Significant restriction of the delivered dose uniformity criteria in the revised USP Chapter for Aerosols <601>

USP proposes more restrictive criteria for delivered dose uniformity (DDU)

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This is the second of two articles published by Inhalation, presenting opinions from representatives of IPAC-RS on the proposed revised and new USP Chapters for Aerosols <601> and <5>.

The June 2011 issue of the Pharmacopeial Forum [Pharm Forum 2011; 37(4)] contains a 110-page re-write (an in-process-revision) of USP General Chapter <601>, which had been known under the title of *"Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers"* but is now called *"Product Performance Tests—Nasal And Inhalation Aerosols, Sprays, And Powders."* Some of the revisions were discussed in our first of two articles, published in *Inhalation,* February 2012. In this article, one of the most critical aspects of the USP proposal – the new acceptance criteria for delivered dose uniformity (DDU) of orally inhaled products (OIPs) is discussed. The complete text of the revised Chapter <601> is accessible online upon free registration at www.usppf.com.

The new USP criteria represent a significant restriction of the existing USP requirements, as can be seen from a simple comparison of the limits in Table 1. An expanded table, which includes a comparison to the European DDU requirements, is available in a poster developed by IPAC-RS.[1]

The new USP test closely resembles that of the FDA 1998 Draft FDA Guidance for Industry *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation,*[2] although not completely and with different legal/regulatory implications. Are these more restrictive requirements sensible? To answer that question, we only need to look at the work done in response to the 1998 Draft FDA Guidance, as will be discussed below.

Importantly, there has been no evidence (either given by USP or in the public literature) that the DDU performance of marketed MDIs and DPIs is somehow deficient or is adversely impacting safety or efficacy of these products. Nor has USP made any attempt to compare the proposed specifications to the capability of orally inhaled products (OIPs) on the market and under development. The increase in stringency, therefore, appears arbitrary.

DDU performance of MDIs/DPIs compared to 1998 FDA Draft Guidance

The 1998 FDA Draft Guidance requirements were considered by the inhalation industry to be excessively stringent and thus spawned a cross-industry collaboration between the International Pharmaceutical Aerosol Consortium and the Inhalation Technology Focus Group (ITFG) of the American Association of Pharmaceutical Scientists (AAPS). As one of its first tasks, the collaboration collected an extensive, blinded database of DDU determinations from a large number of products on the market and under development. Results of the database analysis indicated that the FDA DDU criteria were not suitable for the majority of orally inhaled products.[3] Subsequently, a broader industry consortium (IPAC-RS) expanded that database and compared the actual DDU criteria for products approved by FDA as safe and efficacious, with the Draft Guidance's limits, via operating characteristic curves (OCCs). In general, an OCC depicts the probability of passing a particular test based on the underlying data's characteristics, such as batch mean and standard deviation. An example is depicted in Figure 1.

Results of the IPAC-RS DDU analyses are presented in Figures 2 and 3. Both indicate that the FDA Guidance limits are too restrictive for current aerosol technology (Figure 2) and that the FDA had often granted deviations from the Guidance criteria, resulting in the OCCs

Table 1

A summary of the DDU requirements for MDIs and DPIs (Tier 1) in the previous USP <601>, the 2011 in-process revision USP <601> and the 1998 Draft FDA MDI/DPI Guidance

Previous USP <601> DDU Criteria *(Tier 1)*	New USP DDU Criteria (2011) *(Tier 1)*	FDA 1998 DDU Criteria *(Tier 1)*
Delivered dose uniformity Sample 1 dose from each of 10 separate inhalers. Pass if: • No more than 1 of 10 doses is outside 75-125% label claim (LC) • No dose outside 65-135% LC If 2-3 of 10 doses are outside 75-125% LC, and no dose outside 65-135% LC, go to tier 2 by sampling 20 additional inhalers, 1 dose from each. Otherwise, fail.	**Delivered dose uniformity** Sample 2 doses (beginning and end) from each of 10 separate inhalers. Pass if: • No more than 2 of 20 doses are outside 80-120% LC • None outside 75-125% LC • The mean of beginning doses within 85-115% LC • The mean of end doses within 85-115% LC If 3-6 of the 20 doses are outside 80-120% LC, none outside 75-125% LC, and the means for beginning and end are within 85%-115% LC, go to tier 2 by sampling 20 additional inhalers, 2 doses from each (beginning and end). Otherwise, fail.	**Dose content uniformity** Sample 1 dose from each of 10 inhalers. Pass if: • No more than 1 of 10 doses is outside 80-120% LC • None is outside 75-125% LC • The mean of the 10 doses is within 85-115% LC. If 2-3 doses are outside 80-120% LC, none outside 75-125% LC, and the mean is within 85-115% LC, go to tier 2 by sampling 20 additional inhalers, 1 dose from each. Otherwise, fail.
DDU over the entire contents Sample 1 inhaler, 10 doses Pass if: • At least 9 of 10 doses within 75-125% LC • No dose outside 65-135% LC If 2-3 doses outside 75-125% LC, and no dose outside 65-135% LC, go to tier 2 by sampling 2 additional inhalers, 10 doses from each. Otherwise, fail.		**Dose content uniformity through container life** Sample 3 inhalers, 3 doses from each (beginning, middle and end of container) Pass if: • No more than 1 of 9 doses is outside 80-120% LC • None is outside 75-125% LC • The mean of each of the beginning, middle and end doses are all within 85-115% LC. If 2-3 doses are outside 80-120% LC, none outside 75-125% LC, and all three means are within 85-115% LC, go to tier 2 by sampling 6 additional inhalers, 3 doses from each. Otherwise, fail.

shifted to the right relative to the OCC based on the Guidance DDU specifications (red line in Figure 3).

There have also been presentations and articles which clarify that the zero-tolerance component of the test (allowing no values outside certain limits) penalizes increased testing even when the underlying product quality does not change.[6] The zero-tolerance component leads, therefore, to minimalistic testing, contrary to the intentions of current paradigms such as Quality-by-Design, i.e. understanding process and product, process analytical technologies and other modern pharmaceutical approaches to product quality.

How does the new USP DDU test differ from the 1998 FDA Guidance test?

The second and third column of Table 1 illustrate that, despite similar limits used in both cases, there is a difference in the structure of the DDU test in the revised USP <601> and in the Draft FDA Guidance. Namely, the through-container-life component is assessed in a separate test by the FDA Draft Guidance but is integrated into the overall DDU test in the revised <601>. This means the total number of doses tested in the first tier is 20 for the revised <601> and 16 to 19 for the FDA Guidance (depending on the way the two parts of the

Figure 1

An example of an operating characteristic curve (OCC). As batch variability increases, the probability to pass a test decreases.

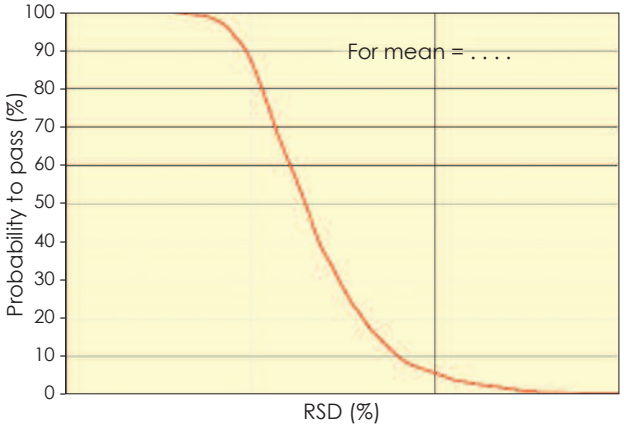


Figure 2

Delivered dose uniformity (DDU) determinations[4]

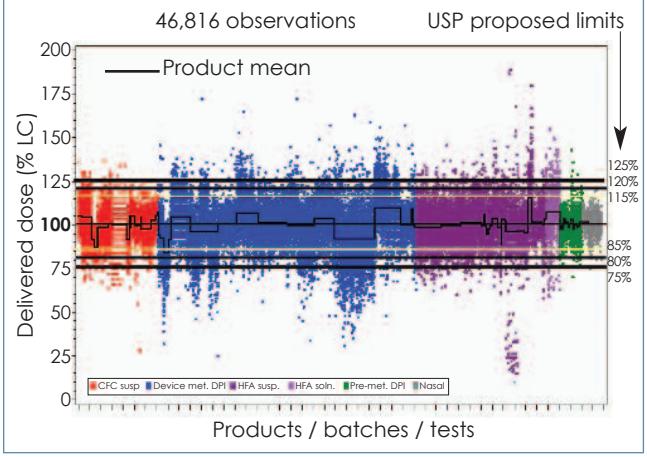
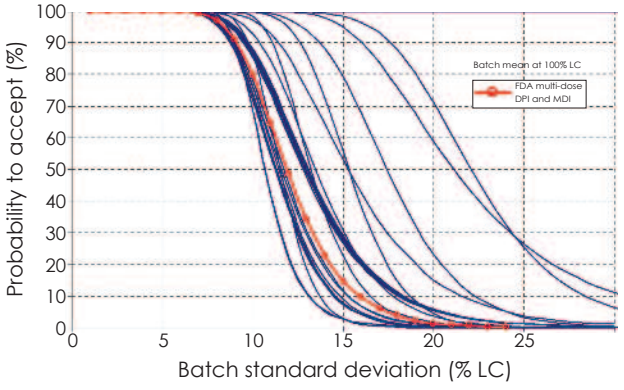


Figure 3

OCCs for DDU criteria of 24 MDIs & DPIs approved by FDA in 1990-2003 (thin blue lines, some overlapping) compared to the FDA Draft Guidance DDU criteria[5] (red line). Batch mean on target.



FDA DDU test are combined). The larger sample size will translate into a slightly more stringent USP test. On the other hand, the FDA Guidance test has an additional condition for the mean value of middle doses, absent in the revised <601>. This difference will likely have a negligible effect on the test's outcomes, because through-life trends are typically monotonic and will be captured by the end-dose testing. Overall, therefore, the revised USP <601> DDU test will behave very similarly to, or somewhat stricter than, the 1998 FDA Draft Guidance test. The analyses and conclusions presented in the previous section, focusing on the FDA test, would apply to the revised USP test – if applied to a batch once.

The principal difference between the FDA and USP tests, however, lies in the legal standing of the USP standards. As explained in our first article, USP standards are mandatory.[7] There is no negotiation, review of product-specific data or consideration of therapeutic indication. Moreover, USP standards must be met whenever a product is tested (even if multiple times), meaning that chances of failure are increased multiple-fold (even if the product quality remains the same). If a product marketed in the US fails to meet USP standards, the product is considered adulterated, with substantive negative consequences and repercussions.

What would be an alternative?

In the IPAC-RS comments submitted to USP, it was recommended that USP maintain the original criteria in <601>. If the need for revisions is warranted, a public dialogue with all relevant stakeholders should be initiated. Such dialogue should be given sufficient time and an appropriate interactive forum. This forum should address three general areas: a) whether and why revisions are needed (rationale); b) the appropriate form of future USP tests and standards (sample-based or product/population-based, which do not depend on sample size); and c) appropriate factors for defining acceptance criteria for a given product class (clinical information, safety information, product history, existing regulatory requirements, etc.)—and the manner for arriving at such acceptance criteria.

USP organized an Aerosols Workshop on December 12-13, 2011 to discuss the proposed changes. At the time this article was written, the workshop had not yet taken place. Our hope is that the workshop initiates a meaningful dialogue. Yet due to the limited time designated for open deliberations, further discussion will most likely be required.

What you can do as an inhalation product developer/sponsor

As an inhalation product developer or sponsor, you have multiple ways to respond to the proposed USP changes:

Options related to your product.

Option 1: Do nothing – simply wait for the USP standards to come into effect (which may be on August 1, 2013, unless the USP Aerosol Subcommittee decides that this aspect of the revised chapters is not ready for finalization). If you are considering this option and are interested in the impact that the new USP standards may have for your products, simulations of repeated USP DDU tests on your product(s) could be conducted—based on your product's typical batch mean, variability of batch means (e.g., range of batch means) and your typical batch standard deviation. As a shortcut for these calculations/simulations, simply check for any observations of a delivered dose value outside the new USP zero-tolerance limits (75-125% label claim [LC]). Each such observation means a failed test and thus a failed batch of product. Lack of values outside these limits, however, does not mean passing the USP test—rather a more complete evaluation and calculations to determine the outcome of individual tests and the overall frequency/probability of failing/passing would be required. If your product(s) can pass the new USP DDU test 100% of the time, no matter how many times or when it is tested, Option 1 could be advisable. However, if the pass rate is less than 100%, imagine every "failed" test leading to a recall because the product can now be considered adulterated. Keep in mind that compliance with public pharmacopeial standards is mandatory in the US (regardless of whatever other criteria were established with the FDA approval) and is often mandatory in other countries that follow USP standards.

Option 2: To stay within the law and minimize the chances of having an adulterated product, a product-specific monograph could be prepared for inclusion in the USP document, specifically defining the requisite criteria. Individual pharmacopeial product monographs are not only considered public standard but supersede the requirements of general chapters such as <601>.

Option 3: A redesign or modification of the manufacturing process and/or the product could be considered, if technologically and economically feasible. The goal should be reduction of delivered dose variability to a level that allows the product to pass the USP DDU test routinely with sufficiently high certainty.

Options for changing the DDU requirements.

There are also long-term and near-term options that focus on efforts to proactively change the published DDU requirements in USP <601>.

Long-term options: a) Wait for the next USP cycle (2015-2020), volunteer to serve on the Aerosol Subcommittee of the USP Pharmaceutical Dosage Form, hope that your application gets accepted (there are currently only six seats on that subcommittee), and then develop a better approach that would be agreeable to all the other experts on the committee. b) Attend the next USP Aerosol Workshop (assuming USP would organize a follow-up aerosol workshop to continue the discussion started in December 2011) and raise your questions and concerns directly with USP.

Near-term options: a) Send written comments and communications to the USP. b) Join IPAC-RS to work with other companies and organizations in the development of better approaches and to build consensus with USP and other stakeholders.

There are clearly approaches that companies could undertake in reaction to the proposed changes in the USP chapters. Among the aforementioned options, you and your company have a choice to make. Our recommendation is for you to engage in the near term approach along with other interested industry colleagues.

References

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2. FDA CDER Draft Guidance for Industry. Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation. 1998. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070573.pdf

3. See www.ipacrs.com/PDFs/Initial_Assessment_of_Dose.PDF for specifics.

4. Adapted from a presentation at RDD-IX, available at www.ipacrs.com/PDFs/RDD_IX_DDU.PPT

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6. Zero-Tolerance Criteria Do Not Assure Product Quality. Murphy JR, Griffiths KL. Pharm.Tech. 2006; 30(1): 52-60. www.pharmtech.com/pharmtech/content/printContentPopup.jsp?id=283486.

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The first article in this two-part series, "A critical evaluation of the revised and new USP Chapters for Aerosols: <601> and <5> [Pharm Forum 2011; 37(4)," was published in *Inhalation* February 2012 and can be found on the *Inhalation* website: www.inhalationmag.com.