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PROCESS VALIDATION OF EQUIPMENT PURIFICATION IN THE PRODUCTION OF ANTIBIOTICS OF CEFALOPARIN SERIES IN JV LLC JURABEK

R. A. Khusainova*, K.A. Ubaydullaev, S. Kh. Kariev and M. O. Akromov

Tashkent Pharmaceutical Institute.

*Corresponding Author: R. A. Khusainova

Tashkent Pharmaceutical Institute.

ABSTRACT

Currently, in practice, "Good Manufacturing Practice for Medicinal Products (GMP)" is one of the most important document defining the requirements for the production and quality control of drugs for humans and animals. This means that the condition for ensuring the quality of drugs is their production in accordance with the rules of GMP. In this regard, the development of new highly sensitive, rapid and reasonably economical methods of chemical control of the purity of the surface of pharmaceutical equipment should be considered an urgent problem. The purpose of the work was to create a complex of highly sensitive, selective and express methods of chemical control of the purity of pharmaceutical production equipment using the example of cephalosporins using chromatographic methods of analysis, as well as developing approaches to validating the cleaning process of equipment.

KEYWORDS: GMP, Ceffast, Vitaxon, Intralin, DM-20, acceptance criterion.

INTRODUCTION

The Validation Master Plan (VMP) was first requested by the Pharmaceutical Inspection Convention (PIC/S) instruction PI 006-1 "Principles of Qualification and Validation in Pharmaceutical Manufacture" for the first time.[1] Carrying out all validation operations is a rather complex multidisciplinary problem, requiring the cooperation of experts from a number of specialties. It is therefore extremely important that they have VMP at their disposal,[2] which:

- Establishes separate parts of validation
- Determines the nature and extent of testing for each part
- Provides test procedures and protocols
- Distributes official duties
- Distributes responsibility for reports and documentation requirements

The manufacturer should develop the VMP in such a way as to describe all its validation operations that will take place over a specific period (usually one year).[3] If we are talking about the description of validations associated with a new production unit (or a valid unit after reconstruction), it is recommended to develop an independent VMP.

The introduction of rules of good manufacturing practice is a guarantee of risk reduction in the production of medicines. The most important way to ensure GMP requirements is validation work. Validation is a documented procedure that gives a high degree of confidence that a particular process, method, or system will consistently produce results that meet predetermined acceptance criteria.[4]

In the production of products intended for further medical use, it is necessary to ensure their microbiological purity. The presence of foreign microorganisms in the final product may affect its quality. Even a small content of pathogenic microorganisms or toxic metabolites can make a product toxic.[5]

Validation of equipment cleaning processes in the manufacture of medicines is important to confirm the effectiveness of the procedure and to avoid contamination of the product. Insufficient or improperly selected equipment washing is one of the common causes of contamination.[6]

The main method of maintaining the cleanliness of industrial equipment is the integration of the cleaning mechanism into the equipment itself. This can be achieved by using pressure, heat, steam, mechanical cleaning, or chemical reagents. Before chemical or high-temperature cleaning, large particles are removed using steam or water cleaning under high pressure. For automatic cleaning systems, alkaline disinfectants and detergents are mainly used. Sodium hydroxide is widely used. Such caustic alkalis remove organic residues without affecting the equipment. It is important that the

cleaning process is approved (by the equipment manufacturer).[7]

When analyzing the quality of equipment preparation for work, the degree of chemical (presence of pharmaceutical substances, auxiliary substances and detergents) and microbiological purity are usually evaluated. A traditional method for determining the effectiveness of cleaning procedures is laboratory testing for the presence of traces of a product or material in samples of the last rinsing of process equipment.[8]

MATERIALS AND METHODS

The object of the study is Vitaxon powder for preparing injection solution at 0.5 and 1.0 g (active ingredient ceftriaxone sodium salt is easily soluble in water). "Intralin" powder for preparing injection solution at 0.5 and 1.0 g (active ingredient is cefazolin sodium salt which easily soluble in water), "Ceffast" powder for the preparation of injection solution of 0.5 and 1.0 g (the active ingredient - cefotaxime sodium salt - easily soluble in water). All samples of antibiotics analyzed according to obstacle to the requirements of the FS project, developed by the author.

• The amount above the indicated substances was determined by HPLC. Chromatograms were obtained on a UV-spectrophotometer HPLS 1260 instrument from Agilent Technologies (Germany)
• Cleaning procedures for DM-20 filling machine

The development of the validation program and the assessment of validation parameters are presented below using the example of evaluating the effectiveness of the cleaning procedure of the packaging machine DM-20 (hereinafter referred to as DM-20) used in the chemical and pharmaceutical industry. For the process of cleaning validation, the dispenser bunker was chosen, since it is a device of pharmaceutical production that is complex in design and contains difficult-to-access elements for effective cleaning. DM-20 consists of parts in contact with the product: dispenser hopper, Teflon tube, intermediate agitator, metering wheel and dispenser body.[1,2]

Dosing of sterile powders for preparing an injection solution in vials is a complex and rather laborious process, involving a large number of operations: loading sterile powders into a bin, mixing, feeding powders in dosing, capping, rolling protective caps, as well as transporting and unloading.

The essence of the dosing process in the DM-20 device is as follows: in a sterile room, powders will be loaded into the hopper, mixed and fed through a Teflon tube into the dosing wheel, resulting in powders placed in bottles, closed with stoppers and sent to packaging and labeling.

The validation of the DM-20 purification process was carried out with regard to the efficiency of removing residues from the content of active ingredient.

The validation of the DM-20 purification process was performed by the grouping method: we group similar drugs according to their characteristics and conduct validation for only one representative of the group.

For the selection of the most representative products are taken into account:
1. The similarity of the physical characteristics of the product (the solubility in water of the active ingredient, the presence in the composition of the product of coloring matter);
2. Relation to the list of potent substances.

For validating to the cleaning process, the following were selected:
1. "Vitaxon" powder for the preparation of an injection solution of 0.5 and 1.0 g (the active ingredient is ceftriaxone sodium salt - easily soluble in water);
2. "Intralin" powder for the preparation of an injection solution of 0.5 and 1.0 g (the active ingredient is Cefazolin sodium salt - easily soluble in water);
3. "Ceffast" powder for the preparation of an injection solution of 0.5 and 1.0 g (the active ingredient - cefotaxime sodium salt - is easily soluble in water).[4]

Validation measures for the purification of DM-20 were carried out in three stages in accordance with Table 1.

Table 1: The steps of validating the DM-20 purification process.

Validation stage	Equipment position	The name of the product that was last produced on this equipment
I stage		«Vitaxon»
II stage	DM-20	«Intralin»
III stage		«Ceffast»

Methods for sampling residues from the surface of the equipment are presented in Table. 2

Table 2: Sampling methods.

Parts of the DM-20 in contact with the product	Active substance sampling methods	
	Direct sampling (smear method)	Analysis of the last wash water (washout method)
Dispenser Hopper	+	+
Teflon tube		+
Intermediate Stirrer	+	+
Dosing wheel	+	+
Dispenser housing		+

Data to determine the total allowable limit of residues of drugs across the entire inner surface of DM-20 before starting the manufacture of a subsequent product was determined after calculating the total allowable limit of residues of drugs on surfaces in contact with the product of all equipment items involved in the production of these drugs.

The calculation of the limits of the residues of the active substances is established on the basis of the therapeutic or pharmacological effect of the residue. Data for the determination of residues of active substances in the product are presented in table 3.

Table 3: Data definitions of residues of active substances in the product.

Product name	Critical parameter (substance content)	TD (mg)	Maximum Daily Dose LDD (mg)	Safety factor SF	Batch size BS (kg)
"Ceffast"	Cefotaxime	1000	12000		50
"Vitaxone"	Ceftriaxone	2000	4000	1/1000	75
"Intralin"	Cefasoline	1000	6000		60

The total allowable limit of residues of active substances on the surface throughout the production equipment before starting the manufacture of the following preparation was calculated by the formula:

$$MAC = \frac{TD \times SF \times BS}{LDD}$$

Where:
TD – individual therapeutic dose of the controlled product;
SF – safety factor of the next manufactured product;
BS – batch size of the subsequent product;
LDD – maximum daily dose of the subsequent product.
The results are presented in table 4.

Table 4: The total allowable limit of residues of active substances on the surface throughout the production equipment.

The name of the active active substance	Minimum MAC	Maximum total allowable limit for residues of active substances on the internal surface of equipment, mg		
		Subsequent drug "Vitaxone"	Subsequent drug "Intralin"	Subsequent drug "Ceffast"
Ceftriaxone	20000	-	20000	8333,3
Cefazolin	18750	18750	-	4166,7
Cefotaxime	10000	18750	10000	-

The maximum limit of residues of active substances on the surface of DM-20 is presented in Table. five.

Table 5: The total allowable limit of residues of active substances on the surface of DM-20.

The name of the active active substance	Minimum MAC, mg
Ceftriaxone	5495
Cefazolin	5151
Cefotaxime	2747

Acceptance criterion for equipment purity is the concentration of the residue of active substances in a sample (COST [mg/ml] or [ppm]) on the surface of equipment measuring 0.0025 m^2 by direct sampling, is presented in Table. 6. The total surface area of the equipment is 9.1 m^2.

Table 6: Acceptance criterion of the content of residues of active substances in the sample.

The surface area of the equipment in contact with the active substance	Acceptance criteria		
	The maximum allowable content of residues of active substances in the sample, mg / ml		
	Ceftriaxone	Cefazolin	Cefotaxime
Dispenser Hopper Intermediate Stirrer Dosing wheel	0,002	0,002	0,001

Since the limit of quantitative evaluation of the analytical method used is 5 ppm, therefore, the results will be obtained with sufficient accuracy and correctness. The criterion of acceptability for the purity of the equipment is the concentration of the residue of active substances in the sample (Cost [g/ml] or [ppm]), determined using the last rinse method, is presented in Table. 7. The sample volume of the residue is carried out in a volume of 52 liters (V=52 dm3), and the sample is not diluted.

Table 7: Acceptance criterion of the content of residues of active substances in the sample.

The surface area of the equipment in contact with the active substance	Acceptance criteria		
	The maximum allowable content of residues of active substances in the sample, mg / ml		
	Ceftriaxone	Cefazoline	Cefotaxime
Dispenser Hopper Teflon tube Intermediate Stirrer Dosing wheel Dispenser housing	0,002	0,002	0,001

Since the limit of quantitative evaluation of the analytical method used is 5 ppm, therefore, the results will be obtained with sufficient accuracy and correctness.[5]

At each stage, the validation program was repeated three times (in parallel with the production of three consecutive industrial batches of the product).

The considered equipment of the new generation, designed according to the rules of GMP and GOST R 52896-2007. The automatic system of cleaning is built in the equipment (sir-sink). Water is used as a detergent for injections.

Parts of DM-20 that are in contact with the product are treated as follows: the inner surface of DM-20 (dispenser hopper, Teflon tube, intermediate agitator, metering wheel) is rinsed with injection water at a temperature not lower than 80 ° C for 20 minutes; for 2 minutes, maintain the equipment for 5 minutes for spontaneous discharge of water from the inner walls.

Determination of the quantitative content of active substances in washes was carried out by HPLC methods in accordance with the methods of quantitative determination of these drugs in washes presented in Chapters 3 and 4. The obtained results satisfy the stated acceptance criterion and indicate a high degree of cleaning equipment surfaces contaminating with products (Table 8). As can be seen, the concentration of the active substance in the last rinsing liquid at each stage of the validation process of cleaning equipment surfaces in contact with the product does not exceed the maximum allowable amount stated in the acceptance criteria. The degree of cleaning equipment is satisfactory.

Table 8: The results of quantitative determination of the content of medicinal substances in samples.

Medicinal substances	Content of active substances, mkg / ml	
	Smear method	Wash Method
Ceftriaxone	0,73 ± 0,03	0,81 ±0,04
Cefazolin	0,64 ±0,05	0,69 ±0,04
Cefotaxime	0,78 ± 0,04	0,88 ± 0,03

For the production of "Ceffast", the total allowable limit of residues of active substances on the surface of DM-20 is 2747 µg, A_{total} = 91000 cm². Sampling of the residue is performed using the washout method with an A_{sample}=25 cm², in a volume of 25 ml (V = 0.025 dm³), and the sample is not diluted (F=l). Substituting the listed values in the ratio, we calculate the necessary limit of quantitative evaluation by the formula:

$$QL_{rez} \leq MAC_{rez} \times Recovery \times \frac{A_{sample}}{A_{total}} \times \frac{F}{V} = 2747 \times 0,8 \times \frac{25}{91000} \times \frac{1}{0,025} = 241,5 \ (ppm)$$

This criterion already corresponds to the actual limit of quantitative evaluation of the analytical method, so that the results will be obtained with sufficient accuracy and correctness.

For the production of Ceffast, the value of the maximum total allowable limit (MAC_{rez}) of residues is 2747 μg, A_{total}=91000 cm^2. Sampling of the residue is performed using the last rinse method A_{total}=91000 cm^2, in a volume of 52 liters (V = 52 dm^3), and the sample is not diluted (F=l). Substituting the listed values in the ratio, we calculate the necessary limit of quantitative evaluation by the formula:

$$QL_{rez} \leq MAC_{rez} \times Recovery \times \frac{A_{sample}}{A_{total}} \times \frac{F}{V} = 2747 \times 0,8 \times \frac{91000}{91000} \times \frac{1}{52} = 42,3 \, (ppm)$$

The limit of quantification of the analytical method used is 5 ppm.

An important issue is the evaluation of the effectiveness of cleaning procedures in relation to the removal of residues of detergents. Detergents are not included in the product. They are intended only to facilitate the cleaning of equipment and should not remain on the equipment after the last rinsing, therefore, it is necessary to establish permissible limits for the content of detergent after cleaning, for which you need to know their composition. Ideally, detergent residues should not be detected.

If the obtained results do not meet the acceptance criterion, the purification validation should not be repeated. It is necessary to once again evaluate the effectiveness of the cleaning process, the work of the operators, the equipment used to optimize the cleaning process. Before carrying out secondary validation, it is necessary to adjust the cleaning process (detergents, temperature of the washing liquid, cleaning operations), modify the equipment or retrain the operators.

CONCLUSION

1. A program has been developed to validate the process of cleaning equipment and justified its use in in-process control of chemical and pharmaceutical production. Acceptance criteria are set on the example of equipment for mixing and dosing of powders in the production of cephalosporins.
2. The results of validation may raise the degree of quality assurance, or indicate the need to improve production conditions.

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