Content Uniformity

The large amount of potentially useful work on computer simulation of the performance of various sampling tests by Flann[1] is to be applauded. The nonconventional, complex "operating characteristic" curves and the admittedly arbitrary measures used for reliability and robustness are to be lamented because they do not adequately summarize the data. Although the author refers to the two standard texts on variables sampling and several drug sampling papers, he does not subscribe to their use of "percentage defective" because he somehow feels the concept is not appropriate for drugs. This feeling produces the features mentioned above, so it deserves close scrutiny.

The author says (pp. 191, 192) that, for practical reasons, in the absence of pharmacological dose–response data ". . . pharmaceutical chemists have, for years, temporized . . . [by using] percentage of defectives . . . or outsiders, this classification implies that all units within the range are pharmacologically equally satisfactory and those outside the range are equally unsatisfactory." The word "equally" is the hinge upon which the matter turns. The author interprets it strictly, while most chemists (and others) interpret it loosely, in a practical sense.

Admittedly, the units within the specified range do differ in potency but, if the range is small enough, the resultant effect on patients would be swamped by other variations. The question then becomes: "How small must the range be for each drug?" The answer depends on, first, the dose–response curve and, second, the proportion that the drug content variation contributes to the *total* response variation composed of intrapatient variation in absorption, distribution, response, metabolism, and elimination as well as drug content variation.

The only study touching on this topic that comes to mind was one[2] in which aspirin at nine dose levels, at 2.5% intervals, was given to 20 fasted, young males *per os*. The authors stated that ". . . it is obvious that the inter-dose variation is quite trivial compared to that related to inter-individual divergencies and time-dependent individual differences."

However, this lack of definite information for many drugs is no reason to abandon the use of percentage of outsiders; the use of mean and standard deviation suffers from the same lack. What multiplier of the standard deviation is appropriate and what limit is best?

An advantage of the use of percentage of outsiders is that its interpretation is the same for any reasonable shape of a lot's distribution of unit drug content. Since, as Flann states, "There is ample evidence that an appreciable proportion of the many distributions of drug content are significantly nonnormal," the application of the mean and standard deviation (so easy for normal distributions) becomes more complicated and uncertain. For instance, with a mean of 100% label claim and a standard deviation of 5.8%, the theoretical number of single-dose units (per 100,000 units) beyond the ±15% limits is 1000 for a normal distribution (Flann, Table I), 60 for the platykurtic distribution defined in his Table IV, and 2000 for the leptokurtic distribution—the patients would think these are hardly lots of equal quality.

Another viewpoint of the nonnormality feature shows that three product lots with identical means of 100% label claim and the same percentage of outsiders, 1%, but with differently shaped distributions have standard deviations of 5.8% for normal, 7.0% for platykurtic, and 5.0% for leptokurtic distributions. The producers could say: "Here are three lots of equal quality. Why should the platykurtic one be more likely to be rejected, as would happen by the standard deviation test?" The use of percentage outsiders as the measure of uniformity seems fairer to both producer and consumer.

Finally, the reduction from two parameters, mean and standard deviation, to characterize content uniformity to one parameter, percentage outsiders, will simplify the analysis of the data and lead to a comprehensible presentation of results. The use of percentage outsiders has been vindicated so the author can, in good conscience, use his valuable simulation data to evaluate the various sampling tests.

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Received August 5, 1974.

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Tablet Strength Testing

The following comments are in response to Dr. Newton's letter in the "Open Forum" section of the April 1974 issue of *J. Pharm. Sci.*

Dr. Newton *did not* criticize our experimental procedure, the analysis of the data generated, and the conclusions that we drew, but he suggested that our effort was misplaced. It is rather unfortunate that Dr. Newton misunderstood the objectives of our study[1], which we felt were apparent in the title and in the first two paragraphs of the paper. Nowhere do we mention that the study pertained to the stress phenomena within a tablet characterized by its tensile, compressive, and shear components. Dr. Newton, as a matter of fact, has studied and published on these mechanisms[2]. We felt that his work was adequate.

In any event, we feel that both objectives are essential for the growth of pharmaceutical sciences. On one hand, the testing and comparing of several tablet testers presently available on the market would lead to the knowledge of their performance in one's own laboratory, so that one becomes aware of the advantages and disadvantages associated with the testers. This knowledge should be disseminated and shared by others in the field. On the other hand, a study of the physical laws governing the mechanisms would lead to the development of new instruments to be marketed in the future. In either case, statistical inference should be used to arrive at valid conclusions.

Dr. Newton appears to have misunderstood the variation reported in our paper. He stated that the variation was limited and contradicted what one might expect. Table I of our paper consists of *geometric* means and geometric standard errors, as indicated in the footnote to the table. The use and presentation of the geometric means and geometric standard errors are appropriate because initially the data were transformed to logarithms for the purpose of *stabilizing* the variances.

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Received August 15, 1974.

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[2] J. T. Fell and J. M. Newton, *ibid.*, **59**, 688(1970).