Enquiry

Demonstration of Uniformity of Dosage Units using Large Sample Sizes

Proposal for a new general chapter in the European Pharmacopoeia

In order to take advantage of increased batch control offered by process analytical technology (PAT) tools, for example large sample sizes used for the control of uniformity of dosage units, a new Ph. Eur. general chapter 2.9.47. Demonstration of uniformity of dosage units using large sample sizes is proposed (see ***PA/PH/Exp. PAT/T (11) 1 ANP****, below).*

The scientific considerations of the Ph. Eur. PAT Working Party are published in the annex in the form of a scientific article submitted by the rapporteurs for the project.

Please take account of the notice at the start of the section Draft monographs and general texts for comment, on page 297 of this issue of Pharmeuropa.

Comments on the proposed general chapter 2.9.47 should be submitted by 30 June 2011.

Reference: PA/PH/EXP. PAT/T (11) 1 ANP

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2.9.47. DEMONSTRATION OF UNIFORMITY OF DOSAGE UNITS USING LARGE SAMPLE SIZES

Compliance with general chapter *2.9.40. Uniformity of dosage units* can be demonstrated with the following procedures when the determination is performed on a large sample size ($n > 30$).

Option I (parametric)

SAMPLING PROCEDURE

The consistency of dosage units is evaluated by content uniformity or mass variation as prescribed in Table 2.9.40.-1. Calculate the acceptance value (*AV*) using the formula and definitions presented in general chapter *2.9.40*. Use the acceptability constant (*k*) defined in Table 2.9.47.-1.

Table 2.9.47.-1. – *Acceptability constant applicable to large samples*

Sample size *(n)*	**Acceptability constant *(k)***
≥ 50	1.91
≥ 75	1.87
≥ 100	1.84
≥ 150	1.81
≥ 200	1.79
≥ 300	1.77
≥ 500	1.75
≥ 1000	1.73
≥ 2000	1.72
≥ 5000	1.71
≥ 10 000	1.70

CRITERIA

Apply the following criteria, unless otherwise specified.

The requirements for dosage form uniformity are met if:

(1) the acceptance value (*AV*) is less than or equal to $L1$; and

(2) in the calculation of acceptance value (*AV*) under content uniformity or under mass variation, the number of individual dosage units (*c2*) with a content less than $(1 - L2 \times 0.01)M$ or more than $(1 + L2 \times 0.01)M$ is within the limit defined in Table 2.9.47.-2.

Table 2.9.47.-2. – *Acceptable number of dosage units (c2) with a content less than (1 - L2 × 0.01)M or more than (1 + L2 × 0.01)M*

n	< 500	≥ 500	≥ 1000	≥ 2000	≥ 5000	≥ 10 000
c2	0	1	2	6	16	34

Option II (non-parametric)

SAMPLING PROCEDURE

The consistency of dosage units is evaluated by content uniformity or mass variation as prescribed in Table 2.9.40.-1. Assay or weigh the units individually. Count the number of units outside the targets $T \pm L1$ (= *c1*) and $T \pm L2$ (= *c2*) respectively, and evaluate if *c1* and *c2* are within the limits that are defined in Table 2.9.47.-3.

Unless otherwise specified, $L1$ is 15.0 and $L2$ is 25.0.

Table 2.9.47.-3. – *Acceptable number of dosage units outside T ± L1 (= c1) and T ± L2 (= c2) for a given sample size n.*

n	≥ 35	≥ 60	≥ 80	≥ 100	≥ 120	≥ 150	≥ 200
c1	1	2	3	4	5	6	8
c2	0	0	0	0	0	0	0

n	≥ 300	≥ 500	≥ 1000	≥ 2000	≥ 5000	≥ 10 000
c1	13	23	47	95	239	479
c2	0	1	2	6	16	34

Annex

Evaluation of Uniformity of Dosage Units using Large Sample Sizes

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ABSTRACT

Recent developments in analytical technology have made possible the fast determination of unit content in a large number of dosage units from a batch using non-destructive analytical methods. These measurement techniques are often referred to as Process Analytical Technology (PAT). Using such methodology, a better understanding of the manufacturing process and a closer control of the drug product is obtained, as compared with the use of traditional analytical methods. The increased process control that is achieved by PAT is attractive both from the patient's point of view (improved product quality) and from the industry's point of view (increased production efficacy, less batch rejection).

Acceptable batch quality is demonstrated by compliance with the drug product specification. Usually, several of the tests of a specification refer to pharmacopoeial test methodologies and acceptance criteria. One such test is the harmonised Ph. Eur. general chapter 2.9.40. Uniformity of dosage units (UDU). To take full advantage of the increased batch control that is gained by PAT in general and a large sample size in particular, it should be legitimate to demonstrate batch compliance with UDU using other acceptance criteria than those applicable to small samples (n = 30). In this paper, a proposal for two new sets of test criteria is presented, applicable to sample sizes larger than 30. The proposal is intended for PAT applications, but is applicable also to traditional analytical methods. The test criteria would be stand-alone alternatives to the current criteria, and it would not be acceptable to re-evaluate a batch against these criteria if it already failed the UDU test for n = 30. The sampling plan has to be pre-defined and the sample should be representative of the batch.

1. INTRODUCTION

To ensure the consistency of dosage units, each unit in a batch should have an active substance content within a narrow range around the label claim [1]. Ph. Eur. general chapter *2.9.40. Uniformity of dosage units* (UDU) is the recommended test to demonstrate this critical property in a batch of drug product. The general chapter was introduced in Supplement 5.2 of the Ph. Eur., and is harmonised with the USP and JP. The earlier Ph. Eur. general chapters *2.9.5. Uniformity of mass of single-dose preparations* and *2.9.6 Uniformity of content of single-dose preparations* (content uniformity, CU) are still applicable to existing drug products that were approved before the introduction of UDU. UDU is considered superior to CU in that acceptable and non-acceptable batches, respectively, are more precisely judged using the more recent method. The performance of the old and the new general chapters has been discussed by Limberg and Savsek [2].

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It is acknowledged that the evaluation of a small sample will only provide an estimate of the batch quality. There is always a small risk that a highly variable batch would pass the UDU test and be released. Likewise, there is always a risk that a good quality batch would fail the UDU test and be rejected. Increasing the sample size leads to a more precise estimate of the batch variability.

Recently, concern has been raised that the UDU requirements may discourage the use of modern analytical techniques that are fast and non-destructive, often referred to as Process Analytical Technology (PAT) [3-7]. With certain PAT methods, much larger sample sizes are obtained compared to traditional analytical methods. The increased process control that may be achieved when using PAT is attractive both from the patient's point of view (improved product quality) and from the industry's point of view (increased production efficacy, less batch rejection). It is therefore unfortunate that a pharmacopoeial requirement may be regarded as a disincentive to the implementation of such analytical methods.

The main concern with the UDU test when applied to large samples is the requirement that no single result of the test sample is outside $\pm L2$ % of the reference value M ('sample average'; for a precise definition of M, refer to Ph. Eur. general chapter *2.9.40*; $L2 = 25.0$, unless otherwise specified). Such an absolute requirement is included in both the CU and the UDU tests. The requirement was established to disclose batches with largely deviating units, even if the sample mean and the overall sample variance are acceptable. This 'safety net' does not assume normal distribution in the sample or in the batch, and it seems reasonable enough not to allow any largely deviating units in a small sample. In our test proposal, a small number of largely deviating units is allowed for large sample sizes.

Another concern with the UDU test is that the improved precision of the batch estimate as a direct result of increasing the sample size beyond $n = 30$ is not taken into account in the evaluation criteria. The UDU test already applies a smaller acceptability constant k to the larger sample size ($k = 2.4$ when $n = 10$; $k = 2.0$ when $n = 30$). Thus, a larger sample standard deviation s is allowed in the calculation of the acceptance value AV when evaluating the larger sample size, provided that sample mean is the same in both samples. In the smaller sample, it is acknowledged that the provided estimate is poor, and a greater security margin is needed to evaluate if the batch is acceptable. In the present proposal for interpretation of the UDU test when applied to large samples, this principle is continued as the sample size increases beyond 30 units.

2. MATERIALS AND METHODS

The test characteristics of the UDU test were analysed in order to establish new test criteria for larger sample sizes. The test characteristics were analysed separately with respect to the calculation of the acceptance value *AV* and the requirement that no single unit is outside ± *L*2 % of the reference value *M*. The new proposals were evaluated by Monte-Carlo simulation of a selection of sample sizes from a selection of batches with relevant properties (normal, bimodal or long-tailed distributions).

2.1. The calculation of the acceptability constant *k*

Calculation of the acceptability constant *k* involves the probability that a given proportion of the batch complies with a specified range (± *L*1) around the batch average. The statistical parameter is dependent on the sample size, but it is independent of the sample size relative to the batch size, provided that the batch size is still much larger than the sample size. It is however assumed that the sample is representative for the entire batch.

In UDU testing, the required proportion of a batch (coverage, fraction, β) that is within a specified range around the target is determined with a suitable level of probability (confidence level, γ). Assuming that the batch is normally distributed, the prescribed UDU acceptability constants $k = 2.4$ ($n = 10$) and $k = 2.0$ ($n = 30$) imply $\gamma = 84$ % and $\beta = 91$ %. For each sample size, other combinations of γ and β would return *k* values of 2.4 and 2.0, respectively, but $\gamma = 84$ % and $\beta = 91$ % is the only combination that returns both $k = 2.4$ ($n = 10$) and $k = 2.0$ ($n = 30$). Still assuming that the batch is normally distributed, acceptability constants *k* can be calculated for various sample sizes *n* by adopting $\gamma = 0.84$ and $\beta = 0.91$:

$$k(n,\beta,\gamma) = Z_{(1-\beta)/2}\sqrt{\frac{n-1/n}{\chi^2_{\gamma,n-1}}}$$

where $Z_{(1-\beta)/2}$ is the critical value of the normal distribution and $\chi^2_{\gamma,\,n-1}$ is the critical value of the chi-square distribution with *n-1* degrees of freedom [8].

When applying $\beta = 0.91$ and $\gamma = 0.84$, k_∞ converges towards 1.6943 as the sample size *n* approaches the batch size. In practice, this implies that when the batch mean is on target ($M = \bar{X}$) and *L*1 = 15.0, then the acceptable variability according to UDU, expressed as % RSD (σ), is given by: $AV = L1 = k{\cdot}s \Rightarrow \sigma = L1/k_\infty = 15.0/1.6943 = 8.85$ %. As the sample size decreases, a greater safety margin is required to accept the batch based on the sample variability. Calculated *k* for a selection of *n* is presented in Table 1 in section 3.1 below.

2.2. The evaluation of largely deviating units

2.2.1. Acceptance criteria based on the characteristics of the UDU test

For the purpose of detecting the presence of largely deviating units, a non-parametric test is proposed. Following Sandell *et al.* [3], it is possible to calculate the fraction of units outside ± *L*2 % of the reference value *M* for a batch that has a 50 % probability to pass the current UDU test. The probability that all 30 units comply with the requirement is given by $P = (1 - f)^{30}$, where *f* is the proportion of the batch that is outside $M \pm L2$. Equating *P* with 0.5 results in $f = 0.02284$. In other words, in a borderline batch where the proportion of units outside ± *L*2 % of *M* is 2.284 %, there is a 50 % probability to pass the UDU test with respect to largely deviating units in the sample. In the following, the transition point of a test is defined as the fraction of largely deviating units corresponding to 50 % probability of passing the test. It is assumed that the number of units outside ± *L*2 % of *M* in a sample is binomially distributed: $Y \sim \text{Bin}(n, p)$ (sample size *n*, $p = 0.02284$). Note, however, that no specific assumption is required regarding the distribution of individual dosage units within a batch. Assuming that 2.284 % is the proper acceptability transition point, from the viewpoint of quality, the acceptable number of non-compliant units *c2* for a given sample size *n* has been calculated. These results are presented in Table 2 in section 3.2 below. For each sample size n, the cumulative binomial distribution $P(Y \le c2; n, p)$ defines the largest integer *c2* that corresponds to a probability to accept of $P \le 0.5$. An example of the calculation is presented in Figure 1 for sample sizes $n = 250$ and $n = 1000$. From the cumulative distributions it is evident that a 250 or 1000 units sample with 5 and 22 largely deviating units, respectively, would fail the current test criterion for largely deviating units with a probability of slightly less than 50 % ($P \approx 49$), whereas a sample with 6 and 23 largely deviating units, respectively, would fail the test with a probability greater than 50 % (approximately 65 and 57 %, respectively). Consequently, 5 and 22 largely deviating units, respectively, should be acceptable in a 250 or 1000 units sample if the alternative tests should be equally stringent for a borderline batch.

2.2.2. Alternative acceptance criteria with stricter conditions of acceptance

From the clinical efficacy and safety point of view, it may not seem reasonable to allow a batch to contain as much as 2.284 % of units with more than 125 % or less than 75 % of target (when *L*2 = 25.0). Assuming the cut-off is redefined at a point where the current probability to release a batch is $P = 0.75$, then the calculation above yields $f = 9.544{\cdot}10^{-3}$, i.e. 0.954 % of the batch is outside the range. Similarly, a cut-off corresponding to $P = 0.9$ would yield $f = 3.506{\cdot}10^{-3}$, i.e. 0.351 % of the batch is outside the range. The corresponding acceptable number of largely deviating units, *c2*, for a selection of sample size *n* is presented in Tables 3 and 4 in section 3.2 below.

2.3. Alternative to the calculation of an acceptance value: non-parametric test

Reference is made to Sandell *et al.* [3], where a detailed description of this approach is provided. In a batch that has a 50 % probability to pass the UDU test (the indifference point, transition point), the proportion of units within the acceptable range ± *L*1 around target (coverage) is 95.2 %. The number of units outside target (*Y*) in a sample is binomially distributed: $Y \sim \text{Bin}(n, p)$, where *n* is sample size and $p = (1 - 95.2\ \%) = 0.048$. Still assuming the transition point at the coverage of 95.2 %, the acceptable number of non-compliant units *c1* for a given sample size *n* has been calculated. For each sample size n, the cumulative binomial distribution $P(Y \le c1; n, p)$ defines the highest integer *c1* that corresponds to a probability to accept of $P \le 0.5$.

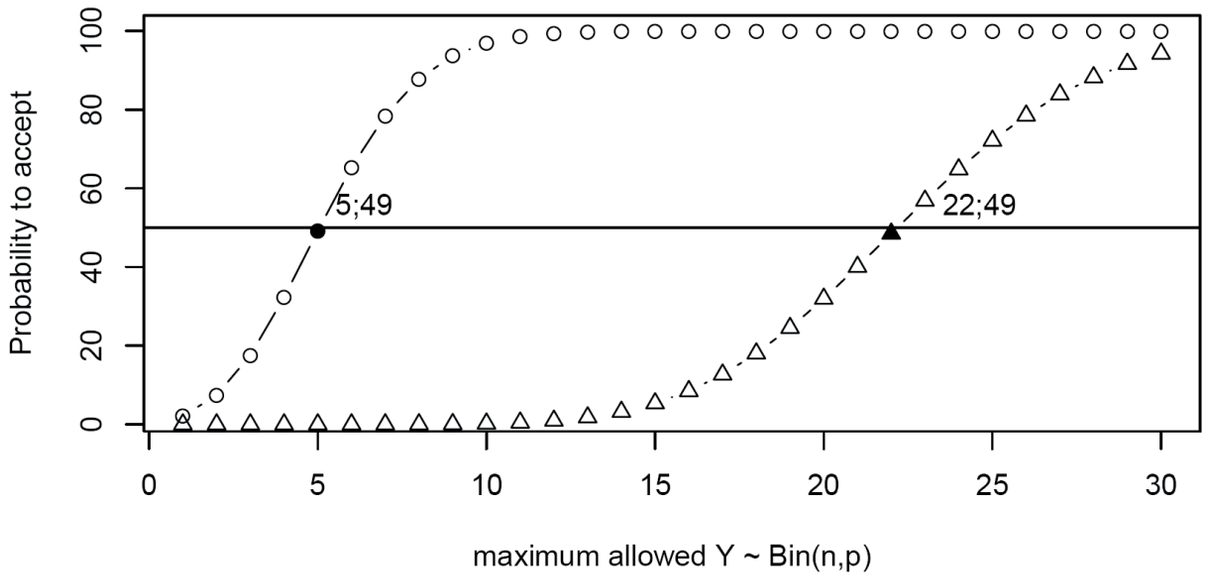

Figure 1 – *Example calculation of c2 for n = 250 (circles) and n = 1 000 (triangles). p = 0.02284. The numbers adjacent to the filled points represent the maximum allowed deviating units and the corresponding probability to accept (≤ 50 %).*

Calculated *c1* for a selection of *n* is presented in Table 5 in section 3.3 below.

2.4. Monte-Carlo simulations

The operating characteristic curve (OC curve) for a test demonstrates how the probability to pass the test decreases as the batch variability increases. OC curves for several alternative tests and sample sizes were calculated by a Monte-Carlo simulation. A representative and illustrative selection of OC curves is presented in section 3.4 below to illustrate the performance of the different test methodologies that are discussed in this paper.

In principle, for a specific batch distribution an explicit formula could be provided to calculate this probability. Nevertheless, a direct Monte-Carlo simulation is more robust and versatile in this respect, allowing the straightforward evaluation of any desired batch distribution that is subjected to a certain set of test conditions.

In this procedure, first, a batch distribution is specified. The distribution can be arbitrarily complex, e.g. a mixture of different distributions. Then, a prescribed number of units are randomly generated according to the specified distribution. This randomly generated sample is tested according to the chosen criteria. The cycle of random sample generation and testing is repeated many times (e.g. 10 000 times). Finally, the probability for a batch with such distribution to pass the test is then estimated as the ratio of the total number of cases where the random sample passed the test, to the total number of simulations.

The simulations were performed within the R software environment for statistical computing [9]. Actual source code used will be available upon request.

3. RESULTS AND DISCUSSION

3.1. The calculation of the acceptability constant *k*

The required proportion of a batch that is within a specified range around the batch average (or target) could easily generate lengthy discussions among industry and the authorities. What proportion of the batch (coverage, fraction, β) should fall within the acceptable range, and what is a suitable level of probability (confidence level, γ) that the estimate provided by the sample is actually the true batch property? Such discussions are outside the scope of this paper. The authors assume that the test properties (β, γ) that are true for the UDU test should be the same regardless of sample size. Calculated *k* for a selection of *n* is presented in Table 1.

Table 1 – *Acceptability constant k applicable to large samples*

Sample size, *n*	**Acceptability constant, *k***
≥ 50	1.91
≥ 75	1.87
≥ 100	1.84
≥ 150	1.81
≥ 200	1.79
≥ 300	1.77
≥ 500	1.75
≥ 1000	1.73
≥ 2000	1.72
≥ 5000	1.71
≥ 10 000	1.70

3.2. The evaluation of largely deviating units

The purpose of this requirement is first and foremost to disclose largely deviating units in a batch that is not normally distributed, possibly indicating poor process control. Even in a normally distributed batch, however, there is a small proportion of largely deviating units. When the sample size increases, there is an increasing risk that largely deviating units are included in the sample even for good quality batches. Therefore, the acceptable number of largely deviating units, *c2*, should reflect the sample size.

Table 2 – *Acceptable number of dosage units, c2, with a content less than (1 - L2 × 0.01)M or more than (1 + L2 × 0.01)M, in samples from a batch that has a 50 % probability to pass the current criteria for n = 30 in Ph. Eur. general chapter 2.9.40.*

n (exact)	< 75	≥ 75	≥ 117	≥ 161	≥ 292	≥ 467	≥ 993	≥ 2000	≥ 4997	≥ 9992
n (rounded)	< 75	≥ 75	≥ 150	≥ 200	≥ 300	≥ 500	≥ 1000	≥ 2000	≥ 5000	≥ 10 000
c2	0	1	2	4	6	10	22	45	113	227

Table 3 – *c2 when the transition point is set at where the current probability to release a batch is 75 %.*

n (exact)	< 176	≥ 176	≥ 280	≥ 490	≥ 908	≥ 1956	≥ 4995	≥ 9919
n (rounded)	< 200	≥ 200	≥ 300	≥ 500	≥ 1000	≥ 2000	≥ 5000	≥ 10 000
c2	0	1	2	4	8	18	47	94

Table 4 – *c2 when the transition point is set at where the current probability to release a batch is 90 %.*

n (exact)	< 479	≥ 479	≥ 763	≥ 1903	≥ 4754	≥ 9888
n (rounded)	< 500	≥ 500	≥ 1000	≥ 2000	≥ 5000	≥ 10 000
c2	0	1	2	6	16	34

Calculated *c2* for a selection of *n* is presented in Table 2. The various *n* have been rounded in order to establish suitable sets of acceptance criteria (*AV* + *c2*, or *c1* + *c2* in section 3.3 below). Although the rounding introduces a small error compared to the calculated *n*, the use of the exact *n* with three or four significant numbers would leave the impression of a clear statistical basis for the criteria. It is explained in the Introduction that this is not the truth.

Alternative acceptance criteria *c2* for largely deviating units that, within UDU, correspond to borderline batch acceptance probabilities of 75 % and 90 %, respectively, are presented in Tables 3 and 4. It should be recognised that this would represent a tightening of the requirement as compared to UDU. Reference is made to the discussion in section 2.2.2 above.

3.3. Alternative to the calculation of an acceptance value: non-parametric test

In the alternative test procedure, there is an acceptable number of units *c1* for a given sample size *n* that fall outside the established acceptable range around target. Compared to the original test that was proposed by Sandell *et al.* [3], two changes are however proposed: 1) the test is applicable to all sample sizes $n > 30$, whereas it was initially intended for samples sizes $n \geq 100$ only; and 2) a second test criterion is included to disclose batches with too many largely deviating units. The value of the second test criterion is discussed in section 3.2 above. The proposed test criteria for the largely deviating units are the same as those presented in Table 4 in section 3.2 above. In the test, the assay (or weight) of individual units is determined. The number of units outside target $T \pm L1$ (= *c1*) and $T \pm L2$ (= *c2*), respectively, is counted, and the batch is accepted if *c1* and *c2* are within the limits that are defined in Table 5.

3.4. Comparison of the operating characteristics of the current acceptance criteria and the proposed criteria

Typical examples of batch distributions that have been simulated in order to compare the performance of different test criteria are illustrated in Figure 2.

3.4.1. Normally distributed batches

OC curves for normally distributed batches with varying content uniformity, expressed as relative standard deviation, are presented in Figure 3. Each of the batches has been evaluated on increasing sample sizes by three sets of acceptance criteria: in the top panel, the current UDU is compared with the criteria of Tables 1 and 2; in the middle panel, the current UDU is compared with the criteria of Table 1 and the stricter criteria for largely deviating units of Table 4; in the lower panel, the current UDU is compared with the non-parametric test criteria of Table 5. It is evident that the larger the sample size, the more precise is the estimation of the batch variability. This is illustrated by a steeper OC curve. In other words, for a batch with acceptable variability, the probability to pass the test would increase as the sample size increases. Conversely, for a batch with unacceptable variability, the probability to

Table 5 – *Acceptable number of dosage units outside T ± L1 (= c1) and T ± L2 (= c2) for a given sample size n.*

n (exact)	≥ 35	≥ 56	≥ 77	≥ 97	≥ 118	≥ 139	≥ 181	≥ 285	≥ 493	≥ 993	≥ 1993	≥ 4993	≥ 9993
n (rounded)	≥ 35	≥ 60	≥ 80	≥ 100	≥ 120	≥ 150	≥ 200	≥ 300	≥ 500	≥ 1000	≥ 2000	≥ 5000	≥ 10 000
c1	1	2	3	4	5	6	8	13	23	47	95	239	479
c2	0	0	0	0	0	0	0	0	1	2	6	16	34

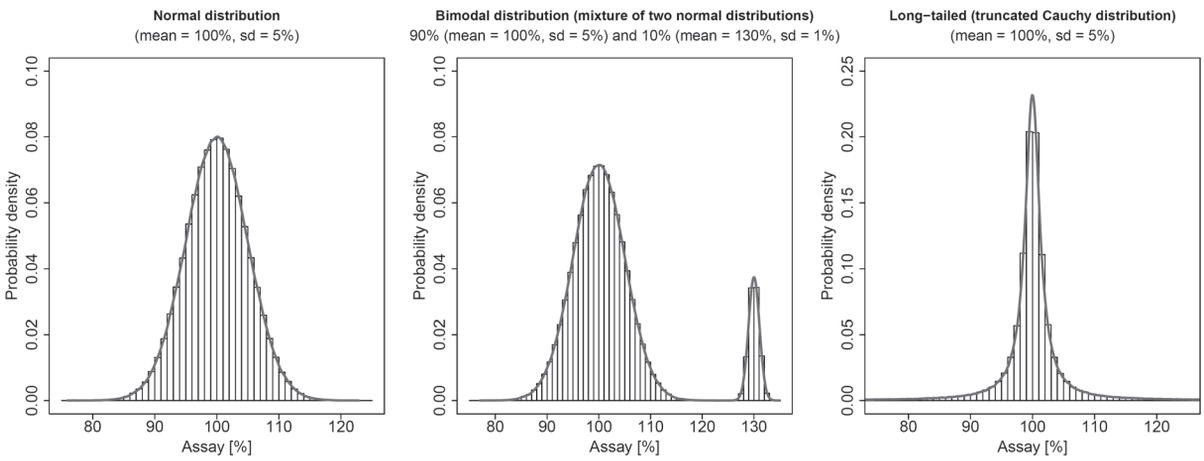

Figure 2 – *Typical example of normal distribution (left), bimodal distribution (middle) and long-tailed Cauchy distribution (right).*

pass the test would decrease as the sample size increases. It was explained in section 2.1 above, that an on-target batch variability resulting in a RSD of 8.85 % is considered acceptable, according to UDU. Less variability is accepted in batches with off-target mean, but this is not illustrated by the selection of OC curves below. From the middle panel, it is evident that for a normally distributed batch, the *AV* alone is in large responsible for the sample evaluation. However, even in the normally distributed batch, there is a certain proportion of largely deviating units, resulting in a slightly lower probability to pass the test when the more stringent criterion for largely deviating units in Table 4 is applied. From the lower panel, the general picture of the sample size and precision of the estimation of the batch is the same, but the test criteria are somewhat stricter than the acceptance values of Table 1. This could be explained by the different sets of coverage and confidence level that was used in the establishment of the two alternative tests, discussed in sections 2.1 and 2.3 above.

3.4.2. Bimodal batches

OC curves for bimodal batches are presented in Figures 4 and 5. The greater part of the batch is on target (mean = 100 %, RSD = 5 %), but there is a certain proportion of largely deviating units (mean = 130 %, RSD = 1 %). Increasing proportions from 0 to 15 % of largely deviating units are represented in the figures by the abscissa of the OC curve. In Figure 4, each of the batches has been evaluated by the acceptance criteria of the current UDU and the criteria that are described for increasing sample sizes in Tables 1 and 2. The figure demonstrates that the proposed acceptance criteria are much more stringent than the current UDU with respect to disclosing bimodal batches with a significant proportion of largely deviating units. In Figure 5, the increasingly stringent test criteria that are presented in Table 1 and in Tables 2 to 4, and the *AV* criterion alone (Table 1), are compared. It is evident that the bimodal batches are exposed by the alternative criteria for largely deviating units.

3.4.3. Long-tailed distributions

OC curves for batches with a long-tailed Cauchy distribution are presented in Figure 6. Batch variability is represented by increasing standard deviation along the abscissa. Each of the batches has been evaluated by the acceptance criteria that are described in Table 1 and Tables 2 to 4, respectively. The figure demonstrates that a smaller standard deviation is allowed in a batch with a long-tailed distribution compared to a normally distributed batch, due to the greater proportion of largely deviating units in the long-tailed batch (compare to Figure 3 above). Thus, the acceptance value *AV* alone is not suitable to disclose such batches, having an unacceptable proportion of largely deviating units.

4. CONCLUSION

The two alternative UDU tests proposed here should resolve the problems that have been addressed regarding the applicability of the harmonised UDU test when applied to large sample sizes. Moreover, the proposed test criteria are at least equally stringent as the requirements of Ph. Eur. general chapter *2.9.40*. In the light of the improved process control that can be achieved when using PAT methodology, the acceptance criteria for largely deviating units presented in Table 4 are proposed, although this would represent a narrowing of the acceptance criteria of the UDU test for sample size $n = 30$. Although the proposed test originally has been motivated by PAT applications, it is applicable also to traditional analytical methods. As Ph. Eur. general chapter *2.9.40* has been harmonised within the Pharmacopoeial Discussion Group (PDG), it is not proposed to change the existing chapter *2.9.40*. Instead, it is proposed to publish a separate general chapter in the Ph. Eur. to provide guidance on how to interpret the requirements of Ph. Eur. general chapter *2.9.40* when the sample size is larger than 30 (see draft general chapter *2.9.47. Demonstration of uniformity of dosage units using large sample sizes*). Depending on the analytical methodology and sample size available, and the purpose of the analysis (e.g. market surveillance on a limited number of samples available or batch release), uniformity of dosage units could be evaluated by a pre-selected set of test criteria: the current criteria for $n = 30$, or any of the proposed criteria for larger sample sizes.

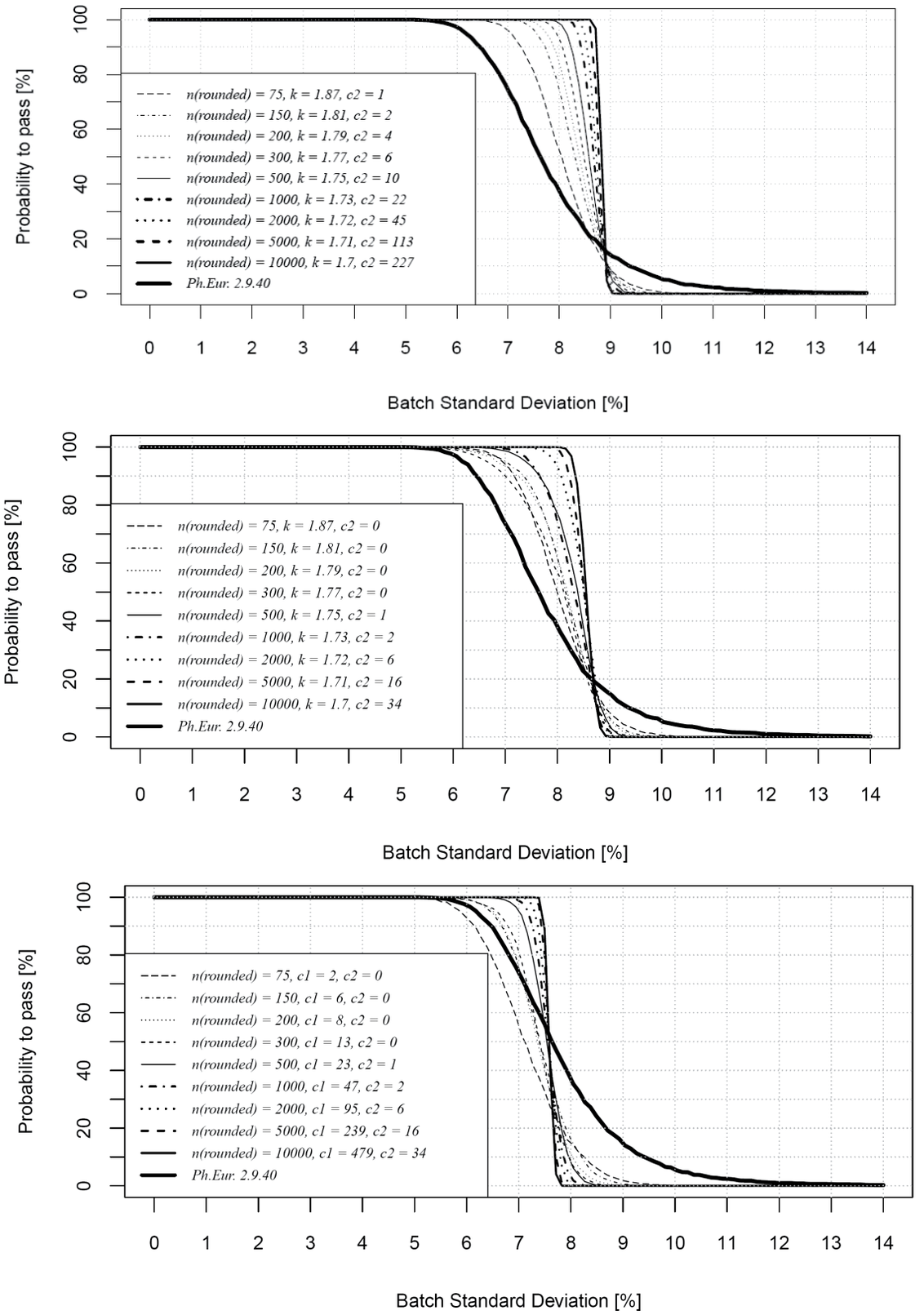

Figure 3 – *Operating characteristic curves for normally distributed batches with varying content uniformity, expressed as relative standard deviation. Top panel: The batches were evaluated by the acceptance criteria of the current UDU and the criteria that are described for increasing sample sizes in Tables 1 and 2. Middle panel: The batches were evaluated by the acceptance criteria of the current UDU and the criteria that are described for increasing sample sizes in Tables 1 and 4 (corresponding to the proposed Option I). Lower panel: The batches were evaluated by the acceptance criteria of the current UDU and the criteria that are described for increasing sample sizes in Table 5 (corresponding to the proposed Option II).*

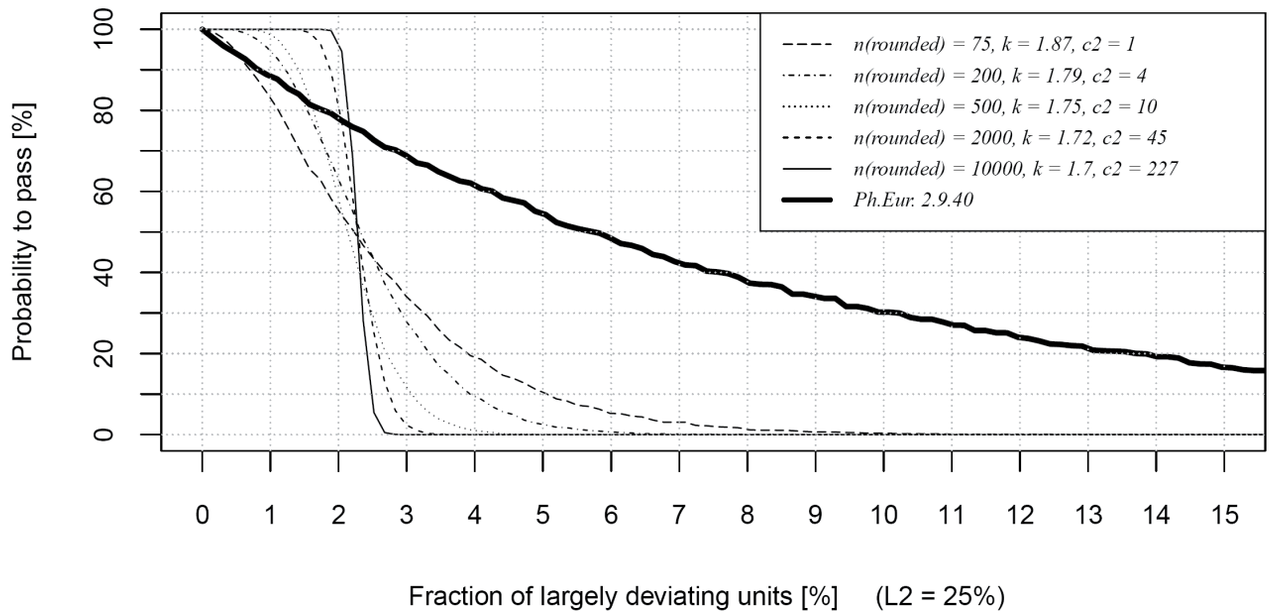

Figure 4 – *Operating characteristic curves for bimodal batches with varying proportion of largely deviating units. The batches were evaluated by the acceptance criteria of the current UDU and the criteria that are described for increasing sample sizes in Tables 1 and 2. Note that such batches have a high probability to yield an AV < L1 and pass the current UDU, possibly testing 10 units only.*

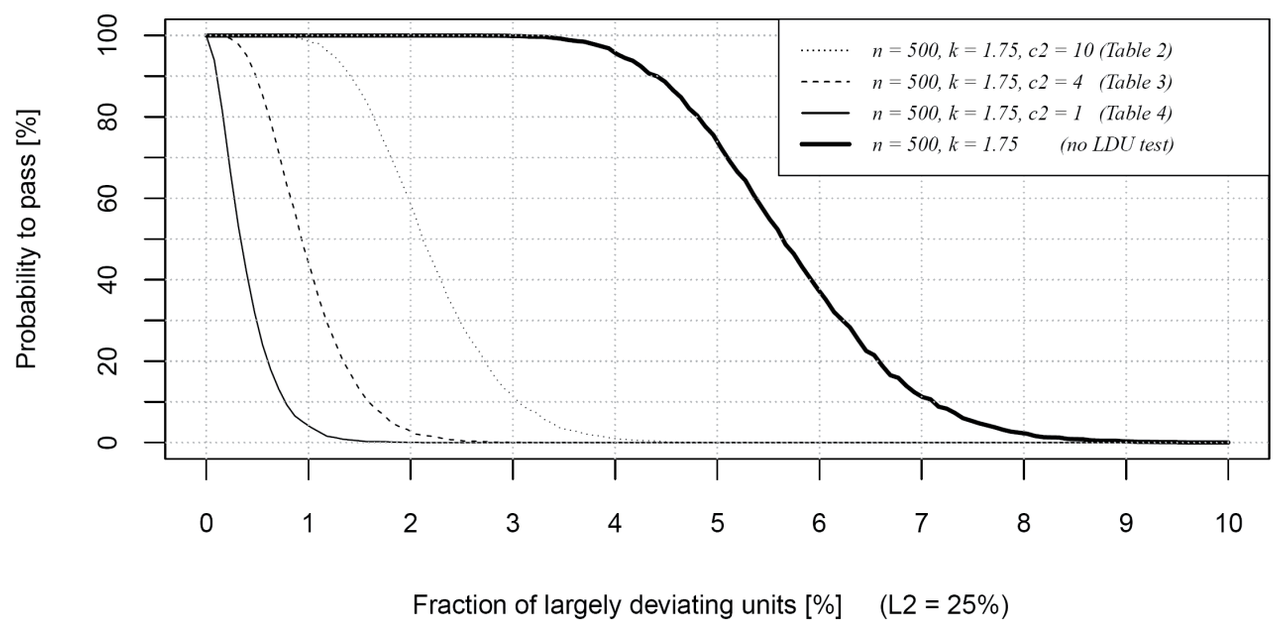

Figure 5 – *Operating characteristic curves for bimodal batches that were evaluated by the increasingly stringent acceptance criteria presented in Tables 2 to 4, and the corresponding OC curve for the batches evaluated by the acceptance criteria of Table 1 alone. Sample size n = 500.*

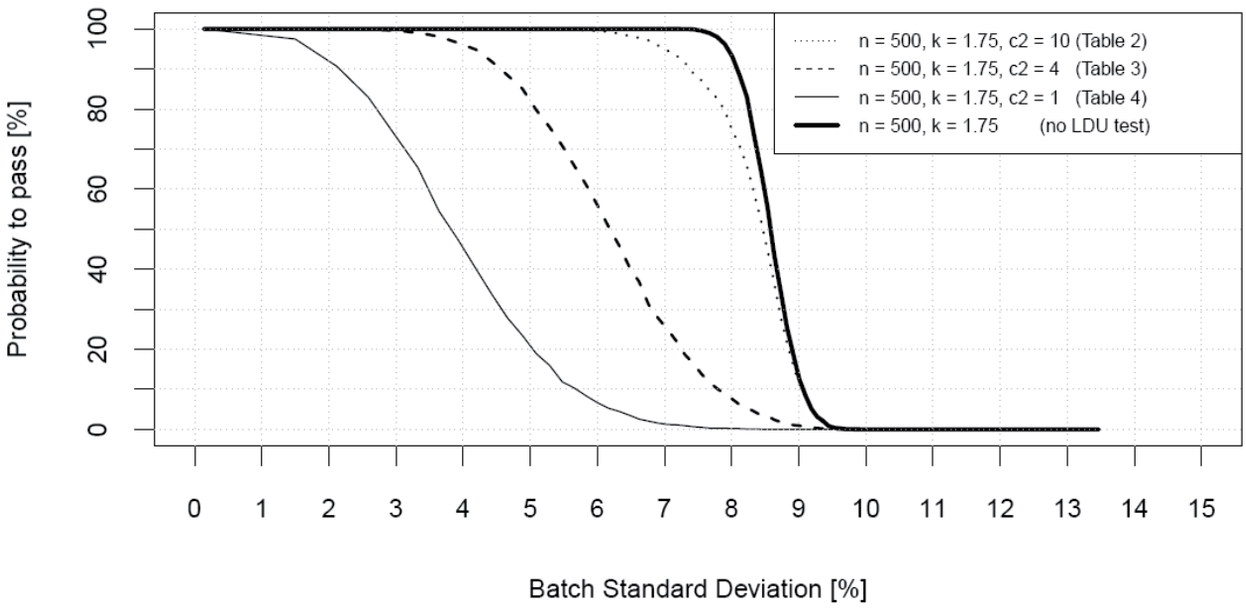

Figure 6 – *Operating characteristic curves for batches with long-tailed Cauchy distributions. The batches were evaluated by the increasingly stringent acceptance criteria presented in Table 1 and Tables 2 to 4, respectively.*

5. REFERENCES

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