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Study of Stability and Expiration Date of Intralin Powder in Bottles 0.5 and 1.0 G

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Abstract- **The study of antibiotics as a potential drug, in addition in order to develop effective methods for assessing quality in preclinical stage includes the establishment of stability and expiry date. This study regulatory requirement is necessary to establish the time during which the substance remains unchanged physical, chemical, biological properties, i.e. suitable to all requirements of regulatory documentation. Justification of the established expiry date of the substance is included in the section of the registration dossier on the methods of quality assessment. The purpose of this study is to establish the expectancy duration and stability of the antibiotics of the cephalosparin group of a number produced by "Jurabek Laboratories" JV LLC.**

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I. Introduction

Stability (sustainability) is a factor in the quality of medicines. The criterion for the stability of a medicinal substance is the preservation of its quality, i.e. appearance, solubility, authenticity, good quality and quantitative content. The decrease in the quantitative content of the pharmacologically active substance in the drug confirms its instability. The decrease in the quantitative content of the drug by 10% should not occur within 3-4 years in the finished dosage forms.

To increase stability, chemical processes occurring during storage of drugs are investigated and methods are created to inhibit these processes. The solution of these problems is possible only on the basis of the development of methods for analyzing medicinal substances in the presence of their decomposition products. The results of these studies are taken into account when developing the technology of obtaining drugs and ND.

Products of organic synthesis make up a significant part of the arsenal of medicines of modern medicine. Despite the significant number of drugs used in medical practice, the search for more effective and safe ones is constantly underway. Largely, this refers to groups of drugs used to treat inflammatory processes caused by bacterial microflora [1, 2].

II. Material and Methods

Material of the study is the substance "Intralin" - (cefazolin sodium salt/5-thia-1-azabicyclo [4.2.0] octa-2-en-2-carboxy, 3-[[(5-methyl-1,3,4-thiadiazole-2-yl) thio] methyl]-8-oxo-7-[[(1H-tetrazole-1-yl) acetyl] amino]-, sodium salt (βY-trans)-) 0.5 or 1,0 g, powder for the preparation of injection solutions released by JV "Jurabek Laboratories" LLC.

The experiments were carried out on 3 series of antibiotics obtained in the laboratory by the methods. All samples of antibiotics were pre-analyzed in accordance with the requirements of the FS project developed by the author.

- IR spectra were obtained by Protégé 460 "Nicolet Instruments Corporation" (USA);
- UV spectra were obtained by UV-spectrophotometer 8453 by Agilent Technologies (Germany);
- HPLC chromatograms were obtained by UV-spectrophotometer HPLS 1260 by Agilent Technologies (Germany);
- Used thermostat TOVL-80.
- Auxiliary equipment and reagents were also used in the work.
- Used reagents, solvents, indicators that meet the requirements of the Global Fund XI ed. Test methods for authenticity and quantification, developed earlier by the authors.

In determining the expiration dates, they were guided by the requirements of the Global Fund XI and the Interim Instruction I-42-2-82. According to these documents, the establishment of stability is possible using the following methods:

– Test under long-term storage conditions;
– Testing under conditions of "accelerated aging" according to the Interim Instruction I 42-2-82.

The method of "accelerated aging", based on the law of van't Hoff, establishes the relationship between the shelf life of the substance and storage temperature

$$C = A^{\frac{tэ-txp}{10}} \frac{tэ - txp}{10}$$

Where, experimental substance series:

tэ is the temperature of experimental storage.

t_{xp} - storage temperature.

A is the temperature coefficient of the chemical reaction rate when the temperature increases by 10 °C (assumed 2) [3].

Investigations were carried out on 3 series of cefazolin substance (040113, 070113, 100113) at an

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experimental storage temperature of 60 °C. Samples were placed in vials of 0.5 or 1.0 g of the drug from a glass tube of the type FO-1-15 or 00-1-20 according to TU 64-2-10-87 or imported in accordance with ISO 8362-1 and ISO 8362-4, hermetically sealed with stoppers of rubber stamps I-51ili 52-599 / 1, or IR-119po TU 38.006108-90 or imported according to ISO 8362-2, compressed with aluminum caps of type K-2, as per ISO 6462-686 or imported according to ISO 8362-6. Quality control was carried out at time intervals (11.5 days), equivalent to 6 months of storage in natural conditions according to the indicators given in table 1 [4,5].

Table 1: Specification: "Intralin 0.5 or 1.0 g" powder for the preparation of injection solution produced by J V Jurabek Laboratories LLC Uzbekistan

Indicators	Methods	Standard
Description	Visual	Powder white or almost white, very hygroscopic
Solubility	Visual	Easily soluble in water, very little soluble in 96% alcohol
Authenticity	Infrared spectrometry	1. IR absorption spectrum of drug sample obtained in disks with potassium bromide (about 2 mg of the drug in 200 mg of potassium bromide) from 4000 to 450 cm "should correspond to the spectrum of the RSO cefazolin sodium salt (about 2 mg of the RSO cefazolin sodium salt in 200 mg of potassium bromide).
	UV Spectrophotometer	2. The ultraviolet absorption spectrum of the solution in the region from 220 to 350 nm should have an absorption maximum at a wavelength of 272+2 nm.
	Chemical reactions	3. The drug gives a characteristic reaction to sodium.
Quantitative content	HPCL	From 850 to 1050 mcg, calculated on the dry matter

The results of the experiment (Table 2) showed that the cefazolin substance remains stable for 69 days of experimental storage, which corresponds to 1104 days of storage under natural conditions, calculated according to the van't-Hoff rule:

$$C = A^{\frac{t_э - t_{хр}}{10}} = 2^{\frac{60-20}{10}} = 16 - 16 \cdot 69 = 1104 \text{ сут.}$$

compliance rate.
Hence, the shelf life, which is 3 years.
Storage temperature, which allows to ensure the established shelf life is:

$$t_{хр} = t_э + \frac{10}{lgA} \cdot lg\frac{C_э}{C} = 60 + \frac{10}{lg2} \cdot lg\frac{69}{1104} = 20\,°C$$

The maximum allowable storage temperature is:

$$t_{макс.доп.} = 20\,° + \frac{10}{lgA} \cdot lg\frac{C_э}{2 \cdot 365} = 20 + \frac{10}{lg2} \cdot lg\frac{1104}{730} = 26\,°C$$

Thus, as a result of the studies conducted by the method of "accelerated aging", the shelf life and temperature storage of the cefazolin substance has been established.

Thus, a preliminary shelf life of 3 years can be established.

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Table 2: The results of studies on the stability of drug cefazolin by the method of "accelerated aging"

Series	Life expectancy, in days	Description	Authenticity			Quantitative content, %
			IR-spectrum	UV spectrum	Characteristic reaction to sodium	
1	2	3	4	5	6	7
040113	0	White or almost white crystalline powder; odorless	The spectrum corresponds to the spectrum of RSO cefazolin	Maximum at 272+2 nm.	Yellow precipitate	99,9
	11,5	- // -	- // -	- // -	- // -	99,85
	23	- // -	- // -	- // -	- // -	99,86
	34,5	- // -	- // -	- // -	- // -	99,84
	46	- // -	- // -	- // -	- // -	99,96
	57,5	- // -	- // -	- // -	- // -	99,75
	69	- // -	- // -	- // -	- // -	99,71
070113	0	White or almost white crystalline powder; odorless	The spectrum corresponds to the spectrum of cefazolin RSO	Maximum at 272 + 2 nm.	Yellow precipitate	99,95
	11,5	- // -	- // -	- // -	- // -	99,97
	23	- // -	- // -	- // -	- // -	99,85
	34,5	- // -	- // -	- // -	- // -	99,84
	46	- // -	- // -	- // -	- // -	99,85
	57,5	- // -	- // -	- // -	- // -	99,72
	69	- // -	- // -	- // -	- // -	99,70
100113	0	White or almost white crystalline powder; odorless	The spectrum corresponds to the spectrum of cefazolin RSO	Maximum at 272+2 nm.	Yellow precipitate	99,90
	11,5	- // -	- // -	- // -	- // -	99,85
	23	- // -	- // -	- // -	- // -	99,82
	34,5	- // -	- // -	- // -	- // -	99,91
	46	- // -	- // -	- // -	- // -	99,93
	57,5	- // -	- // -	- // -	- // -	99,75
	69	- // -	- // -	- // -	- // -	99,72

The study of the stability of cefazolin was also carried out by the method of long-term storage. For this, cefazolin series 151210, 171210, and 201210 were stored in dry and dark place that ground-glass jars with ground glass stoppers at room temperature. Quality control was carried out on the main indicators, at intervals equal to 1 year of storage. Studies (tab. 3) showed that the stability of the substance cefazolin in long-term storage conditions is maintained for at least 3 years.

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Table 3: The results of studies on the stability of drug cefazolin in vivo

Series	Expiry date, in years	Description	Authenticity			Quantitative content, %
			IR spectrum	UF spectrum	characteristicre actiontosodium	
1	2	3	4	5	6	7
151210		White or almost white crystalline powder; odorless	The spectrum corresponds to the spectrum of cefazolin RSO	Maximum at 272+2 nm.	Yellow precipitate	99,40
	1	- // -	- // -	- // -	- // -	99,81
	2	- // -	- // -	- // -	- // -	99,79
	3	- // -	- // -	- // -	- // -	99,72
171210	0	White or almost white crystalline powder; odorless	The spectrum corresponds to the spectrum of cefazolin RSO	Maximum at 272+2 nm.	Yellow precipitate	99,81
	1	- // -	- // -	- // -	- // -	99,78
	2	- // -	- // -	- // -	- // -	99,73
	3	- // -	- // -	- // -	- // -	99,69
201210	0	White or almost white crystalline powder; without smell	The spectrum corresponds to the spectrum of cefazolin RSO	Maximum at 272+2 nm.	Yellow precipitate	99,87
	1	- // -	- // -	- // -	- // -	99,81
	2	- // -	- // -	- // -	- // -	99,78
	3	- // -	- // -	- // -	- // -	99,75

III. Conclusion

1. It was found that the stability and shelf life of the investigated drug, established by the method of "accelerated aging" at a temperature of 60 °C, is not less than 3 years, and the storage temperature is from 20 to 26 °C.
2. It is established that the substance of cefazolin in the conditions of long-term storage at room temperature in a dark place is not less than 3 years.

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5. In accordance with modern requirements, in accordance with the General technical regulation on the safety of medicinal products (Appendix to the Decree of the KMRUz dated October 27, 2016 No. 365).

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