch is considered as failed. The acceptance criteria for these multistage tests are given in Table 1 and Table 2. For the scope of this manuscript, robustness is defined as obtaining a low probability value for passing the initial stage and failing in the subsequent stages of multi-stage testing USP tests. We also assume that the goal of the manufacturing process is the ability to manufacture dosage units with a mean value of 100% of drug content when tested for content uniformity. Simulations are implemented using computer programs using random numbers to approximate the passing probability of these multistage tests. The simulated random values generated account for the variability which is expected from experimental results. Simulations are a great tool as they help to approximate the experimental results in a faster and effective way without actually performing the experiment.

Simulations were used to assess the robustness of acceptance criteria in USP multistage testing for different combinations of mean and standard deviation values.

Material and methods

For content uniformity, simulated data was generated to model the mean value of drug content. In case of dissolution, simulated data represented the cumulative

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Table 1. USP <905> content uniformity acceptance criteria (USP<905>, 2011)

Stage 1	Stage 2
N = 10 units Acceptance value (AV) is not more than 15 AV = $\lvert M - \bar{X} \rvert + k * sd$ where $\bar{X}$ = Mean of 10 units sd = Standard deviation of 10 units k = 2.4	Stage 1 AV > 15 N = 30 units (10 from Stage 1 and additional 20 units) AV value not more than 15 AV = $\lvert M - \bar{X} \rvert + k * sd$ where $\bar{X}$ = Mean of 30 units sd = Standard deviation of 30 units k = 2.0 75% * M < All 30 units individually < 125% M
M (case 1): when T ≤ 101.5	If 98.5% ≤ $\bar{X}$ ≤ T, then M = $\bar{X}$ (AV = k * sd) If $\bar{X}$ < 98.5%, then (AV = 98.5 – $\bar{X}$ + k * sd) M = 98.5% If $\bar{X}$ > T, then (AV = $\bar{X}$ – 101.5 + k * sd) M = 101.5%
M (case 2): when T > 101.5	If 98.5% ≤ $\bar{X}$ ≤ 101.5%, then M = $\bar{X}$ (AV = k * sd) If $\bar{X}$ < 98.5%, then (AV = 98.5 – $\bar{X}$ + k*sd) M = 98.5% If $\bar{X}$ > 101.5%, then (AV = $\bar{X}$ – 101.5 + k * sd) M = 101.5%

T – Target content per dosage unit at time of manufacture, expressed as percentage of label claim. T is generally 100% or manufacturer's approved target content per dosage unit.

Table 2. USP <711> dissolution test acceptance criteria for immediate release dosage forms (USP<711>, 2011)

Stage of dissolution	Units tested	Acceptance criteria
S_1	6	Each unit is not less than Q + 5%
S_2	6	For 12 units a) Average of (S_1+ S_2) is equal to or greater than Q b) No unit (S_1+ S_2) is less than Q - 15%
S_3	12	For 24 units a) Average of (S_1+ S_2+ S_3) is equal to or greater than Q b) No more than 2 units are less than Q – 15 % c) No unit is less than Q – 25 %

amount of drug released at the end of dissolution. In both cases simulated data was generated using specified mean and standard deviation. The normal distribution was considered to represent high-quality material materials manufactured under controlled conditions (Lunney and Anderson, 2009). Mean and standard deviation are the parameters that determine the shape of this distribution.

a) USP<905> simulation

Simulations were performed using custom written code in R, which is available as free software (The R Project for Statistical Computing, 2025). The code works by checking whether the simulated data meets the USP specified conditions at each stage. The schematic outline of the code is shown in Figure 1 and Figure 2. The passing probability is then calculated using the following equation:

$$\frac{Number\ of\ times\ simulated\ data\ meeting\ acceptance\ criteria}{Number\ of\ simulations} \quad (1)$$

The advantage of simulations is that they provide an opportunity to estimate the probability of passing each stage, irrespective of the outcome in the initial stage of the test. The simulation was performed under the assumption that the underlying distribution of content uniformity results was from a normal distribution. Different means (90, 95 to 105, and 110) at a range of standard deviation values (1 to 10) were used for simulation. Fig. *3* shows the probability of passing USP 905 when the simulation was performed at mean 100 at standard deviation values ranging from 1 to 10, whereas Fig. *4* shows the probability of passing USP 905 in the first stage but failing in the second stage. The simulation results matched with the reported USP 905 probability (Bergum et al., 2015). Compiled R code for USP 905, the probability of passing at first stage and failing in second stage are included in the supporting

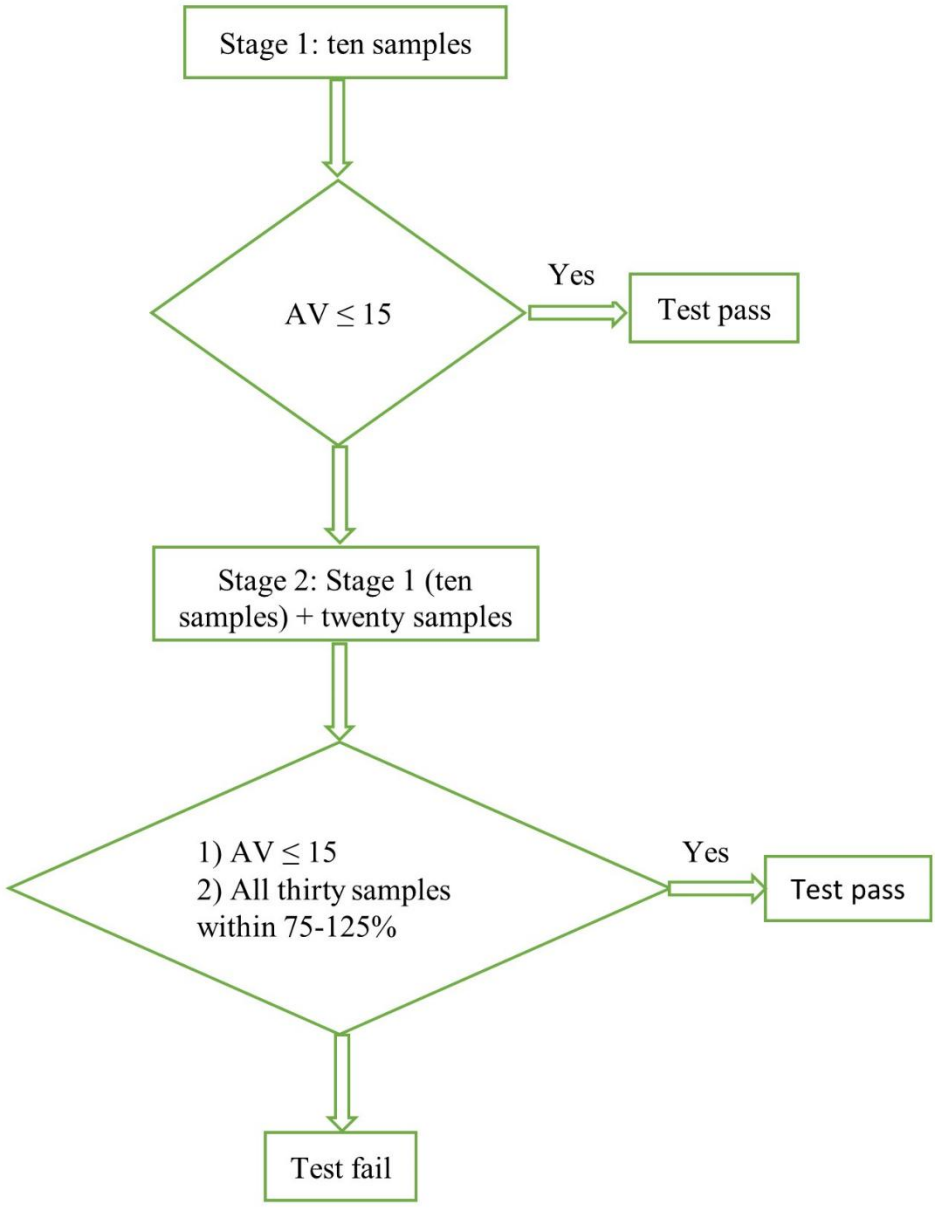

Fig. 1. Schematic outline for simulation for USP<905> content uniformity test. The process is repeated for large number of times to accurately estimate the probability of passing USP content uniformity test. In case of robustness testing, content uniformity test is continued irrespective of the result in the first stage.

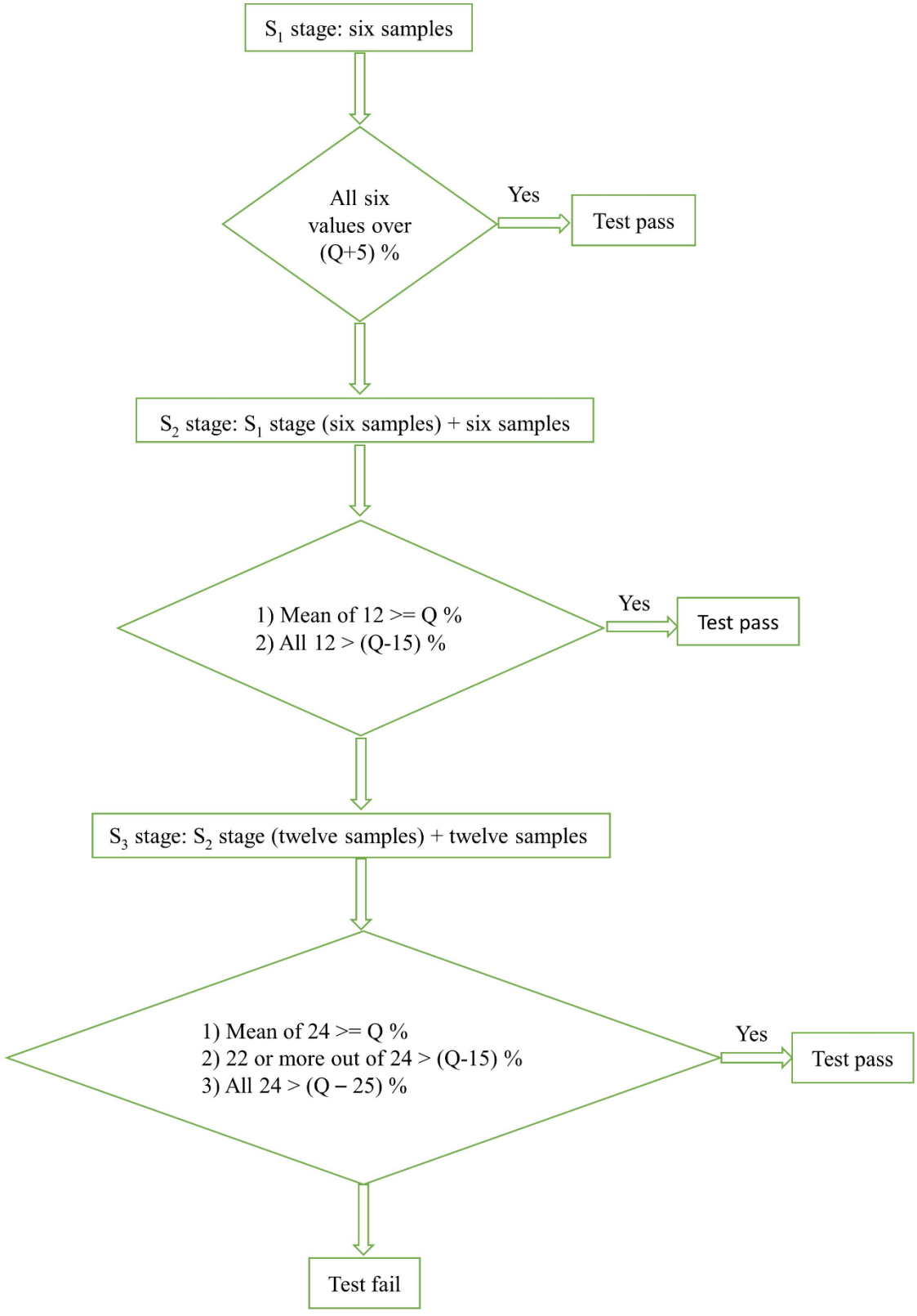

Fig. 2. Schematic outline for simulation for USP<711> dissolution test. The process is repeated for large number of times to accurately estimate the probability of passing USP dissolution test. In case of robustness testing, dissolution test is continued irrespective of the result in the initial (first and second) stages.

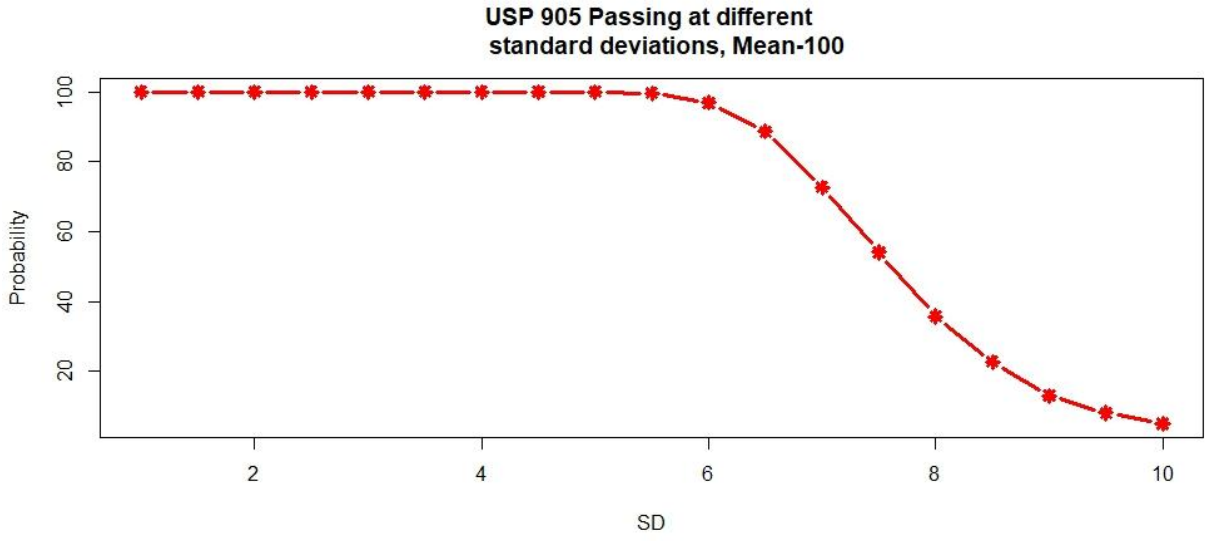

Fig. 3. Plot showing probability of passing USP<905> at standard deviation (1 to 10).

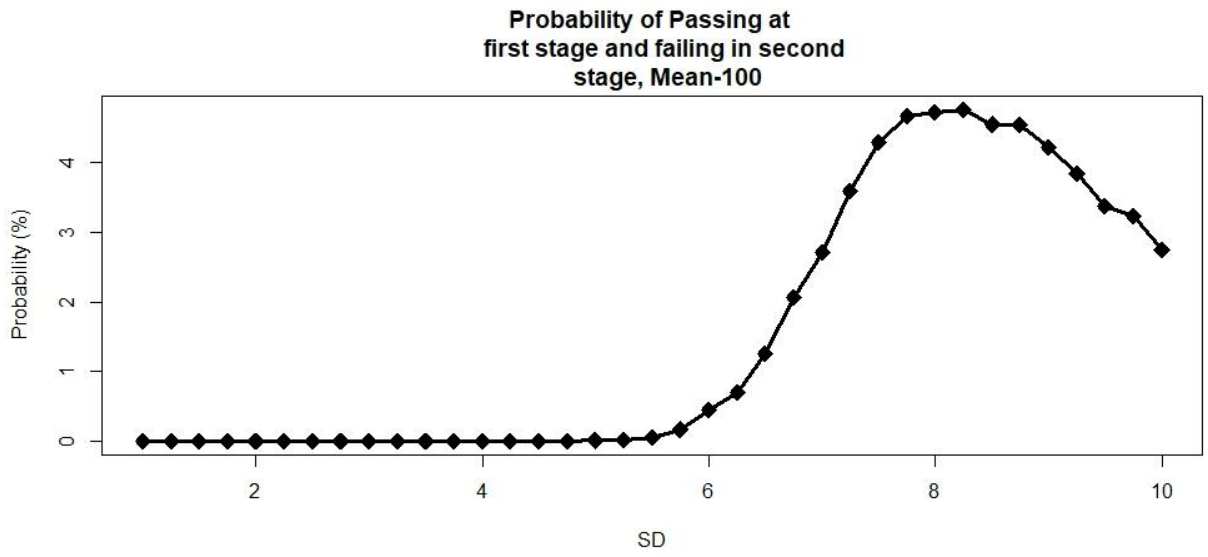

Fig. 4. Plot showing probability of passing in first stage and failing in second stage.

information. In both these R codes, by changing the mean value to the required value, probability can be estimated.

Even though the probability of passing the test decreased as standard deviation increased as seen in Fig. 3, it was observed that the probability of passing in first stage and failing in second increases as standard deviation increases to 8 and then decreases as standard deviation increases to 10 as seen in Fig. 4. The plausible reason for this can be explained by standard deviation. It was found that the first stage standard deviation for ten samples was found to less when compared to thirty samples tested in the second stage.

b) USP <711> simulation

The passing probability of S_1 stage can be estimated either by exact mathematical formula or by using simulation. Simulation was employed to calculate the probability of passing since S_2 criteria is tested on failing S_1, S_3 criteria is tested conditioned on failing S_2. When the number of simulations is large, an accurate estimate of passing probability can be obtained (Dumont et al., 2007).

Simulation was performed at mean values (75 and 80) at different standard deviation values (1 to 10). Fig. *5* shows the probability of passing at different standard

deviations when mean was 80. The results for passing probability from the simulation matched with the reported values (Wang, 2007). Compiled R code for USP<711>, probability of passing in the first stage and failing in the second stage and probability of passing in the first two stages while failing in the third stage are included in the supporting information. In these R codes, by changing the mean value, robustness at specific mean and standard deviation values can be estimated.

Results and discussion

From the simulation it can be inferred that for USP<905> content uniformity tests, as the mean increases above 100 and as the standard deviation varied between 6 to 8, higher probability values were observed leading to lower robustness under these conditions. The results of simulations are shown in Figure 4. Simulations for USP<711> were performed at mean values of 75 and 80, and the results are shown in Table 3.

Conclusion

Based on results from the simulation, it can be observed that in USP<711> multistep dissolution tests are robust with respect to the acceptance criteria. In case of USP<905> content uniformity test, robustness depends on the mean and standard deviation values used in the simulation. Based on simulation results, which are shown in Fig. 6 it can be concluded that for mean values from 95 to 98, 102 to 105 second stage testing should be performed for standard deviation values over 5 irrespective of the first stage results. In case of mean values 99 and 101, second stage testing should be performed for standard deviation values over 6 irrespective of the first stage results. For mean value of 110, second stage testing should be performed irrespective of first stage result for standard deviation values from 3 to 8. For mean value of 100, second stage testing should be performed irrespective of first stage result for standard deviation values above 6. In case of a mean value of 90, no such conclusion could be made.

Table 3. Probability at different standard deviations (prb (%) refers to probability of passing in S_1 stage and failing S_2 stage, whereas prb1(%) refers to probability of passing in S_1 and S_2 stage, but failing in S_3 stage)

	Mean = 80		Mean = 75	
stdev	Prb (%)	Prb1 (%)	Prb (%)	Prb1 (%)
1	0	0	0	0
1.5	0	0	0	0
2	0	0	0	0
2.5	0	0	0	0
3	0	0	0	0
3.5	0	0	0	0
4	0	0	0	0
4.5	0	0	0	0
5	0	0	0	0
5.5	0	0	0	0
6	0	0	0	0
6.5	0.01	0	0	0
7	0	0	0	0
7.5	0.06	0	0	0
8	0.05	0	0	0
8.5	0.06	0	0.02	0
9	0.11	0	0.02	0
9.5	0.17	0	0.03	0
10	0.21	0.01	0.02	0

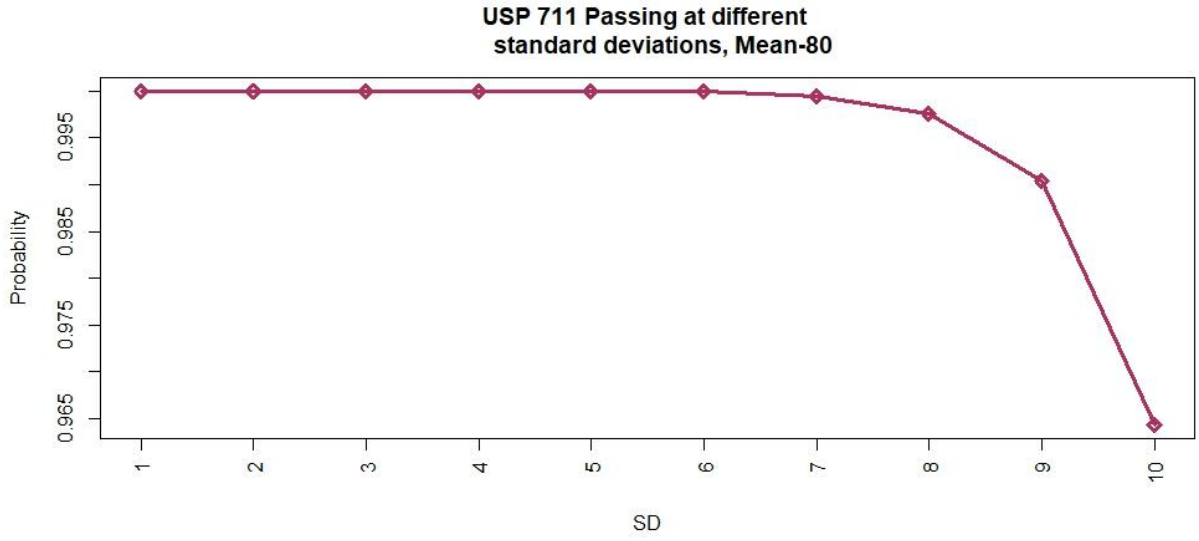

Fig. 5. Plot showing probability of passing USP<711>.

Supporting information:

Compiled R codes for USP<711>, USP<711> robustness, USP<905> and USP<905> robustness tests.

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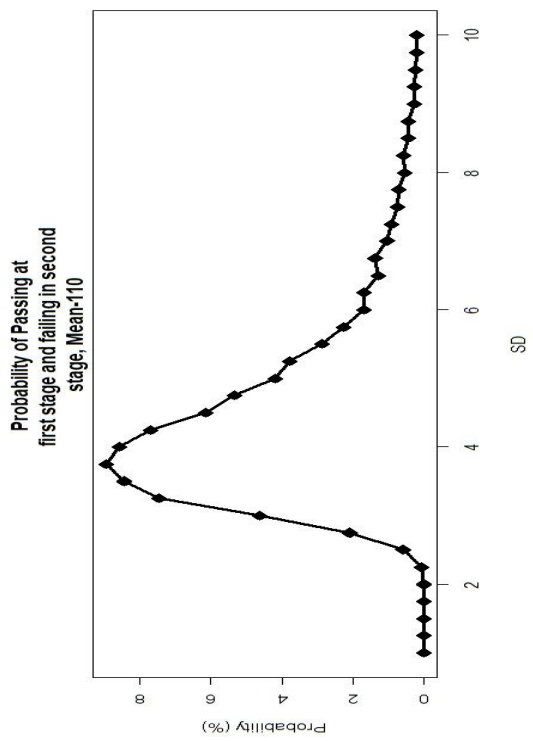
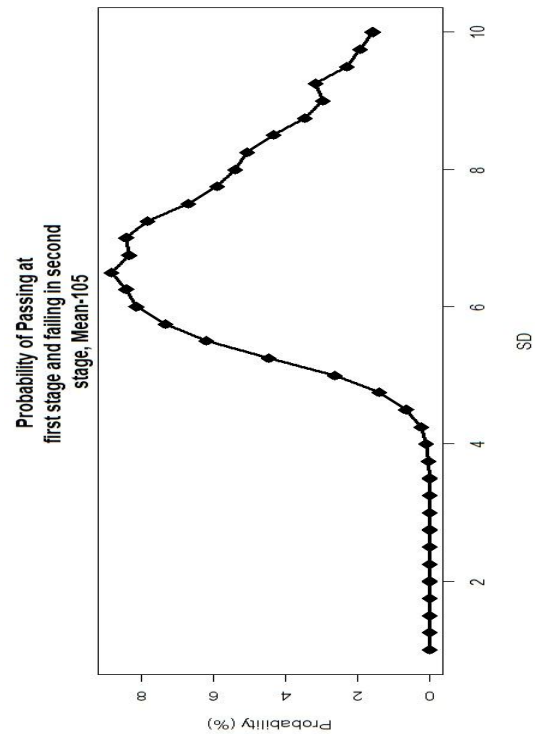
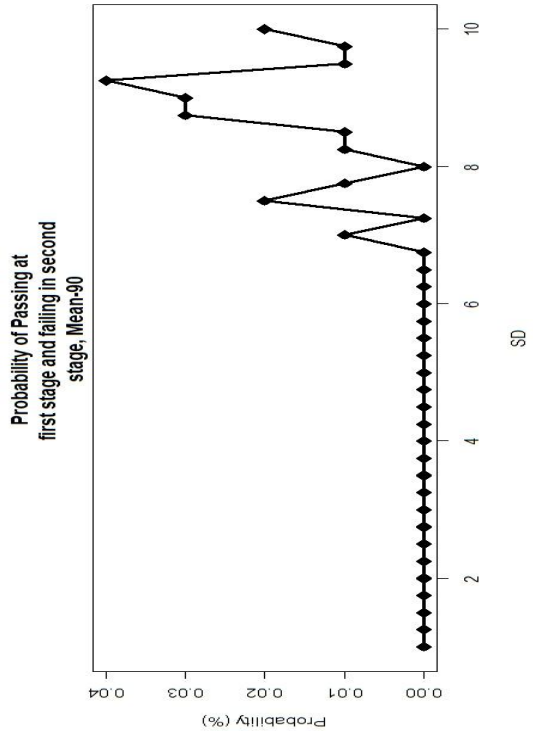
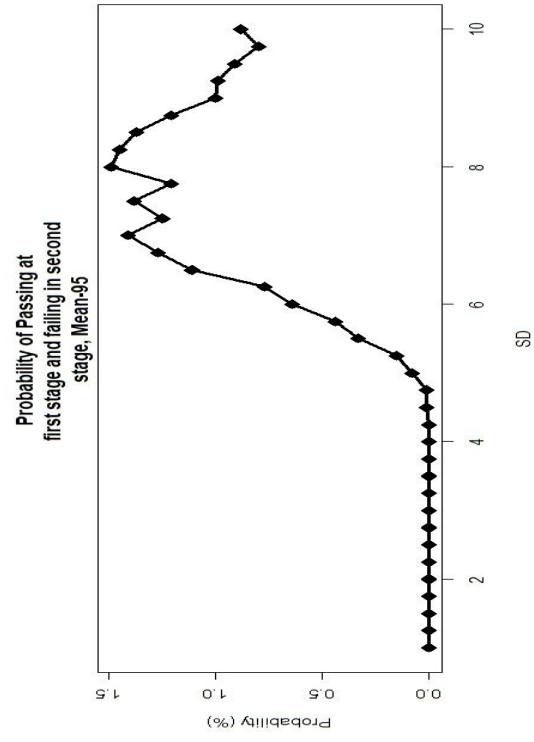
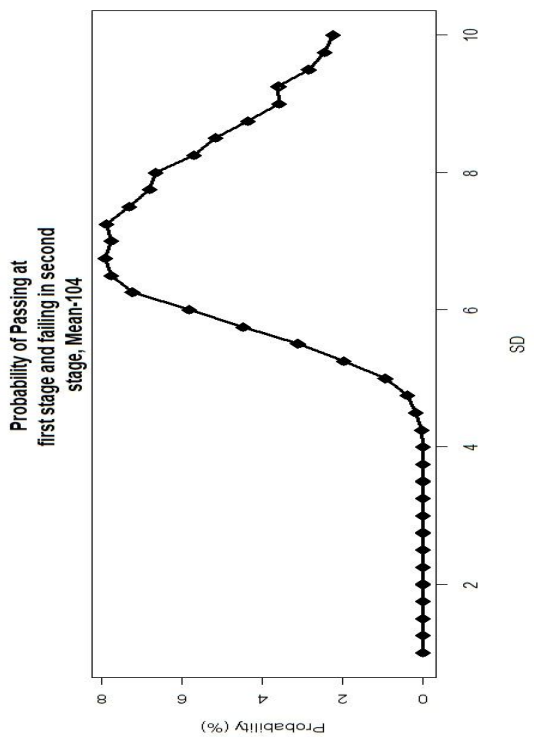
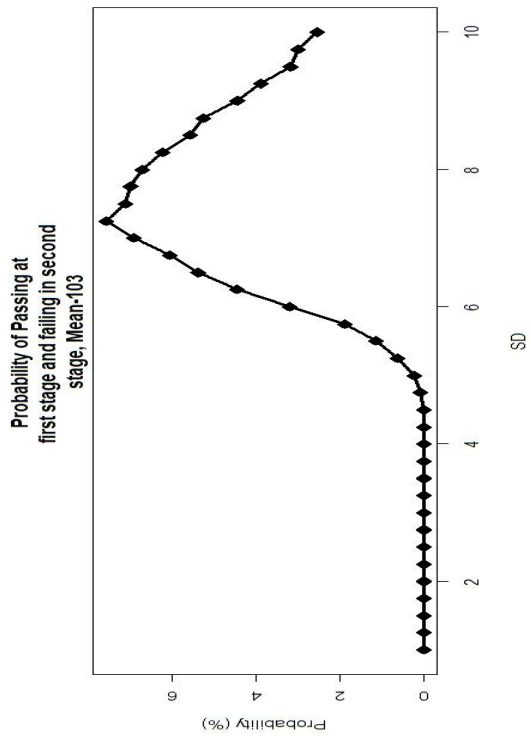

Probability of Passing at first stage and failing in second stage, Mean-110
Probability (%)
SD

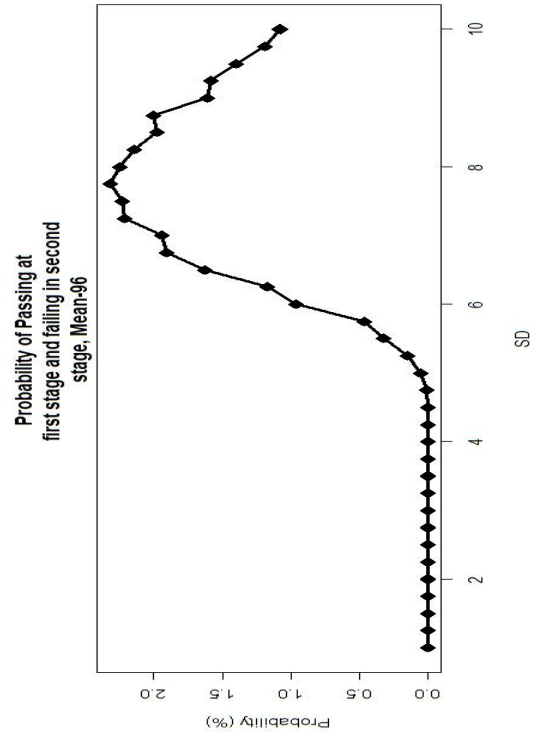

Probability of Passing at first stage and failing in second stage, Mean-105
Probability (%)
SD

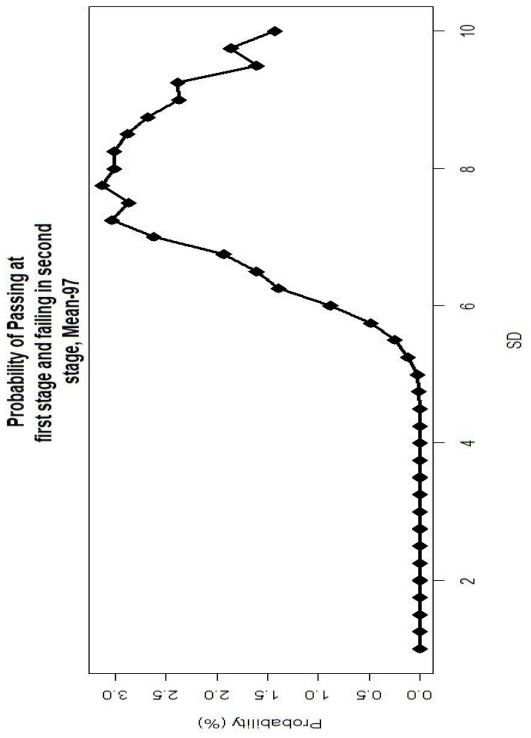

Probability of Passing at first stage and failing in second stage, Mean-90
Probability (%)
SD


Probability of Passing at first stage and failing in second stage, Mean-95
Probability (%)
SD


Probability of Passing at first stage and failing in second stage, Mean-104
Probability (%)
SD


Probability of Passing at first stage and failing in second stage, Mean-103
Probability (%)
SD


Probability of Passing at first stage and failing in second stage, Mean-96
Probability (%)
SD


Probability of Passing at first stage and failing in second stage, Mean-97
Probability (%)
SD

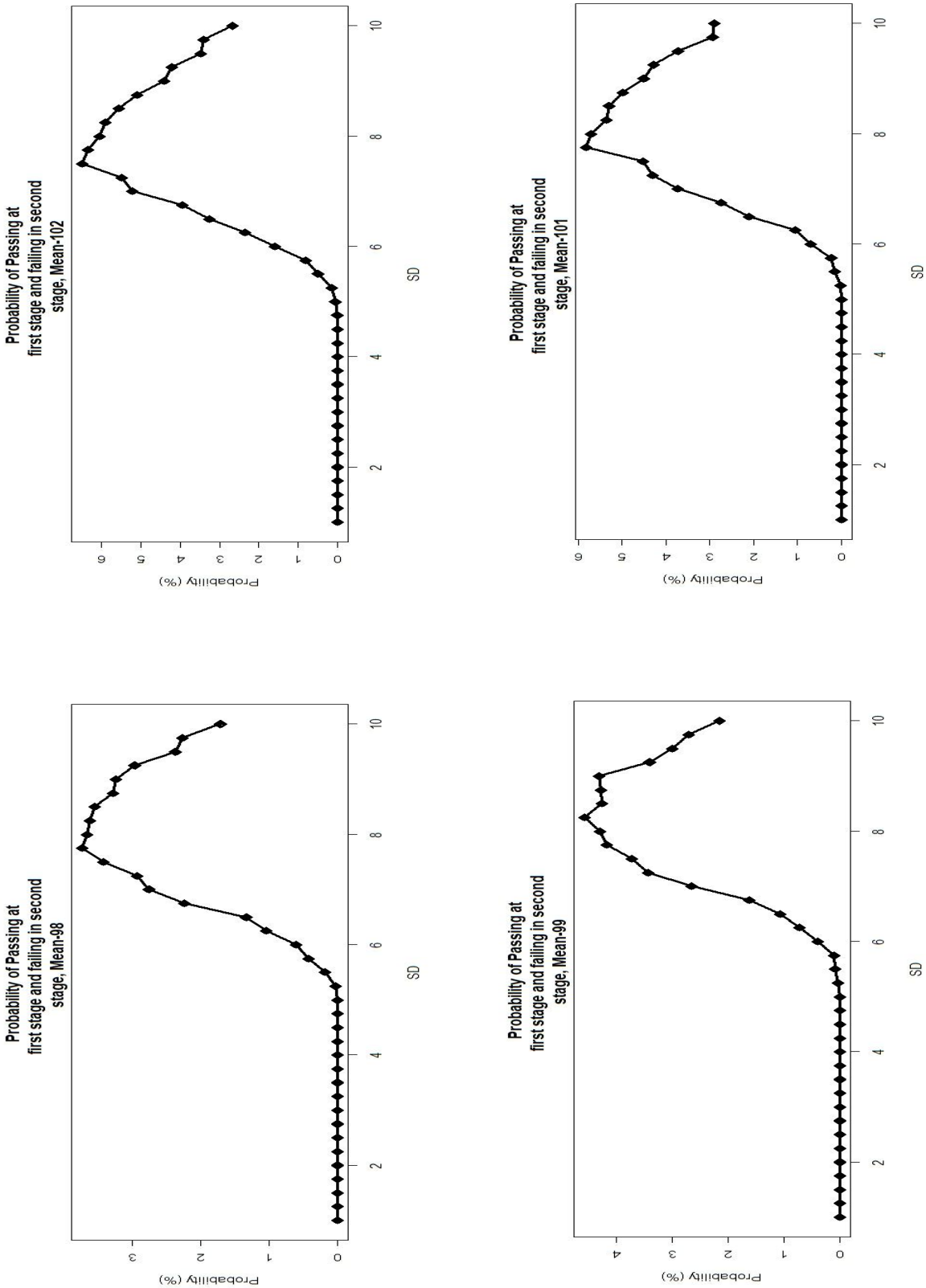


Fig. 6. USP <711> robustness at different mean and standard deviation

Резиме

Тестирање на робусност во повеќестепено тестирање на USP со помош на симулации

Прасант Самбарају

Независен истражувач, Хајдерабад, Индија

Клучни зборови: воедначеност на содржина, дисолуција, симулација, веројатност, робустност

Воедначеноста на содржината и дисолуцијата се повеќестепени тестови кои се специфицирани од Американската фармакопеа (USP) за да се осигура дека фармацевтскиот производ ги исполнува наведените стандарди. Еден производствен процес е во согласност со регулативата, само ако ги исполнува критериумите за прифаќање за сите тестови наведени во USP. Проценката на веројатноста за исполнување, односно неисполнување на овие критериуми за прифаќање се користи од страна на производителите за да се евалуира квалитетот на овие производи. Ова истражување има за цел да користи статистички симулации за да создаде нова мерка на веројатност за да се процени робусноста на овие повеќестепени тестови. Врз основа на резултатите од симулациите, беше забележано дека критериумите за прифаќање на повеќестепените тестирања за тестот за дисолуција на USP беа робусни, додека пак за USP робусноста на тестот за воедначеност на содржината беше поврзана со вредностите на средната и стандардната девијација користени во симулацијата.