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Content uniformity and assay requirements in current regulations

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Abstract

The acceptance of a tablet batch is based both on the content uniformity test and on the assay. It is shown that these two characteristics are not independent, and the acceptance criteria for them are not even consistent. For content uniformity range three methods of calculation are compared: the present European Pharmacopoeia method, a tolerance range method with improved k tolerance factor and a one-way random effects analysis of variance model. To resolve the inconsistency several options are discussed: applying the holistic content uniformity range alone; using content uniformity standard deviation and assay mean simultaneously or applying a criterion based on Taguchi's quadratic loss function.

Keywords: Content uniformity; Assay; Acceptance criteria; Tolerance range; Pharmacopoeia; Random effects ANOVA; Taguchi's quadratic loss function

1. Introduction

Pharmaceutical products prior to their approval for market authorization are evaluated/tested according to their quality test specification (QTS). Tests, described in the QTS contain physical tests (appearance, average mass, etc.), chemical tests (assay, purity, etc.), and pharmaceutical tests (dissolution, content uniformity). Assay and content uniformity (CU) tests are two major aspects of drug quality assessment, discussed in this paper. Assay value reflects the mean active content in a production batch. The content uniformity test shows the distribution of the active content within the production batch.

While most quality attributes are regulated in the Pharmacopoeias [1,2] and various Guidelines [3], the assay requirements are dictated – at least in Europe – by a European Directive [4]. The European Pharmacopoeia (Ph. Eur.) [1] and the US Pharmacopeia (USP) [2] slightly differ regarding the content uniformity requirements, their harmonization is in progress. The European Pharmacopoeia has introduced a significant change in the calculation of the content uniformity values and in their acceptance criteria in 2005. The US Pharmacopeia has declared that it will apply the new requirements published in the European Pharmacopoeia in early 2007.

This paper enlightens some of the inconsistencies of the assay and CU requirements present in the current European Pharmacopoeia This paper deals with the regulation concerning solid dosage units, mentioned further for brevity mostly as tablets.

2. Current regulations

2.1. Assay

The aim of the assay is to prove that the mean active content of the product batch is close to its label claim. The assay tests are published in the pharmacopoeia monographs (if any) individually. For example, the USP monographs are published for the pharmaceutical dosage forms individually, whereas the European Pharmacopoeia monographs deal with the active pharmaceutical ingredient (API) individually and for the finished dosage forms only general descriptions are available. The assay limits for medicines are defined by law in Europe [4]: at release the maximum acceptable deviation from the label claim shall not exceed ±5%. Interestingly, it is not regulated how the average is made up: neither the number of the tablets representing the population, nor the number of parallel measurements is given.

The US requirements are dictated either in the USP or, if no monograph exists, a draft Food and Drug Administration

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(FDA) Guidance has to be considered. According to the guide the assay value is suggested to be in the ±5% range of label claim on release and in ±10% through shelf-life [3]. Details for the implementation are also not given.

2.2. Content uniformity (CU)

The content uniformity tests are used for proving the uniform distribution of the active content in a production batch. It is performed by measuring the active content of n individual dosage units.

The European Pharmacopoeia had loose criteria for content uniformity till July 1, 2005 [5]. It gave criteria only for the measured individual active contents, no requirements for the average and the standard deviation were given. The number of the random taken dosage units was set to 10, and uniformity was accepted, if the individual values were found to be in the range of 85–115% of the calculated average. If one of the values was outside the 85–115% but within the 75–125% range additional 20 randomly taken dosage units had to be analyzed. If not more than one individual dosage unit of the total 30 was outside the 85–115% and none were outside the 75–125% range, the product met the requirements of the test.

After July 1, 2005 the European Pharmacopoeia introduced a new legislation of the content uniformity [1]. This tolerance interval-based legislation is more complex than the previous versions. An acceptance value is computed and is compared to a permissible limit. The new version is showed in Table 1.

The requirement of content uniformity is fulfilled if the acceptance value (AV) of the first 10 dosage units is less than, or equal to $L1$. If it is greater, then together with the next 20 samples the final AV must be less than, or equal to $L1$ ($n = 30$). The individual contents must be in the range of $(100 - L2)M$ and $(100 + L2)M$. This is superior to the previous version, since it contains *some kind* of expectation for the average and the standard deviation.

Table 1
Calculation of the acceptance value ($AV = |M - \bar{X}| + ks$) according to the current Ph. Eur.

AV	Acceptance value
M	Reference value 98.5% if $\bar{X} < 98.5\%$ $\bar{X}$ if $\bar{X}$ is between 98.5–101.5% 101.5% if $\bar{X} > 101.5\%$
$\bar{X}$	Mean of individual contents
n	Number of samples
k	Acceptability constant (tolerance factor) $k = 2.4$ if $n = 10$ $k = 2.0$ if $n = 30$
s	Sample standard deviation
$L1$	Limit for the acceptance range $L1 = 15$
$L2$	Limit for the individual units $L2 = 25$

The acceptance value (AV) is calculated as the sum of two components, namely the difference of the observed mean and the reference value ($|M - \bar{X}|$) and the width of the tolerance interval (ks). Thus, the decision on accepting/rejecting a batch depends not only on the width of this interval but also on the shift of the mean from the nominal value.

The US requirements are determined in the USP [2]. To ensure the consistency of dosage units, each measured unit in a batch should have an active content within the given range around the label claim. Ten randomly taken units represent the batch. The individual results should be between 85% and 115% of label claim, with a RSD < 6.0%. If one of the samples is out of the 85–115% but is within 75–125% boundaries then additional 20 units must be measured. For the total of the 30 values, the following applies: the individual results should be between 85 and 115% with the RSD < 7.8%, one outlier is permitted, but should be between 75 and 125% of the label claim. USP is planning to adopt the current European Pharmacopoeia regulations.

3. Discussion

3.1. Content uniformity method

The content uniformity is related to the idea of tolerance interval. One may ask what the range is in which the content of most tablets or capsules (e.g. 95% of them) occur at high (e.g. 95%) probability. In other words most of the patients should obtain a dose of the active ingredient not deviating from the label claim more than the specified value (15%). Specifically the β, content tolerance interval with U upper and L lower limits, respectively, should contain at least β part of the population with γ degree of confidence (probability): $P[P[L < x < U] \geq \beta] = \gamma$ [6]. This interval can be obtained from a random sample of the population (measuring the individual content of a certain number of tablets) as $\bar{x} - ks < x < \bar{x} + ks$, where x is the random variable (content of individual tablets), $\bar{x}$ and s are the mean and the standard deviation of the random sample, respectively. The k tolerance factor depends on the degrees of freedom of the s standard deviation, on the β content and γ probability.

This approach assumes a single source of variation, thus would be directly applicable if there were no measurement uncertainties. Unfortunately the content values are accessible only through chemical analysis subject to measurement errors. As the purpose is to calculate tolerance interval for the true active content, the s standard deviation should stand for the variability of the dosage units.

In the content uniformity measurements, however there are two sources of variation: variability of the dosage units (inhomogeneity) and the measurement (analytical) error. The adequate approach for this problem is the one-way random-effects ANOVA (analysis of variance), enabling the separation of the variability sources. The model is $y_{ij} = \mu + \alpha_i + \varepsilon_{ij}$, where y_{ij} is the jth measurement result on the ith dosage unit of the batch, μ the centre of fluctuation, α_i the deviation in the content of the ith dosage unit from the centre (effect of the A random factor) and ε_{ij} is the measurement error in the jth measurement of the ith dosage unit. The estimated variance of the inhomo-

geneity is calculated as $\hat{\sigma}_A^2 = (S_A^2 - S_R^2)/p$, where S_A^2 is the mean square between tablets, S_R^2 is the mean square attributed to the analytical error and p is the number of repeated analyses. This experimental design would require repeated measurements of each dosage unit, which is not typical in content uniformity analysis, thus generally $p = 1$, therefore S_R^2 may not be evaluated. The estimated analytical error variance should be taken from the validation study of the applied analytical method.

Calculation of the tolerance interval in the context of one-way random-effects ANOVA model is not simple. One complication is that the estimated variance of the tablet diversity is calculated as the difference of the mean square variances in the content uniformity test and that of the measurement error, and it does not behave like the squared standard deviation of a simple set of measurements (not distributed as $\chi^2\sigma^2/\nu$). The Satterthwaite-approximation [7] has to be used which leads to non-integer degrees of freedom causing elevated computational difficulties. In addition, because the degrees of freedom depend on the actual values of the standard deviations, it may not be tabulated for general use, but (together with the resulting k tolerance factor) has to be calculated for the actual content uniformity measurement (for the actual combination of observed standard deviation and estimated measurement error). Since the estimated variance of the tablet diversity is calculated as the difference of two mean squares, there is a nonzero probability of finding this difference negative. The second type of complication arises from the two-sided nature of the required tolerance interval, for which there are only approximation methods available here as well.

Based of the comparative study of Wang and Iyer [8] Howe's two-sided tolerance factor approximation [9] has been chosen for our calculations.

3.2. Reconsidering the content uniformity calculations

3.2.1. Computation methods

In order to demonstrate the difference between the interval calculation concepts three different methods have been applied to calculate the width of the tolerance intervals assuming different observed content uniformity standard deviation values and measurement errors.

The first method (method I) is the method proposed by the European Pharmacopoeia content uniformity regulation with k factor of 2.4 and s standard deviation obtained in the content uniformity measurements. This method mathematically assumes a single source of variation, not considering the one-way random factor ANOVA model. Two possible corrections of the European Pharmacopoeia method have been investigated and shown below.

In method II the same concept has been used as in the European Pharmacopoeia, but the value of the k factor is based on statistically more sound consideration. The value of 4.44 has been chosen from the two-sided tolerance interval table [10] for $n = 10$, $\beta = 0.99$ (99% content) and $\gamma = 0.95$ (95% probability). In this method only the tolerance factor has been corrected but still a single source of variation is considered only, therefore measurement error and inhomogeneity cannot be separately assigned.

In method III the correct one-way random effects model based tolerance intervals have been applied. Therefore, the k tolerance factor is not constant; it depends on the actual values of the observed standard deviation of content uniformity and that of measurement error ($n = 10$, $\beta = 0.99$, $\gamma = 0.95$).

3.2.2. Computation results

Table 2 shows the one-sided widths (ks) of the intervals calculated in the above mentioned three different ways, with different variance component values. Total RSD% of the content uniformity test is the relative standard deviation observed (evaluated) from content uniformity measurements, and this is the only standard deviation used for methods I and II. The total RSD% of the content uniformity test reflects the sum of two variances, namely that of the tablet inhomogeneity and analytical error. When applying method III the two variances are separated. The RSD% of the analytical method (used in method III) reflects the fluctuation due to analytical error.

For example if the total RSD% of the content uniformity test is 3%, and the RSD% of the analytical method is 1%, the original European Pharmacopoeia method calculates the range of

Table 2
One-sided widths of the intervals (ks) in percent of label claim

Total RSD% of the content uniformity test	(I) Ph. Eur.	(II) One variance	(III) One-way random model[a] (RSD% of the analytical method)						
	$k = 2.40$	$k = 4.44$	0.25	0.50	1.00	1.50	2.00	2.50	3.00
0.50	1.20	2.22	2.22						
1.00	2.40	4.44	4.44	3.63					
1.50	3.60	6.66	6.67	6.15	4.32				
2.00	4.80	8.88	8.89	8.51	7.27	4.64			
2.50	6.00	11.10	11.11	10.81	9.86	8.07	4.69		
3.00	7.20	13.32	13.33	13.08	12.30	10.90	8.64	6.96	
3.50	8.40	15.54[b]	15.56[b]	15.34[b]	14.68	13.52	11.74	10.54	3.94
4.00	9.60	17.76[b]	17.78[b]	17.59[b]	17.02[b]	16.02[b]	14.54	13.57	9.28
5.00	12.00	22.20[b]	22.22[b]	22.07[b]	21.62[b]	20.84[b]	19.71[b]	19.00[b]	16.13[b]
6.00	14.40	26.64[b]	26.67[b]	26.54[b]	26.16[b]	25.52[b]	24.61[b]	24.03[b]	21.81[b]

[a] The ranges are function of the analytical variability with this method.
[b] Intervals outlying the ±15% range.

tablet contents (around the mean) to be ±7.2%, while the modified European Pharmacopoeia method (method II, with $k = 4.44$) gives a more realistic approximation for the real value of the range (±13.32%), and the proposed new method (method III) proves it to be ±12.30%. The higher the total error the wider the range for methods I and II become. Using method III, the higher the analytical error (provided that the level of inhomogeneity is constant), the narrower the range for the true active content of the tablets is (as the effect of measurement error is subtracted from the experienced total fluctuation).

It can be seen from the results that the European Pharmacopoeia intervals are unreasonably narrow, compared to the intervals with the correct tolerance factor. As the range ($\bar{x} \pm ks$) needs to be within the nominal ±15%, this error can lead to accepting batches where the major proportion of the dosage units is not contained within 85–115% of the label claim. In addition the calculated intervals reflect the variability of the measured contents of the dosage units, not the true active contents.

Results with method II (single source of variation, in fact coupling the two sources in an inappropriate way, but with the correct k factor) are better from compliance aspects. These intervals also reflect the variability of the measured contents of the dosage units, not the true active contents. Thus if the analytical error is large (the analytical error is of similar size to the variability of the tablets), it widens the calculated range beyond the acceptable level leading to the rejection of appropriate products.

The tolerance intervals for the one-way random model (method III) regard both the tablet variability and the analytical error separately. With this method the calculated intervals reflect the true active content of a product batch. As a result, these intervals are wider than those calculated using the original European Pharmacopoeia rule (I), but narrower than the more established modified European Pharmacopoeia (II).

The proposed method is more reliable, as the model is statistically more sound, but in practice may be problematic to use due to computation demand (the tolerance factors is a function of the variability sources). This could be made easy for the manufacturers by supplying tabulated factors covering practically occurring cases.

According to the current European Pharmacopoeia regulation the acceptance value is calculated as the sum of two components, namely the difference of the observed mean and the reference value ($|M - \bar{X}|$) and the width of the tolerance interval (ks). Thus, the decision on accepting/rejecting a batch depends not only on the width of this interval but also on the shift of the mean from the nominal value. Table 3 shows the size of allowable shift for the three different methods.

It can be seen from the results that a significant shift is allowed to occur even with the corrected methods. The smaller the observed content uniformity standard deviation, the larger the shift can be. Using the current Ph. Eur method, the allowed shift can be severe. Method II with the corrected tolerance factor allows smaller deviations from the nominal value. The shift changes with the variance of the analytical error when using the intervals based on the one-way random model (method III). The intervals for the true content of product are narrow due to the separation of the measurement error. The larger measurement error takes larger part in the resulting variability, so the tolerance intervals are narrower increasing the allowed shift of the mean.

For example, if the measured RSD of the content uniformity test is 3.0% then according to the European Pharmacopoeia the calculated width of the content range is ±7.2% (Table 2). As such, the average can still shift from the label claim by 7.8%. If the stricter k factor (4.44) is applied, the calculated width of the content range is ±13.3% and a much smaller, 1.68% shift of the average is possible. Using the one-way random model, the allowed shift varies from 1.67% to 8.04%, depending on the relation of measurement uncertainty to the total variation.

3.3. Doubts in consistency of content uniformity and assay

The acceptance of a tablet batch (among others) is based both on the content uniformity test and on the assay. In the previous section it was shown that these two characteristics are not independent, the shift in mean value (the assay) influences the position of the tolerance range (the content uniformity test result). Therefore, it could be preferable to use two independent (may be mentioned as orthogonal) characteristics.

Table 3
Allowable deviation of the mean from the nominal content (percent of label claim)

Total RSD% of the content uniformity test	(I) Ph. Eur.	(II) One variance	(III) One-way random model[a] (RSD% of the analytical method)						
	$k = 2.40$	$k = 4.44$	0.25	0.50	1.00	1.50	2.00	2.50	3.00
0.50	13.80	12.78	12.78						
1.00	12.60	10.56	10.56	11.37					
1.50	11.40	8.34	8.33	8.85	10.68				
2.00	10.20	6.12	6.11	6.49	7.73	10.36			
2.50	9.00	3.90	3.89	4.19	5.14	6.93	10.31		
3.00	7.80	1.68	1.67	1.92	2.70	4.10	6.36	8.04	
3.50	6.60	0.00	0.00	0.00	0.32	1.48	3.26	4.46	11.06
4.00	5.40	0.00	0.00	0.00	0.00	0.00	0.46	1.43	5.72
5.00	3.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
6.00	0.60	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

[a] The ranges are function of the analytical variability with this method.

In general, an industrial product is of good quality if the fluctuation of its characteristic (e.g. active content in drug products) is small and the average value of the characteristic is close to the nominal value. These are well characterized by two independent parameters of the assumed normal distribution: variance and expected value, namely the variance is preferably small; the expected value should be close to the nominal. The estimates of these two parameters (sample variance and sample mean) are statistically independent variables.

The assay reflects the sample mean in a correct way in the context of independent characteristics. Contrarily the current content uniformity test tries to represent a consolidated index of drug product quality, reflecting both the mean and the variance. These two properties can be verified independently. In that case the fluctuation may be characterised as some kind of interval around the mean characteristic only, without paying attention to the nominal value in the acceptance requirements.

The philosophy behind the present definition of the content uniformity tests is that the authorities want to assure that the consumer will receive a drug product having active content not seriously deviating from the nominal dose value (within 15%). This philosophy makes the check of the mean assay value (shift of the mean content from label claim) unnecessary. In this approach, the shift of the mean content is of no interest, because the patient is affected only by the true active content of the few tablets that she/he takes.

3.4. Proposals for applicable decision criteria

There are several possible solutions for the mentioned problems.

(a) The current content uniformity regulations can be followed, because this holistic approach fully respects the patients' compliance aspect, thus it may serve as a synthetic index of the quality of a drug product alone. The calculation of the tolerance range is to be performed in a statistically sound way (method III), however. In accordance with this approach the assay becomes unnecessary, therefore it can be omitted from the QTS. It is worth mentioning that the requirement of obtaining most of tablets at high probability in the ±15% range is dictated by non-statistical arguments.

(b) There are several cases where the mean of a characteristic and the fluctuation is examined side by side. In other industries where mass product is manufactured (e.g. food, household goods, etc.) both requirements are set independently [11]. The philosophy behind this regulation is fair business in addition to assuring the single customer/consumer. The company is not allowed to deliver product of lower content in average, even if it is able to manufacture it at low fluctuation. Most generally orthogonal characteristics are preferred in decisions. This approach may be useful not only for regulatory purposes, but it helps in quality improvement, because different measures are required if the mean or the variance is

Table 4
Analytical application of the proposed criteria

	Well-controlled product	Products in early stage of development	
		I	II
Parameter			
Average content, $\bar{X}$ (%)	100.50	102.00	103.50
RSD of the content uniformity test (%)	2.00	4.00	5.00
RSD of the analytical method (%)	0.50	2.00	2.50
Decisions with the different criteria			
Current Ph. Eur. method (method I)			
Tolerance factor (k)	2.40	2.40	2.40
Acceptance value (AV)	4.80	10.10	14.00
Decision	Acceptable	Acceptable	Acceptable
Content uniformity method with different tolerance factor (method II)			
Tolerance factor (k)	4.44	4.44	4.44
Acceptance value (AV)	9.38	19.76	25.70
Decision	Acceptable	Unacceptable	Unacceptable
(a) Content uniformity method with revised tolerance factor calculation (method III)			
Tolerance factor (k)	5.67	6.41	7.60
Width of tolerance range	8.51	14.54	19.00
Acceptance value (AV)	9.01	16.54	22.50
Decision	Acceptable	Acceptable	Unacceptable
(b) Orthogonal criteria			
Mean deviation (%)	0.50	2.00	3.50
Width of tolerance range (%)	8.51	14.54	19.00
Decision	Acceptable	Acceptable	Unacceptable
(c) Taguchi's loss function			
Core of the loss function ($\%^2$)	4.25	20.00	37.25
Decision	Acceptable	Acceptable	Unacceptable

found to be improper. If this (orthogonal criteria) approach is followed, requirements are to be set for both in QTS, e.g. the mean value of the assay should not deviate more that 5% of the label claim (preferably demonstrated by two one-sided *t*-test); the $\pm ks$ width of the tolerance range (for instance $n = 10$, $\beta = 0.99$, $\gamma = 0.95$) should not exceed the ±15% limits.

(c) If one wants to express the goodness of the product with a single property, however, Taguchi's quadratic loss function – widely accepted in quality engineering – may be used (see the Appendix A for the explanation of the loss function). In that case requirement is to be specified for the $s^2 + (\bar{x} - T)^2$ core of the loss function, e.g. it should not exceed $36(\%^2)$, which is roughly equivalent to the ±5% (assay), ±15% (content uniformity range) criterion in option (b).

3.5. Example of analytical application of the proposed criteria

The slightly different characteristics of the proposed decision criteria are presented on hypothetical examples based on practically occurring content uniformity and assay data using HPLC measurement methods. In Table 4 three different hypothetical products are shown, a well-controlled and two products in early stage of development. The table contains the measured parameters and the decisions arrived at using the different criteria. The first three blocks of the table show the different tolerance interval calculation methods for the content uniformity approach (methods I–III). According to regulation, in order to accept the batch, the acceptance value must be less than or equal to 15. The batch in the third column is not accepted by methods II and III. With the orthogonal criteria (b) the requirements are set side by side for the mean (±5%) and the tolerance range (±15%). These values are derived from the current regulatory conventions. The criterion based on Taguchi's loss function uses the limit $36\%^2$ for the core of the loss function, again derived from the convention. The different decision characteristics can be seen in the table, the content uniformity approach with the statistically correct tolerance range calculation (a) is stricter than method (b) or (c). The tolerance range calculation method II is even more restrictive.

With these settings (±5% for assay and ±15% for the tolerance range, $36\%^2$ for the core of the loss function) the orthogonal decision criteria (b) and Taguchi's loss function (c) are not strict enough compared to the holistic approach (a) thus fine tuning of the acceptability parameters is required.

4. Conclusion

The European Pharmacopoeia (and in the future the US Pharmacopeia as well) criteria on the assay and content uniformity test have to be satisfied to accept a batch. The current content uniformity criterion is of holistic nature. It reflects both the extent of fluctuation and the deviation of the mean from the label claim, and fully respects the patients' compliance aspect. Its statistical background is not well defined, however.

We argue for consistent use of criteria. One option is the application of content uniformity criterion alone (without the assay requirement). It could be more preferable for the development or control of the manufacturing process to use two statistically independent criteria, one for the mean (assay) value and another one for the extent of variation (inhomogeneity). The two statistically independent criteria may be synthesized in a novel way as well (Taguchi's loss function).

The calculation of tolerance range for content uniformity criterion is in flaw. The proper model would be the one-way random effects model, which explicitly considers two sources of variation (inhomogeneity and measurement error). If this model is considered too demanding, an acceptable alternative approximate solution can be used. This is similar to the current official method assuming a single source of variation by merging the two sources, but the *k* tolerance factor calculation method has to be improved, resulting in a value of 4.44.

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Appendix A. Taguchi's loss function

If y is the quality characteristic of interest, the loss (expressed in financial categories due to quality deficiency) for an actual part (tablet in our context) is expressed as

$$L(y) = k(y - T)^2$$

where T is the target value (label claim in our context) according to Taguchi [12]. For the population the expected loss is calculated as

$$E[L(y)] = k[\sigma^2 + (\mu - T)^2]$$

where σ^2 is the variance, μ is the expected value (centre of fluctuation). From the sample (assay and content uniformity measurements) the expected loss is estimated as

$$\bar{L} = k[s^2 + (\bar{x} - T)^2]$$

The expected loss reflects both the extent of variation and the mean value shift in a single function. While the expression itself is qualitatively obvious (if either the extent of variation or the mean shift is increased, the quality is suffered), its additional feature is that is it gives useful and interpretable quantity, giving the financial loss due to quality. For that the k value is to be assigned as loss for unit deviation to $(y - T)$, in our context for a unit deviation in content.

This k value (with a different meaning to the tolerance factor used in the main body of the paper) may not be relevant for the decision criterion on accepting/rejecting a tablet batch, the term in square brackets (core) is sufficient.

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