

Dose Content Uniformity - Parametric Tolerance Interval Test for Aerosol Products

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This topic is being brought to ACPS as an "awareness" topic.

CDER has published two guidances for chemistry, manufacturing and controls (CMC) documentation of orally inhaled and nasal drug products (OINDP). In October 1998, a draft guidance for industry entitled *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products - CMC Documentation*, was published. In May 1999, a draft guidance for industry entitled *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - CMC Documentation*, was published, and the final guidance was published in July 2002. These guidances include recommendations for dose content uniformity (DCU) or spray content uniformity (SCU), also referred to as delivered dose uniformity. Metered doses of drug discharged from the actuator of an MDI, DPI, or nasal spray should meet the recommended acceptance criteria stated in these guidances to assure uniformity of drug delivery of doses within a container, and among containers and batches. At the present time, CDER recommends that DCU from MDIs and DPIs, and SCU from nasal sprays, be determined using nonparametric tests. For example, at tier 1 for MDIs, the emitted dose (the minimum dose approved in the labeling) of not more than 1 of 10 canisters are outside of 80 - 120 percent of label claim and none of the 10 are outside of 75 - 125 percent. The test is not completely nonparametric - the mean of the 10 containers at the various lifestages of testing is not outside 85 - 115 percent. As noted above, MDIs, which are multidose products, should also meet a DCU through container life test. This test measures the metered dose at beginning, middle and end lifestages, to assess whether the product delivers the labeled number of full medication doses throughout the life of the MDI. This test also includes nonparametric and parametric elements.

Recently, parametric approaches have been developed for content uniformity testing. In 1996, a parametric approach became official in the *Japanese Pharmacopoeia*. The parametric approach was subsequently discussed by the Pharmacopoeial Discussion Group (composed of representatives of the *European Pharmacopoeia*, the *Japanese Pharmacopoeia*, and the *United States Pharmacopoeia*), the Statistics Working Group of PhRMA, and an ICH/PDG Task Force. Neither the nonparametric (with certain parametric elements) approach recommended by FDA, nor the parametric approaches discussed by the above organizations, is based on statistical hypotheses. Rather, they specify a decision rule.

Dr. Walter Hauck of Thomas Jefferson University proposed a parametric tolerance interval approach based on a statistical hypothesis. The approach specifies a maximum consumer risk, a minimum coverage probability, and a target interval. The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) then prepared a proposal entitled *A Parametric Tolerance Interval Test for*

Improved Control of Delivered Dose Uniformity of Orally Inhaled and Nasal Drug Products (15 November 2001). This report is based on the Hauck approach, and incorporates additional features based on the current FDA DCU test and DCU through container life test. The report was submitted to FDA with a request that the agency replace the DCU and DCU through container life tests, as well as the SCU and SCU through container life tests in the two draft FDA CMC guidances for OINDP.

ISSUES FOR RESOLUTION:

Conceptually, OPS finds the approach proposed by IPAC-RS to be acceptable. However, a number of issues remain to be resolved prior to possible acceptance of the approach. These include the following:

1. The appropriate level of consumer risk (alpha) is less than or equal to 5 percent. Simulations reveal that with the present values of acceptability coefficients (k_1 , k_2 , and f) stated in the report, the estimated level of consumer risk exceeds 5 percent. This problem must be corrected.
2. The quality standards proposed in the IPAC-RS report (85 percent coverage, target interval equal to 75 - 125 percent of label claim) are claimed to be based on the current FDA DCU acceptance rule. A maximum consumer risk of 5 percent was assumed. However, the IPAC-RS quality standards are not the same as current agency standards. The IPAC-RS approach exhibits a higher acceptance probability for products with low or borderline quality, e.g., large batch standard deviation (IPAC-RS Parametric Tolerance Interval Test report, 15 November 2001, updated September 2002, Fig. D, p. 12). To date the agency has not defined its quality standards in terms of a parametric tolerance interval test, and issues remain concerning the differences between the two approaches.
3. The IPAC-RS approach eliminates the "zero tolerance criterion," i.e., no unit in the sample delivers a dose outside the limits of 75 - 125 percent of label claim. The zero tolerance criterion may be of value for skewed or heavy-tailed data. Moreover, the FDA acceptance rule recommends that 90 percent of the tested samples must be within 80 - 120 percent of label claim.
4. Robustness of the IPAC-RS approach must be established for non-normally distributed data when the batch is at or below the proposed limiting coverage of 85 percent.
5. OPS has concerns about proper sampling of containers for the DCU test. DCU standards should assure the limiting quality of the batch. These standards should apply to the performance of samples from containers randomly selected from the batch. At present, sampling standards are not a component of the DCU review process. Furthermore, appropriate sampling schemes may differ among applicants and among OINDP dosage forms.

6. Based on a judicial decision, a manufacturing process in which the batch failure rate is 10 percent or more may be considered to be not under control. OPS would like to understand the current commercially available drug product production batch failure rate, and if feasible, relate it to the coverage, tolerance limits or the magnitude of a zero tolerance criterion of the sample, in order to develop a DCU quality standard that assures no more than a 10 percent batch failure rate.

QUESTIONS FOR DISCUSSION:

1. Does ACPS agree that a parametric tolerance interval test is conceptually acceptable as a replacement for the agency's nonparametric (with certain parametric elements) DCU and DCU through container life tests for OINDPs?
2. Does ACPS feel that DCU quality standards should provide assurance that batch failure rates do not exceed a specified level?

BACKGROUND DOCUMENTS:

1. Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products - Chemistry, Manufacturing, and Controls Documentation, October 1998.
<<http://www.fda.gov/cder/guidance/2180dft.pdf>>
2. Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing, and Controls Documentation, July 2002.
<<http://www.fda.gov/cder/guidance/4234fnl.pdf>>
3. 10. Content Uniformity Test, *The Japanese Pharmacopoeia*, Thirteenth Edition, April 1996, p. 25
4. RL Williams, WP Adams, G Poochikian, WW Hauck. Content Uniformity and Dose Uniformity: Current Approaches, Statistical Analyses, and Presentation of an Alternative Approach, with Special Reference to Oral Inhalation and Nasal Drug Products. *Pharm Res*, 2002; 19:359-66.
5. B Olsson, D Sandell. Delivered Dose Uniformity Testing: IPAC-RS Advocacy and Justification. *Respiratory Drug Delivery VIII Proceedings*, 2002, Vol. I, pp. 115-22.
6. WW Hauck. An Independent Assessment of IPAC-RS' Proposal. *Respiratory Drug Delivery VIII Proceedings*, 2002, Vol. I, pp. 123-7.
7. IPAC-RS. A Parametric Tolerance Interval Test for Improved Control of Delivered Dose Uniformity of Orally Inhaled and Nasal Drug Products. 15 November 2001, Updated September 2002.
http://www.ipacrs.com/PDFs/ipac-rs_DDU_Proposal.pdf