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A.S. KALYKOVA[1,2], D.V. BARINOV[1], Z.B. SAKIPOVA[2], L.N. IBRAGIMOVA[2], O.V. CHSHUKINA[1], A.A. AZEMBAYEV[1]

[1]JSC "Scientific Centre for Anti-Infectious Drugs", Almaty c., Kazakhstan,

[2]Kazakh National Medical University n.a. S.D. Asfendiyarov, Almaty c., Kazakhstan

VALIDATION OF MANUFACTURING PROCESS FOR ORAL DOSAGE FORM WITH IODINE ADDUCTS

Kalykova A.S.

Validation technology for liquid dosage forms with iodine adducts – FS-1 medical substance was carried out under the scale pilot production.

Material and methods. *Studies of physical and chemical parameters of raw materials, intermediates and products were performed by spectrophotometric and titrimetric assays. The results were processed using the software "Statistica 12" and Shewhart control charts.*

Results and discussions. *For the validation of the technological process of FS-1 drug production were examined three manufactured successive pilot-scale batches of drug – 05251013, 06011113, 07061113 in the volume 40±2 L of each. The regulatory documents, regulating the production process was created. Comparable data on the technological parameters of the three batches was obtained and confirmed the stability of the production process of FS-1 solution intended for oral administration.*

Conclusions. *Thus, the transfer of technology production from laboratory to pilot model successfully carried out, which is confirmed by validation studies.*

Key words: *FS-1 substance, iodine adducts, validation of manufacturing process, control charts, solution per oral use.*

The drug of FS-1 is a nano-ion complex formed by proteins and carbohydrates, metal salts and intercalated therein iodine [1]. Experimental studies of drug activity in vitro and in vivo [2, 3, 4] have shown a wide range of its antibacterial action. The drug has a bactericidal activity against gram-positive and gram-negative bacteria (Mycobacterium tuberculosis, Brucella species, staphylococci), to antibiotic-resistant strains, in particular, against the methicillin-resistant Staphylococcus aureus (MRSA).

The technology is based on the complexation reaction, which proceeds in four stages, the first of which is interaction of carbohydrates and proteins from the metal salts, the second stage of intercalation is 5-95% of the required amount of iodine in the complex is formed in the first reaction step of complexation with certain ionic strength, a third step reacting the complexing proteins containing at least one terminal aminoacid with electron donating functional groups, the fourth step is the intercalation of the remaining amount of iodine into antimicrobial agent [1].

The process of synthesis of the drug successfully worked out in laboratory conditions and transferable of technology in the pilot-scale conditions. To ensure the production of quality products in accordance with the requirements of GMP Annex 15 is necessary to conduct the validation work. In connection with this task of the present work is the transfer of production technology of liquid oral dosage forms of FS-1 and its validation.

Material and methods

Used in the manufacture of FS-1, drug substance were obtained in the experimental production of "Scientific Center for Anti-infectious Drugs," in the same conditions, transfer of technology of the investigational product has been made with the use line for the production of liquid dosage forms (Linde, Germany and Sklochem, Czech Republic).

Studies of physical and chemical parameters of raw materials, intermediates and products were performed on the following equipment: IR spectrophotometer Nicolet 6700 Thermo Scientific (USA), UV spectrophotometer Lambda 35 PerkinElmer (USA), PP-50 Sartorius (Germany), pH-meter Sartorius PB-11 (Germany), balance BL120S Sartorius (Germany) and viscometer VPZh-4m (Russia).

The results were processed using the software "Statistica 12" and Shewhart control charts.

Results and discussion

Using risk analysis conducted at the stages of technology transfer, validation of production processes and quality control of the product were determined control points and technological parameters (fig. 1).

For the validation of the technological process of FS-1 drug production were examined three manufactured successive pilot-scale batches of drug – 05251013, 06011113, 07061113 in the volume 40±2 L of each. Before the start of the validation process work, a number of measures was provided for the qualification of technological and laboratory equipment, as well as all the used analytical methods.

We have developed a validation plan for the production process of the drug under study (table 1). The main critical stage is the preparation of working solutions and synthesis of FS-1 medical substance. In the preparation of working solutions was

Контакты: Калыкова Асем Сериковна, магистр биотехнологии, докторант модуля «Фармацевт-технолог», Казахский национальный медицинский университет им. С.Д. Асфендиярова, г. Алматы. Тел. +7 747 615 17 74, e-mail: asemai@mail.ru

Contacts: Assem Serikovna Kalykova, M.Sc. in biotechnology, PhD-student of "Pharmacist-technologist" department, Kazakh National Medical University n.a. S.D. Asfendiyarov, Almaty c. Ph. +7 747 615 17 74, e-mail: asemai@mail.ru

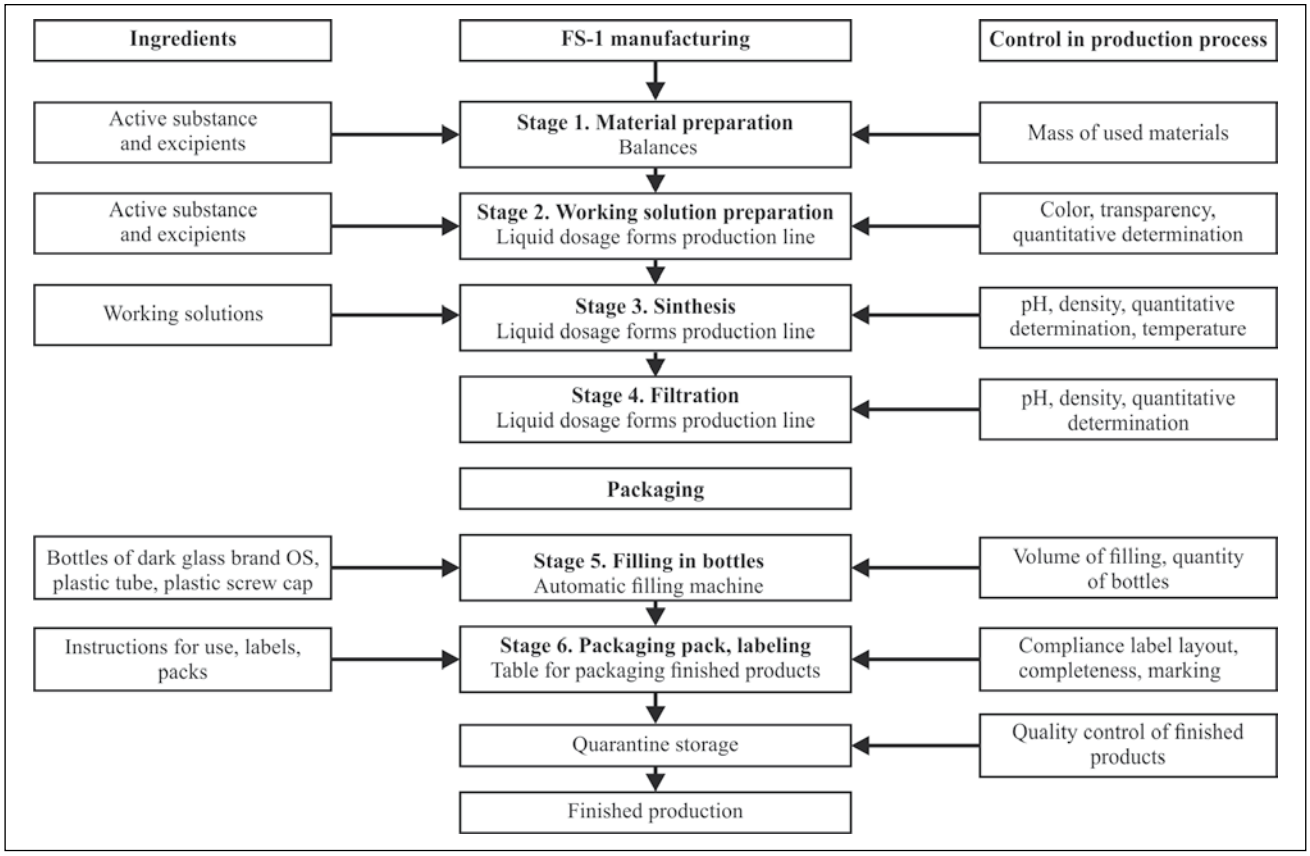

Figure 1 – Technological chart of "FS-1 solution per oral use" production

Table 1 – **Validation plan of technological process for "FS-1 solution per oral use" manufacturing**

№	Stage of the process	Parameters	Acceptable criteria	Quantity of Sampling
1	Stage 1 Weighting	Mass of used materials	0,5±2%	1
2	Stage 2 Working solution preparation	Transparency Color Uniformity Quantitative determination	According to WAND, ND	9 9 9 9
3	Stage 3 FS-1 synthesis	Temperature conditions pH Density Quantitative determination Uniformity Description	According to WAND, ND	9 9 9 9 9 9
4	Stage 4 Filtration	Microbiological purity Description pH Density Quantitative determination	According to WAND, ND	9 9 9 9 9
5	Stage 5 Packaging and labeling	Does not meet the terms of filling, mistakes in the marking batch number and expiration date, label mistaking	According to WAND, ND	10

investigated following technological parameters: transparency, color, uniformity, quantitative content. Control of the synthesis was performed using the quality indicators described in the analytical regulatory document (WAND), as well as investigating technical parameters: mixing speed, temperature and time of administration of the ingredients. Sampling was carried out in reactors using samplers at 9 points from the top, middle and bottom with three samples. Regulated standards of studied

technological parameters strictly comply with the approved regulatory documents.

Based on obtained data (fig. 2-5) can evaluate the validity of FS-1 production process. Shewhart control charts indicate that the data obtained are in the range 3σ and regulated within predetermined standards described in the standard documen-

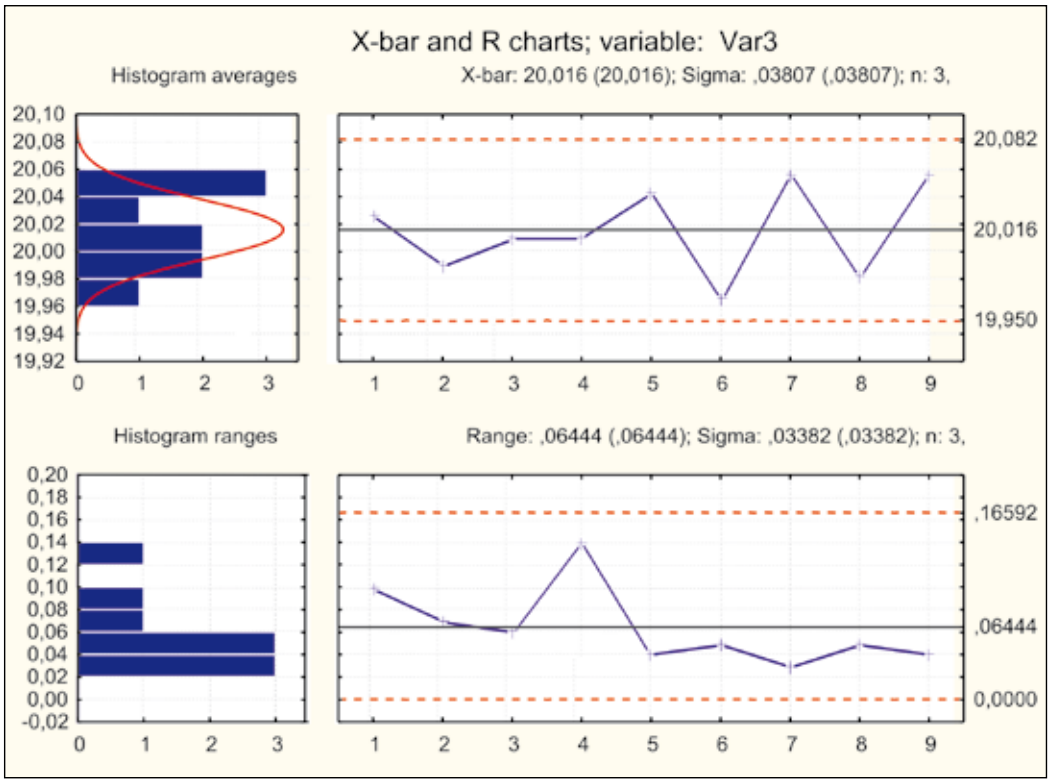

Figure 2 – Control chart of quantitative determination API (FS-1 solution)

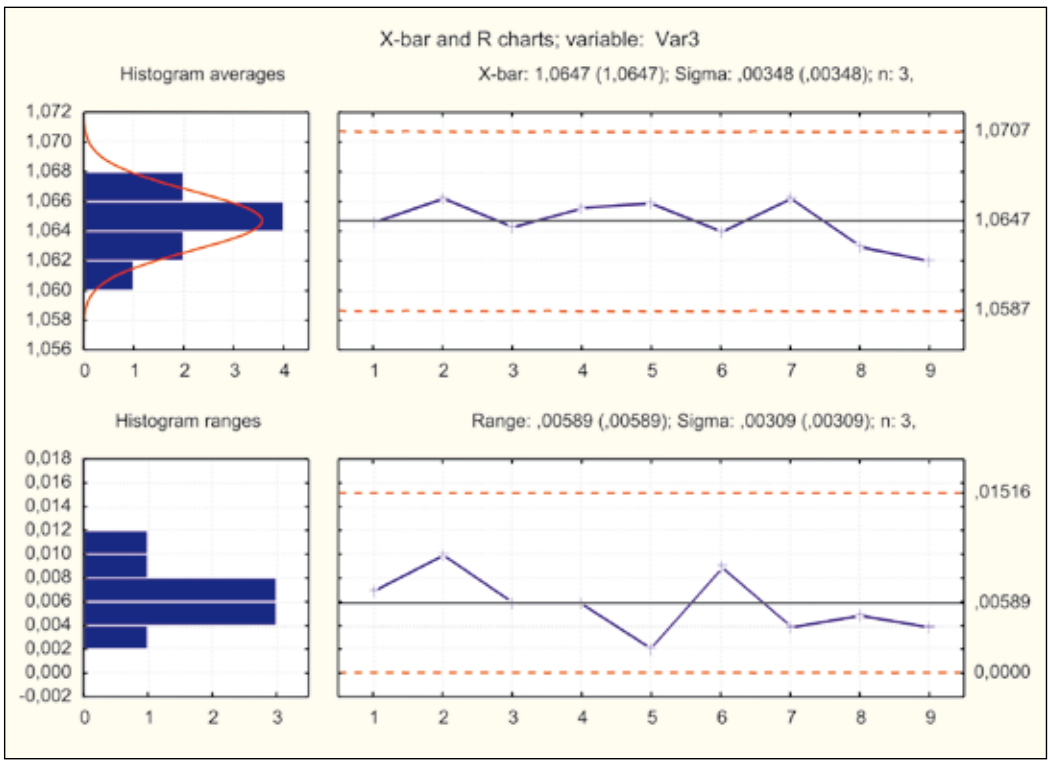

Figure 3 – Control chart of density (FS-1 solution)

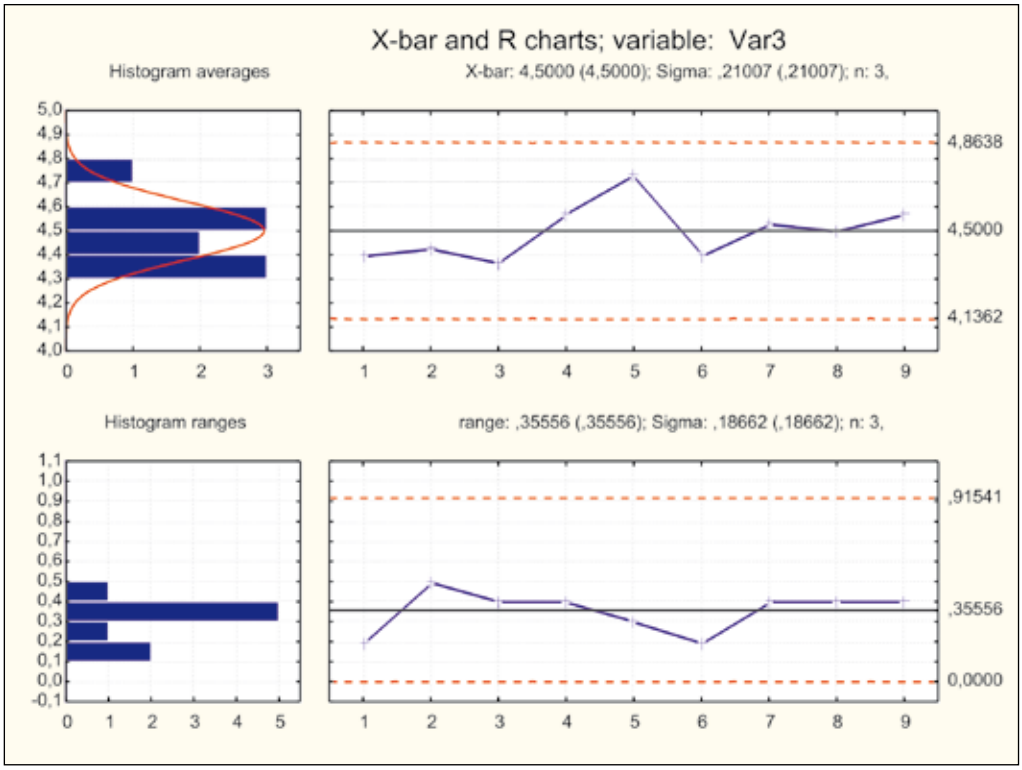

Figure 4 – Control chart of pH (FS-1 solution)

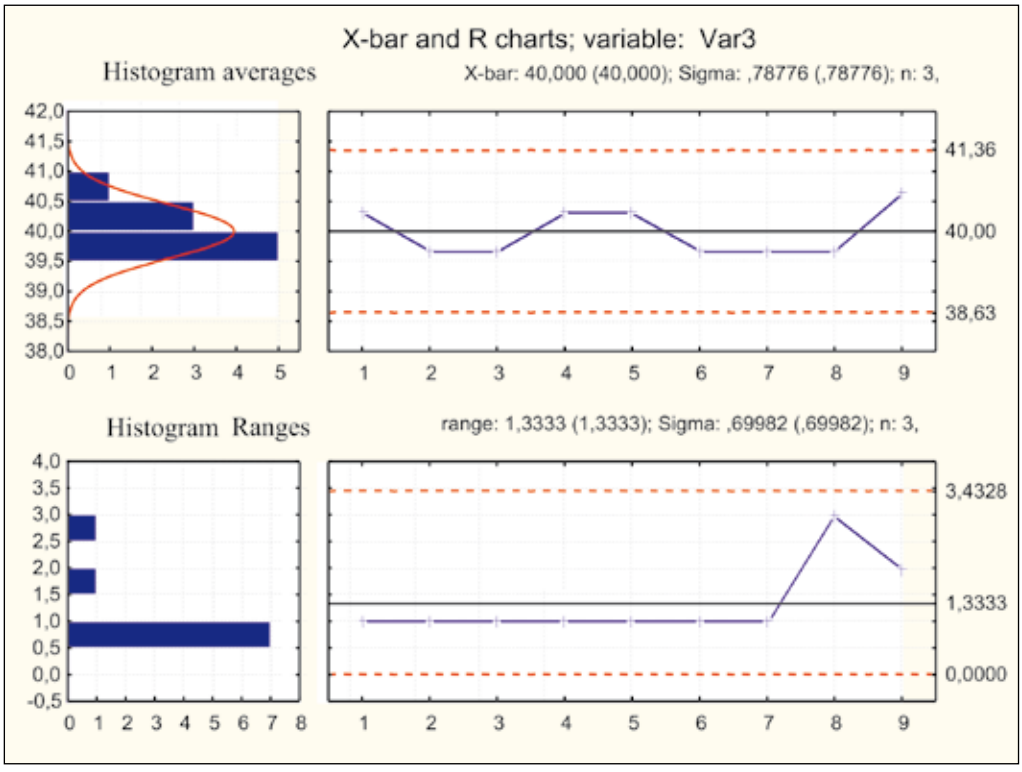

Figure 5 – Control chart of reactor mixing speed

tation, the relative standard deviation of the results does not exceed 2% (table 2).

Based on the study has been designed experimental-industrial batch-record for manufacturing process of FS-1.

Thus, the transfer of technology production from laboratory to pilot model successfully carried out, which is confirmed by validation studies. The obtained data allow us to assert the stability of the technological process and product quality

Table 2 – **Process parameters results**

Indicator	Units of measure	Min mean	Max mean	M	RSD,%
Quantitative determination	mg/ml	19,93	20,08	20,016	0,04388
pH	-	4,2	4,9	4,5	0,192154
density	g/sm^3	1,06	1,07	1,0647	0,00314
Stirring speed	rpm	38	42	40	0,78446

meets quality specifications and requirements of the State Pharmacopoeia of the Republic of Kazakhstan.

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ТҰЖЫРЫМ

А.С. ҚАЛЫҚОВА[1,2], Д.В. БАРИНОВ[1], З.Б. САҚЫПОВА[2], Л.Н. ИБРАГИМОВА[2], О.В. ЩУКИНА[1], А.А. ӘЗІМБАЕВ[1]

[1]Инфекцияға қарсы препараттардың ғылыми орталығы, Алматы қ.,

[2]С.Ж. Асфендияров атындағы Қазақ Ұлттық Медицина Университеті, Алматы қ.

ЙОД АДДУКТІ НЕГІЗІНДЕ ПЕРОРАЛЬДІ ДӘРІЛІК ҚАЛЫПТЫҢ ӨНДІРІСТІК ВАЛИДАЦИЯСЫ

Өнеркәсіптік-тәжірибелік өндіріс ауқымында йод аддукті негізінде ФС1 дәрілік препаратының сұйық дәрілік түрін алудың технологиялық валидациясы жасалынды.

Материал және әдістері. Шикізаттар және нысандарға (материалдар) физика-химиялық көрсеткіштері бойынша зерттеу спектрофотометриялық және титртеу әдістері бойынша жүргізілді. Нәтижелері «Statistica 12» бағдарламасының көмегімен «Statistica 12» бақылау диаграммаларын пайдаланып өңделді.

Нәтижелері және талқылауы. ФС-1 дәрілік қалыптың технологиялық өндірістік үрдісіне валидация жүргізу үшін дәрілік қалыптың кезекпен өндірілген көлемдері 40±2 л ден болатын үш сериясы-05251013, 06011113, 07061113 зерттелген болатын. Зерттеу нәтижесінде өндірістік үрдісті реттейтін нормативті құжат әзірленді.Зерттелініп отырған үш сынақ сериясының технологиялық параметрлері салыстырылды және ішке қолдануға арналған ФС-1 сұйық дәрілік қалыптың технологиялық өндірістік үрдісінің тұрақтылығы анықталды.

Қорытынды. ФС-1 дәрілік қалыптың өндірілу технологиясы лабораториялық модельден өндірістік-тәжірибелік модельге сәтті түрде ауыстырылды және ол валидация зерттеуімен расталған.

Негізгі сөздер: *ФС-1 субстанциясы, өндірістік үрдістің валидациясы, сынақ карталары, ішке қолдануға арналған сұйықтық.*

РЕЗЮМЕ

А.С. КАЛЫКОВА [1,2], Д.В. БАРИНОВ[1], З.Б. САКИПОВА[2], Л.Н. ИБРАГИМОВА[2], О.В. ЩУКИНА[1], А.А. АЗЕМБАЕВ[1]

[1]АО «Научный центр противоинфекционных препаратов», г. Алматы,

[2]Казахский национальный медицинский университет им. С.Д. Асфендиярова, г. Алматы

ВАЛИДАЦИЯ ПРОИЗВОДСТВА ПЕРОРАЛЬНОЙ ЛЕКАРСТВЕННОЙ ФОРМЫ НА ОСНОВЕ АДДУКТОВ ЙОДА

Проведена валидация технологии получения жидкой лекарственной формы на основе аддуктов йода – лекарственного препарата ФС-1 в масштабе опытно-промышленного производства.

Материал и методы. Исследования физико-химических параметров материалов и продуктов проводились спектрофотометрическими и титриметрическими методами. Обработку результатов осуществляли при помощи программы «Statistica 12» с использованием контрольных карт Шухарта.

Результаты и обсуждение. Для проведения валидации технологического процесса производства препарата ФС-1 были исследованы три последовательно произведенные опытно-промышленные серии препарата – 05251013, 06011113, 07061113 в объеме 40±2 л каждая. В результате проведенных исследований разработана нормативная документация, регламентирующая производственный процесс. Получены сопоставимые данные по технологическим параметрам трех исследуемых серий, и подтверждена стабильность технологического процесса производства раствора ФС-1, предназначенного для приема внутрь.

Вывод. Таким образом, успешно проведен перенос технологии производства препарата ФС-1 с лабораторной модели на опытно-промышленную, что подтверждено валидационным его исследованием.

Ключевые слова: *субстанция ФС-1, валидация производственных процессов, контрольные карты, раствор для приема внутрь.*

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