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Methodology for the validation of analytical methods involved in uniformity of dosage units tests

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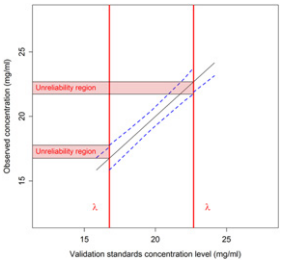
HIGHLIGHTS

- Methodology to validate methods for uniformity of dosage units tests.
- Valid methods will ensure to make the correct decisions with high probability.
- A Quality by Design compliant validation methodology for UDU assays.
- Analytical Target Profile is defined for UDU assays.
- Application to the validation of an HPLC-UV and NIRS method.

GRAPHICAL ABSTRACT



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ABSTRACT

Validation of analytical methods is required prior to their routine use. In addition, the current implementation of the Quality by Design (QbD) framework in the pharmaceutical industries aims at improving the quality of the end products starting from its early design stage. However, no regulatory guideline or none of the published methodologies to assess method validation propose decision methodologies that effectively take into account the final purpose of developed analytical methods. In this work a solution is proposed for the specific case of validating analytical methods involved in the assessment of the content uniformity or uniformity of dosage units of a batch of pharmaceutical drug products as proposed in the European or US pharmacopoeias. This methodology uses statistical tolerance intervals as decision tools. Moreover it adequately defines the Analytical Target Profile of analytical methods in order to obtain analytical methods that allow to make correct decisions about Content uniformity or uniformity of dosage units with high probability. The applicability of the proposed methodology is further illustrated using an HPLC-UV assay as well as a near infra-red spectrophotometric method.

1. Introduction

A critical property of a batch of drug product is to ensure that each of its units must have active product ingredient (API) content close to the product label claim. This evaluation is required by pharmacopoeias through the harmonized chapters about uniformity of dosage units (UDU) (e.g. chapter 2.9.40 of the European Pharmacopoeia [1] or chapter ⟨905⟩ of the United States Pharmacopoeia [2]). For products that were approved before the introduction of UDU, the general chapter about content uniformity (CU) (e.g. chapter 2.9.6 of the European Pharmacopoeia [3]) is still applicable. In addition, a proposal of a new general chapter for the European Pharmacopoeia has been introduced: chapter 2.9.47 demonstration of uniformity of dosage units using large sample sizes [4] in order to take into account the increased batch control that is performed by process analytical technology (PAT) tools.

To assess if a batch of drug product complies with these regulatory expectations, analytical procedures either chromatographic based or spectroscopic ones are used to analyse the drug product units. These analytical procedures should

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Table 1
Sample size (n) and acceptability constant (k) used in the assessment of the uniformity of dosage units (UDU) test.

n	10	30	50	75	100	150	200	300	500	1000	2000	5000	10,000
k	2.4	2	1.91	1.87	1.84	1.81	1.79	1.77	1.75	1.73	1.72	1.71	1.7

be validated by complying with the general requirements of ICH Q2 [5].

The purpose of method validation is to ensure that the analytical procedures that will be used routinely are fit for their intended purpose. However, there is no guideline on the way to decide about the validity of analytical procedures. This is in contradiction with the explicit rules found in the pharmacopoeias to assess UDU or CU for a batch. The key purpose of analytical methods involved in UDU or CU is to allow making the correct decision about compliance of the batches with respect to the rules found in the European or US Pharmacopoeias. Therefore the validity of these analytical methods should be judged on their ability to achieve this final aim.

The objective of this work is to propose a methodology using statistical tolerance intervals to decide about the validity of analytical methods that is fit with the final objective of these procedures involved in CU and UDU. Furthermore, this methodology is fully coherent with the actual Quality by Design (QbD) paradigm recently adopted for pharmaceutical industries [6] and allows to properly define the Analytical Target Profile (ATP [7,8]) of the analytical methods involved in UDU and CU.

2. Computations

All computations and simulations were performed with R v2.11.1 (CRAN, http://cran.r-project.org) and RStudio v0.92.44 (http://www.rstudio.org/).

3. Simulations

The following simulations were performed to find the probability values β_{UDU} that will be needed to assess the validity of analytical method used for UDU tests (see Section 5). Analytical methods with bias ranging from 1 to 20 and intermediate precision standard deviation ranging from 1 to 20 were simulated. The results simulated from the analytical method were generated from the model described below:

$$x_i = 100 + \delta + \varepsilon_i \quad (1)$$

where x_i is the result of the ith measurement, δ is the method bias, and ε_i is the intermediate precision random error supposed to be normally distributed $N(0, \sigma^2_{I.P.})$.

Then the decision rule for UDU defined in the pharmacopoeias is applied with sample sizes defined in Table 1 for the case of small sample sizes [1,2] as well as for the case of large sample sizes [4]. For each simulated analytical method defined by its known bias and standard deviation and for each sample size, the UDU test is simulated 2000 times. In each simulation, the acceptance value (AV) is computed as defined in the pharmacopoeia and is compared to the 15% limit to evaluate compliance to the UDU test requirements [1,2]. The probability p that simulated AV values are equal or smaller than 15% is then computed. This probability p represents the probability to correctly declare the UDU test compliant as well as the probability to correctly declare this test as not compliant. In addition the probability β_{UDU} to have a single result inside the ±15% limit is also computed. β_{UDU} is the probability allowing to make the correct decision about the compliance to the UDU test with p probability. The p probabilities were settled at 0.50, 0.75, 0.90, 0.95 and 0.99. These p probabilities represent the probability to correctly declare the UDU test as compliant or not compliant depending on the situation studied. For instance for $p = 0.95$, these simulations allow to find the probability β_{UDU} that will correctly declare the UDU test as compliant. This probability β_{UDU} is the minimum probability that must have a single result of an analytical method to be within the 15% limit that allows to declare correctly the UDU test as compliant (β^+_{UDU}) or not compliant (β^-_{UDU}) with p chances. The validation of the analytical methods involved for UDU tests should then be performed using these β_{UDU} probability values as explained in the following sections.

Table 2
Content uniformity (CU) case: probability values of β^+_{CU} and of β^-_{CU} for each future result obtained by an analytical method required to correctly declaring the method as valid in the case of truly compliant batches and truly non compliant batches, respectively. p: probability of correctly complying or failing the CU test. n: sample size planned to be used in the CU test.

n	p				
	0.5	0.75	0.9	0.95	0.99
10					
β^+_{CU}	0.9330	0.9716	0.9895	0.9949	0.9990
β^-_{CU}	0.1622	0.2474	0.3369	0.3941	0.5043
30					
β^+_{CU}	0.9772	0.9905	0.9965	0.9983	0.9997
β^-_{CU}	0.0553	0.0872	0.1235	0.1485	0.2016

4. Content uniformity

Prior to the application of the harmonized chapter about uniformity of dosage units [1,2], the general chapter concerning content uniformity (CU) [3] was applied to demonstrate the quality of batches of drug products. CU is still applicable for to existing drug products that were approved before adoption of UDU. For newly developed products the CU rule will not anymore be applicable. A question that is still interesting concerns the validity of analytical methods that are routinely applied to assess CU in existing production processes. Analytical methods that are involved in CU tests should allow to correctly declaring batches as compliant by following the CU rule found in pharmacopoeias.

4.1. Decision methodology

For tablets, the rule states that if each of the 10 individual dosage units content is between 85% and 115% of the average content then the batch is compliant [3]. Analytical methods involved in CU should then ensure that they can reliably answer this requirement.

The dosage units content x_i falling within the [85%; 115%] limits follow a binomial distribution $x_i \sim Bin(n, \beta^+_{CU})$ where n is the sample size set at $n = 10$ and β^+_{CU} is the probability to have a single dosage unit content within [85%; 115%] limits. If it is required that the analytical procedure must correctly declare batches as compliant 95% of the times, then the following equation must be resolved for β^+_{CU}:

$$\beta^{+10}_{CU} = 0.95 \Leftrightarrow \beta^+_{CU} = \sqrt[10]{0.95} = 0.9948838 \cong 0.995 \quad (2)$$

This means that in order to declare an analytical method as valid it has to be demonstrated that for samples with concentration levels at the label claim (100%) there is 99.5% probability to obtain each analytical result with the analytical method within the limits of [85%; 115%]. Table 2 provides different values of β^+_{CU} for different probability values p of correctly passing the CU test.