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ATTESTATION OF A TEST SAMPLE OF PIRACETAM TO DETERMINE THE ACCOMPANYING IMPURITIES WITHIN THE PROFESSIONAL TESTING PROGRAM

Abstract: *The attestation of the test sample to determine the accompanying impurities in testing a professional testing program. The attribute value has obtained the content of the accompanying impurities in the test sample of piracetam. Confirmed the homogeneity and stability of the piracetam content test sample accompanying impurities. Criteria for evaluating participants' results were developed, testing a professional testing program to determine the content of the accompanying impurities. Forms of tables have been developed to populate the test results participants.*

Key words: *professional testing program, test sample, certification, high-performance liquid chromatography, suitability testing chromatographic system, evaluation criteria.*

Language: *English*

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Introduction

Medicines Quality Control Laboratories have a great responsibility for authorized government agencies and customers to provide right and accurate analytical research findings that base their conclusions on the quality of medicines. Therefore, such laboratories must continuously confirm their competence and the reliability of the data they receive following the officially recognized mechanisms and demonstrate it to both the state accredited accrediting bodies and directly to the customers. One of the standards and accepted ways of doing this is the participation of the laboratory in inter-laboratory comparative tests [1, p.9].

There are many programs in the world between comparative laboratory tests for control laboratories in various fields - medical, food, environmental, and others. In the pharmaceutical area, popular overseas relative research programs are being developed and implemented by such well-known international

organizations as the European Directorate for Quality of Medicinal Products (EDQM), the World Health Organization (WHO), and others. However, for most Ukrainian laboratories, participation in these programs involves some difficulties - material (cost of the involvement in the program), logistics (time and cost of delivery of test samples from abroad), and language (understanding and providing information in English only).

Therefore, in Ukraine since 2001, a national program for laboratory comparisons, called the Professional Testing Program of Laboratories for Quality Assurance in Medicinal Products (PTP), has been developed and successfully implemented in 2001 and has 13 annual rounds of testing. This program has some peculiarities in comparison with its foreign counterparts, in particular, regarding approaches to the choice of testing method, attestation of test samples provided to test participants, and criteria for evaluating the results of participants. Unlike most similar programs that evaluate the effects of testing the participants on the statistical 3s-criterion, the PTP proceed from the specific pharmacopoeial requirements to the actual drugs described in the pharmacopeia in formulating their evaluation criteria. Controlling laboratories of pharmaceutical enterprises, state and independent laboratories for quality control of drugs, both domestic and from abroad, take part in the PTP.

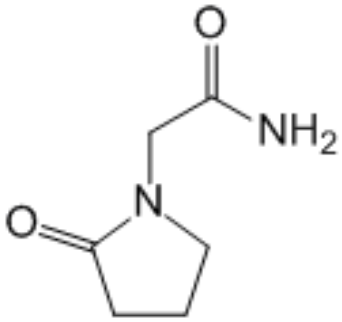
According to the concept of PTP, when the attestation of the testing sample (TS) is taken, it is necessary not only to determine the attributable value of a specific quality characteristic and the level of uncertainty with which this value is obtained but also to make sure that the attested TS provides an opportunity to trace the compliance of participants with pharmacopoeial requirements. Thus, with a sufficient degree of reliability to obtain the test results are in line with the test results. Besides, according to the methodology with which the certification is conducted and following the results of the accreditation, form a protocol for filling in the test participants to monitor the quality of the test participants test and identify violations and non-compliance with pharmacopoeial requirements [1,p.15;2,p.33;3,p.876;4,p.1085;5,p.29;6,p.10;7,p.5;8 ,p.92;9,p.41;10,p.13;11,p.436;12,p.85;13,p.3; 14,p.13;15,p.112;16,p.23; 17,p.532]. .

The purpose of this work is to certify the test sample of piracetam. Accompanying impurities in the test sample of piracetam should be determined. Also, there is a strong need for the study of the homogeneity and stability of the test sample of piracetam. The reproducibility of the test of the suitability of the chromatographic system is important to be determined.

The experimental part.

Piracetam. Pharmacopoeial quality indicators.

Piracetam substance was selected as a candidate for PTP certification. Piracetam is a nootropic drug, historically the first and foremost representative of this group of drugs. Chemically, it is a derivative of pyrrolidone and is the ancestor of the group of "racetam", a class of psychoactive nootropic substances which have the pyrrolidone core.



The pharmacopoeial quality requirements of this substance are represented in the Piracetam monograph included in Ph.Eur. and SPU (National Pharmacopeia of Ukraine).

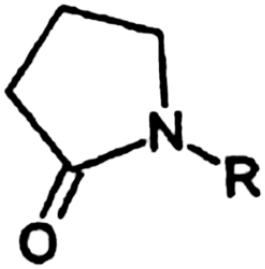
Properties: Powder is white or almost white. Easily soluble in water P, soluble in ethanol (96%) P.

Quality/purity indicators are transparency of solution; the color of the solution; accompanying impurities; heavy metals; weight loss on drying; ash sulfates.

Quantitative determination.

Famous impurities

Specified impurities: A, B, C, D.



- A. R=H : pyrrolidone - 2-one (2-pyrrolidone),
- B. R=$CH_2 - CO - O - CH_3$: methyl (2-oxopyrrolidin-1-yl) acetate,
- C. R=$CH_2 - CO - O - C_2H_5$: ethyl (2-oxopyrrolidin-1-yl) acetate,

- D. R=$CH_2 - CO_2H$: (2-Oxopyrrolidin-1-yl) acetic acid.

Equipment:

Scales analytical MC 210 S, firms Sartorius, Germany.

Scales analytical AUW220D, from Shimadzu, Japan.

713 pH Meter, Metrohm, Switzerland.

Chromatograph with diode-matrix detector Waters Aliance.

Measuring dishes of accuracy of class A for solution preparation.

Chromatographic columns:

- Column 1: Waters XTerraRP 18,4.6 * 250 mm, 5 μm with pre-column;

- Column 2: Agilent Zorbax Eclipse XDB-C18, 4.6 * 250 mm, 5 μm with pre-column;

- Column 3: Supelco Discovery C18, 4.6 * 250 mm, 5 μm with front column (1);

Standard sample:

Pharmacopoeial standard samples of SPU of piracetam with a content of the basic substance 99.8% (uncertainty of attestation does not exceed 0.5%).

Reagents:

Water P;

Acetonitrile P;

Dicalium Hydrophosphate P;

Phosphoric acid diluted R.

Test sample:

The substance used was Piracetam, a product of the People's Republic of China, provided by the Health Pharmaceutical Company LLC, Ukraine, 20110520, as a test sample.

Methods

The determination of the accompanying impurities was carried out according to the method of the indicator "Compound impurities" of the monograph of SPU "Piracetam", in accordance with the requirements of the general article of the SPU "2.3.29. Liquid chromatography "[16,p.21], SPU" 2.2.46.Chromatographic separation methods ".

Accompanying impurities. Liquid chromatography (2.2.29).

Test solution (a). 50.0 mg of the substance was dissolved in a mixture of acetonitrile P1 - water P (10:90) and brought the volume of the solution with a mixture of solvents up to 100.0 ml.

Comparison solution (a). 5 mg of the substance and 10 μl of 2 - pyrrolidone P were dissolved in acetonitrile P1 - water P (10:90), and the solution volume was adjusted to 100.0 ml with the same solvent mixture.

Comparison solution (b). 1.0 ml of the test solution (a) was adjusted with acetonitrile P1 - water P (10:90) to a volume of 100.0 ml. 5 ml of the resulting solution was adjusted with a mixture of acetonitrile P1 - water P (10:90) to a volume of 50 ml.

Column:

-size: 0.25 m × 4.6 mm;

-stationary phase: silica gel for chromatography, octadecyl silyl, end-capped P (5 μm.).

Verification of the suitability of the chromatographic system

According to the SPU, the Chromatographic System Verification Test (CSVT) is an integral part of the procedure and is used to ensure the required quality of the chromatographic system.

The method of the indicator "Compound impurities" of the monograph of SPU "Piracetam" regulates only two parameters of CSVT, which is determined from the chromatograph of the comparison solution (a):

- a degree of separation of at least 3.0 between the peaks of piracetam and impurity A;

- symmetry coefficient: no more than 2.0 for the piracetam peak.

However, under the requirements of the general article Ph.Eur./SPU "2.2.29. Liquid chromatography "typically uses parameters such as nominal efficiency, retention factor (mass partition coefficient), degree of separation, relative retention, and symmetry coefficient to evaluate the functioning of the column, as well as, in tests for the content of accompanying impurities, except should be controlled by such an important parameter as the limit of quantification (LQ). It should be observed that the pharmacopoeial requirements [15, p. 111], LQ should be no more than the boundaries that are not taken into account. According to the method of the Piracetam monograph [17,p.532], the unaccounted limit is 0.05%, that is, the LQ should be no more than 0.05%, from which it follows that the calculated S / N ratio should be not less than 20. The calculation of these parameters for various analytical columns is given in table 1.

For the reliable certification of the substance piracetam as a TS for testing on the indicator "Compound impurities", it is necessary to analyze the sample, which is certified on as many chromatographic columns as possible. Also, the method of indicator should be checked. Therefore, the suitability of the chromatographic system, which is an integral part of the technique, was tested for six chromatographic columns. The results of the definition, as well as the regulation (if any), are given in Table 1, where bold indicates the parameters of the CSVT that do not meet the requirements.

It turned out that not all columns with the sorbent type, particle size, and geometric parameters that meet the requirements of the method meet the needs of the suitability of the chromatographic system. The following studies were performed on columns 2 and 6, which do not meet the requirements.

According to the information above, when testing in PTP, it was necessary to monitor how test participants understand the requirements for CSVT and comply with them. Thus, on the basis of the CSVT data obtained from the TS certification of piracetam, tables on the performance of CSVT for the chromatograph of the comparison solution (a) (Table 2) and the comparison solution (b) (Table 3) were developed and were included in the testing protocol.

Determination of the content of the accompanying impurities in TS of piracetam

The presence of impurities in the substance of piracetam was determined by the method of the indicator "Compound impurities" monograph SPU "Piracetam" on columns 2 and 6. Initially, two parallel determinations of three samples of the sample, selected from different packing cities, thereby determining the homogeneity of the sample. Also, the stability of the substance piracetam over time was monitored at intervals of about one month and three months, respectively. The results of determining the content of impurities are shown in table 4.

As can be seen from the table, no accompanying impurities in the TS of piracetam were found. The same conclusion was reproduced by the results of all definitions, thus confirming that the piracetam was homogeneous and stable over the testing.

Conclusion.

According to the results of the certification, it can be concluded that the TS of piracetam complies with the requirements of SPU of "Piracetam" monograph due to the content of the accompanying impurities. There are no accompanying impurities. It means that their content does not exceed the unaccounted for limit (0.05%).

Test participants should draw the same conclusion to obtain satisfactory test results in PTP.

Table 1. Parameters of the suitability of the chromatographic system

	Time of staying	Number of theoretical plates	Staying factor (k)	Symmetry coefficient (As)	Measure of separation (Rs)	Signal	MKV,%
Reglamentation	-	-	-	Less than 2	Less than 3	Less than 20	Less than 0,05
Column 1	3,248	6278	0,624	0,98	1,40	22	0,045
Column 2	3,177	8638	0,59	1,84	3,03	27	0,037
Column 3	3,641	5812	0,82	1,23	1,63	16	0,063
Column 4	3,978	7297	1,00	1,31	2,21	30	0,033
Column 5	2,96	5356	0,48	1,48	2,12	15	0,067
Column 6	3,245	7563	0,622	1,16	3,16	25	0,04

Table 2. CSVT from chromatograms of comparison solution (a) to be filled by participants

Sample, mg	Volume of pirolidone, ml	Number of theoretical plates	Staying factor (k)	Symmetry coefficient (As)	Measure of separation (Rs)

Table 3. CSVT from chromatograms of comparison solution (b) to be filled by participants

Dilution	Peaks square	An average value of peak square	Relation S/N	Limit of quantative determination

Table 4. The results of the determination of the accompanying impurities in TS of piracetam

The date of the experiment	Availability of chromatographic system	Content of individual impurities	Sum of impurities	Result
11.08.2019	Fit for	An additional peaks are absent on chromatograms	Absent	No impurities
17.08.2019	Fit for	An additional peaks are absent on chromatograms	Absent	No impurities
06.09.2019	Fit for	An additional peaks are absent on chromatograms	Absent	No impurities
18.01.2020	Fit for	An additional peaks are absent on chromatograms	Absent	No impurities

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