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COMMUNICATIONS

Assessment of 75/75 Rule: FDA Viewpoint

Keyphrases □ Bioavailability—studies involving subjects with intersubject coefficient of variation, assessment of 75/75 Rule, FDA viewpoint □ Bioequivalence—bioavailability studies involving subjects with intersubject coefficient of variation, assessment of 75/75 Rule, FDA viewpoint.

To the Editor:

Recently, the new 75/75 specification proposed by the FDA for Bioequivalency Studies came under criticism (1) as being scientifically invalid and unpredictable in bioavailability studies involving subjects with intersubject coefficient of variation (*CV*) of 60% and intrasubject *CV* of 20–30%. Similar criticism also has been launched at the FDA for application of the 75/75 Rule in establishing an *in vitro–in vivo* correlation. Although the FDA does not disagree with the calculated results on hypothetical problems in the published article and the application of the Pittman–Morgan test when appropriate, the authors of the proposed FDA rule do disagree with the underlying assumptions of the author, *i.e.*, that such large variations are the norm in bioequivalency studies.

It has been observed by the FDA that for the large majority of drugs for which bioavailability bioequivalence data are submitted as part of a New Drug Application, the coefficient of variation is generally <40%, assuming that a properly validated analytical assay is employed. To substantiate the latter claims, a review of FDA reports over a 5-year period by a primary FDA contractor (2) is summarized in Table I. The FDA review reveals that the coefficients of variation among 106 total drug products involving 12 drug entities were generally well within the 40% range. Only in the case of diphenhydramine (Table I) was

Table I—Summary of Bioavailability Studies [a]

Drug	Number of Products Tested	*CV*, % (C_{max})[b]	*CV*, % (*AUC*)[b]	Number of Products with *CV* >40%
Phenytoin	a. 6	14–33	16–45	1
	b. 6	19–24	19–26	0
Meprobamate	a. 6	6–21	12–26	0
	b. 6	15–24	22–37	0
Chlorothiazide	6	—	30–46[c]	1
Acetazolamide	4	19–36	17–30	0
Propylthiouracil	6	16–23	16–29	0
Warfarin	5	10–20	9–13	0
Griseofulvin	a. 6	21–40	14–26	0
	b. 6	27–46	24–30	1
Diphenhydramine	a. 6	14–54	35–67	4
	b. 6	36–48	40–62	5
Tolbutamide	7	12–20	18–24	0
Phenobarbital	6	16–23	21–34	0
Sulfisoxazole	a. 6	5–13	7–16	0
	b. 6	15–25	20–32	0
Trichlormethiazide	a. 5	30–35	26–35	0
	b. 5	17–25	11–26	0

[a] Studies performed under FDA Contract 223-77-3011. The total number of drug products tested was 106. The total number of drug products exceeding 40% *CV* was 12. [b] Range of *CV* values for peak plasma level (C_{max}) and area under the curve (*AUC*). [c] Range of *CV* for total cumulative urinary excretion.

Table II—Proportion of 1000 Simulated Studies with 12 Hypothetical Drugs Meeting 75/75 Rule [a]

Drug	N[b]	Intersubject *CV* TP[c]	Intersubject *CV* RP[d]	Intrasubject *CV*	Proportion of 1000 Studies Meeting 75/75 Criterion							
					p[e] = 0	p = 0.3	p = 0.4	p = 0.5	p = 0.6	p = 0.7	p = 0.8	p = 0.9
Case 1	24	60	60	30	0.15	0.19	0.22	0.26	0.30	0.35	0.43	0.52
Case 2	24	40	40	30	0.72	0.78	0.79	0.81	0.84	0.86	0.88	0.90
Case 3	24	60	40	30	0.29	0.32	0.34	0.36	0.38	0.39	0.41	0.43
Case 4	12	60	60	20	0.24	0.29	0.32	0.35	0.40	0.47	0.54	0.66
Case 5	12	40	40	20	0.55	0.63	0.66	0.69	0.73	0.79	0.82	0.88
Case 6	12	60	40	20	0.38	0.44	0.45	0.47	0.51	0.53	0.56	0.59
Case 7	12	30	30	15	0.74	—	—	0.87	—	0.91	—	0.98
Case 8	12	15	15	13	1.00	1.00	—	1.00	—	1.00	—	1.00
Case 9	12	30	15	13	0.84	—	—	0.86	—	0.88	—	0.89
Case 10	12	30	30	10	0.68	—	—	0.86	—	0.94	—	0.99
Case 11	12	15	15	10	1.00	1.00	—	1.00	—	1.00	—	1.00
Case 12	12	30	15	10	0.80	—	—	0.86	—	0.89	—	0.91

[a] Portion of Table II, *i.e.*, drugs 1–6, published by Haynes (1) drugs 7–12 was generated by Dr. Haynes at the request of Dr. Purich for presentation at the 1981 International Industrial Pharmacy Conference, Austin, Tex. [b] N is the number of subjects. [c] TP is the test product. [d] RP is the reference product. [e] Correlation coefficients between *AUC* values for test and reference products in the same individual.

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a significant problem encountered in utilizing the 75/75 Rule. Of 106 drug products tested in 18 bioavailability studies, 94 products had <40% *CV*.

The author of the original article pointed out that given a true correlation coefficient, $\rho = 0.90$, the probability of success utilizing the 75/75 Rule was 90% in bioavailability trials involving 24 subjects where the intersubject *CV* is 40% for both the test and reference drug, and the intrasubject *CV* is 30%. The probability of success of applying the 75/75 Rule will significantly increase when the inter- and intrasubject variations are reduced to <40 and 30%, respectively (Table II) (2). The proportion of 1000 studies involving as few as 12 subjects meeting the 75/75 Rule utilizing drugs with an intersubject *CV* of <40% and an intrasubject *CV* of <20% is >88%, and 98% with inter- and intrasubject *CV*s of 30 and 15%, respectively.

The application of the 75/75 Rule is only valid for drugs having a well-defined reference standard that has reproducible pharmacokinetic properties in terms of absorption and clearance. Drugs having a large coefficient of variation associated with extensive first-pass metabolism are often required to undergo multiple-dose steady-state study comparisons or other more appropriate study design as a basis of drug approval. To achieve these results, the FDA often utilizes an oral solution as a basis of comparison where the reference drug has poor bioavailability. Also, the 75/75 Rule is only applied in conjunction with a proper analysis of variance and the FDA relies on additional data analyses.

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FDA 75/75 Rule: A Response

Keyphrases □ Bioavailability—studies involving subjects with intersubject coefficient of variation, FDA 75/75 Rule □ Bioequivalance—studies involving subjects with intersubject coefficient of variation, FDA 75/75 Rule

To the Editor:

Dr. Cabana's communication (1) refers to an article (2) that is critical on statistical grounds of the FDA Division of Biopharmaceutic's proposed 75/75 Rule for bioequivalency studies. We emphasize that the point deserving discussion here is not the rigor of the 75/75 Rule, but rather, the fatal flaws inherent in its form. The same flaws would exist even if the rule were less rigorous (50/50) or more rigorous (90/90), because it would retain the same undesirable form: the dispersion of certain ratios. We applaud the vast majority of the pharmacokinetic–bioavailability–bioequivalency regulations and guidelines as contributing to the improvement of health care; we also are glad to see that the FDA accepts the Pitman–Morgan *F*-test as the proper test for equality of test-product and reference-product variation in crossover bioavailability–bioequivalency studies. This *F*-test is described in the statistical literature as "uniformly most powerful" (3); therefore, no other test of variation in a study can have as much statistical power for detection of true differences in standard deviations. The word uniform indicates that this superiority holds for differences of all magnitudes.

In essence we agree with the communication (1) which states that the intersubject coefficient of variation (*CV*) of 40% used previously (2) is not the norm. The choice of 40% per se is not critical; however, the question is whether the results would be much different at a 35% *CV*. Such large coefficients of variation reflect the skewness of the distributions. It also should be noted that the intrasubject *CV* is 20 or 30%, common values for the error term in the analysis of variance (ANOVA).

The performance in a certain region of a proposed statistical test, such as the 75/75 Rule, generally is not very interesting to the statistician designers and the users of such a rule. The main interest in the performance of the proposed test centers on how the more variable drug products are treated by the test—whether they are treated fairly in this respect. The number of such drug products is not negligible, accounting for ≥10% (depending on a cutoff *CV* of 35 or 40%) of drugs studied, according to Dr. Cabana's Table I (1). (If other parameters for a test product have unacceptable values, they should not obscure the point under consideration.) "Are they treated fairly?" is the question addressed earlier (2) for the case of equal averages, and the answer is that they are not. For example, according to the 75/75 Rule, a test product for chlorothiazide with a variation of *AUC* values that is 50% greater than the variation of the reference product *AUC* values usually has a greater chance of being declared bioequivalent than does a test product for phenytoin with the same variation as its reference product.

The main flaw of the 75/75 Rule lies in the fact that the degree of dispersion of the ratio depends on the dispersion or both products, test and reference, without distinction. Thus, a test product which fails the 75/75 Rule in a study may do so because the reference product standard deviation is relatively large—the reference product should fail the dispersion test in that study. For example, for the 12 drugs in Dr. Cabana's Table I (1), suppose that in each study a test product always had the smallest coefficient of variation shown for that drug and the reference product had the largest coefficient of variation—both products with the same average. The unadjusted *F*-values would be, for the *AUC* columns of Table I (1): 7.9, 1.9, 4.7, 2.8, 2.4, 3.1, 3.3, 2.1, 3.4, 1.6, 3.7, 2.4, 1.8, 2.6, 5.2, 2.6. 1.8, and 5.6. Superior uniformity would be indicated for such test products but probably many would fail the 75/75 Rule falsely, because the greater variability is that of the reference products.

The statement that the 75/75 Rule "is only applied in conjunction with a proper analysis of variance" (1) implies a remedy, probably subjective, but the fatal flaws remain; the rule should be withdrawn. Furthermore, since the performance of the 75/75 Rule is affected by differences in the two mean *AUC*s (for test and reference materials),

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