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VALIDATION RESEARCHES OF THE PRODUCTION PROCESS OF THE GLUCOSE MEDICINE INFUSION SOLUTION

Goal. *The purpose of the work is to carry out validation researches of the technological process of production of glucose solution for infusions using the bracketing approach for batches of different volumes and fullness the filling of containers.*

Techniques. *The object of the research is the manufacturing process for the manufacture of glucose infusion solution 50 mg / ml. Data collection was carried out on the basis of series production protocols, protocols for analysis of of raw materials and supplies, intermediate and finished products, series packaging protocols, other protocol and registration documentation of the drug production process. Validation studies were carried out at all stages of the technological process with the determination of critical parameters, confirming the quality of the product under the investigated parameters and the reproducibility of the results when the initial parameters were changed, such asy: preparation of raw materials, solution preparation, filtration of solution, filling and capping of vials, sterilization, inspection, packaging.*

Results. *The technological scheme for the production of the drug Glucose solution for infusion of 50 mg / ml was determined. Validation studies and data collection were carried out on 3 industrial series, determined by the bracketing method: 2000 l with a dosage of 200 ml of medicine per bottle (min. series size, min. dosage), 5000 l and a filling volume of 400 ml (min. series size for bottles of 400 ml), 10000 l with packaging in bottles of 500 ml (max. series size, max. dosage).*

The obtained research results indicate the reproducibility and normativity of the quality indicators of intermediate and finished products in accordance with the regulatory documentation and declared acceptance criteria for all investigated release forms of 200 ml, 400 ml and 500 ml in glass bottles. The results of validation examinations of the technological process for preparing a solution for glucose infusion solution of 50 mg / ml is representative of the intermediate parameters of drug production and are determined to be satisfactory to ensure stable quality indicators.

Scientific novelty. *The results of validation researches were obtained using a scientifically based approach to the selection of limit values, risk analysis and determination of critical parameters.*

Practical value. *The results of the study are of practical importance for organizing the validation of the technological process for the production of medicines with several dosages, volumes of production series, various sizes of container filling, in order to reduce the number of tests to save resources and time.*

Key words: *technological process, validation, bracketing approach, acceptance criteria.*

Introduction. To this date, glucose remains an indispensable medicinal preparation for deintoxication to remove toxins from the body, to monitoring of filling of physiological fluid losses, and is an easily absorbed source of valuable nutrition that increases the body's energy reserves and improves its function, especially in extreme medicine. For infusion solutions, as dosage drug formulations for parenteral administration, special requirements (apyrogenicity, sterility, stability, absence of mechanical inclusions) are wanted, as well as specific requirements that need to be implemented into the technological processes of specific technological stages, inasmuch during introducing into the blood channel parenteral drugs should perform their functional purpose, as well as they have to completely eliminate from the body without accumulating [1].

In the industrial production of parenteral medicinal products, should be taken into account: ISO standards, guidelines and requirements of good manufacturing practice [2, 3] - GMP requirements for sterile drugs, in particular: identification of points related to minimization of

contamination risks; microbiological - pyrogenic objects; general requirements for pharmaceutical production - greening, air locks; sterile materials, staffing requirements; separate areas for operations: component preparation, product preparation, filling, sealing, sterilization, etc.; purity level; filtered air; laminar airflow, air flow rate, number of air changes, air samples; compliance with standards; workplace and environment; technology; barriers and automated systems [4].

The organization of the production of infusion solutions requires special approaches to ensure the quality and special sterility of drug preparations that are designed to support the life's activity of cells, organs and physiological properties of human blood. Therefore, an effectively organized validation of technological processes by international standards is an obligate component of the life cycle of drug preparation production, one of the processes in the quality management system of modern pharmaceutical companies and combines the approaches outlined in the rules of Good Manufacturing Practice (GMP) and ISO standards 9001 [2, 3]. Validation of technological processes in accordance with the requirements of good manufacturing practice is carried out with the purpose of documented confirmation that the process carried out within the established parameters can occur with adequate efficiency and reproducibility for the production of the medicinal product in accordance with previously established specifications and quality indicators [5].

Solutions for glucose based infusions are commercially produced in glass or polymeric containers of various volumes: 100 ml, 200 ml, 250 ml, 500 ml, 1000 ml, 2000 ml, 3000 ml, 5000 ml. The sizes of batches can collect from 1000 liters to 15000 liters or even more. Considering the fact that on the pharmaceutical enterprise are possible several sizes of production batches in manufacturing and a large number of possible variants of prepacking are used, were determined that carrying out complete validation of a glucose infusion solution of 50 mg / ml is quite complex and requires proper provision of the validation process with the necessary resources - specialized equipment, highly qualified specialists and considerable costs for conducting experiments. Therefore, it is appropriate to use a bracketing method that will solve the problem of excessive costs in order to save resources during the organizing the process for serial production of the drug preparation, and to facilitate the validation during the scaling of the process [6].

In instructions of various regulatory authorities are not provided clear guidance on the number of series for validation studies or certain methods for determination and justifying of the number of industrial batches of medicinal products having several sizes of batches in manufacturing and the large number of possible dosage options. But the critical aspect is rationalisation of the number of the series based on knowledge of the drug and process, large-scale/clinical manufacturing experience, control strategy, overall process risk, and statistical assurance/confidence [7]. Leading guides of the process validation recommend approaches contained using bracketing in case of the manufactoring of drug preparations in containers of different sizes or for different filling completeness for the same system container / closure. In the case of the validation of technology of preparation with several doses, using of bracketing is only possible provided that the composition of preparation with the several doses is identical or very similar. Scheme / protocol of research, which provides during the validation of the experiment process only those series, ewhich are characterized by the limit values of certain predefined and substantiated characteristics, such as force of action (dosage), batch size, packing size, provides that validation for any limit values is representative for intermediate values [5, 8].

Analysis of recent studies and publications has shown that general requirements for the organization of validation of technological processes of drug preparation manufactoring are shown in a number of regulatory documents [3, 5, 8]. Was developed the algorithm of validation of technological process of production of sterile medicine drugs with determination of critical parameters of technological process and establishment of tolerable deviations of quality indicators [9, 10]. In the literature are briefly presented validation tests of model series of the medicine drug Pharmasulin H, solution for injection, 100 IU / ml in vials and cartridges of 3 ml. As a confirmation of the predicted results of the implementation, was described a scheme of validation of the technological process of industrial manufactoring of Sinart preparation, solution for injections 200 mg / ml [1]. In foreign publications, information of the results of validation experiments of solutions for parenteral using is very limited. Thus the ranges of technology process parameters for injectable solutions, which have to be validated, at enterprise Hikma, USA, have been developed in accordance with standards and guidelines [11, 12]. However, an analysis of recent literary data has proved that there is an absence of validation studies in scientific publications, which were conducted within the production processes of sterile infusion solutions, in particular using the bracketing approach.

Statement of the problem. The purpose of the work is to conduct validation studies of the technological process of manufactoring of glucose solution for infusions using the bracketing approach for batches of different volumes and fullness filling of containers.

Research materials and methods. The object of the study is the manufacturing process of producing a solution for glucose infusions of 50 mg / ml. A validation plan using the bracketing approach was developed based on the data obtained from the industrial production series. Validation researches were carried out at all stages of the process with the determination of critical parameters that would confirm the product quality by the under studied parameter and the reproducibility of the results in case of changing the initial parameters, namely: preparation of raw materials, solution preparation, filtration of solution, filling and sealing of vials, sterilization, inspection, marking, packaging.

Data were collected on the basis of batch production protocols, protocols for analysis of initial feedstock and materials, intermediate and finished production, batch packing protocols, other protocol and registration documentation of the manufacturing of a glucose solution for infusion of 50 mg / ml.

The solution for infusion was prepared by the following technology: glucose is weighed and mass by weight is controlled. Water for injection of a predetermined temperature and a portion of glucose are taken into the reactor. The solution is stirred at a certain speed of the stirrer until complete dissolution of the active substance. Prepared solution is controlled according to the specification for intermediate products. After accordance with the results of the control with the established quality indicators, the solution is submitted for filtration. The prepared solution is filtered on the filtration equipment through a cascade of filters with a pore diameter of 0.6 μm and 0.22 μm, while the temperature of the solution and the pressure on the filters are controled. The filtered solution is poured into vials and sealed. The vials are sterilized in an autoclave according to the pharmacopoeial regime at 121 ° C for 15 minutes [13]. Control of the hermiticity of the vials and the absence of mechanical inclusions in the solution is carried out on the automatic inspection machine of lines of inspection, marking and packaging, at that controlling the hermiticity of the

vials, the absence of visible mechanical inclusions in the solution, the appearance of the vials. Marking and packaging of vials is carried out on the line of inspection, marking and packaging.

Research results. For the development of a validation plan using the bracketing method, a variety of batch sizes and packing was taken into account, namely the industrial release of a medicinal product in 200 ml, 400 ml and 500 ml glass vials, which are produced in a size of industrial series of 2000 l - for volume of filling in primary packaging in 200 ml, 5000 l for containers of all sizes, and 10000 l for 400 ml and 500 ml vials. For the selection of the extreme points of the parameters, all risks for the accuracy of the validation and quality assurance of the product were evaluated, and the choice of batch size (maximum or minimum) was stipulated, which ensured the reliability of the results and their reproducibility in case of changing these parameters. Technological chart of manufactoring of glucose drug preparation, solution for infusions, is presented in Fig. 1. The solution for all types of packing is prepared according to one scheme and using one technological equipment. The difference in the parameters in stage 3 "Filling and sealing the vials", where the working time and the amount of output depends on the size of the batch and the volume of the container.

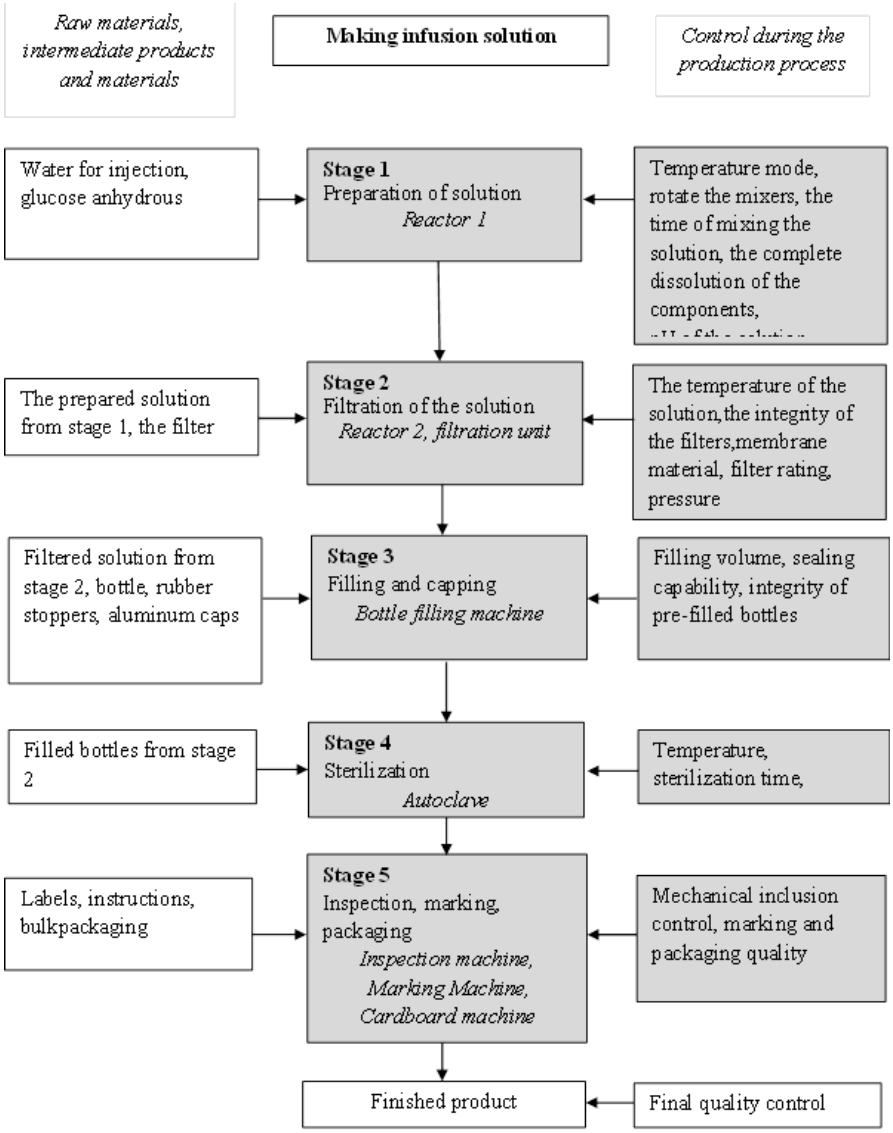

Fig. 1. **Technological scheme of the production of glucose 50 mg / ml, solution for infusions**
** It is indicated with gray colour the critical stages and critical points of control in the manufacturing process*

Inasmuch as the validation is performed in "the worst case scenario", differentiated for each product and batch size, therefore specific characteristics, parameters and their ranges have been established for successful validation work, with the observance of which the technological process is stable and reproducible (Table 1).

Table 1

Scheme of validation of industrial series characterized by limit values of defined and validated characteristics, such as batch size and container volume

Production	Critical limit values		Critical quality attribute	Acceptance criteria
	Batch size	Container volume		
Preparation of solution	2000 l (min for 200 ml) 10000 l (max for 400 ml, 500 ml)	-	Description	Transparent colorless liquid
			Transparency	It must be transparent
			Color	It must be colorless
			pH	From 4.0 to 6.5
			Quantitative content	Not less than 47.5 mg and not more than 52.5 mg in 1 ml
Filtration, filling and capping of vials	5000 liters (max for dosing 200 ml)	200 ml (min)	Bioloading of the solution before sterilization	Not more than 10 CFU / 100 ml
			Extractable volume	Not less than 100,0 ml
Sterilization	10000 l or 20000 vials (max)	500 ml (max)	Sterilization time	At least 15 minutes
			Sterilization temperature	121 ° C-124 ° C
			Sterility of the solution	Must be sterile
Inspection, marking, packaging	(max) 25 thousand v. 200 ml or 25 thousand v. 400 ml, or 20 thousand v. 500 ml each	All volumes 200 ml 400 ml 500 ml	Impermeability	They must be airtight
			No visible particles in solution	Almost none
			Appearance	Must appropriate

As can be seen from the data in Table 1, industrial series with limit values of 2 parameters were selected for validation researches - the batch size and filling capacity of the container (dosage), namely a series with a production size of 2000 l with a dosage of 200 ml per vial (min - batch size, min - dosage), 5000 l and filling volume 400 ml (min - batch size for 400 ml vials), 10000 l with packing into 500 ml vials (max - batch size, max - dosage) . Were determined that the selected limit values are representative of the series with intermediate values. Critical elements of the manufactoring process are identified during the risk assessment:

- Validation of the "Solution Preparation" stage: the preparation process is exactly the same for all volumes of the batch. Sampling was performed from three horizons of solution in the reactor. One sample was taken from each level. The sampling points are presented in Figs. 2.

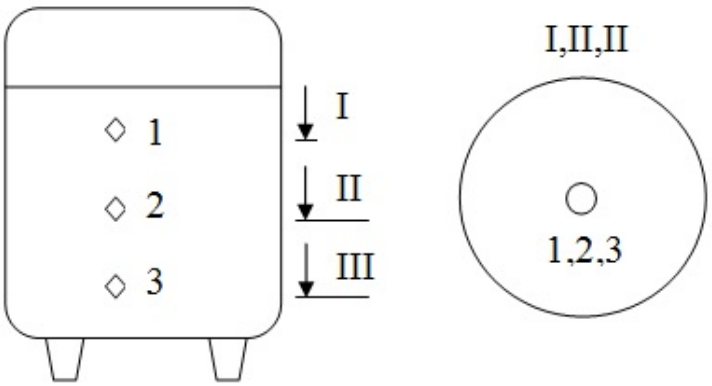

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Fig. 2. **Scheme of points for collecting samples from the reactor for preparing solutson**

- Validation of the "Solution Filtration" step: purification of the solution from microorganisms and mechanical inclusions was performed by filtration of the solution through a filter system with a final filter with a pore size not exceeding 0.22 μm.

- Validation of the “Filling and sealing of vials” stage: tests were performed for the maximum produced series volume for all doses of vials 200 ml, 400 ml and 500 ml vials. Sampling was carried out at regular intervals during the bottling of a series of preparation for validation exams according to the indicator “Extractable volume”. Also selected one vial from the each batch to determine the "Bioburden solution before sterilization".

- Validation of the "Sterilization" stage: one sample of at least 20 vials of each batch of preparation was selected to monitor the "Sterility Indicator".

- Validation of the "Inspection, Marking, Packaging" stage: Researches of the process of the "Control of the hermeticity of the vials" were performed for 100 ml and 400 ml marginal volumes of packing within the qualification of the inspection machine. During the validation of the process "Control of vials on mechanical impurities" were prepared Knapp-series of 250 vials, 80 of which had a known load of mechanical impurities. The Knapp series was viewed 10 times by operators, then checked on an inspection machine.

The results of the validation studies at the "Solution Preparation" stage show the uniformity of the solution throughout the reactor volume (Fig. 3).

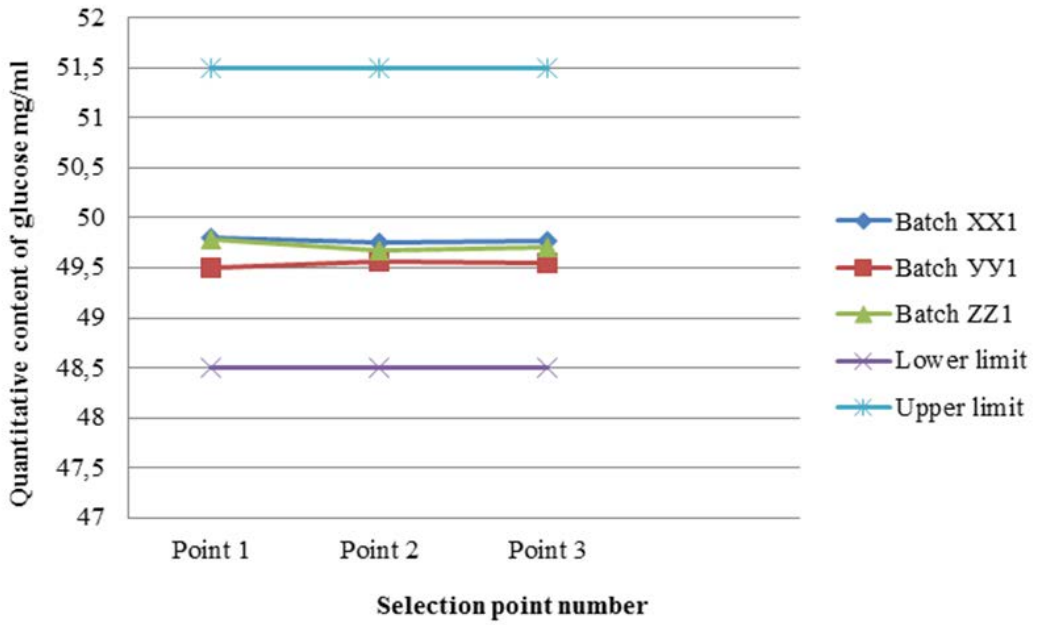

Fig. 3. **The results of the analysis of quantitative determination of glucose at the sampling points in the prepared solution**

The value of the relative standard deviation (RSD) is much smaller than the allowable value and are approximate enough to each other during the determination of the active substance. The results of validation researches are presented in Table 2.

Table 2

Control points in the manufacturing process and summary test results obtained during the validation of the process of manufacturing glucose infusion solution 50 mg / ml

Production	Parameter	Units	Acceptance criteria	Batch XX1 2000 l	Batch УУ1 5000 l	Batch ZZ1 10000 l
Preparation of solution	Weight of glucose monohydrate	kg	Accordingly TI/SMP	548,85	548,85	329,31
	Mass of water for injection	kg		9620,0	9620,0	5772,0
	Water temperature for injection in the reactor before loading of glucose monohydrate	°C	Not higher than 60-65	60	60	60
	Mixing time after loading Glucose monohydrate	min	Not less than 20	20	20	20
	Rotate of the mixer	rpm	60	60	60	60
	Water temperature for injection in the reactor after cooling	°C	20-25	23	24	23
	Rotate of the mixer	rpm	60	60	60	60
	Quantitative glucose content	mg / ml	From 48.5 to 51.5	49,8	49,5	49,8
Preparation of	pH	-	From 4.0 to 6.5	6,1	6,0	6,0

solution	Transparency	-	The solution should be transparent	+	+	+
	Color	-	The solution should be colorless	+	+	+
Solution filtration	Filter element rating (F4) on pre-filter	Mm	Not more than 0.45	0,6	0,6	0,6
	Filter element rating (F5) of the final filter	Mm	Not more than 0.2	0,2	0,2	0,2
Filling and sealing of vials	Control of the extractable volume of the drug	G	Not less than the above	214,9-219,4	409,5-415,4	509,3-515,3
	Control of the extractable volume of the drug	Ml	Not less than the above	206,9-217,4	405,9-415,3	504,7-518,5
	Bioloading	-	≤10 CFU / 100 ml	App.	App.	App.
Sterilization of vials	Temperature	^{o}C	121+3	122	122	122
	Sterilization time	Min	15	15	15	15
	Pressure	Bar_a	3,2	3,2	3,2	3,2
	Sterility	-	Must be sterile	App.	App.	App.
Control of impermeability, mechanical inclusions and appearance of vials	Absence of mechanical inclusions and impermeability of vials	-	According to TI/SMP	App.	App.	App.
Marking of vials	Control on labels conformity of the image of the pharmaceutical code according to the sample, in IP / PP	-	According to PI/SPP	App.	App.	App.
	Control of conformity of batches number and expiration date in IP / PP and on labels			App.	App.	App.
	Controls the definition of the batch and the expiration date on the label			App.	App.	App.
	Quality control of labeling on the vial, incl. orientation of the label on the bottle (vertical)			App.	App.	App.
	Control of conformity of the pharmaceutical code on the label and in the IU / PU			App.	App.	App.
	Control of conformity of the name of the drug, its concentration and volume on the group labels in accordance with the stated in the IU / PU			App.	App.	App.

Group vial packing	Controls the definition of the batch and the expiration date group label	-	According to PI/SPP	App.	App.	App.
	Control of the presence of instructions in group packing			App.	App.	App.
	Control of conformity of the pharmaceutical code to the instructions and the IU / PU			App.	App.	App.
	Control the number of vials in a group box			App.	App.	App.
Quality control finished product	Quantitative glucose content	mg / ml	From 48.5 to 51.5	49,7	49,9	50,0
	pH	-	From 4.0 to 6.5	6,1	6,0	6,0
	5-hydroxy-methylfurfural and related impurities	-	The optical density is not more than 0.25	0,0505	0,0675	0,0635
	Control of the extractable volume of the drug	ml	Not less than the above	AA= 212,8 Min= 206,9 Max= 217,4	AA= 412,2 Min= 407,8 Max= 419,0	AA= 511,8 Min= 505,9 Max= 516,3
		Index	C=0	0	0	0
		Index	Cpl ≥ 1,33	2,52	1,41	1,98
		RSD	≤6%	0,8	1,18	0,8
	Determination of sterility of the solution after the sterilization stage	-	The solution should be sterile	Sterile	Sterile	Sterile

As can be seen from Table 2, the results of the researches indicate the reproducibility and standard nature of the intermediate and finished products in accordance with the guidelines and declared eligibility criteria.

Conclusions. It is determined that a vital medicine drug Glucose solution for infusion is produced in containers of different volumes of filling from 100 ml to 5000 ml. The wide variability of dosage and volume of industrial series complicates carrying out of classical full validation, which requires proper support of the validation process with special equipment, highly qualified specialists and considerable costs to perform full-scale studies.

It was established that the guidelines of the various regulatory authorities do not provide clear guidance on the number of series for validation researches or specific methods for identifying and justifying the number of industrial batches of medicinal products having multiple batch sizes in production and a large number of possible dosage options. Leading guides of technological process validation recommend approaches which use bracketing approach to reduce test volume based on selective studies of production batches in containers of different sizes or different filling completeness.

In the course of the research, the selection of industrial series of manufactoring of medicine drug for validation researches on the limit values of the critical characteristics of the product is substantiated.

The results of the researches show the reproducibility and standardization of quality indicators of intermediate and finished products in accordance with the normative documentation and declared acceptance criteria for all investigated release forms of 200 ml, 400 ml and 500 ml in glass vials. The results of the validation tests of the technological process for the producing of a solution for infusion Glucose 50 mg / ml are representative of the intermediate parameters of production of the medicinal drug and are determined to be satisfactory to ensure stable quality indicators.

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ВАЛІДАЦІЙНІ ДОСЛІДЖЕННЯ ПРОЦЕССУ ВИРОБНИЦТВА ЛІКАРСЬКОГО ЗАСОБУ ГЛЮКОЗА РОЗЧИН ДЛЯ ІНФУЗІЙ

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Мета. *Метою роботи є проведення валідаційних досліджень технологічного процесу виробництва розчину глюкози для інфузій із застосуванням підходу брекетингу для серій різних за об`ємом та повноти наповнення контейнерів.*

Методики. *Об`єктом дослідження є виробничий процес виготовлення розчину для інфузій глюкоза 50 мг/мл. Збір даних проведено на підставі протоколів виробництва серій, протоколів аналізу вихідної сировини і матеріалів, проміжної і готової продукції, протоколів упаковки серій, іншої протоколючої та реєстручої документації процесу виробництва лікарського засобу. Валідаційні дослідження проводили на всіх стадіях технологічного процесу з визначенням критичних параметрів, які б підтверджували якість продукту за досліджуваним параметром та відтворюваність результатів при зміні початкових параметрів, а саме: підготовка сировини, приготування розчину, фільтрація розчину, наповнення та укупорка флаконів, стерилізація, інспекція, маркування, пакування.*

Результати. *Визначена технологічна схема виробництва лікарського засобу Глюкоза розчин для інфузій 50 мг/мл. Граничні значення визначено за критичними параметрами як розмір промислової серії та дозування (об'єм наповнення флакону) лікарського засобу. Валідаційні дослідження та збір даних проведено на 3-х промислових серіях,визначених підходом брекетінгу: 2000 л з дозуванням лікарського засобу по 200 мл у флакони (min – розмір серії, min - дозування), 5000 л та об'єм наповнення 400 мл (min – розмір серії для флаконів по 400 мл), 10000 л з фасуванням у флакони по 500 мл (max – розмір серії, max – дозування). Отримані результати досліджень свідчать про відтворюваність і стандартність показників якості напівпродукту і готової продукції відповідно до нормативної документації і задекларованих критеріїв прийнятності для всіх досліджуваних форм випуску по 200 мл, 400 мл та 500 мл у скляних флаконах. Дані результатів валідації технологічного процесу виготовлення розчину для інфузій Глюкози 50 мг/мл є репрезентативнми для проміжних параметрів виробництва лікарського засобу і визначені як задовільні для забезпечення стабільних показників якості.*

Наукова новизна. *Результати валідаційних дослідженнь отримані шляхом науково-обґрунтованого підходу вибору граничних значень, аналізу ризиків та визначення критичних параметрів.*

Практична значимість. *Отримані результати дослідженнь мають практичне значення для організації валідації технологічного процесу виробництва лікарських засобів із кількома дозуваннями, об'ємами виробничих серій, різними розмірами наповнення контейнерів, з метою зменшення обсягу випробувань задля економії ресурсів та часу.*

Ключові слова: *технологічний процес, валідація, підхід із застосуванням брекетингу, критерії прийнятності.*

ВАЛИДАЦИОННЫЕ ИССЛЕДОВАНИЯ ПРОЦЕССА ПРОИЗВОДСТВА ЛЕКАРСТВЕННОГО СРЕДСТВА ГЛЮКОЗА РАСТВОР ДЛЯ ИНФУЗИЙ

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Цель. *Целью работы является проведение валидационных исследований технологического процесса производства раствора глюкозы для инфузий с применением подхода брекетинга для различных серий по объему и полноте наполнения контейнеров.*

Методики. *Объектом исследования был производственный процесс изготовления раствора для инфузий глюкоза 50 мг / мл. Сбор данных проведено на основании протоколов производства серий, протоколов анализа исходного сырья и материалов, промежуточной и готовой продукции, протоколов упаковки серий, другой протокольной и регистрационной документации процесса производства лекарственного средства. Валидационные исследования проводили на всех стадиях технологического процесса с определением критических параметров, подтверждающих качество продукта по исследуемым параметром и воспроизводимость результатов при изменении начальных параметров, а именно: подготовка сырья, приготовление раствора, фильтрация раствора, наполнение и укупорка флаконов, стерилизация, инспекция, маркировки, упаковки.*

Результаты. *Разработана технологическая схема производства лекарственного средства Глюкоза раствор для инфузий 50 мг / мл. Валидационные исследования и сбор данных проведен на 3-х промышленных сериях, определенных подходом брекетинга: 2000 л с дозировкой лекарственного средства по 200 мл во флаконах (*min *- размер серии, min - дозирование), 5000 л и объем наполнения 400 мл (min - размер серии для флаконов по 400 мл), 10000 л с фасовкой во флаконы по 500 мл (max - размер серии, max - дозирование). Полученные результаты исследований свидетельствуют о воспроизводимости и стандартности показателей качества полупродукта и готовой продукции в соответствии с нормативной документацией и задекларированных критериев приемлемости для всех исследуемых форм выпуска по 200 мл, 400 мл и 500 мл в стеклянных флаконах. Данные результатов экзаменов валидации технологического процесса приготовления раствора для инфузий Глюкозы 50 мг/мл является репрезентативными для промежуточных параметров производства лекарственного средства и определены как удовлетворительные для обеспечения стабильных показателей качества.*

Научная новизна. *Результаты валидационных исследований получены путем научно обоснованного подхода выбора предельных значений, анализа рисков и определения критических параметров.*

Практическая значимость. *Полученные результаты исследования имеют практическое значение для организации валидации технологического процесса производства лекарственных средств с несколькими дозировками, объемами производственных серий, различными размерами наполнения контейнеров, с целью уменьшения объема испытаний для экономии ресурсов и времени.*

Ключевые слова: *технологический процесс, валидация, подход с применением брекетинга, критерии приемлемости.*