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CONSTRUCTION OF UPPER CONFIDENCE LIMIT OF COEFFICIENT OF VARIATION FOR CONTENT UNIFORMITY

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ABSTRACT

Relative standard deviation (coefficient of variation) plays an important role in meeting the current compendial requirements for content uniformity. Since the sample RSD value would vary from sample to sample in a population (batch), the scientist would need not only the sample estimate of the RSD but also its 95% two-sided upper confidence limit, for making the proper statistical inference as well as for arriving at the appropriate pharmaceutics decisions. The primary purpose of this paper is to depict the five available methods for determining the confidence limit and to discuss their relative merits and similarities in the context of a content uniformity study associated with Product-C. Suitable tables are furnished to facilitate rapid access to the desired RSD confidence limit.

INTRODUCTION

Content uniformity constitutes one of the cardinal properties of a product dosage-form. However, there is a fundamental distinction between content uniformity and other properties such as, dissolution, disintegration, tablet strength and friability in that, here, the prime interest is the measure of uniformity. A measure of variability among dosage units is indeed an appropriate measure of uniformity. Since content uniformity serves as an index of the degree of homogeneity of the distribution of the active ingredient among the individual dosage units of a drug product, the content uniformity measurement of a sample begins with determining the amount of active ingredient (expressed as a percentage of label claim) in each unit in a sample of several dosage units and then calculating the sample estimate of the relative standard deviation (RSD), often called coefficient of variation (COV) in the statistical literature, by using the formula $100S/\bar{X}$, where S and $\bar{X}$ denote the standard deviation and mean respectively.

It would be appropriate, at the outset, to outline the USP-NF test requirements (1), as follows: (i) Selection of a random sample of 10 dosage units, (ii) determination of the amount of active ingredient in each of the 10 dosage units individually by the prescribed assay procedure, (iii) expression of each assay value as a percentage of label claim, (iv) demonstration of the fact that the assay value of each of the 10 units is indeed within the range of 85% to 115% of the label claim and (v) demonstration of the fact that the RSD value is less than or equal to 6%. [Note that, the required compendial limit of RSD has been set at 7.8% when the number of dosage units in the sample is 30 (1)]. Since the test procedure involves the experimental determination of the RSD value based on the

sample estimates of the standard deviation and the mean, it would be appropriate to take into consideration in the estimation, the experimental variation encountered. As such, the experimenter would need not only the point estimate of the RSD but also its 95% upper confidence limit for arriving at the proper statistical inference as well as at the appropriate pharmaceutics decisions.

The primary purpose of this paper is to present all the five available methods of constructing the 95% two-sided upper confidence limit (95% TSUC limit) of the RSD being considered, to demonstrate the procedures by applying to a real-world study and to provide ready-made tables suitable for rapid access to the desired 95% TSUC limit for a given RSD.

THEORY

Consider a random sample of n dosage units and let their respective assay values be denoted by X_1, X_2,-----, X_n assumed to emanate from a Gaussian distribution with mean μ and variance σ^2. Let the sample estimate of μ be denoted by $\bar{X}$, where $\bar{X} = \Sigma X/n$, and the sample estimate of σ be represented by S, where $S = [\Sigma(X-\bar{X})^2/n-1]^{1/2}$. The sample estimate of COV is defined as S/X which is denoted by σ/μ in the population. The primary purpose of this section is to demonstrate the derivation of the 95% TSUC limit of COV for each of the five available methods of approach, denoted by B, F, M, EX and JK, and to present their respective computational formulations.

Method-B: The derivation of this method essentially follows the Fieller's theorem (2,3,4). Let $S/\bar{X} = B$, where B denotes the fixed parameter of interest. Upon rearrangement, we have, $S-B\bar{X} = 0$. The variance formula for the right hand side of the equation is equal to $[\sigma^2/2(n-1) + B^2\sigma^2/n]$, which is estimated by the

expression, $[S^2/2(n-1) + B^2S^2/n]$. It is known that the following ratio has a T-distribution (2),

$$T = (S-B\bar{X})/[S^2/2(n-1) + B^2S^2/n]^{\frac{1}{2}}$$

Squaring both sides of the equation and rearranging, we have,

$$(S-B\bar{X})^2 - T^2_a[S^2/2(n-1) + B^2S^2/n] = 0$$

where a = the level of significance selected. This is a quadratic equation in B and thus it has two solutions. The larger of the two roots constitutes the 95%(1-a) upper confidence limit, with T_a representing the tabular T-value at .05 level of significance, obtained from an ordinary T-table (5). (Note that, here the upper case T is used instead of the lower case t, generally used.) Explicitly, we have,

$$B^* = \bar{X}SG + G[\bar{X}^2S^2 - GH]^{\frac{1}{2}}$$

where, $G = \bar{X}^2 - T^2_aS^2/n$

$H = S^2 - T^2_aS^2/2(n-1)$

B^* = 95% upper confidence limit

It is, however, more convenient to use the B^* formula expressed as a function of $C = S/\bar{X}$, as follows:

$$B^* = CG^* + CT_aG^*[G^*/2(n-1) + C^2/n]^{\frac{1}{2}}$$

where, $G^* = 1 - C^2T^2_a/n$

C = sample coefficient of variation $(S/\bar{X})$

= RSD/100

and, $T_{.05}$ = 2.2622 for 9 degrees of freedom (n=10) to be used for two-sided 95% confidence limits (5). This is the formula used to generate the 95% TSUC limit for the various values of RSD, presented in Table-B in Addendum-A.

Method-F (6,7): This method is a variation of Method-B in that, the T_a value is replaced by Z_a value (normal deviate) obtained from an ordinary T-table (5) located at the last row of the table for ∞ degrees of freedom. (One could also use a standard normal distribution table (5) for the purpose.) Since the value of Z_a does not

depend upon the sample size (n), there are only two values of Z_a which are of interest in this case, namely, $Z_{0.975} = 1.96$ for a two-sided upper confidence limit and $Z_{0.95} = 1.645$ for a one-sided upper confidence limit. Explicitly, we have, the 95% TSUC limit formula,

$$F^* = CM + CZ_aM[M/2(n-1) + C^2/n]^{\frac{1}{2}}$$

where, $M = 1-C^2Z^2_a/n$

C = Sample coefficient of variation $(S/\bar{X})$

$= RSD/100$

This is the formula used to generate the values in Table-F in Addendum-A.

Method-M (8,9): It is known that the following quantity,

$$\Theta = n[KC^{*2}/C^2][(1 + C^2)/(1 + KC^{*2})]$$

is distributed as X^{*2} (chi-square) probability function with (n-1) degrees of freedom, where, $C^* = S/\bar{X}$, C = population coefficient of variation, n = sample size and $K = (n-1)/n$. For the construction of a 95% upper confidence limit, we start with the following inequality relationship,

$$n[KC^{*2}/C^2][(1 + C^2)/(1 + KC^{*2})] \leq \bar{X}^{*2}_{n-1}.$$

Since we need the confidence limit for C, the population COV, we solve for C from the inequality relationship using the following steps,

(i) $[(nKC^{*2})/(1 + KC^{*2})][1/\bar{X}^{*2}_{n-1}] \leq C^2/(1 + C^2)$

(ii) by taking the reciprocal of both sides of (i) and rearranging we have,

$$[[\bar{X}^{*2}_{n-1}(1 + KC^{*2})]/nKC^{*2}] - 1 \geq 1/C^2$$

(iii) by taking reciprocal of both sides of (ii), substituting $K = (n-1)/n$ and rearranging, we have

$$C \geq [\bar{X}^{*2}_{n-1}(P^{-1} + n^{-1}) - 1]^{-\frac{1}{2}}$$

where, $P = (n-1)C^{*2}$ and, $\bar{X}^{*2}_{0.975} = 2.70$ for 9 degrees of freedom, to be used for a two-sided confidence limit (5). This is the formula (right-hand side) used to generate the values in Table-M in Addendum-A.

Method-EX (6,7): This method is generally known as the exact method and hence the abbreviation "EX". An integral part of the method is the derivation of the probability distribution of the sample COV, $S/\bar{X}$, under the consideration that the original observations emanate from a Gaussian distribution. It takes advantage of the fact that in this distribution the sample estimates of the mean and the standard deviation are independent, and consequently the joint probability distribution of the two estimates is derived from the product of the two individual distributions. Let a sample of n identically and independently distributed observations be from a Gaussian distribution with mean μ and variance σ^2. Explicitly we have,

$$f(\bar{X}_i) = (2\pi\sigma^2)^{-\frac{1}{2}} \exp[-(\bar{X}_i - \mu)^2/2\sigma^2]$$

where i = 1,2,----n. Since the sample COV is scalar invariant, we could consider for simplification the following transformation,

$$Y_i = (\sqrt{n}/\sigma)X_i \qquad i = 1,2,-------n$$

The mean of Y_i is equal to $\sqrt{n}/C$ $(=\mu^*)$ and the variance of Y_i is equal to 1.0. Explicitly, the joint distribution has the following expression,

$$f(S,\bar{Y}) = \exp[-(\bar{Y}-\mu^*)^2/2]S^{n-2}\exp[-S^2/2]/G$$

where, $G = (2\pi)^{\frac{1}{2}}\,\Gamma(n-1/2)2^h$ and $h = (n-3)/2$

Now substituting $S = C^*\bar{Y}$ $(C^* = S/\bar{Y})$ and applying the appropriate Jacobian, we have

$$f(C^*,\bar{Y}) = (C^*\bar{Y})^{n-2}\,|\bar{Y}|\,\exp[-1/2(\bar{Y} - \mu^*)^2 + (C^*\bar{Y})^2]/G.$$

The marginal distribution of C^*, $f(C^*)$ is obtained by integrating the above expression over $\bar{Y}d\bar{Y}$ from $-\infty$ to $+\infty$. Explicitly,

$$f(C^*) = [Q/(1 + C^{*2})^{-n/2}]A_{n-1}[(\sqrt{n}/C)/(1 + C^{*2})^{\frac{1}{2}}]$$

where, $Q = C^{*n-2}\exp[-(\sqrt{n}/C)^2/2(1 + C^{*2})]/G$

and $A_{n-1} = \int_0^\infty z^{n-1}\exp[-1/2(z-b)^2]dz$

where, $b = [\sqrt{n}/C]/(1 + c^{*2})^{\frac{1}{2}}$ (C = population COV)

Now, after inserting the closed-form approximation of

A_{n-1}, into $f(c^*)$, a formidable algebraic expression, covering a half-a-page of algebraic terms, emerges. And yet, one has to use various complex numerical procedures for the evaluation of the probability points of C^*, for given values of C and n. For this very reason appropriate tables (Table-EX) have been provided in Addendum-B for the scientists to obtain the desired values directly. Note that, if for a set of given values of C, n and p (level of significance), the tabular value, denoted by C^{**}, is obtained from Table-EX, then the following integral relationship is satisfied by each of the entries in Table-EX,

$$\int_0^{C^{**}} f(C^*)\, dC^* = p$$

Method-JK: (3,10,11) This is the jackknife method and hence the abbreviation "JK". Since the sample COV is a ratio of two statistics, the derivation of the variance of this non-linear function would invariably result in a complex expression. The jackknife statistic, in such situations, is applicable and it provides a much simpler form of the variance. Let X_1, X_2, ---- X_n be a sample of n observations. Let Q(all) denote the estimator of C, S_{all}/X_{all} based on all the n observations. Let Q(i) denote the estimator, S(i)/X(i), based on the sample size of (n-1), where the i^{th} observation has been deleted. The pseudo values are computed as follows: $Q^*(i) = n[Q(all)] - (n-1)[Q(i)]$, where i = 1, 2,--, n. The jackknife estimate of C is $C^*(JK) = \Sigma Q^*(i)/n$ and the jackknife estimate of the standard deviation of C is $S_C(JK) = [\Sigma[Q(i) - C^*(JK)]^2/n-1]^{\frac{1}{2}}$. It should be noted that since C is a non-linear function one could as well use a linearizing transformation on C, such as the logarithmic transformation, and then apply jackknife procedure to the derived log linear function. Then, at

the end, one could restore the confidence limit in the original units by taking the antilogarithm of the log confidence limit. This procedure is very elaborate and complicated, however. This approach will be called the JK(L) method.

CONTENT UNIFORMITY STUDY: RESULTS AND DISCUSSION

A random sample of ten sterile vials each containing a measured amount of powdered antibiotic Product-C is selected for the content uniformity test. Each vial is individually assayed by the prescribed assay procedure, provided in the monograph and the test is conducted in conformation with the compendial and regulatory requirements. Each of the spectrophotometric assay value is expressed as a percent of the label claim and then the required statistical quantities are computed based on the percentage data, as follows:

n = 10, Range = 97.8-108.8, mean($\bar{x}$)= 103.98,

Standard deviation(S)= 4.1109, COV= $S/\bar{x}$= 0.0395,

RSD= $100S/\bar{x}$= 3.95%.

Table I presents the 95% upper confidence limit computed by using each of the six methods, B, F, M, EX, JK and JK(L), for the two-sided as well as for the one-sided level of significance.

A cursory examination of the results indicates that the sample has indeed met the current compendial requirements. However, if one is interested in making statistical inference about the batch from which the sample was drawn, the magnitude of the 95% TSUC limit has to be examined. Since there are 5 methods of computing the limit, it would be appropriate at this point to discuss the relationships among the methods as depicted in Table-I.

It is clearly observed that the results of Method-M and Method-EX are essentially the same in this case, and it is conclusively shown (6,7) that this relationship

TABLE-I

95% UPPER CONFIDENCE LIMIT FOR RSD

No.	METHOD	N	RSD	TWO-SIDED LOS	ONE-SIDED LOS
1	B	10	3.95*	6.063	5.661
2	F	10	3.95	5.780	5.486
3	M	10	3.95	7.225	6.508
4	EX	10	3.95	7.223	6.505
5	JK	10	3.95	5.180	4.950
6	JK(L)	10	3.95	5.280	5.020

LOS = Level of Significance * expressed in percent

holds also in general. It must, however, be noted that while the computation of Method-M can easily be accomplished with a hand-calculator, the computation of Method-EX cannot be easily accomplished since it involves intricate integral evaluation and complex numerical analysis. Presently the only source of the Method-EX values is the table available in reference (7). The portion of the table relevant to the current compendial requirements is presented in Table-EX in Addendum-B. In practice, however, one should compute both the methods for the purpose of comparison and confirmation of the results. A comparison between Method-B and Method-F clearly shows that the results are fairly close in this case. However, Method-B is distinctly preferable since Method-F requires strict normality assumption of the data (6) which enables it to use the tabular t-value of 1.96 for the infinite degrees of freedom instead of the t-value for the degrees of freedom associated with the sample size. Now, a comparison between Method-M and Method-B indicates that Method-M is more conservative and as such it should be used for batch-to-batch release purposes in production

and manufacturing. However, for formulation research and development, Method-B is most suitable because a conservative method may impose severe restrictions on possible alternative options at this stage of development. The intention of presenting the two jackknife procedures is for the purpose of comparison only. The one-sided limits are provided here only to demonstrate the differences with their respective two-sided counterparts. Unless there is a compelling scientific explanation, one-sided limits should not be used as a general rule.

The interpretation of the results of the two methods, M and B for the Product-C content uniformity study is as follows: If the sample originated from a production release batch, a resampling schedule should be organized based on the current compendial requirements. If, however, the sample pertains to a formulation research and development lot, the retention of the formulation for further development should be the prime consideration.

CONTENTS OF ADDENDUM-A AND ADDENDUM-B TABLES

For each of the three methods, B, F and M, a table of 95% TSUC limits is generated pertaining to a set of RSD values ranging from 0.1 to 10.0 at an increment of 0.1 and to the two sample sizes, 10 and 30, as required by the current compendial document. The computer results are presented in Tables B, F and M in Addendum-A. The tables are extremely useful in that one can directly read off the value of the 95% TSUC limit for a given RSD value and a given sample size, as follows: Let RSD = 2% and n = 10, then the corresponding 95% TSUC limits are 3.07, 2.93 and 3.65 respectively for B, F and M methods. The 95% TSUC limit for an intermediate RSD value can also be obtained from these tables either by

interpolation of the tabular values (see Addendum-C) or by calculating the desired value by using the appropriate formula given in the Theory section. Table-EX is provided in Addendum-B. The C^* values (RSD/100) range from 0.02 to 0.50 at an increment of 0.02. The entries here are the theoretical percentage points of the C^* values and therefore the 95% TSUC limit can only be obtained by the inverse interpolation procedure as shown in the following numerical example: Suppose one wishes to obtain for the sample size of 10, the 95% TSUC limit of 0.04 (RSD/100), then the values in the column labeled 2.5% are searched to find the two values within which 0.04 falls. Based on these two numbers, the following table is constructed,

2.5% Column	95 % TSUC limit
0.03283	0.06
0.04	?
0.04374	0.08

By using the linear interpolation formula given in Addendum-C, we have,

$$95\%\ \text{TSUC limit} = 0.06 + \left[\frac{0.04 - 0.03283}{0.04374 - 0.03283}\right](0.080 - 0.060)$$

$$= 0.07314 \text{ or } 7.314\%.$$

(Note: Multiply the result by 100 to obtain 95% TSUC limit for the RSD).

Addendum-C provides the formulations as well as the numerical examples for the linear and Lagrangian interpolation methods. The latter method provides a high precision numerical approximation for the intermediate values.

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ADDENDUM-A

95% Two-Sided Upper Confidence Limit of RSD Based on Methods B,F and M

RSD	TABLE-B		TABLE-F		TABLE-M		RSD	TABLE-B		TABLE-F		TABLE-M	
	n=10	n=30	n=10	n=30	n=10	n=30		n=10	n=30	n=10	n=30	n=10	n=30
0.1	0.153	0.127	0.146	0.126	0.183	0.134	5.1	7.834	6.475	7.468	6.418	9.341	6.864
0.2	0.307	0.254	0.292	0.251	0.365	0.269	5.2	7.989	6.602	7.615	6.544	9.525	6.998
0.3	0.460	0.381	0.439	0.377	0.548	0.403	5.3	8.143	6.730	7.762	6.670	9.710	7.133
0.4	0.613	0.507	0.585	0.503	0.730	0.538	5.4	8.297	6.857	7.909	6.796	9.894	7.268
0.5	0.767	0.634	0.731	0.629	0.913	0.672	5.5	8.451	6.984	8.056	6.922	10.079	7.403
0.6	0.920	0.761	0.877	0.754	1.096	0.807	5.6	8.606	7.111	8.203	7.048	10.263	7.538
0.7	1.073	0.888	1.023	0.880	1.278	0.941	5.7	8.760	7.238	8.350	7.174	10.448	7.673
0.8	1.227	1.015	1.170	1.006	1.461	1.075	5.8	8.915	7.366	8.497	7.300	10.633	7.808
0.9	1.380	1.142	1.316	1.132	1.643	1.210	5.9	9.069	7.493	8.644	7.427	10.818	7.943
1.0	1.533	1.269	1.462	1.257	1.826	1.344	6.0	9.224	7.620	8.791	7.553	11.003	8.078
1.1	1.687	1.395	1.608	1.383	2.009	1.479	6.1	9.378	7.748	8.938	7.679	11.189	8.213
1.2	1.840	1.522	1.755	1.509	2.191	1.613	6.2	9.533	7.875	9.086	7.805	11.373	8.348
1.3	1.993	1.649	1.901	1.635	2.374	1.748	6.3	9.687	8.002	9.233	7.931	11.558	8.483
1.4	2.147	1.776	2.047	1.760	2.557	1.882	6.4	9.842	8.130	9.380	8.057	11.743	8.619
1.5	2.300	1.903	2.193	1.886	2.739	2.017	6.5	9.997	8.257	9.527	8.184	11.929	8.754
1.6	2.454	2.030	2.340	2.012	2.922	2.151	6.6	10.152	8.384	9.675	8.310	12.114	8.889
1.7	2.607	2.157	2.486	2.138	3.105	2.286	6.7	10.307	8.512	9.822	8.436	12.300	9.024
1.8	2.760	2.284	2.632	2.263	3.288	2.420	6.8	10.461	8.639	9.969	8.562	12.486	9.159
1.9	2.914	2.411	2.778	2.389	3.470	2.555	6.9	10.616	8.767	10.117	8.689	12.671	9.294
2.0	3.067	2.537	2.925	2.515	3.653	2.689	7.0	10.771	8.894	10.264	8.815	12.857	9.430
2.1	3.221	2.664	3.071	2.641	3.836	2.824	7.1	10.926	9.022	10.412	8.941	13.043	9.565
2.2	3.374	2.791	3.217	2.767	4.019	2.958	7.2	11.081	9.149	10.559	9.068	13.229	9.700
2.3	3.528	2.918	3.363	2.892	4.202	3.093	7.3	11.236	9.277	10.707	9.194	13.415	9.836
2.4	3.681	3.045	3.510	3.018	4.385	3.227	7.4	11.392	9.404	10.855	9.320	13.601	9.971
2.5	3.835	3.172	3.656	3.144	4.568	3.362	7.5	11.547	9.532	11.002	9.447	13.788	10.106
2.6	3.988	3.300	3.803	3.270	4.751	3.496	7.6	11.702	9.659	11.150	9.573	13.974	10.242
2.7	4.142	3.426	3.949	3.396	4.934	3.631	7.7	11.857	9.787	11.298	9.700	14.161	10.377
2.8	4.295	3.553	4.095	3.521	5.117	3.765	7.8	12.013	9.915	11.446	9.826	14.347	10.513
2.9	4.449	3.680	4.242	3.647	5.300	3.900	7.9	12.168	10.042	11.594	9.953	14.534	10.648
3.0	4.603	3.807	4.388	3.773	5.483	4.034	8.0	12.324	10.170	11.741	10.079	14.721	10.784
3.1	4.756	3.934	4.535	3.899	5.666	4.169	8.1	12.479	10.297	11.889	10.206	14.908	10.919
3.2	4.910	4.061	4.681	4.025	5.850	4.303	8.2	12.635	10.425	12.037	10.332	15.095	11.055
3.3	5.064	4.188	4.828	4.151	6.033	4.438	8.3	12.790	10.553	12.185	10.459	15.282	11.190
3.4	5.217	4.315	4.974	4.277	6.216	4.573	8.4	12.946	10.681	12.333	10.585	15.470	11.326
3.5	5.371	4.442	5.121	4.402	6.400	4.708	8.5	13.102	10.808	12.482	10.712	15.657	11.462
3.6	5.525	4.569	5.267	4.528	6.583	4.842	8.6	13.258	10.936	12.630	10.838	15.845	11.597
3.7	5.679	4.696	5.414	4.654	6.767	4.977	8.7	13.413	11.064	12.778	10.965	16.032	11.733
3.8	5.832	4.823	5.560	4.780	6.950	5.112	8.8	13.569	11.192	12.926	11.092	16.220	11.869
3.9	5.986	4.950	5.707	4.906	7.134	5.246	8.9	13.725	11.320	13.074	11.218	16.408	12.005
4.0	6.140	5.077	5.854	5.032	7.317	5.381	9.0	13.881	11.447	13.222	11.345	16.596	12.140
4.1	6.294	5.204	6.000	5.158	7.501	5.516	9.1	14.038	11.575	13.371	11.472	16.784	12.276
4.2	6.448	5.331	6.147	5.284	7.685	5.650	9.2	14.194	11.703	13.520	11.598	16.973	12.412
4.3	6.602	5.458	6.294	5.410	7.868	5.785	9.3	14.350	11.831	13.668	11.725	17.161	12.548
4.4	6.756	5.585	6.440	5.536	8.052	5.920	9.4	14.506	11.959	13.817	11.852	17.350	12.684
4.5	6.910	5.712	6.587	5.662	8.236	6.055	9.5	14.663	12.087	13.965	11.979	17.538	12.820
4.6	7.064	5.839	6.734	5.788	8.420	6.189	9.6	14.819	12.215	14.114	12.105	17.727	12.956
4.7	7.218	5.967	6.881	5.914	8.604	6.324	9.7	14.976	12.343	14.263	12.232	17.916	13.092
4.8	7.372	6.094	7.027	6.040	8.788	6.459	9.8	15.132	12.471	14.411	12.359	18.105	13.228
4.9	7.526	6.221	7.174	6.166	8.972	6.594	9.9	15.289	12.599	14.560	12.486	18.294	13.364
5.0	7.680	6.348	7.321	6.292	9.157	6.729	10.0	15.445	12.727	14.709	12.613	18.484	13.500

ADDENDUM-B

95% Two-Sided Upper Confidence Limit of $C^* = S/\bar{X}$ based on Method-EX**

C*(UL)	2.5% n=10	2.5% n=30
0.02	.01095	.01487
0.04	.02190	.02974
0.06	.03283	.04459
0.08	.04374	.05943
0.10	.05463	.07423
0.12	.06547	.08900
0.14	.07628	.10374
0.16	.08704	.11842
0.18	.09775	.13304
0.20	.10841	.14760
0.22	.11900	.16210
0.24	.12953	.17653
0.26	.13997	.19090
0.28	.15033	.20519
0.30	.16062	.21938
0.32	.17090	.23350
0.34	.18100	.24750
0.36	.19100	.26150
0.38	.20090	.27530
0.40	.21070	.28900
0.42	.22050	.30260
0.44	.23010	.31620
0.46	.23960	.32960
0.48	.24910	.34290
0.50	.25840	.35610

C*(UL) = 95% Two-Sided Upper Confidence Limit
"2.5%" implies two-sided limit
** : See text for obtaining C*(UL) by inverse interpolation

ADDENDUM-C

Interpolation Methods

The two most popular methods of interpolation, linear and Lagrangian, are depicted in this section for completeness and for economizing the user's time.

Linear Interpolation

The linear interpolation formula and a numerical example are provided in the following. Let the value of X_0 be known and let $f(X_0)$, the functional value of X_0, be unknown. It is desired to compute $f(X_0)$ by linear interpolation between the two consecutive values of X, X_1, X_2, within which the value of X_0 falls. Then,

$$f(X_0) = f(X_1) + \left[\frac{f(X_2) - f(X_1)}{X_2 - X_1}\right] (X_0 - X_1)$$

Consider the following table, for example:

$X_1 = 0.03283$	$f(X_1) = 0.06$
$X_0 = 0.04$	$f(X_0) = ?$
$X_2 = 0.04374$	$f(X_2) = 0.08$

Then,

$$f(X_0) = 0.06 + \left[\frac{0.08 - 0.06}{0.04374 - 0.03283}\right] (0.04 - 0.03283)$$

$$= 0.07314$$

Lagrangian Interpolation

Consider the following three consecutive values, X_1, X_2 and X_3, of X and their respective functional values, $f(X_1)$, $f(X_2)$ and $f(X_3)$. X_0 is known to fall among the three X values and it is desired to determine $f(X_0)$ through the Lagrangian interpolation procedure, as follows:

$$f(X_0) = f(X_1) \left[\frac{(X_0 - X_2)(X_0 - X_3)}{(X_1 - X_2)(X_1 - X_3)}\right]$$

$$+ f(X_2) \left[\frac{(X_0 - X_1)(X_0 - X_3)}{(X_2 - X_1)(X_2 - X_3)}\right]$$

$$+ f(X_3) \left[\frac{(X_0 - X_1)(X_0 - X_2)}{(X_3 - X_1)(X_3 - X_2)}\right]$$

Numerically, for example, consider the following table:

$X_1 = 0.20$	$f(X_1) = 0.34202$
$X_2 = 0.25$	$f(X_2) = 0.42262$
$X_3 = 0.30$	$f(X_3) = 0.50000$

Need to find $f(X_0)$ for $X_0 = .22$

$$f(X_0) = (0.34202)\left[\frac{(X_0 - 0.25)(X_0 - 0.30)}{(0.20-0.25)(0.20-0.30)}\right]$$

$$+ \quad (0.42262)\left[\frac{(X_0 - 0.20)(X_0 - 0.30)}{(0.25-0.20)(0.25-0.30)}\right]$$

$$+ \quad (0.50000)\left[\frac{(X_0 - 0.20)(X_0 - 0.25)}{(0.30-0.20)(0.30-0.25)}\right]$$

$$= (68.404(X_0 - 0.25)(X_0 - 0.30)$$
$$- (169.048)(X_0 - 0.20)(X_0 - 0.30)$$
$$+ (100.00)(X_0 - 0.20)(X_0 - 0.25)$$

For, $X_0 = 0.22$, the formula yields, $f(X_0) = 0.37465$.