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Uniformity of content requirements for tablets and capsules

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Present pharmacopoeial requirements for uniformity of content of tablets and capsules are based on tests by attributes. A test for uniformity of content based on the root mean square deviation about target (s_T) is more reliable than the pharmacopoeial tests and has the added convenience of using a single statistic to control both the mean content and the variation about the mean. Implications of the use of the statistic s_T in uniformity requirements are discussed.

Present pharmacopoeial requirements relating to uniformity of content of active substance in tablets and capsules are based on tests by attributes and are stated in terms of limits for the fraction of defectives of the type 'not more than x out of a sample of y shall deviate by more than z per cent. . .'. This approach may have been adopted because of uncertainties regarding the distribution of dosage units in batches, the use of small sample sizes and the tedium of calculating appropriate statistical parameters. The older methods for uniformity of content tended to rely on small sample sizes and simple assay procedures in order to reduce the cost and time of testing. In recent years, the difficulties in computation have been greatly reduced by the widespread availability of electronic calculators, while the growth in the use of instrumental and automated analytical methods has made possible an increase in the sample sizes used in tests of uniformity.

If a sample of ten or more items is used, a requirement which takes into account the variability of the quantity being measured, by use of a statistic such as standard deviation, makes better use of the available data than does a requirement based on a fraction of defectives, and the probability of a wrong decision is greatly reduced. Tests by variables are generally accepted as more reliable tests of dispersion than are tests by attributes (Flann 1974). It seems desirable, therefore, for future standards for therapeutic goods to make use of tests by variables in requirements for uniformity of content.

Current pharmacopoeial uniformity of content requirements

The British Pharmacopoeia (B.P.) has uniformity of content requirements for certain tablet formulations which are framed with reference to the mean of the experimentally determined contents of individual tablets. Typically, the contents of active substance for 9 out of 10 tablets are required to be within a specified percentage of the mean of the 10 individual assay results. A separate bulk assay is used to ensure that the tablets comply with the limits for content of active substance given in the monograph. The B.P., therefore, has limits for the mean content and the variation of the contents of individual tablets about the mean which are independent of each other. For example, the monograph for digoxin tablets in the 1980 B.P. specifies that 9 out of 10 tablets have contents which are between 80 and 120% of the mean content and that the contents of all 10 tablets are within 75 and 125% of the mean. A bulk assay is carried out on a pooled sample of 25 tablets, and the limits for the content of the bulked tablet sample are 90 to 110% of the stated content.

The United States Pharmacopeia (U.S.P.) states uniformity of content requirements for tablets in terms of the average of the limits specified in the potency definition in the individual monograph and uses a two stage sampling plan with inner limits of 85 to 115% and outer limits of 75 to 125% of stated content. The requirements are met if all 10 tablets have contents which fall within the inner limits. If not more than one tablet has a content which falls between the inner and outer limits, a further 20 tablets are assayed individually, and the contents of each must fall within the inner limits. Similar, but rather more lenient, U.S.P. requirements apply to capsules, with the contents of one out of 10 or 3 out of 30 units being permitted to fall between the inner and outer limits. In addition to uniformity of content requirements, separate requirements are set for mean content,

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based on the assay of a pooled sample of dosage units. In the case of digoxin tablets U.S.P., 20 tablets are used for the bulk assay, and the limits set are 92·0 to 108·0% of stated content. In the U.S.P. XX a correction procedure has been introduced to compensate for any bias of the uniformity of content method with regard to the assay procedure. The U.S.P. requirements, therefore, differ from those of the B.P. in that they refer the variation in individual tablet contents to the stated content rather than to the experimentally determined mean. Both the B.P. and the U.S.P. tests for uniformity of content use separate samples of tablets to determine mean content and variation in content.

If the assumption is made that the sample is normally distributed, the B.P. requirements for uniformity of content can be considered to indicate a limiting value for permitted standard deviation of individual tablet contents. In the case of digoxin tablets, the B.P. specifies that at least 90% of the tablets in the sample must have contents of active substance which are within ±20% of the mean of those contents. In a normal distribution, 90% of the population lies within ±1·645 standard deviations of the mean, so that the limit for permitted standard deviation in this case is 20/1·645 or 12·16. This argument makes sweeping assumptions about the distribution of a small sample but illustrates the implications of the B.P. requirements.

The purpose of a uniformity of content requirement is to protect the consumer against excessive variation in the product concerned. The type of requirement used by the B.P. is rather lenient when the mean content is substantially different from the stated content, and the chance of unacceptable variation is greatly increased. The U.S.P. requirements also have a potential for combining an off-target mean content with a comparatively large inter-tablet variation. When separate limits are set for the mean content and the standard deviation of the individual tablet contents, the least desirable case where a product complies with the requirements is when both statistics are at these limits. For example, consider the case where limits of 90 to 110% of the target value (stated content) are set for the mean, and the limit for the standard deviation of the individual tablet contents is 10%. If individual tablet contents were normally distributed, a batch of tablets which gave a mean of 100% and a standard deviation of 10 in a test for uniformity of content would be expected to have 4·55% of its population with contents differing from the stated content by more than 20% and 0·27% of its population differing from this target value by more than 30%.

However, if the mean was either 90% or 110% of stated content, then with a standard deviation of 10, 16·0% of the population would be expected to deviate from the target value by more than 20%, and 2·28% by more than 30%. In the second instance, the chance of the consumer receiving a tablet with a content of active substance differing appreciably from that stated is greatly increased.

Alternatives to the pharmacopoeial tests

It seems unreasonable, and not in the interests of the consumer, for the criteria for uniformity of content to be independent of the value for the mean, and consideration has therefore been given to methods of expressing limits so that the permissible standard deviation of individual results is reduced when the mean deviates appreciably from the target value (stated content of active substance in the case of uniformity of content). One way of doing this is to impose a linear condition of the type

$$|x - T| + Bs \leqslant A$$

where x is the mean of the individual tablet contents, T the target, s the standard deviation, A the limit and B a constant. Following the previous example, if A and B have the values of 10 and 1·0 and the results are calculated as percentages of the stated content, so that T is 100, the maximum permitted value for s falls from 10 at 100% potency to zero at 90% or 110% potency. With a requirement of this sort, none of the population would be permitted to deviate by more than ±20% from the target when the deviation of the mean from target reached about 6·5%. This sort of requirement would place unreasonable constraints on manufacturers in cases when the mean was off-target but within acceptable limits.

A statistic which has been used at N.B.S.L. for several years in the assessment of uniformity is the root mean square deviation about target. This is similar to standard deviation but the deviations are measured from the target rather than the mean. The statistic has been assigned the symbol s_T and is defined as:

$$s_T = \sqrt{[\Sigma(x - T)^2/n]}$$

It can be shown that:

$$s_T = \sqrt{[s^2(n - 1)/n + (x - T)^2]}$$

so that s_T can readily be calculated from the standard deviation and the deviation of the mean from the target value.

The statistic s_T has characteristics that are helpful in the framing of uniformity requirements, and gives the added convenience of using a single statistic to control both the mean and the variation about the mean. Suggestions for its use in uniformity of content specifications have been made by Pocock & Rhodes (1974). These authors refer to the statistic as relative standard deviation. Use of this type of requirement has also been considered by Flann (1974). Uniformity of content requirements which use this statistic resemble those of the U.S.P. in that deviation from target is considered rather than deviation from mean.

Comparisons between the three types of uniformity requirements mentioned above are shown in Figs 1 and 2. In each Fig., curve A corresponds

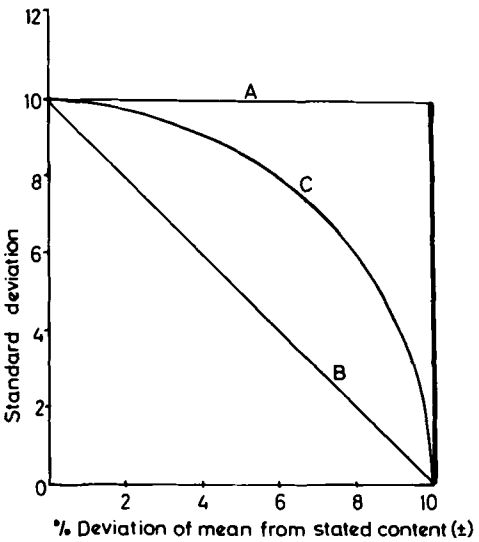

FIG. 1. Variation of permitted standard deviation with deviation of the mean from target. Curve A $|\bar{x} - T| = 10$; $s = 10$. Curve B $|\bar{x} - T| + s = 10$. Curve C $s_T = 10$.

to the case where the mean is restricted to 90–110% of the stated content, and the standard deviation to 10%, that is

$$|x - T| \leqslant 10; s \leqslant 10.$$

This is analogous to the concept used by the B.P.

Curve B corresponds to a requirement that the standard deviation plus the value of the deviation of the mean from target is not more than 10, that is

$$s + |x - T| \leqslant 10$$

This type of requirement is considered to be too restrictive for manufacturing industry.

Curve C corresponds to a requirement that the value of s_T is not more than 10, that is

$$\sqrt{[\Sigma(x - T)^2/n]} \leqslant 10$$

where the sample size is large, so that $(n - 1)/n$ can be considered as unity.

Fig. 1 shows the limit of s when the mean is allowed to vary over the permitted range. In each case, the region below the curve corresponds to the conditions which meet the uniformity of content requirements.

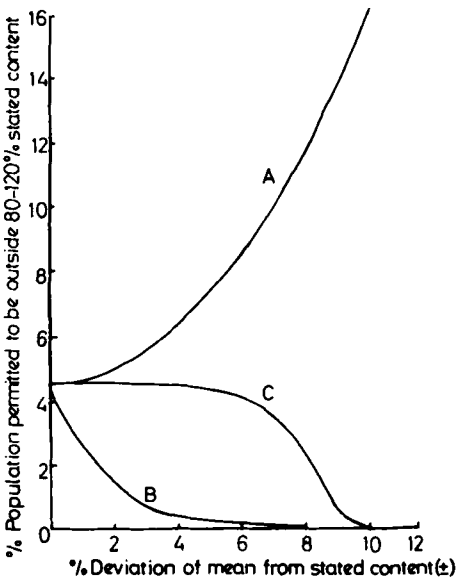

FIG. 2. Variation of percentage of population outside 80–120 per cent of target with deviation of mean from stated content. Curve A $|\bar{x} - T| = 10$; $s = 10$. Curve B $|\bar{x} - T| + s = 10$. Curve C $s_T = 10$.

It is apparent that the statistic s_T produces a characteristic which provides a suitable trade-off between the distance of the mean from the target and the permitted standard deviation. The permitted standard deviation is at a maximum when the mean coincides with the target, and decreases with increasing separation of the mean and the target. Fig. 2 shows the percentages of a population permitted to deviate by more than ±20% from the stated content. As the mean deviates from the stated content the proportion of units permitted to deviate by more than ±20% of the target rises rapidly in case A and falls rapidly in case B. It can be seen that curve C is flatter than the other two and permits a relatively constant proportion of outlying units up to a deviation from target of about

6%, after which the characteristic decreases to zero. It is considered that case C, representing the use of the statistic s_T, offers a suitable compromise between the principles of protecting the consumer and allowing reasonable latitude to the manufacturer.

If a single unit assay of adequate specificity is available, use of a separate bulk assay for potency is unnecessary—the value for potency can be obtained from the mean derived from the potency test for uniformity of content. When this procedure is adopted it is, of course, necessary for the single unit assay to have negligible bias with respect to a conventional bulk assay and be reasonably rapid to perform. The Australian requirement for uniformity of content of digoxin tablets (*Therapeutic Goods Order No.* 1, 1975) is that the value of s_T is not more than 10·0. A sample of 30 tablets is used, and a separate bulk assay for potency is not considered necessary. It is felt that this approach has advantages over those used by the B.P. and the U.S.P. to control uniformity of content of digoxin tablets.

The comparison of the s_T test with pharmacopoeial tests has been made on the assumption that the sample is representative of the whole population. From the data reported by Flann, it would appear that the s_T test also compares favourably with tests by attributes when applied to samples from populations with non-normal distributions. A further discussion of this matter will be presented at a later date.

Implications of the use of the statistic s_T *in uniformity requirements*

In Fig. 1, characteristics B and C reach zero standard deviation when the deviation from target is 10%. In real situations, there will always be a variation about the mean content for any sample of tablets or capsules. This implies that a uniformity of content requirement based on the statistic s_T could result in narrower limits for mean content of active substance than those given in some pharmacopoeial monographs. For example, in the case represented by curve C in Fig. 1, where the limit for s_T is 10, an estimated standard deviation of 5 would give a limit for deviation of the mean from the target of 8·66%, giving effective mean content limits of 91·3 to 108·7% (the linear condition, represented by curve B, would give effective limits of 95–105% if the standard deviation was 5.)

In practical situations, the limits would be rather more lenient because of the relatively small sample size, and the radius of curve C in Fig. 1 would be increased by a factor of $\sqrt{[n/(n-1)]}$. Figs 3 and 4 show uniformity of content data obtained by N.B.S.L. for digoxin and for corticosteroid tablets.

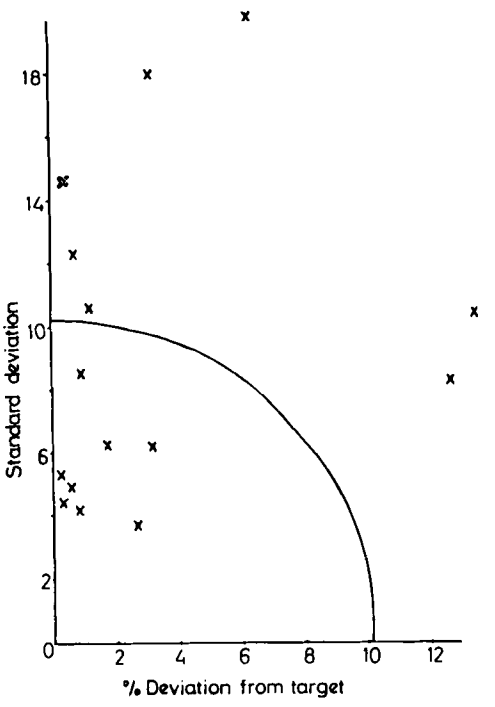

FIG. 3. Uniformity of content data for 15 samples of digoxin tablets.

The assay procedures used had negligible bias with regard to the corresponding bulk assay procedures. In each Fig., the standard deviation of the individual tablet contents is plotted against deviation

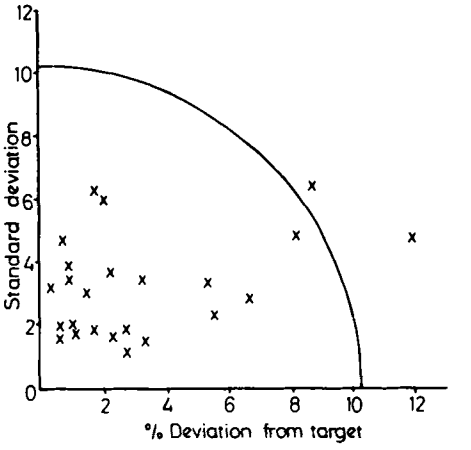

FIG. 4. Uniformity of content data for 25 samples of corticosteroid tablets.

of the mean of these contents from target, each point represents a sample of one brand of tablets, and the continuous curve represents the limit for $s_T = 10$. The value of s_T for a sample is given by the expression 10 AB/AC where AB is the distance from the origin to the data point and AC is the distance from the origin to the limit curve. Fig. 3 presents data obtained from 15 brands of digoxin tablets during the survey of this type of product conducted some years ago by N.B.S.L. In all cases, 100 single tablet assays were carried out. In 5 of the samples which fall outside the limit for s_T the deviation from target is much less than 10% but the samples fail because of the very high standard deviations. Data from those digoxin samples with deviations of mean from target of less than 8% and standard deviations of more than 8% are presented in Table 1. In the Table, comparison has been made between the s_T test and the pharmacopoeial tests with regard to the number of samples rejected. For the purposes of this comparison, the one hundred tablet samples used have been considered in sequences of ten, in the order they were analysed, and the pharmacopoeial criteria applied to each sequence. In the case of the U.S.P. test, sequences of 30 results were considered when one unit in ten was between the inner and outer limits. Sequences of 30 tablets, corresponding to the sample size in the Australian standard, were considered in the case of the s_T test. The worst dose value for each sample and for those sequences from each sample which passed the B.P. test have also been included. The data show that some sequences of tablets passed the B.P. test in all samples. The U.S.P. test rejected three samples completely, with one sequence passing in sample C and 5 and 4 respectively in samples A and B. The s_T test completely rejected four samples, passed two out of three sequences from Sample A and one out of three from sample B.

As would be expected, the number of tablets in each sample with contents differing by more than 30% from the target increased with increasing standard deviation. These data provide some indication of the comparative reliabilities of the different tests as applied to this small group of samples. The B.P. test performed rather badly, the combination of small sample size and independent limits enabling samples with poor uniformity of content to pass the test. It should be noted that the samples considered in Table 1 had mean contents which were well within the B.P. limits of 90 to 110%. Larger numbers of outliers would be expected for tablet lots with deviations from mean which were closer to the B.P. limits. The U.S.P. test was more selective than that of the B.P. and was comparatively severe on sample A because some sequences of 30 tablets contained two tablets with contents of digoxin which were just outside the inner limits. All brands that failed the uniformity of content test in this survey have now been removed from the market.

Fig. 4 presents data on 25 samples of 5 mg corticosteroid tablets (prednisone or prednisolone). In each case, 50 single tablet assays were carried out. Most samples had values of s_T which were much less than 10. Both samples with deviations from target of between 8 and 10% would have passed a test with the limits $|x - T| \leqslant 10$; $s \leqslant 10$. Of these samples, that which passed the s_T test also complied with U.S.P. requirements, while the other failed both the s_T and U.S.P. tests. Overall, both standard deviation and deviation from target made significant contributions to the individual values of s_T for this group of samples.

Ideally, the chance of obtaining a normally distributed sample can be increased by assaying a large number of tablets. In practice, the cost and speed of analysis are important factors and it will not be feasible for a laboratory to assay very large numbers of tablets in uniformity of content tests on a routine basis. A compromise is therefore necessary between the ideality of testing large numbers of units and the realities of laboratory workload.

Table 1. Uniformity of content data for digoxin tablets.

Sample	Mean content, per cent of label claim	s_T (100 units)	No. of sequences of 10 units passing		No. of sequences of 30 units passing s_T test	No. of units with contents > 30% from target	Worst dose passing B.P. test, per cent of target	Worst dose (100 units) per cent of target
			B.P. test	U.S.P. test				
A	101·0	8·58	10	5	2	0	120	120
B	98·8	10·62	8	4	1	1	120	137
C	99·3	12·33	7	1	0	2	124	131
D	99·7	14·79	4	0	0	5	129	149
E	103·1	18·30	3	0	0	8	127	164
F	106·3	20·78	3	0	0	5	129	238

In the Australian requirements for digoxin tablets, a sample size of 30 is used. This is considered to be a reasonable compromise between uncertainty of sample distribution and cost and speed of testing. Future Australian uniformity of content requirements for other types of formulation may specify a smaller sample size. In the case of corticosteroid formulations it seems likely that a sample size of 20 tablets may be appropriate as the increase in reliability would seem not to justify the additional workload in this case. However, reduction of the number of units tested to 10 would produce too great a decrease in reliability. Flann (1974) has drawn attention to the relatively large improvement in reliability obtained in using 20 rather than 10 assays and has illustrated this with the operating characteristic (O.C.) curves for a number of uniformity of content tests. These O.C. curves include three dimensional representations with probability of the sample passing the test plotted against both deviation of the mean from target value and standard deviation. In the case of the test which is equivalent to the use of s_T, Flann quotes estimated reliabilities 32, 58 and 65% respectively for 10, 20 and 30 single unit assays. There is therefore an 81% relative increase in relability in going from 10 to 20 assays but only a further 12% when the number of assays is increased from 20 to 30.

The comparative reliability of a test corresponding to the first part of the U.S.P. test (10 assays, all results within inner limits) is 19% and that of a test corresponding to the second part of the U.S.P. test (30 assays, not more than one result between the inner and outer limits) is 58%. Flann's comparison of earlier pharmacopoeial tests (U.S.P. XVIII and N.F. XIII) gives reliabilities of between 16 and 30% compared with 65% for tests based on measurement of variables. The proposal by Pocock & Rhodes to set appropriate conditions for the use of s_T depending on the nature of the formulation seems reasonable. However, in the case of tablets these conditions will often relate to sample size rather than the limit for s_T. A limiting value for s_T of 10 reflects common pharmacopoeial bulk assay limits in that the maximum permissible deviation from target is 10%.

Flann considers that, ideally, there should be a pharmacological basis for the definition of quality of a batch of a dosage form. Pharmacopoeial and other estimates of batch quality make use of the concept of a percentage of defectives, that is the percentage of dosage units with either weights or contents of active substance falling beyond specified limits. This concept implies that all dosage units falling within the specified range are equally acceptable from the point of view of therapeutic efficacy while those falling outside the limits are all equally unsatisfactory. In reality, variation in content of active substance will be reflected in corresponding variation in blood concentrations and pharmacological response. Flann mentions that this reasoning 'suggests the use of a simple function of the deviation of unit content from label claim as a measure of unit quality and the pooled magnitude as a measure of lot quality'

Use of a requirement which is framed with reference to mean content of active substance and the standard deviation of individual contents has the advantage that both these quantities are familiar and provide suitable descriptive parameters for each batch of a dosage form. Mean blood level (pharmacological effect) will in general be proportional to mean content of active substance in the dosage units and standard deviation of the blood levels will in general be proportional to the standard deviation of the individual contents of active substance.

The information given in this paper illustrates the usefulness of the s_T statistic in setting suitable limits for uniformity of content of pharmaceutical preparations and providing appropriate protection for the consumer. The statistic is based on familiar quantities and gives a test for uniformity of content of greater reliability than current pharmacopoeial tests. Calculation of the statistic is straightforward, given the widespread use of electronic calculators. It seems appropriate to make use of uniformity of content requirements based on the application of this statistic in future standards for Therapeutic Goods.

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