An overview of Bayesian approaches to content uniformity

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Introduction: Content Uniformity

Before a batch of a newly manufactured drug product is released to consumers, **content uniformity testing is used to establish that the dosage units of a drug product consistently contain the specified amount of drug** (active pharmaceutical ingredient). For dosage units from a batch to be of uniform content, the amount of active pharmaceutical ingredient in the dosage units of a batch must be reasonably close to the intended (target) dose, thus avoiding the patient risk of under/over dosing. Tests of content uniformity assess the assayed results of a sample of units from a batch against a predetermined set of criteria. The United States Pharmacopeia (USP) chapters provide testing standards for content uniformity that are used by more than 140 countries. **The specifics of most modern USP content uniformity tests may be found in USP<905> for solid dosage units**, USP<3> for topical and transdermal drug products, and USP<601> for aerosols, nasal sprays, metered-dose inhalers, and dry-powder inhalers. In addition, the approach discussed in ASTM E2810 (the CuDAL approach) and the PTI-TOST have been suggested as techniques for batch release.

Content uniformity tests by regulatory agencies are not Bayesian in nature. USP-recommended tests include the so-called zero-tolerance counting tests (how many units in the sample are acceptable) and ad-hoc mean-centered statistical intervals. As these test methods are not associated with exact hypotheses nor do they consider the test size, collected data from a manufactured batch either meet or do not meet USP-based acceptance criteria. **Bayesian content-uniformity methods, however, allow for statistical inference to be made based upon a test of two hypotheses through the probability that the units from within the tested batch meet the acceptance criteria.** Further, a Bayesian approach to examine historical data provides a useful means to assess batch and process performance against any content-uniformity tests while addressing more complex data structures when applying these tests.

Figure 1 shows an operating characteristic (OC) curve for USP<905> Uniformity of Dosage Units. The OC curve shows the conditional probability that a batch will meet the acceptance criteria of USP<905>, given the true mean (μ) and true standard deviation (σ) of a batch.

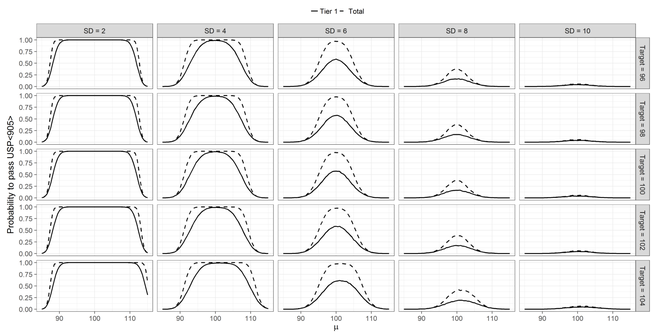

Figure 1. OC Curve for USP<905> Uniformity of Dosage Units.

Issues with USP<905>

Some common issues with USP<905>:

- **Hypothesis:** If a batch meets the conditions of USP<905>, what may be said about the content uniformity of units from the batch?

Not much.

There are no formal statistical hypotheses to compare.

There are no assumptions regarding the statistical distribution of the content of dosage units.

- **Probability statement:** Given $\boldsymbol{X}=\{X_1, X_2, \ldots, X_n\}$ from n units from a batch, what is the probability a batch meets USP<905>? What is the probability that $L < X_i < U$?

This is not assessed by USP<905>. Given $\boldsymbol{X}$, units either meet or do not meet USP<905>.

The CuDAL approach

Bergum and Li (2007) published a novel method called CuDAL (content uniformity and dissolution acceptance limits) to estimate a lower bound for the probability that a random sample from a batch would pass the USP <905> standard for content uniformity with statistical confidence.

Based on a random sample of size n of solid dosage units from a batch and a given confidence level, the CuDAL calculation involves the creation of a simultaneous 100(1-α)% frequentist confidence region for (μ, σ). If the operating characteristic probabilities (see Figure 1) are all larger than p_0 for the set of every (μ, σ) in the confidence region, then with 100(1-α)% confidence, the acceptance probability for a random sample from the tested manufactured batch is at least p_0.

The Bergum and Li CuDAL method was incorporated into ASTM E2709 and E2810.

CuDAL provides *confidence* that, conditioned on a sample $\boldsymbol{X}$ from the batch, another random sample from the same batch will meet USP<905>.

Bayesian CuDAL

Lewis and Fan (2016) show that the classical statistical approach to ASTM E2810 is conservative at each step of construction, leading to overly restrictive acceptance limits

Using Bayesian methods, Lewis and Fan (2016) create a 100(1-α)% credible limit for the USP<905> OC (Figure 1), vastly improving upon the testing acceptance limits.

In essence, Lewis and Fan's method calculates the ***posterior predictive probability*** that a different sample from the same batch will meet with USP<905>; i.e., **Pr(Batch meets USP<905> | $\boldsymbol{X}$).**

Advantages over original CuDAL:

- Less conservative approach. Given the same data, the original CuDAL is overly conservative.
- Can incorporate prior information. At the very least, may incorporate *vaguely-informative* priors on model parameters.
- Easily adaptable to incorporate features in the data collection, including components of variability.

One issue still remains:

CuDAL (Bayesian or otherwise) does not characterize units within a batch. That is, even if Pr(Batch meets USP<905> | $\boldsymbol{X}$) > p_0, no information is provided about the likely content of a randomly selected dosage unit from the batch.

Two one-sided Parametric Tolerance Interval test (PTIT)

The PTIT was proposed by Lostrito (2005) and compares to hypotheses. Let p = proportion of units from a batch, $0 < p < 1$.

H_0: Fewer than 100(1+p)/2% of units lie at or above L% or fewer than 100(1+p)/2% of units lie at or below U%.

H_a: At least 100(1+p)/2% of units lie at or above L% and at least 100(1+p)/2% of units lie at or below U%.

Using a two one-sided tolerance interval testing approach, if H_a is declared, then at least 100p% of units from the batch fall between L and U with 100(1-α)% confidence. Figure 2 shows the OC curves for a PTIT with L=85% and U=115%.

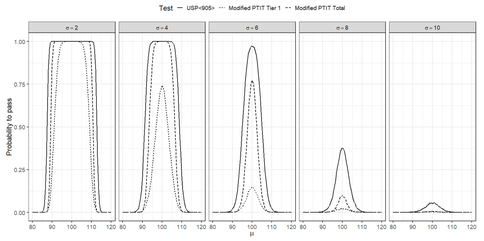

Figure 2. OC curves for modified PTIT with n_1=10 samples in tier 1, n_2 = 20 additional samples in tier 2, L=85, and U=115.

Bayesian PTIT

The PTIT may be translated into a Bayesian setting by calculating Bayesian 100p% beta-content tolerance intervals (see Krishnamoorthy and Mathew, 2009).

In addition, a two-sided test may be constructed from the ***posterior probability*** Pr($L < X_i < U \mid \boldsymbol{X}$) > p_0.

Advantages over original PTIT:

- Can incorporate prior information.
- Easily adaptable to incorporate features in the data collection, including components of variability.

Notable works

Lewis and Novick (2012) construct a PTIT for inhaled products that captures the within-unit correlation.

Novick and Hudson-Curtis (2018a, 2018b) construct a two variance-component PTIT for solid dosage units, assuming a time/location effect in the sampling.

Predicting future batch peformance

After measure the content uniformity of dosage units from M batches, we can predict the success rate of a future batch through the ***posterior predictive probability*** (LeBlond and Mockus, 2014) by calculating $Assurance = \Pr \int (Success|\theta)\, \pi(\theta|X) d\theta$.

The posterior predictive distribution may be used to calculate the probability of success of the costs of business.

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