Use of the Bergum Method and MS Excel to Determine The Probability of Passing the USP Content Uniformity Test

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Using the Bergum Method and the MS Excel software program, the author determines the probability of passing the USP Content Uniformity test.

One of the most well-known basic principles of quality assurance is that quality cannot be inspected or tested into a finished product. That is, reliable product quality means more than just meeting the specifications. If 100 random samples are taken and tested, then a partial number of samples will pass the test depending on the overall quality variability. The number of samples passing the test will readily increase and subsequently approach 100 (= 100%) when the quality parameters are more and more consistent and centrally within the specifications.

Companies want assurance that any sample taken from a product lot has a high percentage (say 95%) of passing the official tests. Such a high percentage—in terms of a high probability for a sample to pass the official tests—will be established through setting new tightened specifications. These specifications, *i.e.*, the new acceptance limits, will be the benchmark for each particular product quality.

James S. Bergum's 1990 paper entitled "Constructing Acceptance Limits for Multiple Stage Tests," introduced the method by which to compute the probability of passing the multiple-stage tests for a sample. Bergum's method is one of the most important tools for content uniformity assessment. In this article, the probability of passing the USP content uniformity test for tablets and capsules according to Sampling Plan 1 (one assay is performed on each of *L* locations) in Bergum's paper and the corresponding MS Excel computations are discussed.

Formula 1 for Excel calculation for tablet content uniformity

Formula 1

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=MAX((FDIST(10/((0.06^2)*(1 + 10* (Mean/Sigma)^2)),(1 + 10*(Mean/Sigma)^2)^2/
(1 + 2*10*(Mean/Sigma)^2),10 − 1)) + ((NORMSDIST((Mean −85)/Sigma) +
NORMSDIST((115 − Mean)/Sigma) − 1)^10) − 1,(FDIST(30/((0.078^2)*(1 +
30*(Mean/Sigma)^2)),(1 + 30* (Mean/Sigma)^2)^2/(1 + 2*30* (Mean/Sigma)^2),30 −
1)) + ((NORMSDIST((Mean − 85)/Sigma) + NORMSDIST((115 − Mean)/Sigma) − 1)^30
+ COMBIN(30,1)*((NORMSDIST((Mean − 85)/Sigma) + NORMSDIST((115 − Mean)/Sigma)
− 1)^29)*(((NORMSDIST((Mean −75)/Sigma) − NORMSDIST((Mean − 85)/Sigma)) +
(NORMSDIST((125 − Mean)/Sigma) − NORMSDIST((115 − Mean)/Sigma)))^1)) − 1,0)
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The above formula may be downloaded from the *Pharmaceutical Technology* Web site (www.pharmtech.com).

Content uniformity of tablets

As described in the *United States Pharmacopeia*, the short procedure used to determine the content uniformity test result is as follows:

- Acceptance criteria stage 1. Assay 10 tablets. Pass if both of the following criteria are met: relative standard deviation (RSD) ≤ 6.0% and no value is outside 85–115% of claim. Fail if one or more values are outside 75–125% of claim. Otherwise, go to stage 2.
- Acceptance criteria stage 2. Assay 20 more tablets. Pass if for all 30 tablets the following criteria are met: RSD ≤ 7.8%, no more than one value is outside 85–115% of claim, and no

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Table I: Probability of passing the USP content uniformity test for tablets (%).

	Sigma = 2			Sigma = 4			Sigma = 6		
Mean	Bergum	Excel	Simulation	Bergum	Excel	Simulation	Bergum	Excel	Simulation
86	2.5	2.5	2.5	0.0	0.0	0.6	0.0	0.0	0.2
90	98.5	98.5	99.1	26.8	26.8	36.8	0.0	0.0	9.0
94	100.0	100.0	100.0	94.8	94.8	96.8	34.7	34.7	53.7
98	100.0	100.0	100.0	100.0	100.0	100.0	88.4	88.4	92.0
100	100.0	100.0	100.0	100.0	100.0	100.0	93.4	93.4	95.7
102	100.0	100.0	100.0	100.0	100.0	100.0	89.6	89.6	92.9
106	100.0	100.0	100.0	94.8	94.8	97.0	38.8	38.8	55.8
110	98.5	98.5	99.1	32.4	32.4	36.4	0.9	0.9	10.0
114	2.5	2.5	2.5	0.4	0.4	0.5	0.0	0.0	0.3

Table II: Probability of passing the USP content uniformity test for capsulses (%).

	Sigma = 3		Sigma = 5		Sigma = 7	
Mean	Bergum	Excel	Bergum	Excel	Bergum	Excel
86	6.6	6.6	0.0	0.0	0.0	0.0
90	94.7	94.7	27.0	27.0	0.0	0.0
94	100.0	100.0	97.6	97.6	27.2	27.2
98	100.0	100.0	100.0	100.0	73.6	73.6
100	100.0	100.0	100.0	100.0	80.0	80.0
102	100.0	100.0	100.0	100.0	82.0	82.0
106	100.0	100.0	97.6	97.6	52.3	52.3
110	94.7	94.7	43.6	43.6	0.1	0.1
114	6.8	6.8	0.0	0.0	0.0	0.0

value is outside 75–125% of claim. Otherwise, fail.

Probability bound. To determine the probability of passing the *USP* criteria, the following variables are defined: C_{11} is the event that criterion 1 in stage 1 is met, C_{12} is the event that criterion 2 in stage 1 is met, C_{21} is the event that criterion 1 in stage 2 is met, and C_{22} is the event that criterion 2 in stage 2 is met.

Using these definitions, Prob(passing *USP* criteria) = Prob(first 10 tablets meet USP stage 1 criteria or all 30 tablets meet the USP stage 2 criteria) ⩾ MAX{Prob(first 10 tablets meet USP stage 1 criteria), Prob(all 30 tablets meet USP stage 2 criteria)} ⩾ MAX {Prob(C_{11}) + Prob(C_{12}) − 1, Prob(C_{21}) + Prob(C_{22}) − 1}

Probability of passing tablet content uniformity. Prob (C_{12}) and Prob (C_{22}) are associated with binomial distribution as follows: Let A be an individual assay result. Prob (C_{12}) is a function of Prob($85 \leqslant A \leqslant 115$), sample size, and the number of tablet(s) outside 85–115% of claim. The binomial probability density function is defined as

$$\text{Prob} = \frac{n!}{(n-k)!k!} p_1^{n-k} p_2^{k} \qquad [1]$$

in which n is the sample size (10 tablets), k is the number of tablets outside the 85–115% range but still within 75–125% of claim, $n!$ is n factorial, p_1 is the probability that an assay result is within 85–115% of claim, and p_2 is the probability that an assay result is within 75–85% of claim or is 115–125% of claim.

Using Equation 1,

$$\text{Prob}(C_{12}) = \frac{n!}{(n-k)!k!} p_1^{n-k} p_2^{k} = \frac{10!}{10!} p_1^{10} p_2^{0} = p_1^{10} \qquad [2]$$

If A is an individual assay result, then Prob (C_{22}) is a function of Prob($75 \leqslant A \leqslant 85$) and Prob($115 \leqslant A \leqslant 125$), sample size, and the number of tablet(s) falling within 75–85% or 115–125% of claim. Prob(C_{22}) can be determined as follows:

$$\text{Prob}(C_{22}) = \frac{30!}{30!} p_1^{30} p_2^{0} + \frac{30!}{29!} p_1^{29} p_2^{1} = p_1^{30} + 30 p_1^{29} p_2 \qquad [3]$$

in which p_1 is the probability that an assay result is 85–115% of claim and p_2 is the probability that an assay result is 75–85% of claim or 115–125% of claim.

Prob (C_{11}) and Prob (C_{21}) are associated with the noncentral F distribution of sample size/CV^2 (n/CV^2) and also the noncentral T distribution of

$$\frac{\sqrt{n}}{\text{CV}} \qquad [4]$$

To compute the noncentral F probability, Bergum used Johnson and Kotz's method to approximate a noncentral F distribution from a central F distribution critical value on the basis of the following relationship (4):

$$F(\nu, df, 0) = \frac{1}{1+\lambda} F(1, df, \lambda) \qquad [5]$$

in which $F(\nu, df, 0)$ and $F(1, df, \lambda)$ are central and noncentral F distribution critical values, respectively, with ν, df, and 1 degrees of freedom and

$$\nu = \frac{(1+\lambda)^2}{1+2\lambda}$$

$$\lambda = n\left(\frac{\mu}{\sigma}\right)^2 \qquad [6]$$

Therefore, PROBF(x, ν_1, ν_2, λ) = PROBF($x/(1+\lambda)$, ν, ν_2, 0) and PROBF (n/CV^2, ν_1, ν_2, λ) = PROBF((n/CV^2)/(1 + λ), ν, ν_2, 0). PROBF(x, ν_1, ν_2, λ) is the probability density function for noncentral F distribution at variable x (= n/CV^2) with ν_1 and ν_2 degrees of freedom and a noncentrality parameter λ. PROBF($x/(1+\lambda)$, ν, ν_2, 0) is the probability density function for central F distribution at a variable $x/(1+\lambda)$ [= (n/CV^2)/(1 + λ)] with ν and ν_2 degrees of freedom and a noncentrality parameter of λ.

Table III: Comparisons of probability by Bergum's CuDAL software and Excel for tablets ($n = 10$). Acceptance limits for tablet content uniformity.*

Mean (% claim)	Critical % CV	Probability by Excel
95.0	2.23	95.15
96.0	2.43	95.08
97.0	2.63	94.92
98.0	2.82	94.91
99.0	3.00	95.00
100.0	3.17	95.07
101.0	2.94	95.02
102.0	2.70	95.14
103.0	2.47	95.10
104.0	2.25	94.88
105.0	2.02	95.07

*Meeting limits guarantees with 90% assurance that at least 95% (by Bergum software) of all samples tested for content uniformity will pass the USP test.

Table IV: Comparisons of probability by Bergum's CuDALsoftware and Excel for tablets ($n = 30$). Acceptance limits for tablet content uniformity.*

Mean (% claim)	Critical % CV	Probability by Excel
95.0	3.15	95.06
96.0	3.43	95.04
97.0	3.70	95.08
98.0	3.97	94.97
99.0	4.21	94.95
100.0	4.39	95.03
101.0	4.13	94.98
102.0	3.81	95.05
103.0	3.49	94.98
104.0	3.17	94.96
105.0	2.85	95.06

*Meeting limits guarantees with 90% assurance that at least 95% (by Bergum software) of all samples tested for content uniformity will pass the USP test.

Table V: Comparisons of probability by Bergum's CuDAL software and Excel for capsules ($n = 10$). Acceptance limits for capsule content uniformity.*

Mean (% claim)	Critical % CV	Probability by Excel
95.0	2.80	94.97
96.0	3.04	95.03
97.0	3.27	94.98
98.0	3.46	95.03
99.0	3.60	94.92
100.0	3.68	94.98
101.0	3.61	95.08
102.0	3.36	94.95
103.0	3.08	95.10
104.0	2.81	94.94
105.0	2.53	95.07

*Meeting limits guarantees with 90% assurance that at least 95% (by Bergum software) of all samples tested for content uniformity will pass the USP test.

Formulae (parts 1 and 2) for Excel calculation for capsules

Part1

=(FDIST(10/((0.06^2)*(1 + 10*(Mean/Sigma)^2)),(1 + 10*(Mean/Sigma)^2)^2/(1 + 2*10*(Mean/Sigma)^2),10 − 1)) + ((NORMSDIST((Mean − 85)/Sigma) + NORMSDIST((115 − Mean)/Sigma) − 1)^10+COMBIN(10,1)* ((NORMSDIST((Mean − 85)/Sigma) + NORMSDIST((115 − Mean)/Sigma) − 1)^9)*(((NORMSDIST((Mean − 75)/Sigma) − NORMSDIST((Mean − 85)/Sigma)) + (NORMSDIST((125 − Mean)/Sigma) − NORMSDIST((115 − Mean)/Sigma)))^1)) − 1

Part2

=(FDIST(30/((0.078^2)*(1 + 30* (Mean/Sigma)^2)),(1 + 30*(Mean/ Sigma)^2)^2/ (1 + 2*30*(Mean/ Sigma) ^2),30-1)) + ((NORMSDIST((Mean − 85)/Sigma) + NORMSDIST((115 − Mean)/Sigma) − 1)^30 + COMBIN (30,1)*((NORMSDIST((Mean − 85)/ Sigma) + NORMSDIST((115 − Mean)/ Sigma) − 1)^29)*(((NORMSDIST ((Mean − 75)/Sigma) − NORMSDIST ((Mean-85)/Sigma)) + (NORMSDIST ((125 − Mean)/Sigma) − NORMSDIST((115 − Mean)/Sigma)))^1) + COMBIN(30,2)*((NORMSDIST((Mean − 85)/Sigma) + NORMSDIST((115 − Mean)/Sigma) − 1)^28)*(((NORMSDIST((Mean-75)/Sigma) − NORMSDIST((Mean − 85)/Sigma)) + (NORMSDIST ((125-Mean)/Sigma) − NORMSDIST((115-Mean)/Sigma)))^2) + COMBIN(30,3)*((NORMSDIST((Mean − 85)/Sigma) + NORMSDIST ((115 − Mean)/Sigma)-1)^27)* (((NORMSDIST ((Mean − 75)/Sigma) − NORMSDIST((Mean -85)/Sigma)) + (NORMSDIST ((125-Mean)/Sigma) − NORMSDIST((115 − Mean)/Sigma))) ^3)) − 1

The above formulae may be downloaded from the *Pharmaceutical Technology* Web site (www.pharmtech.com).

To compute Prob(C_{11}) or Prob(C_{21}), an MS Excel formula is derived from

PROBF($(n/CV^2)/(1 + \lambda), \nu, \nu_2, 0$) as follows:

Prob(C_{11}) = PROBF($(n/CV^2)/(1 + \lambda), \nu, \nu_2, 0$) = PROBF($(10/CV^2)/(1 + \lambda),(1 + \lambda)^2/(1 + 2\lambda), 10 - 1, 0$) = FDIST(10/((0.06^2)*(1 + 10*(Mean/Sigma)^2)),(1 + 10*(Mean/Sigma)^2)^2/(1 + 2*10*(Mean/Sigma)^2), 10 − 1)

Prob(C_{21}) = PROBF($(30/CV^2)/(1 + \lambda), (1 + \lambda)^2/(1 + 2\lambda), 30 - 1, 0$) = FDIST(30/((0.078^2)*(1 + 30*(Mean/Sigma)^2)), (1 + 30*(Mean/Sigma)^2)^2/(1 + 2*30*(Mean/Sigma)^2), 30 − 1)

For example, if Sigma (the population standard deviation) and Mean (the mean) are substituted by 6 and 100 respectively, the results are

Prob(C_{11}) = FDIST(10/((0.06^2)*(1 + 10*(100/6)^2)), (1 + 10*(100/6)^2)^2/(1 + 2*10*(100/6)^2), 10 − 1) = 56.24%

Prob(C_{21}) = FDIST(30/((0.078^2)*(1 + 30*(100/6)^2)), (1 + 30*(100/6)^2)^2/(1 + 2*30*(100/6)^2), 30 − 1) = 98.81%

Using Microsoft Excel

To compute the probability, one must transform the locations at 75, 85, 115, and 125% of claim into the corresponding Z scores using the population mean μ and standard deviation σ. To calculate the Z score:

$$Z = \frac{x - \mu}{\sigma} \qquad [7]$$

in which x is the critical location value (*i.e.*, 75, 85, 115, or 125% of claim) at which the Z score is calculated.

The probability at a given Z score may be obtained with the Excel formula:

=NORMSDIST(Z) = NORMSDIST $((x - \mu)/\sigma)$

Finding p_1 and p_2 is essential. For example, if $\sigma = 6$ and $\mu = 100$ (maximum σ required by USP content uniformity is 10), p_1 is the area between 85% and 115%

of claim, and its calculation in Excel is as follows:

=NORMSDIST ((115 − 100)/6)
− NORMSDIST((85 − 100)/6)
= 0.98758

For p_2, the calculation in Excel is

=(NORMSDIST((125 − 100)/6) −
NORMSDIST((115 − 100)/6)) +
(NORMSDIST((85 − 100)/6)
−NORMSDIST((75 − 100)/6)) =
0.01239

Therefore,

$$\mathrm{MAX}\{\mathrm{Prob}(C_{11}) + \mathrm{Prob}(C_{12}) - 1, \mathrm{Prob}(C_{21}) + \mathrm{Prob}(C_{22}) - 1\}$$
$$= \mathrm{MAX}\{0.5624 + p_1^{10} - 1, 0.9881 + p_1^{30} + 30p_1^{29}p_2 - 1\}$$
$$= \mathrm{MAX}(p_1^{10} - 0.4376, p_1^{30} + 30p_1^{29}p_2 - 0.0119) = \mathrm{MAX}(0.98758^{10} - 0.4376, 0.98758^{30} + 30^{*}0.98758^{29*} 0.01239 - 0.0119) = \mathrm{MAX}(0.4449, 0.9341) = 0.9341 = 93.41\%$$

Note that from the substitution above, $\mathrm{Prob}(C_{11}) = 56.24\%$ and $\mathrm{Prob}(C_{21}) = 98.81\%$. From the probability criteria above, a complete MS Excel formula for the tablet content uniformity (CU) is derived in sidebar "Formula for Excel calculation for tablet content uniformity" (see opening page). After simulation, the results from both formulae (conventional and Excel) are always equal for the same sets of population mean and standard deviation. Table I shows the comparisons of the results from the Bergum method (in Bergum and Simulation columns).

Content uniformity of capsules

As described in *USP*, the short procedure to determine the content uniformity test result is as follows:

- Acceptance criteria stage 1. Assay 10 capsules. Pass if both of the following criteria are met: RSD ≤ 6.0% and no more than one value is outside 85–115% of claim. Fail if one or more values are outside 75–125% of claim. Otherwise, go to stage 2.
- Acceptance criteria stage 2. Assay 20 more capsules. Pass if, for all 30 capsules, the following criteria are met: RSD ≤ 7.8% and no more than three values are outside 85–115% of claim and no value is outside 75–125% of claim. Otherwise, fail.

Probability bound. To determine the probability of passing the USP criteria, the following variables are defined: C_{11} is the event that criterion 1 in stage 1 is met; C_{12} is the event that criterion 2 in stage 1 is met; C_{21} is the event that criterion 1 in stage 2 is met; and C_{22} is the event that criterion 2 in stage 2 is met. Then

$$\mathrm{Prob(passing\ USP)} \geqslant \mathrm{MAX}\{\mathrm{Prob}(C_{11}) + \mathrm{Prob}(C_{12}) - 1, \mathrm{Prob}(C_{21}) + \mathrm{Prob}(C_{22}) - 1\}$$

Probability of passing capsule content uniformity. The probability of passing capsule content uniformity can be calculated as follows:

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$$\text{Prob}(C_{12}) = \frac{10!}{10!}p_1^{10}p_2^{0} + \frac{10!}{9!}p_1^{9}p_2^{1} = p_1^{10} + 10p_1^{9}p_2 \quad [8]$$

$$\text{Prob}(C_{22}) = \frac{30!}{30!}p_1^{30}p_2^{0} + \frac{30!}{29!}p_1^{29}p_2^{1} + \frac{30!}{28!2!}p_1^{28}p_2^{2} + \frac{30!}{27!3!}p_1^{27}p_2^{3} = p_1^{30} + 30p_1^{29}p_2 + 435p_1^{28}p_2^{2} + 4060p_1^{27}p_2^{3} \quad [9]$$

in which p_1 is the probability that an assay result is in the range 85–115% of daim; p_2 is the probability that an assay result is in the range 75–85% of claim or 115–125% of claim.

Using Microsoft Excel. For example, if sigma = 7 and population mean = 100, p_1 and p_2 are 0.967876 and 0.031769, respectively. So

$$\text{MAX}\{\text{Prob}(C_{11}) + \text{Prob}(C_{12}) - 1, \text{Prob}(C_{21}) + \text{Prob}(C_{22}) - 1\} = \text{MAX}\{0.3230 + p_1^{10} + p_1^{9}p_2 - 1, 0.8253 + p_1^{30} + 30p_1^{29}p_2 + 435p_1^{28}p_2^{2} + 4060p_1^{27}p_2^{3} - 1\} = \text{MAX}(0.2813, 0.8004) = 0.8004 = 80.04\%$$

Note that from the substitution above, Prob(C_{11}) = 32.30% and Prob(C_{21}) = 82.53%. Using the probability criteria, a complete Excel formula for capsule content uniformity is derived as Formula II: Probability of passing capsule CU test = MAX(Part1,Part2,0), in which Part 1 and Part 2 are as shown in the sidebar "Formulae (Parts 1 and 2) for Excel calculation for capsules" (see page 90).

Evaluation of sample data

The probability of passing the test normally depends on the population mean and SD. In fact, these population parameters are unknown and can only be estimated using the sample data. To calculate the lower bound on the probability of a future sample passing the USP content uniformity test, one must calculate the sample mean, RSD, and sample size from a batch using Sampling Plan 1 (one result from each location).

Suppose a content uniformity test result from the first stage (n = 10) has a mean of 98% of label claim (LC) and RSD = 2.5%. Using Bergum's table (see Table III), a critical RSD value of 2.81% is required for a sample mean of 98% LC to ensure with 90% assurance that at least 95% of all samples tested for content uniformity will pass the USP test. The probability for this particular test result to meet the USP acceptance criteria can be computed using MS Excel as follows:

Upper(0.90^0.5)*100% Confidence Limit (Mean1)
= $\bar{x}$ + UB*NORMSINV(1 − (1 − 0.90^0.5)/2)/n^0.5

Lower(0.90^0.5)*100% Confidence Limit (Mean2)
= $\bar{x}$ − UB*NORMSINV(1 − (1 − 0.90^0.5)/2)/n^0.5(0.90^0.5)*100 %
Confidence Limit for SD (UB)
= SD*((n − 1)/(CHIINV(0.90^0.5, n − 1)))^0.5

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in which $\bar{x}$ is the sample mean = 98% LC; SD is the sample standard deviation = RSD* $\bar{x}$/100 = 2.5 × 98 ÷ 100 = 2.45% LC; *n* is the sample size = 10; (0.90^0.5)*100% = 94.87% (see below); and UB is the upper bound.

Substituting the above parameters, the results are

Mean1 = 100.47% LC
Mean2 = 95.53% LC
UB = 4.01 % LC

Substituting these values into Formula I gives

Prob1 − (Substitution: Mean1 = 100.47, UB = 4.01)
= 100.00%
Prob2 − (Substitution: Mean2 = 95.53, UB = 4.01) = 99.23%

Therefore, the expected probability of passing the USP test will be MIN(Prob1, Prob2) = 99.23%. Note that because the sample RSD is 2.5, which is less than 2.81, the lower bound on the probability will be greater than 95%. The 90% assurance is simultaneously based on 94.87% confidence on the mean and SD (*i.e.,* 94.87 × 94.87 ÷ 100 = 90%).

When a 95% overall assurance is required, the following formulae are used:

Upper (0.95^0.5)*100% Confidence Limit (Mean1)
= $\bar{x}$ + UB*NORMSINV(1 − (1 − 0.95^0.5)/2)/*n*^0.5

Lower (0.95^0.5)*100% Confidence Limit (Mean2)
= $\bar{x}$ − UB*NORMSINV(1 − (1 − 0.95^0.5)/2)/*n*^0.5
(0.95^0.5)*100% Confidence Limit for SD(UB)
= SD*((n − 1)/(CHIINV(0.95^0.5,n-1)))^0.5

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The expected probability (95% assurance) of passing USP test is MIN(Prob1, Prob2) = MIN(99.95%, 93.62%) = 93.62%.

The calculation is conducted the same way for capsules: Find Mean1, Mean2, and UB, then substitute these values into Formula II and finally MIN(Prob1, Prob2).

Conclusion

To have reliable product quality, one must set a benchmarking (*i.e.,* tightened) acceptance limit that reflects a high probability of passing the official standard test. The USP content uniformity test is a multiple-stage test. These types of tests contain different acceptance criteria for each stage. Determining the probability of passing these tests requires knowing the population parameters that are unknown in actual applications. However, one can estimate the population parameters on the basis of samples results. With its statistical and mathematical functions, MS Excel software is a useful tool for computing these estimates as well as computing the probabilities of passing the official test using the Bergum method.

Acknowledgment

This article is solely intended to support James Bergum's method. Although his method is available on CD, the author's intention to use MS Excel to compute the probability of passing the test

is just to provide an alternative of computation. Finally, the author is very grateful to the reviewer of this paper for his very helpful comments.

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