Available Online at http://www.recentscientific.com

ISSN: 0976-3031

International Journal of Recent Scientific Research
Vol. 6, Issue, 7, pp.5040-5045, July, 2015

International Journal of Recent Scientific Research

RESEARCH ARTICLE

SAMPLE SIZE ESTIMATION FOR HIGHLY VARIABLE DRUGS USING REFERENCE SCALED AVERAGE BIOEQUIVALENCE CRITERIA

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ARTICLE INFO

Article History:

Received 2nd, June, 2015
Received in revised form 10th, June, 2015
Accepted 4th, July, 2015
Published online 28th, July, 2015

Key words:

Highly Variable Drugs, Reference Scaled Average Bioequivalence Criteria, and Sample Size Estimation.

ABSTRACT

Determining the optimal sample size for a study assures an adequate power to detect statistical significance. Hence, it is a critical step in the design of a planned research protocol. Using too many participants in a study is expensive and exposes more number of subjects to procedure. Similarly, if study is underpowered, it will be statistically inconclusive and may make the whole protocol a failure. This paper covers the essentials in calculating sample size for highly variable drug study designs. Sample size computation for highly variable drugs was done incompliance to the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) for reference scaled average bioequivalence (RSABE) studies. To elucidate the complicated features and the relationship between sample size, within-subject variability of reference product, within subject standard deviation of reference product and intra-subject variability comparing test versus reference products. Partial replicate (reference replicate) and full replicate studies were simulated in estimating the sample size for yielding 80% and 90% statistical powers.

INTRODUCTION

The evaluation of bioequivalence for highly variable drugs and drug products frustrated the pharmaceutical industry for many years. It was difficult to demonstrate bioequivalence (BE) unless distressingly many subjects were included in the investigations. Highly variable drugs (HVDs) are defined as those for which within-subject variability (%CV) of reference product in bioequivalence measures is 30% or greater. Because of this high variability, studies designed to show whether generic highly variable drugs are bioequivalent to their corresponding highly variable reference drugs may need to enrol large numbers of subjects even when the products have no significant mean differences.

Several factors influence the sample size needed to meet the regulatory criteria for acceptable BE. First, each one-sided test is carried out at the 5% level of significance, which corresponds to a 90% CI. The 5% level of significance represents the type I error rate (α), which is the probability of incorrectly deeming as bioequivalent two formulations whose true (population) GMR fails to meet the BE limits. The second factor influencing sample size is study power, defined as the likelihood or chance of correctly demonstrating bioequivalence when it, in fact, exists. A third factor influencing sample size is the test/reference bioequivalence measure ratios. If the true test/reference ratio differs from unity, the overall power to show BE is reduced at any given sample size, resulting in an increase in the number of study subjects needed. Other factors influencing sample size include the study design and the expected within-subject variability. For example, a replicate four-way crossover bioequivalence study design, in which each subject receives the test and reference products twice, requires fewer subjects than a two-way crossover bioequivalence study design. As within-subject variability increases, the number of subjects needed in a crossover design will also increase, assuming that all other factors remain constant. Thus, bioequivalence study sample size is calculated based on a type I error rate of 5% per test, the desired study power, and the best estimates of test/reference ratios and within-subject variability as explained in detail in the below mentioned formula for estimating sample size[1].

$$\mathbf{n_e \geq 2 * \left[t_{(\alpha,2n-2)} + t_{(\beta,2n-2)} \right]^2 * [CV/(v-\delta)]^2} \quad \text{..... (1)}$$

where,

n	:	Sample size as per pilot study.
CV	:	Coefficient of variation (intra- subject variability comparing test versus reference) of that PK parameter which has maximum variability.
v	:	Log of bioequivalence limit (0.8 or 1.25) i.e. 20% difference (In general 10% difference is considered. In case of highly variable drugs go for 5% difference of Generic Vs Innovator).

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δ : Absolute value of expected/ observed difference.
α : Level of significance, generally 5%.
β : Probability of Type II error.

Table I Sample size consideration for FDA in three period studies

Power – 80%							
GMR CV%	**0.85**	**0.90**	**0.95**	**1.00**	**1.05**	**1.10**	**1.15**
30	230	62	30	18	30	53	122
32	72	32	20	16	20	30	51
34	63	32	20	15	20	29	47
35	59	32	20	15	20	27	45
36	56	30	20	15	20	27	42
38	51	29	20	15	20	27	39
40	47	29	20	15	20	26	38
42	44	27	20	15	20	26	36
44	42	27	20	15	20	26	35
45	41	26	20	15	18	26	33
46	39	26	20	15	18	24	33
48	38	26	20	15	18	24	32
50	36	26	20	15	18	24	32
52	35	26	20	15	18	24	30
54	35	24	20	15	18	23	30
55	35	24	20	15	18	23	30
56	33	24	20	15	18	23	29
58	33	24	20	15	18	23	29
60	32	24	20	15	18	23	29
62	32	24	20	15	20	23	29
64	32	24	20	17	20	23	29
65	32	24	20	17	20	23	27
66	30	24	20	17	20	23	27
68	30	24	20	17	20	23	27
70	30	24	20	17	20	23	27
72	30	24	20	17	20	23	27
74	30	24	20	17	20	23	27
75	30	24	20	17	20	23	27
76	30	24	20	17	20	23	27
78	30	24	20	17	20	23	27
80	30	24	20	17	20	23	27
82	29	24	20	17	20	23	27
84	29	24	20	18	20	23	27
85	29	24	20	18	20	23	27
86	29	24	20	18	20	23	27
88	29	24	21	18	20	23	27
90	29	24	21	18	21	24	27
92	29	24	21	18	21	24	27
94	29	24	21	18	21	24	27
95	29	24	21	18	21	24	27
96	30	24	21	18	21	24	27
98	30	24	21	18	21	24	27
100	30	24	21	18	21	24	27
105	30	26	23	20	23	26	29
110	30	26	23	20	23	26	27

CV%: Intra-subject variability comparing test versus reference.
GMR: Ratio of geometric mean.

Power – 90%							
GMR CV%	**0.85**	**0.90**	**0.95**	**1.00**	**1.05**	**1.10**	**1.15**
30	317	86	41	26	41	72	168
32	99	45	27	22	27	41	71
34	86	44	27	22	27	39	63
35	81	42	27	22	27	38	60
36	77	41	27	22	26	38	59
38	73	39	27	22	26	36	54
40	65	38	26	22	26	35	51
42	60	38	26	22	26	35	48
44	57	36	26	22	26	33	47
45	56	36	26	22	26	33	47
46	54	36	26	22	26	33	45
48	51	35	26	22	26	33	44
50	50	35	26	20	26	32	42
52	48	33	26	20	26	32	42
54	47	33	26	21	26	32	41
55	47	33	26	21	26	32	41
56	45	33	26	21	26	32	41
58	45	33	26	21	26	32	39
60	44	33	26	21	26	32	39
62	44	33	26	21	26	32	38
64	42	32	26	21	26	30	38
65	42	32	26	21	26	30	38
66	42	32	26	21	26	30	38
68	41	32	26	21	26	30	38
70	41	32	26	23	26	30	38
72	41	32	26	23	26	30	38
74	41	32	27	23	26	30	36
75	41	32	27	23	29	30	36
76	41	32	27	23	26	32	36
78	41	32	27	23	27	32	36
80	41	32	27	23	27	32	36
82	40	32	27	23	27	32	36
84	40	33	27	24	27	32	36
85	40	33	27	24	27	32	36
86	40	33	27	24	27	32	36
88	39	33	27	24	27	32	36
90	39	33	27	24	27	32	36
92	39	33	29	24	29	32	36
94	27	33	29	24	29	32	38
95	41	33	29	24	29	32	38
96	41	33	29	26	29	32	38
98	41	33	29	26	29	33	38
100	41	33	29	26	29	33	38
105	41	35	30	26	30	33	38
110	41	35	30	27	30	33	38

CV%: Intra-subject variability comparing test versus reference.
GMR: Ratio of geometric mean.

Table II. Sample size consideration for FDA in four period studies

Power – 80%							
GMR CV%	**0.85**	**0.90**	**0.95**	**1.00**	**1.05**	**1.10**	**1.15**
30	153	41	20	12	20	35	81
32	48	22	13	9	13	20	34
34	42	21	13	10	13	19	31
35	39	21	13	10	13	19	29
36	37	20	13	10	13	18	28
38	34	19	13	10	13	18	26
40	31	19	13	10	13	17	25
42	29	18	13	10	13	17	24
44	28	18	13	10	12	17	23
45	27	17	13	10	12	17	22
46	26	17	13	10	12	16	22
48	25	17	13	10	12	16	21
50	24	17	13	10	12	16	21
52	23	16	13	10	12	16	20
54	23	16	13	10	12	15	20
55	23	16	13	10	12	15	20
56	22	16	13	10	12	15	19
58	22	16	13	10	12	15	19
60	21	16	13	10	12	15	19
62	21	16	13	10	12	15	19
64	21	16	13	10	12	15	19
65	21	16	13	10	12	15	18
66	20	16	13	11	13	15	18
68	20	16	13	11	13	15	18
70	20	16	13	11	13	15	18
72	20	16	13	11	13	15	18
74	20	16	13	11	13	15	18
75	20	16	13	11	13	15	18
76	20	16	13	11	13	15	18
78	20	16	13	11	13	15	18
80	20	16	13	11	13	15	18
82	19	17	13	12	13	15	18
84	19	16	13	12	13	15	18
85	19	16	14	12	13	15	18
86	19	16	14	12	13	15	18
88	19	16	14	12	13	15	18
90	19	16	14	12	14	16	18

92	19	16	14	12	14	16	18
94	19	16	14	12	14	16	18
95	19	16	14	12	14	16	18
96	19	16	14	12	14	16	18
98	20	16	14	12	14	16	18
100	20	16	14	12	14	16	18
105	20	17	15	13	14	17	18
110	20	17	15	13	15	17	19

CV%: Intra-subject variability comparing test versus reference.
GMR: Ratio of geometric mean.

	Power – 90%						
GMR CV%	**0.85**	**0.90**	**0.95**	**1.00**	**1.05**	**1.10**	**1.15**
30	211	57	27	17	27	48	112
32	66	30	18	13	18	27	47
34	57	29	18	13	18	26	42
35	54	28	18	13	17	26	40
36	51	27	18	13	17	25	39
38	48	26	18	13	17	24	36
40	43	25	17	13	17	23	34
42	40	25	17	13	17	23	32
44	38	24	17	13	17	22	31
45	37	24	17	13	17	22	31
46	36	23	17	13	17	22	30
48	34	23	17	13	17	22	29
50	33	23	17	13	17	21	28
52	32	22	17	13	17	21	28
54	31	22	17	14	17	21	27
55	31	22	17	14	17	21	27
56	30	22	17	14	17	21	27
58	30	22	17	14	17	21	26
60	29	22	17	14	17	21	26
62	29	21	17	14	17	21	25
64	28	21	17	14	17	21	25
65	28	21	17	14	17	20	25
66	28	21	17	14	17	20	25
68	28	21	17	14	17	20	25
70	27	21	17	15	17	20	25
72	27	21	17	15	17	20	25
74	27	21	17	15	17	20	24
75	27	21	18	15	17	20	24
76	27	21	18	15	17	21	24
78	27	21	18	15	18	21	24
80	27	21	18	15	18	21	24
82	27	21	18	15	18	21	24
84	26	22	18	16	18	21	24
85	26	22	18	16	18	21	24
86	26	22	18	16	18	21	24
88	26	22	18	16	18	21	24
90	26	22	18	16	18	21	24
92	26	22	19	16	18	21	24
94	26	22	19	16	19	21	25
95	27	22	19	16	19	21	25
96	27	22	19	17	19	21	25
98	27	22	19	17	19	22	25
100	27	22	19	17	19	22	25
105	27	23	20	17	20	22	25
110	27	23	20	18	20	22	25

CV%: Intra-subject variability comparing test versus reference.
GMR: Ratio of geometric mean.

Procedure for sample size estimation USA submission studies

Calculate the sample size using the formula mentioned in equation (1).

Substitute the 'v' i.e. the log of bioequivalence limit calculated value in equation (1). Obtain log of bioequivalence limit (v) as using the below mentioned formula.

$$[U, L] = exp^{\pm \theta_s * S_{wr}} \quad \text{..... (2)}$$

where, S_{wr} is the within subject standard deviation of reference product i.e., σ_{wR} and θ_s is constant i.e., 0.893 calculated from the equation (5).

Obtain within subject standard deviation of reference product (S_{wr}) using the below mentioned formula [2].

$$S_{wr} = \sqrt{\ln (CV^2 + 1)} \quad \text{..... (3)}$$

where, CV is the intra subject coefficient of variance of reference product.

The formula for obtaining the 95% upper confidence bound [3] for both AUC and C_{max} is as shown below:

$$(\mu_T - \mu_R)^2 - (\theta_S * \sigma_{wR}^2) \leq 0.0000 \quad \text{..... (4)}$$

Table III. Sample size consideration for EMA in three period studies

	Power – 80%						
GMR CV%	**0.85**	**0.90**	**0.95**	**1.00**	**1.05**	**1.10**	**1.15**
30	230	62	30	18	30	53	122
32	171	51	30	20	29	50	102
34	138	53	29	20	29	47	89
35	126	51	29	20	27	45	83
36	116	50	29	20	27	44	78
38	101	47	27	20	27	42	71
40	90	44	27	20	27	41	66
42	81	42	27	20	27	39	62
44	75	41	27	20	27	38	57
45	72	41	27	20	27	38	56
46	69	41	27	20	26	36	54
48	66	39	27	20	26	36	53
50	62	38	27	20	26	37	50
52	68	41	29	21	29	38	54
54	72	44	30	23	30	41	59
55	75	45	32	24	32	42	60
56	77	47	33	24	32	44	63
58	83	51	35	26	35	47	68
60	89	54	38	29	36	50	72
62	95	57	39	30	39	53	77
64	101	62	42	32	42	57	81
65	104	63	44	33	42	59	84
66	107	65	45	33	44	60	86
68	113	69	47	35	47	63	92
70	120	72	50	38	50	68	96
72	126	77	53	39	53	71	102
74	134	81	56	42	54	75	108
75	137	83	57	42	56	77	111
76	141	86	59	44	57	80	114
78	149	90	62	45	60	83	120
80	156	95	65	48	63	87	126
82	164	99	68	51	66	92	132
84	171	104	71	53	71	96	138
85	176	107	72	54	72	98	141
86	180	108	75	56	74	101	144
88	188	114	78	57	77	105	152
90	197	119	81	60	80	110	158
92	206	125	86	63	84	116	165
94	215	129	89	66	87	120	173
95	219	132	90	68	89	123	176
96	224	135	92	68	90	125	180
98	233	141	96	71	95	131	188
100	242	146	101	74	99	135	195
105	267	161	110	81	108	149	215
110	293	177	120	89	119	164	236

CV%: Intra-subject variability comparing test versus reference.
GMR: Ratio of geometric mean.

where, σ^2_{wR} is the population within-subject variance of the reference formulation. θ_s will be obtained based on the below mentioned formula [3].

$$\boldsymbol{\theta_S} = \left[\frac{(\ln(1.25))^2}{\sigma^2_{w0}}\right] \quad \text{..... (5)}$$

θ_s is the scaled average bioequivalence limit and σ^2_{w0} is a predetermined constant set by the regulatory agency i.e., σ_{w0} = 0.25.

Rearranging of equation (4), to obtain the implied limits on $\mu_T - \mu_R$ yields:

$$-\left[\ln(1.25)\frac{\sigma_{wR}}{\sigma_{w0}}\right] \leq \mu_T - \mu_R \leq \left[\ln(1.25)\frac{\sigma_{wR}}{\sigma_{w0}}\right] \quad \text{..... (6)}$$

If $\sigma_{wR}=\sigma_{w0}$, the implied limits are equal to the standard unscaled bioequivalence limits of ±ln (1.25) (0.80 to 1.25).

	Power – 90%						
GMR CV%	0.85	0.90	0.95	1.00	1.05	1.10	1.15
30	317	86	41	26	41	72	168
32	237	78	41	26	39	68	140
34	191	72	39	26	38	63	122
35	174	69	39	26	38	62	114
36	159	68	39	26	38	60	108
38	138	63	38	26	38	57	98
40	123	60	38	26	36	54	90
42	111	59	38	26	36	53	84
44	102	56	36	27	36	51	80
45	99	56	36	27	36	51	77
46	96	54	36	27	36	50	75
48	90	53	36	27	36	50	72
50	86	53	36	27	36	48	69
52	92	56	39	29	38	53	75
54	99	60	42	32	41	56	80
55	102	63	44	33	42	59	83
56	107	65	45	33	44	60	86
58	114	69	48	36	47	65	92
60	122	74	51	38	50	69	98
62	131	78	54	41	54	74	105
64	138	84	57	44	57	78	111
65	143	87	60	44	59	80	116
66	147	89	62	45	60	83	119
68	156	95	65	48	63	87	126
70	165	101	69	51	68	93	134
72	174	105	72	54	71	98	141
74	185	111	77	57	75	104	149
75	189	114	78	59	77	107	153
76	194	117	81	60	80	108	156
78	204	123	84	63	83	114	165
80	215	131	89	66	87	120	173
82	225	137	93	69	92	126	182
84	237	143	98	72	96	132	191
85	243	146	101	74	99	135	195
86	248	150	102	75	101	138	200
88	260	156	107	80	105	146	209
90	272	164	113	83	110	152	219
92	284	171	117	87	116	159	228
94	296	179	122	90	120	165	239
95	303	182	125	92	121	168	243
96	309	186	128	95	125	173	249
98	321	194	132	98	131	180	258
100	335	201	138	102	135	186	269
105	369	222	152	113	149	206	297
110	405	243	167	123	164	225	326

CV%: Intra-subject variability comparing test versus reference.
GMR: Ratio of geometric mean.

If $\sigma_{wR}>\sigma_{w0}$, the implied limits are wider than the standard limits. If $\sigma_{wR}<\sigma_{w0}$, the implied limits are narrower than the standard limits. Calculate the wider bioequivalence limit to substitute the 'v' i.e. the log of bioequivalence limits calculated value in the equation (1) to calculate the sample size with desired power and with the estimates of test/reference ratios.
Refer Table V for wider bioequivalence limit 'v' to substitute in equation (1).

Procedure for sample size estimation EMA submission studies

Calculate the sample size using the formula mentioned in equation (1).

Substitute the 'v' i.e. the log of bioequivalence limit calculated value in equation (1).

Table IV Sample size consideration for EMA in four period studies

	Power – 80%						
GMR CV%	0.85	0.90	0.95	1.00	1.05	1.10	1.15
30	153	41	20	12	20	35	81
32	114	38	20	13	19	33	68
34	92	35	19	13	19	31	59
35	84	34	19	13	19	30	55
36	77	33	19	13	18	29	52
38	67	31	18	13	18	28	47
40	60	29	18	13	18	27	43
42	54	28	18	13	18	26	41
44	50	27	18	13	18	25	38
45	48	27	18	13	18	25	37
46	46	27	18	13	17	24	36
48	44	26	18	13	17	24	35
50	41	25	18	13	17	25	33
52	45	27	19	14	19	25	36
54	48	29	20	15	20	27	39
55	50	30	21	16	21	28	40
56	51	31	22	16	21	29	42
58	55	34	23	17	23	31	45
60	59	36	25	19	24	33	48
62	63	38	26	20	26	35	51
64	67	41	28	21	28	38	54
65	69	42	29	21	28	39	56
66	71	43	30	22	29	40	57
68	75	46	31	23	31	42	61
70	80	48	33	25	33	45	64
72	84	51	35	26	35	47	68
74	89	54	37	28	36	50	72
75	91	55	38	28	37	51	74
76	94	57	39	29	38	53	76
78	99	60	41	30	40	55	80
80	104	63	43	32	42	58	84
82	109	66	45	34	44	61	88
84	114	69	47	35	47	64	92
85	117	71	48	36	48	65	94
86	120	72	50	37	49	67	96
88	125	76	52	38	51	70	101
90	131	79	54	40	53	73	105
92	137	83	57	42	56	77	110
94	143	86	59	44	58	80	115
95	146	88	60	45	59	82	117
96	149	90	61	45	60	83	120
98	155	94	64	47	63	87	125
100	161	97	67	49	66	90	130
105	178	107	73	54	72	99	143
110	195	118	80	59	79	109	157

CV%: Intra-subject variability comparing test versus reference.
GMR: Ratio of geometric mean.

	Power – 90%						
GMR CV%	**0.85**	**0.90**	**0.95**	**1.00**	**1.05**	**1.10**	**1.15**
30	211	57	27	17	27	48	112
32	158	52	27	17	26	45	93
34	127	48	26	17	25	42	81
35	116	46	26	17	25	41	76
36	106	45	26	17	25	40	72
38	92	42	25	17	25	38	65
40	82	40	25	17	24	36	60
42	74	39	25	17	22	35	56
44	68	37	24	18	22	34	53
45	66	37	24	18	24	34	51
46	64	36	24	18	24	33	50
48	60	35	24	18	24	33	48
50	57	35	24	18	24	32	46
52	61	37	26	19	25	35	50
54	66	40	28	21	27	37	53
55	68	42	29	21	28	39	55
56	71	43	30	22	29	40	57
58	76	46	32	24	31	43	61
60	81	49	34	25	33	46	65
62	87	52	36	27	36	49	70
64	92	56	38	29	38	52	74
65	95	58	40	29	39	53	77
66	98	59	41	30	40	55	79
68	104	63	43	32	42	58	84
70	110	67	48	34	45	62	89
72	116	70	48	36	47	65	94
74	123	74	51	38	50	69	99
75	126	76	52	39	51	71	102
76	129	78	54	40	53	72	104
78	136	82	56	42	55	76	110
80	143	87	59	44	58	80	115
82	150	91	62	46	61	84	121
84	158	95	65	48	64	88	127
85	162	97	67	49	66	90	130
86	165	100	68	50	67	92	133
88	173	104	71	53	70	97	139
90	181	109	75	55	73	101	146
92	189	114	78	58	77	106	152
94	197	119	81	60	80	110	159
95	202	121	83	61	82	112	162
96	206	124	85	63	83	115	166
98	214	129	88	65	87	120	172
100	223	134	92	68	90	124	179
105	246	148	101	75	99	137	198
110	270	162	111	82	109	150	217

CV%: Intra-subject variability comparing test versus reference.
GMR: Ratio of geometric mean.

Table VI. BE limit calculation for EMA by using intra variability of reference

Reference CV%	Swr	Upper Limit	BE Limit
0.30	0.294	1.25	0.2231
0.32	0.312	1.27	0.2373
0.34	0.331	1.29	0.2514
0.35	0.340	1.29	0.2584
0.36	0.349	1.30	0.2653
0.38	0.367	1.32	0.2791
0.40	0.385	1.34	0.2928
0.42	0.403	1.36	0.3063
0.44	0.421	1.38	0.3197
0.45	0.429	1.39	0.3264
0.46	0.438	1.40	0.3330
0.48	0.455	1.41	0.3461
≥ 0.50	0.472	1.43	0.3590

S_{wr}: Within subject standard deviation of reference product
CV%: Intra subject variability of reference product

Obtain within subject standard deviation of reference product (S_{wr}) using equation (3).

Obtain bioequivalence limit directly by using the below mentioned formula [4] as given by the regulatory.

$$[U, L] = exp^{\pm k \cdot S_{wr}} \quad \text{..... (7)}$$

where, k = regulatory constant, i.e., 0.760.

Calculate the wider bioequivalence limit to substitute the 'v' i.e. the log of bioequivalence limits calculated value in the equation (1) to calculate the sample size with desired power and with the estimates of test/reference ratios.

If CV ≥ 50% then the bioequivalence limits will be used is 69.84 - 143.19%.

Table V. BE limit calculation for USFDA by using intra variability of reference

Reference CV%	S_{wr}	Upper Limit	BE Limit
0.30	0.294	1.30	0.2621
0.32	0.312	1.32	0.2788
0.34	0.331	1.34	0.2954
0.35	0.340	1.35	0.3036
0.36	0.349	1.37	0.3117
0.38	0.367	1.39	0.3280
0.40	0.385	1.41	0.3440
0.42	0.403	1.43	0.3599
0.44	0.421	1.46	0.3757
0.45	0.429	1.47	0.3835
0.46	0.438	1.48	0.3912
0.48	0.455	1.50	0.4066
0.50	0.472	1.52	0.4218
0.52	0.489	1.55	0.4369
0.54	0.506	1.57	0.4517
0.55	0.514	1.58	0.4591
0.56	0.522	1.59	0.4664
0.58	0.538	1.62	0.4809
0.60	0.555	1.64	0.4952
0.62	0.570	1.66	0.5093
0.64	0.586	1.69	0.5232
0.65	0.594	1.70	0.5301
0.66	0.601	1.71	0.5370
0.68	0.617	1.73	0.5505
0.70	0.631	1.76	0.5639
0.72	0.646	1.78	0.5771
0.74	0.661	1.80	0.5901
0.75	0.668	1.82	0.5966
0.76	0.675	1.83	0.6030
0.78	0.689	1.85	0.6156
0.80	0.703	1.87	0.6281
0.82	0.717	1.90	0.6404
0.84	0.731	1.92	0.6525
0.85	0.737	1.93	0.6585
0.86	0.744	1.94	0.6645
0.88	0.757	1.97	0.6762
0.90	0.770	1.99	0.6879
0.92	0.783	2.01	0.6993
0.94	0.796	2.04	0.7106
0.95	0.802	2.05	0.7162
0.96	0.808	2.06	0.7217

S_{wr}: Within subject standard deviation of reference product
CV%: Intra subject variability of reference product

0.98	0.820	2.08	0.7327
1.00	0.833	2.10	0.7435
1.02	0.844	2.13	0.7541
1.04	0.856	2.15	0.7646
1.05	0.862	2.16	0.7698
1.06	0.868	2.17	0.7750
1.08	0.879	2.19	0.7852
1.10	0.891	2.21	0.7952

S_{wr}: Within subject standard deviation of reference product
CV%: Intra subject variability of reference product

Table VI. BE limit calculation for EMA by using intra variability of reference.

Note[5]

- Full replicate designs: sample size = ~½ of n_e study's sample size.
- Partial replicate designs: sample size = ~¾ of n_e study's sample size.

To obtain the within subject standard deviation of reference product (S_{wr}) or within subject variability of reference product the

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How to cite this article:
Someswara Rao. K *et al*., Sample Size Estimation For Highly Variable Drugs Using Reference Scaled Average Bioequivalence Criteria. *International Journal of Recent Scientific Research Vol. 6, Issue, 7, pp.5040-5045, July, 2015*

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