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Uniformity of dosage units—comparative study of methods and specifications between Eur. Pharm. 3rd and USP 23

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Abstract

Methods and specifications of Eur. Ph. 3rd Ed. and USP 23 for the evaluation of the uniformity of dosage units were compared, in relation to: (i) allowed dispersion of the sample; and (ii) adequability to control the individual contents of active ingredient in relation to the labelled amount. Using the characteristics of the normal distribution curve, we calculate: (1) the highest dispersion allowable, represented by the relative standard deviation of the uniformity of mass of single-dose preparations of Eur. Ph. 3rd Ed., (results were 3.4, 5.1 and 6.8% for $L1 = 5$, $L = 7.5$ and $L = 10$, respectively); and (2) for all the methods studied the allowable units frequency for different intervals of the labelled amount. Differences between the tests of Eur. Ph. 3rd Ed. and USP 23 can lead to acceptance samples with very different individual contents variability, namely if the limit specifications for the strength was $\pm 10\%$. The main reasons for that are: (1) in Eur. Ph. 3rd Ed., the limits are set with reference to the average content of the sample, and in USP 23, they are set with reference to the labelled amount of the active ingredient; and (2), the USP 23 calculates the content of active ingredient in each tablet from the result of the assay, when the weight variation method was used. Taking $\pm 5\%$ of label claim as the specification for the strength of the product, according EEC requirements, the maximum percentage of units outside the range 95–105% of label claim allowed by Eur. Ph. 3rd Ed. and USP 23 tests are similar.

Keywords: Uniformity of content; Uniformity of mass; Single-dose preparations; Pharmaceutical dosage units; Variability

1. Introduction

When considering single-dose preparations, it is fundamental that the patient receives in his individual dose an amount of drug close to that claimed on the label. Because drug content and content uniformity of single-dose preparations depend on a number of processes associated with their manufacture, it is obviously unrealistic to expect every unit of product to possess exactly the same amount of the active ingredient. For that reason, pharmacopeial standards and specifications have been established to provide limits for permissible variations in the amount of active ingredient of individual single-dose units.

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The subject of content uniformity of single-dose units has been considered by a number of authors [1–8]. However, different methodologies and specifications are still prescribed in differents official pharmacopeias like of European Pharmacopeia 3rd (Eur. Pharm. 3rd) [10] and United States Pharmacopeia 23rd (USP 23) [9].

It is the purpose of this paper to point out certain differences which exist between pharmacopeial tests of uniformity of mass and uniformity of content of Eur. Pharm. 3rd and USP 23, analyse them and compare their efficacy.

2. Comparison of the tests

2.1. Scope

The Eur. Pharm. 3rd prescribes two different and alternative tests with different specifications. For single-dose preparations with a content of active ingredient less than 2 mg or less than 2% of the total mass, the test of uniformity of content is prescribed; when the active ingredient to be tested contains more than 2 mg or 2% of total mass, one should use the test of uniformity of mass.

In USP 23, the uniformity of single-dose preparations can be demonstrated by either of two methods, weigh variation or content uniformity. Weigh variation may be applied where the product is a liquid-filled soft capsule, or where the product to be tested contains 50 mg or more of an active ingredient comprising 50% or more, by weight, of the single-dose preparations.

2.2. Methodology and specifications

2.2.1. Uniformity of mass of single-dose preparations of Eur. Pharm. 3rd

This test is based on the use of a representative sample of 20 units weighed individually. The average mass is determined and not more than two of the individual masses deviate from the average mass by more than one percentage deviation (PD) and none deviates by more than twice that percentage that is a function of the average mass and of the pharmaceutical form.

2.2.2. Uniformity of content of single-dose preparations of Eur. Pharm. 3rd

This test is based on the assay of the individual contents of active ingredient of a number of single-units to determine whether the individual contents are within limits set with reference to the average content of the sample. In the first step 10 units was used. If the preparation fails to comply with the test, but the individual contents are within certain limits, the individual contents of another 20 dosage units are determined. Limits vary between three classes of single-dose preparations: (i) tablets, powders for parenteral use and suspensions for injection; (ii) capsules, powders other parenteral use, granules, suppositories and pessaries; and (iii) transdermal patches.

2.2.3. USP 23-uniformity of dosage units, weigh variation method

A total of 10 units are weighed and the average weight is calculated. From the result of the assay obtained by suitable analytical method, the content of active ingredient in each of the 10 units is calculated, assuming homogeneous distribution of the active ingredient. Limits and specifications are the same as the content uniformity method.

2.2.4. USP 23—Uniformity of dosage units, content uniformity method

Like the homonymous test of the Eur. Pharm. 3rd, this test is based on the assay of the individual contents of active ingredient of a number of single-units. However, limits are set not from the average content of the sample, but from the specified amount of active ingredient by unit (label claim). Moreover, a relative standard deviation is specified, which individual contents must comply with.

2.3. Application to cases

For better understanding of the differences between methodology and specifications of the tests of USP 23 and Eur. Pharm. 3rd, these were applied to two hipotetical cases (Figs. 1 and 2). In both cases, the content of active ingredient was 1 mg. In both cases the sample complies with the test when the standards of the Eur. Pharm. 3rd

APPLICATION TO CASES

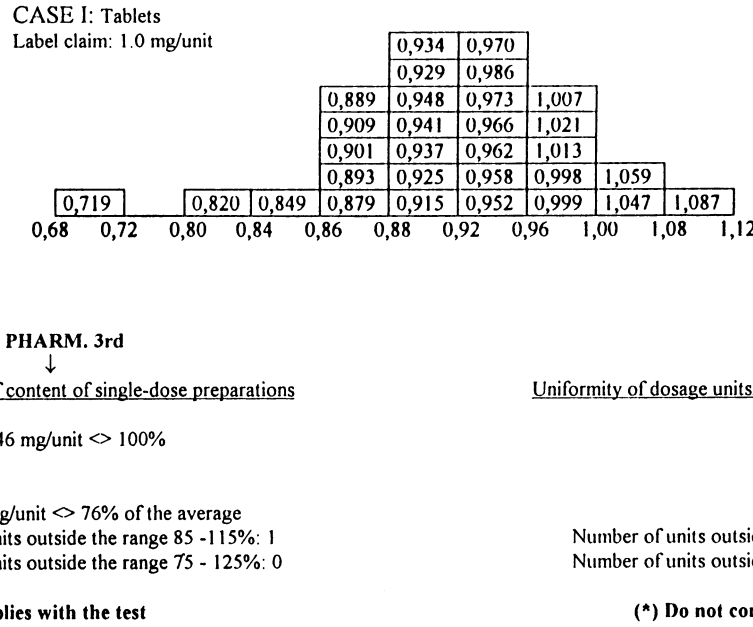

Fig. 1. Differences between methodology and specifications of the tests of uniformity of content of USP 23 and Eur. Pharm. 3rd, were applied to one hipotetical case.

are applied and do not complies with the standards of the USP 23. In the first case, where the determined content is expressed as percentage of label claim, 3 units are outside the range 85–115%. In the second case, the relative standard is more than 7.8%.

3. Analysis of the uniformity specifications of USP 23 and Eur. Pharm. 3rd

3.1. Evaluation of variability allowed by the tests of Eur. Pharm. 3rd

Assuming that the samples used in these tests are representative of their own lots and both have normal distributions, the characteristics of a normal distribution curve were applied to calculate the percentage of units between different ranges. For example, in case II, 68.27% of units is inside the range 91.0–109.0% (Mean $\pm$ 1 SD), 95.45% of units inside the range 82.0–118.0% (Mean $\pm$ 2 SD) and 99.73% of units inside the range 73.0–127% (Mean $\pm$ 3 SD); about 30% of the units are outside the limits of $\pm$ 10% of the label claim. In the same way, it is possible to know the number of outsiders within a range for a specified mean and standard deviation, using a table of normal distribution which correlates the 'percentage exceeding the value' with the standardized value, where standardized value = (value-mean)/SD.

For the test of uniformity of mass of Eur. Pharm. 3rd, it has been verified that 3.4, 5.1 and 6.8% for PD = 5, PD = 7.5 and PD = 10, respectively, are the maximum of standard deviation allowed (Table 1).

The same procedure was used for the test of uniformity of content of the same pharmacopoeia and the results are presented in the Table 2. For the test A, which includes tablets, powders for parenteral use and suspensions for injection, the variability allowed expressed in standard deviation is 8.9%, for $N = 10$ and 8.2% for $N = 30$. For test B, wich includes capsules, powders other than

Table 1
Determined number of units (as % and for $N = 20$) outside differents ranges of the average obtained in the test of Unif. of mass of Eur. Pharm. 3rd, where the characteristics of a normal distribution curve were applied, for samples with differents values of standard deviation (SD) complying with the test of Uniformity of mass of Eur.Pharm. 3rd.

Range =	80–120%[a]		85–115%[a]		90–110%[a]		92.5–107.5%[a]		95–105%[a]		Complies with the test of Unif. of mass of Eur. Pharm. 3rd?		
SD	%	$N = 20$	%	$N = 20$	%	$N = 20$	%	$N = 20$	%	$N = 20$	PD = 5	PD = 7.5	PD = 10
3	<0.005	<0.005	<0.005	<0.005	0.08	0.016	1.2	0.24	9.6	1.92	Yes	Yes	Yes
3.5	<0.005	<0.005	<0.005	<0.005	0.41	0.082	3.2	0.64	15	3	No	Yes	Yes
5.2	<0.005	<0.005	0.39	0.078	5.4	1.08	15	3	34	6.8	No	No	Yes
6	0.08	0.016	1.2	0.24	9.6	1.92	21	4.2	41	8.2	No	No	Yes
6.9	0.38	0.076	3	0.6	15	3	27	5.4	47	9.4	No	No	No

[a] Percentages of the average mass obtained in the test.

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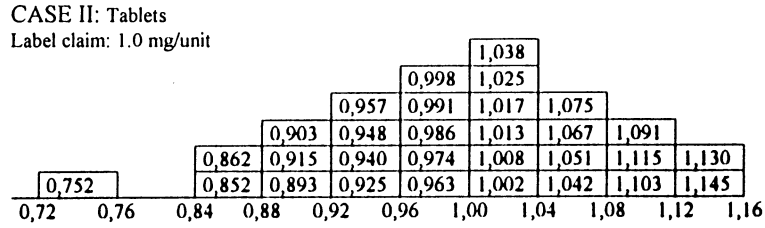

EUR. PHARM. 3rd

↓

Uniformity of content of single-dose preparations

Average: 0.993 mg/unit <> 100%
S = 9.00
S% = 9.0
Min: 0.752 mg/unit <> 75.7% of the average
Number of units outside the range 85 -115%: 1
Number of units outside the range 75 - 125%: 0

Complies with the test

USP 23

↓

Uniformity of dosage units, content uniformity method

Average: 0.993 mg/unit
S = 8.94
S% = 9.0(*)
Min: 0.752 mg/unit
Number of units outside the range 85 -115%: 1
Number of units outside the range 75 - 125%: 0

(*) Do not complies with the test

Fig. 2. Differences between methodology and specifications of the tests of uniformity of content of USP 23 and Eur. Pharm. 3rd were applied to another hipotetical case.

for parenteral use, granules, suppositories and pessaries, the results were 10.1% for $N = 30$ and 11.6% for $N = 10$.

3.2. Adequacy of the different tests studied in relation to the label claim

From Table 3 that resumes the variability allowed for the units of different single-dose preparations by the pharmacopeial tests studied, we can see that for single-units with an average weight of 250 mg or more, the test and specification of the Eur. Pharm. 3rd allow less variability that the USP 23 test. However, since the results obtained in the test of the uniformity of mass of Eur. Pharm. 3rd are not related with the value obtained in the assay, it's possible to obtain a high number of outsiders in the range of 90–100% of label claim, depending of the value determined in the assay. For example, when this value is 90% of the label claim, 50% of the dosage units are outside the range of 90–110%.

Using the methodology already described, it could be seen that for the maximum variability allowed in the USP 23 tests (7.8%), 22.0% of the dosage units are outside the range of 90.0–110.0% of label claim when the determined amount of active ingredient by unit was 97.0% (Table 4). When the value of 95.0% is obtained in the assay, a sample with 30 units with a normal distribution, has more than 3 units outside the range of 85–115% of label claim (and fails the test) and has 28.7% of units outside the range of 90.0–110.0% of label claim.

For samples with the maximum standard deviation allowed by the pharmacopeial tests studied, the Table 5 show the number of outsiders in the range 95.0–105.0%, 90.0–110.0%, 85.0–115.0% and 75.0–125.0% of label claim. When the average of the test was 90% of label claim, it can be seen that the Eur. Pharm. 3rd allows more than 50% of outsiders in the range of 90.0–110.0% of label claim, whereas the USP 23 tests allow only 27.2% on the same range. When the average of

Table 2
Determined number of units (as %, for $N = 10$ and for $N = 30$) outside different ranges of the average obtained in the test of Unif. of content of Eur. Pharm. 3rd, where the characteristics of a normal distribution curve were applied, for samples with different values of SD. Complying with the test of Unif. of content of Eur. Pharm. 3rd.

Range =	75–125%[c]			85–115%[c]			Complies with the test of Unif. Of content of Eur. Pharm. 3rd?			
SD	%	$N = 10$	$N = 30$	%	$N = 10$	$N = 30$	Test A[a]		Test B[b]	
							$N = 10$	$N = 30$	$N = 10$	$N = 30$
7.8	0.14	0.014	0.042	5.4	0.54	1.62	Yes	Yes	Yes	Yes
8.2	0.23	0.023	0.069	6.6	0.66	1.98	Yes	Yes	Yes	Yes
8.3	0.25	0.025	0.075	7.0	0.7	2.1	Yes	No	Yes	Yes
8.9	0.48	0.048	0.144	9.2	0.92	2.76	Yes	No	Yes	Yes
9.0	0.6	0.06	0.18	10	1.0	3.0	No	No	Yes	Yes
10.1	1.3	0 013	0.39	13	1.3	3.9	No	No	Yes	Yes
10.2	1.4	0 014	0.42	14	1.4	4.2	No	No	Yes	No
11.6	3.1	0.31	0.93	19	1.9	5.7	No	No	Yes	No
11.7	3.2	0.32	0.96	20	2.0	6.0	No	No	No	No

[a] Test A, tablets, powders for parenteral use, suspensions for injection.
[b] Test B-Capsules, powders other than parenteral use, granules, suppositories, pessaries.
[c] Percentages of average content obtained in the test.

Table 3
Maximum variability (expressed as RSD) allowed by the pharmacopeial tests studied

	Uniformity of mass Eur. Pharm. 3rd			Uniformity of content of pH. Eur. 3rd				Uniformity of dosage units of USP 23	
				Test A		Test B			
	PD = 5	PD = 7.5	PD = 10	$N = 10$	$N = 30$	$N = 10$	$N = 30$	$N = 10$	$N = 30$
Allowed RSD	3.4[a]	5.1[a]	6.8[a]	8.9[b]	8.2[b]	11.6[b]	10.1[b]	6.0[c]	7.8[c]

[a] Transcribed value from Table 1.
[b] Transcribed value from Table 2.
[c] Official specifications.

the test was 95% of label claim, the Eur. Pharm. 3rd allows about 50% of outsiders in the range of 95%–105% of label claim, which is similar to the value allowable by the USP 23.

4. Discussion and conclusions

Namely for tablets and capsules, pharmacopeial tolerances appear generally to be too wide and do not consider the pharmaceutical manufacturing technology in present. In both pharmacopeias studied, different variabilities are allowed, depending on the pharmaceutical form. From the consumer point of view, these differences are not justified, however he could accept differences in uniformity according to the safety margin of a drug. For tablets and capsules, wherever the Eur. Pharm. 3rd do not prescribe the test of uniformity of content, different variabilities are allowed depending on the average weight. We think that there are not technical reasons for that and the USP 23 does not do it.

Table 4
Determined number of units (as % and for $N = 30$) outside differents ranges of label claim, where the characteristics of a normal distribution curve were applied, for samples with differents values of active ingredient, and with the maximum relative standard deviation allowed by the test of uniformity of dosage units of USP 23

Amount of active ingredient (% of label claim)	RSD = 7.8					Complies with the test of uniformity of dosage units of USP 23
	75–125		85–115		90–110	
	%	$N = 30$	%	$N = 30$	%	
95.0	0.505	0.1515	10.5	3.16	28.7	No
95.5	0.435	0.1305	9.1	2.73	27.2	Yes
97.0	1.115	0.3345	7.05	2.115	22.7	Yes
100.0	0.12	0.036	5.4	1.62	20.0	Yes

Table 5
Determined percentage of units outside the referenced ranges of label claim, for samples with the maximum standard deviation allowed by the pharmacopeial tests studied.

Test	Maximum allowed RSD	Average of the test (% of label claim)	Percentage of outsiders in the range of			
			95–105% of label claim	90–110% of label claim	85–115% of label claim	75–125% of label claim
Unif. of mass of Eur. Pharm. 3 PD = 5	3.4	90	93.0	50.0	7.0	<0.005
		95	50.0	7.0	0.2	<0.005
Unif. of mass of Eur. Pharm. 3 (PD = 7.5)	5.1	90	83.0	50.0	16.5	0.2
		95	50.0	16.7	2.5	<0.005
Unif. of mass of Eur. Pharm. 3 (PD = 10)	6.8	90	77.0	50.2	23.0	1.4
		95	50.0	25.4	9.9	0.2
Unif. of content of Eur. Pharm. 3 Test A	8.9	90	71.8	51.2	28.2	4.6
		95	52.2	33.6	14.3	1.3
Unif. of content of Eur. Pharm. 3 Test B	11.6	90	65.4	54.2	34.6	9.6
		95	54.3	44.0	23.8	9.1
Uniformity of dosage units of USP 23	7.8	95.5	47.5	27.2	10.5	0.4

When the requirements of strength of the product was ± 10%, differences between methodology and specifications of Eur. Ph. 3rd Ed. and USP 23 for the evaluation of the uniformity of dosage units lead to acceptance samples with very different individual contents variability and with a probable number of units outside the range of 90–110% of label claim very different. The main reasons for that are: (1) in Eur. Ph. 3rd Ed., the limits are set with reference to the average content of the sample, and in USP 23, they are set with reference to the labelled amount of the active ingredient; and (2), the USP 23 calculates the content of active ingredient in each dosage unit from the result of the assay, when the weight variation method was used.

When the specifications limits of strength was ± 5%, the probable number of units outside the range of 95–105% of label claim allowable by Eur. Ph. 3rd Ed. and USP 23 are similar.

Results showed that the uniformity of dosage units implemented by the USP 23 is a more reliable procedure to assure the pharmaceutical quality of single-dose preparations, independently of the specifications limits of strength of the product. However, with ± 5% for the specification of strength, according to EEC requirements, the Eur. Ph. 3rd Ed. and USP 23 uniformity tests allows similar dosage unit variabilities.

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