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The following *Brief Scientific Critique of the ICH Proposal on Uniformity of Dosage Units as it Relates to Inhalation Dosage Forms* was prepared by the International Pharmaceutical Aerosol Consortium in response to the proposal on *Uniformity of Dosage Units* put forth by the Japanese Task Force of the Expert Working Group on ICH Topic Q6A. IPAC is an international association of companies that develop and manufacture orally inhaled and nasal drug products for local and systemic treatment of asthma, chronic obstructive pulmonary disease (COPD), rhinitis and migraine, as well as new products for non-respiratory disease indications such as diabetes.

A BRIEF SCIENTIFIC CRITIQUE OF THE ICH PROPOSAL ON UNIFORMITY OF DOSAGE UNITS AS IT RELATES TO INHALATION DOSAGE FORMS

I. Introduction

The ICH proposal on *Uniformity of Dosage Units (*UDU) sets forth the procedure and acceptance criteria for the UDU testing for several dosage forms, including inhalation drug products. Exhibit A contains relevant excerpts from that proposal as it pertains to inhalation dosage forms.

On the other hand, the current US pharmacopeial UDU standards for inhalation drug products are addressed in the USP General Test Chapters <601> and <905> (for a summary of the USP requirements, see Exhibit B).

II. Comparison of Proposed ICH Requirements and Current USP Standards

The basic principles underlying the ICH and USP UDU requirements are quite different. The proposed ICH specification controls dose content variability by establishing a limit on the Acceptance Value, which is a linear combination of the standard deviation and the absolute mean deviation from the target (the proposed limit for the Acceptance Value is ± 25% of the label claim). The proposed ICH UDU test is thus a type of variable test. By comparison, the USP specification controls the variability by establishing a limit on the maximal number of dose content observations outside a certain interval (not more than 1 of 10 observations outside ± 25% of the label claim (3 / 30 for 2nd tier testing)). The USP test is thus an attribute test. Both the ICH and USP specifications prescribe the same outlier criterion, namely that no individual unit is allowed to deviate by more than ± 35% from the label claim.

While the current USP and the proposed ICH specifications employ the same sets of limits (*i.e.*, 25% and 35% of the label claim), it is not straightforward to compare the two tests. The resemblance caused by the fact that the limits happen to coincide may give the impression that they are similarly restrictive. However, because the two specifications use entirely different metrics, there is no simple relation between the implicit requirements of the tests. As discussed above, the USP test metric is the count of observations outside a prescribed set of limits, whereas in the ICH proposal, the test metric is a combination of the sample mean and standard deviation. In this letter, we would like to offer several illustrations of how these respective metrics compare.

To illustrate the application of the proposed ICH specification and to compare it to the USP specification, we first would like to present the following case study. Let us consider a sample from a normal distribution with an observed mean dose content ($\overline{X}$) of 100% of the label claim (*M*). The current USP specification dictates that at least 9 out of 10 units (or at least 90% of the data) must be within ± 25% of the label claim. It can be shown that requiring that at least 90% of the data be within 25% of the label claim corresponds to requiring (on average and when the mean is 100% of the label claim) that the standard deviation is NMT 15.2%.

On the other hand, according to the proposed ICH specification, the Acceptance Value introduced in the UDU proposal is calculated as follows (see Exhibit A for the notation convention):

$$\text{Acceptance Value} = |M - \overline{X}| + ks = |100 - 100| + ks = ks$$

In this case, when $\overline{X}$ = 100% of the label claim, the Acceptance Value equals the product of the pre-set value for the acceptability constant (*k*) and the sample standard deviation (*s*). The acceptability constant *k* is defined to be 2.4 for the Tier 1 testing, while the Acceptance Value should not exceed *L1* = 25.0% (see Exhibit A). Consequently, the proposed ICH specification stipulates, in this example, that the sample standard deviation is NMT 25.0% / 2.4 = 10.4%; (for the 2nd Tier testing, the corresponding figure is 12.5%). A comparison of these limit standard deviations (10.4 and 12.5%) with the one calculated above for the USP test (15.2%) shows that a tighter uniformity is required by the ICH test.

Another way of illustrating the greater stringency of the ICH test is a comparison of average proportions of units falling within ± 25% of the label claim for the different limit standard deviations calculated above (10.4, 12.5, 15.2%). As can be seen from the table below, the ICH test requires a higher proportion of units to fall within the ± 25% limits.

Test	*Limit Standard Deviation, %*	*% units within ±25% of label claim*
ICH Tier 1	10.4	98.4
ICH Tier 2	12.5	95.0
USP	15.2	90.0

This example illustrates that, compared to the current USP specification, the proposed ICH test places much tighter requirement on the acceptable variability of dosage units (although this is not very transparent from the description of the two tests). The consequence of this is that the proposed ICH procedure inevitably leads to a higher rejection rate of any given sample. Thus, the proposed ICH requirements for UDU are more restrictive than those of the current USP.

Let us now compare the ICH and USP tests using a different approach. As mentioned above, the USP test is a variable test, while the proposed ICH test is an attribute test, *i.e.,* the two tests involve different metrics. Comparing tests that use different metrics is best performed by using so-called operating characteristics (OC) curves, where the probability of compliance is graphically displayed as a function of, for example, true standard deviation. The OC curves for the two tests were calculated using a standard method of simulation. Each point is based on 10,000 simulated samples, and the resulting curves are presented in Figure 1 below. These curves show the proportion of samples that on average meet the requirements of each test as a function of true standard deviation (SD), assuming normally distributed data with a true mean at label claim.

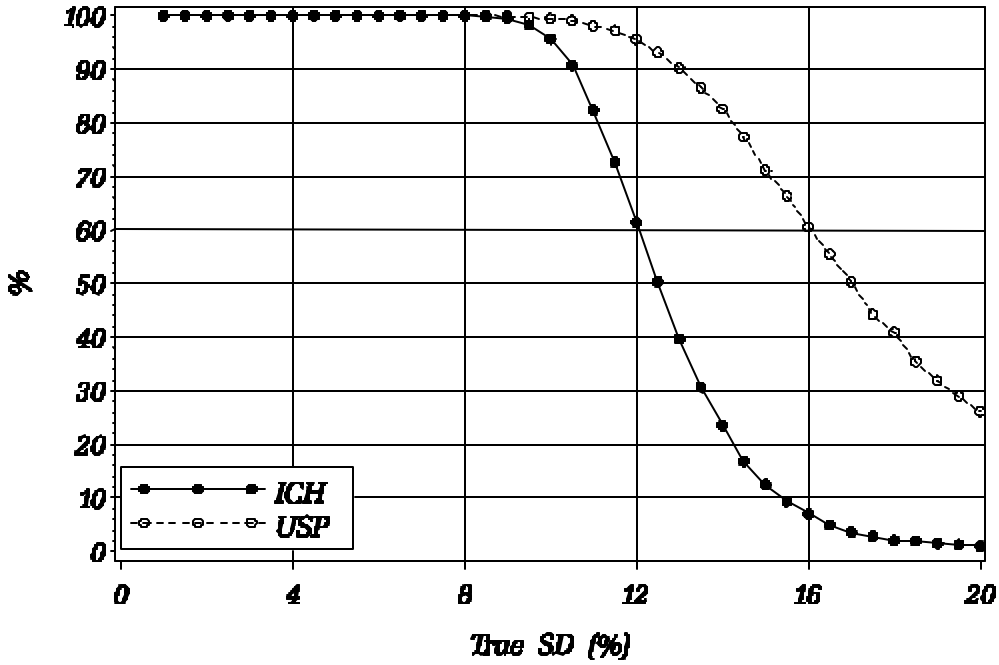

Figure 1. The proportion (%) of samples fulfilling the proposed ICH and current USP UDU requirements as a function of true standard deviation (SD). The true mean is assumed to be at 100% of the label claim.

Figure 1 demonstrates that the proposed ICH requirements are far more stringent than the current USP standards in spite of the superficial similarity of the specification limits. For example, a product with a true SD of 12% and a mean at target (100% of the label claim) will on average pass the USP test in 96% of the tests, while only 61% of the tests on the same product will pass the proposed ICH requirements.

Yet another illustration of the tightening is the following example (again assume that data follow a normal distribution with a mean at 100% of the label claim and an SD of 12%). By means of a simulation study similar to the one above, one can find that it would require a tightening of the USP target interval from 75-125% to 82.5-117.5% to cause the same pass rate in a USP test as that of the proposed ICH test.

Finally, for reference, we present in Figure 2 the OC curves for an off-target product with the true mean at 90% of the label claim. (Identical OC curves are obtained for the case with a true mean at 110% of the label claim.)

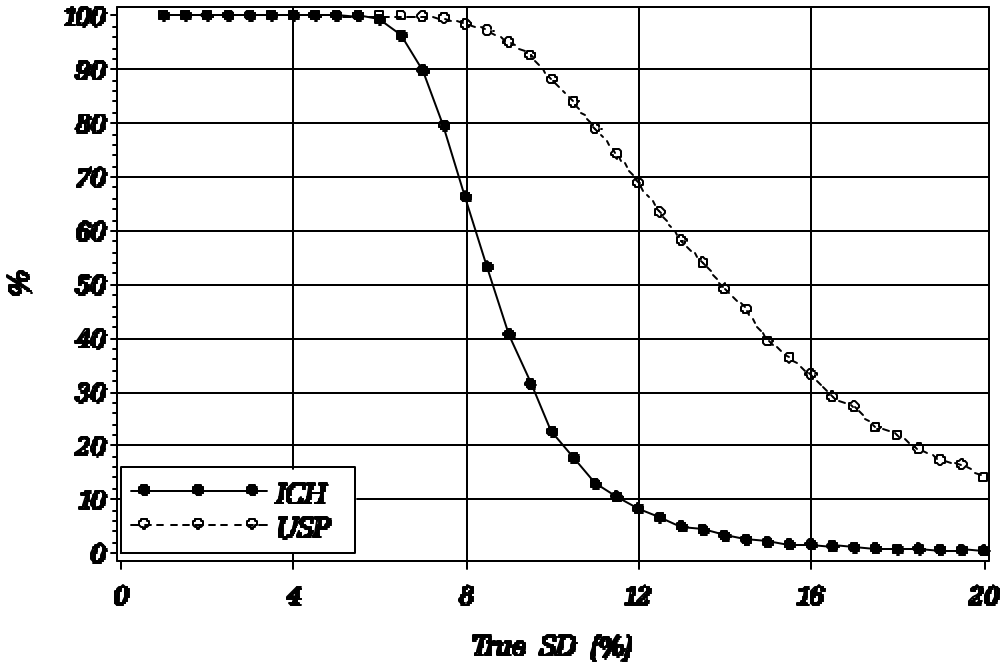

Figure 2. The proportion (%) of samples fulfilling the proposed ICH and current USP UDU requirements as a function of the true standard deviation (SD). The true mean is assumed to be at 90% of the label claim.

Apart from the obvious fact that the pass rate decreases when the true mean deviates from the target, the overall picture is the same as in Figure 1, *i.e.*, the proposed ICH specification in this situation represents a significant tightening over the current USP requirements, just as in the case of a product with the mean at target.

In summary, the OC curves show that the proposed ICH procedure for controlling dose uniformity generally constitutes a far more exacting UDU specification than the current USP specification. However, we acknowledge that the principle of controlling uniformity by means of a variable test (such as the proposed ICH test) is statistically a more powerful method than an attribute test (such as the current USP method). A powerful test has better capability to make the correct decision, *i.e.*, it will more often approve batches with low variability and more often reject batches with high variability. This desirable characteristic of the proposed ICH test is demonstrated by the steeper OC curves for the ICH test in Figures 1 and 2. Thus, a DCU requirement following similar principles as the proposed ICH test may provide an attractive alternative – provided that limits and / or acceptability constants are tuned to reflect the actual capability of inhaled dosage forms that have been proved to provide safe and efficacious therapy – and we support further investigation of this approach.

As we stated in our 22 June 2000 letter to Dr. Aoyagi, the Leader of the Japanese Task Force of the Expert Working Group on ICH Topic Q6A, proposing tightened acceptance criteria for inhaled drug products without justification by relevant data appears to be contrary to the ICH principle of a data-based approach to setting specifications. As an organization comprised of companies with significant expertise in the area of inhalation drug products, IPAC has well founded reasons to believe that the proposed tightening of the pharmacopeial standards is unwarranted by the performance of these products.

III. Conclusion

In this letter, we have provided a brief scientific critique of the ICH UDU proposal and presented a scientific argument in support of our position as stated in the letter to Dr. Aoyagi. We reiterate our position that without consultation of relevant experts, the inclusion of tightened requirements for inhalation dosage forms in the proposal (which is to be published by the USP) would be premature. We respectfully request, therefore, that inhalation dosage forms be excluded from the proposal until specific requirements for these dosage forms are fully considered by the appropriate experts of USP and parties to the Pharmacopeial Discussion Group and the ICH.

EXHIBIT A

Summary of Proposed ICH UDU Specification

Calculation of acceptance value

Acceptance value = $| M - \bar{X} | + ks$

M	If $\bar{X}$ is less than or equal to 100.0%, then M = the greater of 98.5% or $\bar{X}$. If $\bar{X}$ is greater than 100.0%, calculate U, where U is the greater of 101.5% or the target test sample_amount_at the time of manufacture which is normally 100.0% unless otherwise specified in the approved specification or individual monograph. Then, for the acceptance criteria calculation, M is the lesser of $\bar{X}$ or U.
$\bar{X}$	Mean of individual contents (x_1,x_2,…,x_n).
x_1,x_2,…,x_n	Individual contents of the units tested, expressed as a percentage of the label claim.
n	Sample size (number of units in a sample).
k	Acceptability constant. Unless otherwise specified in individual monograph, k=2.4 when the sample size is 10, and k=2.0 when the sample size is 30.
s	Standard deviation of the sample.

$$s = \sqrt{\frac{\sum_{i=1}^{n} (x_i - \bar{X})^2}{n-1}}$$

Criteria

Apply the following criteria, unless otherwise specified in the individual monograph. The requirements are met if the acceptance value of the first 10 dosage units is less than or equal to *L1*%. If the acceptance value is greater than *L1*%, test the next 20 units. The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to L1% and no unit is over the deviation of *L2*% from the calculated value of *M* in **Calculation of acceptance value**.

Unless otherwise specified in the approved specification or individual monograph, *M* is 100.0%. Also, unless otherwise specified in the approved specification or individual monograph, *L1 is* 15.0 and *L2* is 25.0 for all products except for metered dose inhalers and powder dose inhalers for which *L1 is* 25.0 and *L2* is 35.0.

EXHIBIT B

Summary of USP UDU Specification

Tier 1 testing

No more than 1 of the 10 dosage units lies outside the range of 75% to 125% of the label claim and none of the 10 doses is outside the range of 65% to 135% of the label claim. If 2-3 units are outside 75% to 125% of the label claim, but no unit outside 65% to 135% of the label claim, test 20 additional units.

Tier 2 testing

No more than 3 of 30 dosage units are outside the range of 75% to 125% of the label claim and none of the 30 dosage units is outside the range of 65% to 135% of the label claim.