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AN APPROACH TO THE TECHNOLOGICAL PROCESS VALIDATION OF MANUFACTURING MEDICAL DEVICES USING THE EXAMPLE OF INJECTABLE IMPLANTS BASED ON HYALURONIC ACID

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The aim. *Technological process validation of manufacturing medical devices is a necessary condition for confirming the ability to continuously produce high-quality medical devices, reduce or eliminate the number of defects, improve the level of product quality, and is also one of the main requirements for product certification on the European Union market. Given the wide variety of medical device types (from patches to pre-filled syringes), unlike medicinal products, the validation procedure for medical devices does not have clear recommendations and guidelines.*

Materials and methods. *The subject of this article is the determination of the approach to the technological process validation of manufacturing medical devices using the example of injectable implants based on cross-linking hyaluronic acid, based on the experience of batch production of the specified type of products on an industrial scale and the regulatory requirements of Ukraine and the European Union.*

Results. *The article presents information about the nature of hyaluronic acid, its structure, sources and methods of production, and the scope of application.*

Determination of critical points of the technological process was carried out by the method of risk assessment using the approach of forming the Ishikawa diagram, i.e. "analysis of cause-and-effect relationships".

The main stages of the analysis of causal relationships are the following:

– determination of the process that is subject to analysis (obtaining high-quality finished products) and sub-processes that have an impact on the final result;

– determination of the main categories of impact on the process, displayed by blocks on the Ishikawa diagram.

The result of such an analysis is displayed in the form of the above-mentioned diagram Ishikawa ("fishbone"). Sub-processes that have the main influence on it were determined. These elements are the critical points that will be subject to validation. The impact of each of these elements, their key parameters and permissible operating ranges are described in the article.

Conclusions. *The sub-processes that have the main impact on the technological process of manufacturing the medical device are identified. These elements are critical points that are subject to validation. The article describes the impact of each of these elements, their main parameters and permissible operating ranges, and also presents the validation process and confirmation of the validity of the corresponding technology*

Keywords: *technological process, validation, diagram Ishikawa, medical devices, injectable implants, hyaluronic acid*

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1. Introduction

The spectrum of medical devices is very wide and diverse, considering the technology of their manufacture, the method of application, the intended purpose and, especially, the form of release: from ordinary textile plasters to artificial organs, cardiovascular stands, nanomaterials, pre-filled syringes, etc.

One of the most popular and well-known representatives of medical devices today is injectable implants based on hyaluronic acid. Intra-articular and subcutaneous injections of hyaluronic acid are the modern and effective method of therapy, which is used for the treatment of arthrosis of the joints, speeding up the recovery of patients during the rehabilitation period after surgical interventions, reducing the manifestations of skin ageing, facial contouring, etc.

Despite the sufficient experience in the production of these types of medical devices from global manufacturers, each manufacturer of medical devices is obliged to guarantee the safety, effectiveness and quality of their product in order to obtain permission to introduce their product to the desired market [1]. In addition, for the Ukrainian market, the production of this type of medical device is a new and promising direction. One of the primary methods of confirming the above-mentioned indicators at the stage of design and development is the validation of the manufacturing process to confirm that the developed process will ensure constant and uninterrupted production of a quality product while maintaining its specified indicators.

Hyaluronic acid is a natural polysaccharide with a repeating disaccharide unit consisting of D-glucuronic acid

and N-acetyl-D-glucosamine (GlcNAc) connected by glycosidic bonds [2].

Hyaluronic acid was first isolated from the bovine`s eye vitreous by Carl Meyer and John Palmer back in 1934. They managed to identify a high-molecular biopolysaccharide that contained uronic acid. Therefore, they proposed the name "*hyaluronic acid*", combining the words hyaloid (vitreous body) and uronic acid [3].

Hyaluronic acid is present in all vertebrates, it ensures the functionality of joints, namely their elasticity due to the effect of lubrication and the absence of improper friction, and also participates in tissue hydration, adhesion and differentiation of connective tissue cells.

This polysaccharide is actually not an acid but a hyaluronic salt with a sodium cation (sodium hyaluronate) (Fig. 1). In 1986, the term hyaluronan was proposed for this substance according to the modern nomenclature. With the development of science and technology, this compound received different names (Table 1) according to the scope of its application [3].

Today, hyaluronic acid can be obtained in two ways:

– physico-chemical method by extracting from the tissues of mammals, birds and even the umbilical cord of newborn;

– microbial method based on bacteria cultivated in a nutrient medium.

The first is quite expensive and time-consuming due to the need to thoroughly clean the obtained product from protein complexes, other polysaccharides and impurities of animal origin. The second method is more economical, using the bacteria *Pasteurella multocida* or *Streptococcus*. Currently, the method of obtaining hyaluronic acid on an industrial scale by using the bacteria *Streptococcus zooepidemicus*, which synthesises hyaluronic acid as an extracellular capsule [4], has become the most widespread. Considering the wide application of this method, there are also many ways to optimise the synthesis process due to the components of the medium to increase the yield of hyaluronic acid: by two-stage optimisation [5], improving the fermentation process [6], adding lysozyme [7], adding hydrogen peroxide and ascorbate [8] and changing the composition nutrient medium [9].

The chemical structure of synthesised hyaluronic acid is almost identical to the natural hyaluronic acid found in the human body. Considering this, as already mentioned above, its use has become widespread in many areas of medicine: orthopaedics [10–12] (restoring the mobility of joints), cosmetology [13] (moisturising tissues, increasing the lips volume, contour plastic), dermatology [14, 15] (burns treatment, post-thrombotic trophic disorders of the skin), ophthalmology [15–17] (corneal transplant, cataracts treatment, glaucoma), etc.

Reticulated ("cross-linked" or stabilised) hyaluronic acid is the most widely used variation of hyaluronic acid (HA) in medicine primarily because of its increased resistance to the action of hyaluronidase. Accordingly, cross-linked acid (cNA) is today the leader of solutions in the direction of manufacturing injectable implants based on hyaluronic acid of prolonged action.

Table 1

Variations of the names of hyaluronic acid in the literature

Name	Scope of application	Frequency of use, %
Hyaluronic acid	Medicine	60
Na-hyaluronate (sodium hyaluronate)	Pharmacy	10
Hyaluronan	Scientific field	30
Sodium hyaluronan	Some pharmacopoeias	Rarely

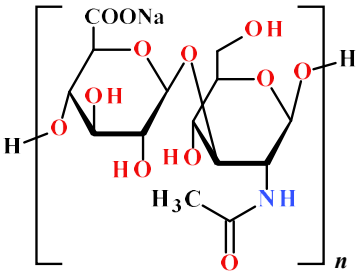


Fig. 1. Structure of sodium hyaluronate

2. Planning (methodology) of research

Synthesis process of cross-linked hyaluronic acid.

Gels based on cross-linked hyaluronic acid differ in the process of cross-linking (stabilisation) and, above all, in the cross-linking agent.

Today, there are injectable implants on the market, for the crosslinking of which two different cross-linking agents are used: 1,4-butanediol diglycidyl ether (BDDE) [18, 19] and divinylsulfone [20]. Both agents work according to the same principle: they react to hydroxyl groups in hyaluronic acid chains. Due to the stitching process, the process of degradation of the implant in the skin tissues is slowed down, and, accordingly, the effect of the medical device is prolonged. In the process of implant synthesis, which is described in this article, BDDE is used as a cross-linking agent.

BDDE is biodegradable, has little toxicity compared to other known cross-linking agents, so it is safer for biomedical applications, which is an absolute advantage for the manufacture of implantable medical devices [18].

The cross-linking of the chains of hyaluronic acid molecules is achieved due to the formation of ether bonds of HA and BDDE molecules, as shown in Fig. 2 [21]. This synthesis occurs only in an alkaline environment. During the reaction, BDDE reacts with the hydroxyl of the hydroxymethyl group $–CH_2OH$ of hyaluronic acid with the formation of cross-linked chains (hydrogel).

In the process of synthesis, there are several key factors that will affect the degree of modification of the hydrogel, its viscosity, rheological properties, which as a result makes it possible to use the product in various medical fields: facial contouring, filling wrinkles, injection into the knee joint to replace synovial fluid etc.

Studies show that the cross-linking index and morphological properties of the gel are affected not only by the concentration of both substances during synthesis, but also by the temperature of the environment, the time of synthesis, and the technology of mixing the gel during cross-linking. In the process of mixing the gel in a large portion in the reactor and mixing parts of the gel with subsequent combining using the same concentrations of BDDE, hyaluronic

acid and auxiliary substances, gels with different cross-linking efficiency are synthesised [22]. The batch-mixed gel was significantly more stable and showed higher resistance to hyaluronidase activity. The level of gel stability is determined by the degree of modification and cross-linking of hyaluronic acid (HA), which can be determined by the method of cleavage of cHA by the enzyme chondroitinase, and the cleavage product is analysed using size-exclusion chromatography in combination with electrospray ionisation mass spectrometry (SEC-ESI-MS) [23].

Accordingly, in the process of developing medical devices, it is necessary to select the parameters of each stage of the production process in order to achieve the necessary characteristics of the hydrogel.

Form of issue of implants.

Injectable implants based on hyaluronic acid are produced in the form of pre-filled syringes. Over the past decade, prefilled syringes have become a very popular method of delivering pharmaceutical products. With a prefilled syringe, the process of administering a medical device or medication can be safer, faster, and easier for the medical staff and the patient as well.

The use of pre-filled syringes reduces the number of necessary steps for injection, thereby reducing the risk of injury to the patient and the doctor, cross-contamination, and also ensures the achievement of dosing accuracy as they are single-use medical devices.

The process of filling gel into syringes is the final stage of production after synthesis. Therefore, before filling syringes with gel, it is necessary to carry out an intermediate control of the product, namely, checking the compliance of the gel specification indicators, such as the concentration of hyaluronic acid, the limit content of BDDE, microbiological purity to avoid the risk of the bacterial endotoxins growth after sterilisation, viscosity, etc.

According to the regulatory requirements of the European Union and Ukraine, injectable implants based on hyaluronic acid are classified as medical devices III risk class. Since hyaluronic acid is administered by injection, it is necessary to confirm the safety and effectiveness of its use for the patient and to minimise any risks of obtaining a product of inappropriate quality during its production.

To achieve the expected characteristics of the finished product on an industrial scale after developing the technological process and establishing the necessary synthesis parameters, it is extremely important to control the critical points of the technological process during the manufacture of each new batch of medical device.

Process validation [24] is a term used in the pharmaceutical industry to demonstrate that the process is subject to close control and that the outcome of the process can be practically guaranteed. Process validation involves demonstrating that, when the technology operates within specified limits, it will consistently produce a product that meets requirements that were determined during the design and development stage. As part of the quality management system, process validation consists in the formation of documentary evidence that a specific procedure ensures the continuous and uninterrupted production of a product that meets predetermined specifications [25]. Validation is carried out by monitoring indicators that are determined precisely at critical points of the technological process. To form their list, it is necessary to assemble a validation group and form a risk assessment according to ISO 14971:2019 [1] to determine those processes that have an impact on the quality of the finished medical device and, accordingly, its safety and effectiveness for the patient.

To identify these critical points, each stage of the technological process has been analysed, and parameters that reflect the correctness of the course and execution of each sub-process to ensure obtaining a high-quality product according to the established specification and affect the achievement of the required product characteristics [26] have been determined. The Ishikawa diagram was used as a tool for such analysis.

Validation of technological process.

In DSTU IEC/ISO 31010:2013 [27] analysis using the Ishikawa diagram is called "analysis of cause-and-effect relationships". The causality analysis group should include a group of experts who have a good knowledge of the subject of analysis to be able to consider all known risks, analyse the relationships between them and product quality, predict any situations that may affect the result of the research process.

The main stages of the analysis of cause-and-effect relationships according to DSTU IEC/ISO 31010:2013 [27] are as follows:

– definition of the process that is subject to analysis and sub-processes that have an impact on the final result; the impact can be both positive and negative depending on the circumstances;

– determination of the main categories of impact on the process, displayed by blocks on the Ishikawa diagram: personnel, equipment, environment, etc.

The result of such analysis is displayed in the form of the above-mentioned diagram Ishikawa in the shape of "fish bone". The Ishikawa diagram is structured by dividing the main categories of influence on the process (represented by lines departing from the fishbone) and secondary sub-processes using additional branches that detail the influence of the main process on the object of analysis.

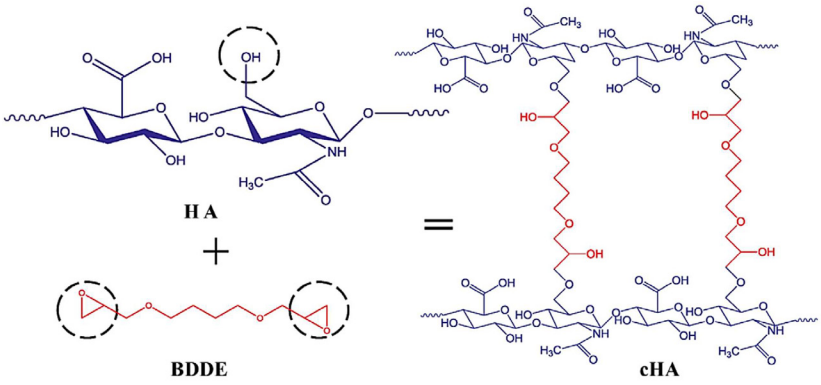


Fig. 2. The process of obtaining cNA due to the cross-linking of chains of HA molecules using BDDE

3. Materials and methods

The subject of analysis in preparation for the validation of the technological process of manufacturing injectable implants based on hyaluronic acid is to obtain a safe and high-quality finished medical device that meets the needs of the user and the declared consumer characteristics. Based on the analysis, the working group determined the criteria/processes that have an impact on the final result, and the sub-processes that must be monitored.

The first criterion was the environment in which the technological process takes place. Namely, its purity level according to ISO 14644-1:2015 [28]. A sub-process that is necessary to minimise the risk of negative impact, in this case, is the periodic control of parameters of clean rooms, which is ensured by periodic qualification.

The next criterion is personnel, namely the presence of the required level of qualifications and job instructions that minimise the risk of error and the human factor.

It is also important to control the equipment used in the technological process, including qualification and calibration of the relevant equipment, and allow only personnel with the appropriate level of qualification to work with it.

The materials used in the technological process have one of the greatest effects on the quality of the finished product. Accordingly, each manufacturer of medical devices must ensure the qualification of suppliers of raw materials according to ISO 13485:2016 [24] and conduct incoming control of each new batch of raw materials from an approved supplier according to the internal specification.

And the most critical is the technological process itself and the formulation of the manufacturing of the medical device. Sub-processes in this case determined the reproducibility of the recipe developed in the laboratory directly at the production site and the correctness of the technological process itself. The reproducibility of the recipe is ensured by the transfer of technology from the development laboratory to production through the production of experimental and industrial batches and quality control of the finished product in accordance with the internal specifications.

For the correct course of the technological process, several sub-processes that have the main influence on it were determined. It is these elements that are the critical points that will be subject to validation:

1. Synthesis: control of the temperature of the solution, speed and time of mixing, time of synthesis and loading of raw materials into the reactor. At this stage, cross-linking of the product occurs (binding of sodium hyaluronate chains with a cross-linking agent). The specified characteristics affect the efficiency and achievement of the required percentage of cross-linking, the rheology of the product and its consumer characteristics.

2. Neutralisation: considering that the synthesis takes place in an acidic environment to activate the cross-linking agent, it is necessary to control the neutralisation stage to achieve the physiological pH level of the finished gel.

3. Dialysis: washing out the remains of the cross-linking agent from the gel. Given that the toxic BDDE is most often used as a crosslinking agent, it is important to maximally wash out the molecules of this substance that have not reacted.

4. Intermediate control: control of the microbial load of the gel before filling the syringes and sterilisation to minimise the risk of a high content of bacterial endotoxins in the finished product; as well as control of the stated amount of hyaluronic acid in the gel.

5. Filling syringes: the volume extracted from the syringe is controlled, which must correspond to the nominal volume declared in the instructions for use.

6. Sterilisation: Treatment of a medical device to destroy pathogenic organisms and biological agents to prevent infection through the medical device.

7. Centrifugation: separation of air from the gel to avoid air bubbles entering the patient's tissues during injection.

A graphical representation of the identified processes and sub-processes is depicted using the Ishikawa diagram in Fig. 3.

These parameters are subject to control for each validation batch. The purpose of validation is to check and document compliance that the process of manufacturing implants in combination with technical means and established requirements can constantly ensure the stable release of finished products of medical devices of appropriate quality in accordance with the requirements of the internal specification. Table 2 presents a list of defined critical points for the validation of the manufacturing process of injectable implants based on cross-linked hyaluronic acid, their parameters, and permissible operating ranges. All permissible ranges were selected practically during the development of the medical device to achieve the required characteristics of the finished product with minimal costs of production resources.

Depending on the stage of the life cycle of the medical device at which the need for validation was identified, one of the following approaches may be chosen:

– prospective validation;
– accompanying validation;
– retrospective validation.

Prospective validation is a validation that is carried out before the start of industrial production of the product, that is, at the stage of design and development. The traditional approach is to carry out validation on experimental and industrial batches, if the process has not yet been scaled to production. In this case, the size of research and industrial batches should be at least 10% of the size of commercial production. The classic approach is to conduct validation on at least three research and industrial lots and form a validation master plan for further validation on industrial lots. That is, accompanying validation.

Accompanying validation is carried out during the industrial production of the product that is already intended for sale, similarly, on at least three batches based on the justification of the number of necessary batches in the validation protocol. For concurrent as well as retrospective validation, it is recommended to perform validation on consecutive batches.

In this case, the following approach was chosen: prospective validation on three experimental and industrial batches before certification and further accompanying validation after certification with the production of maximum volumes of industrial batches for sale.

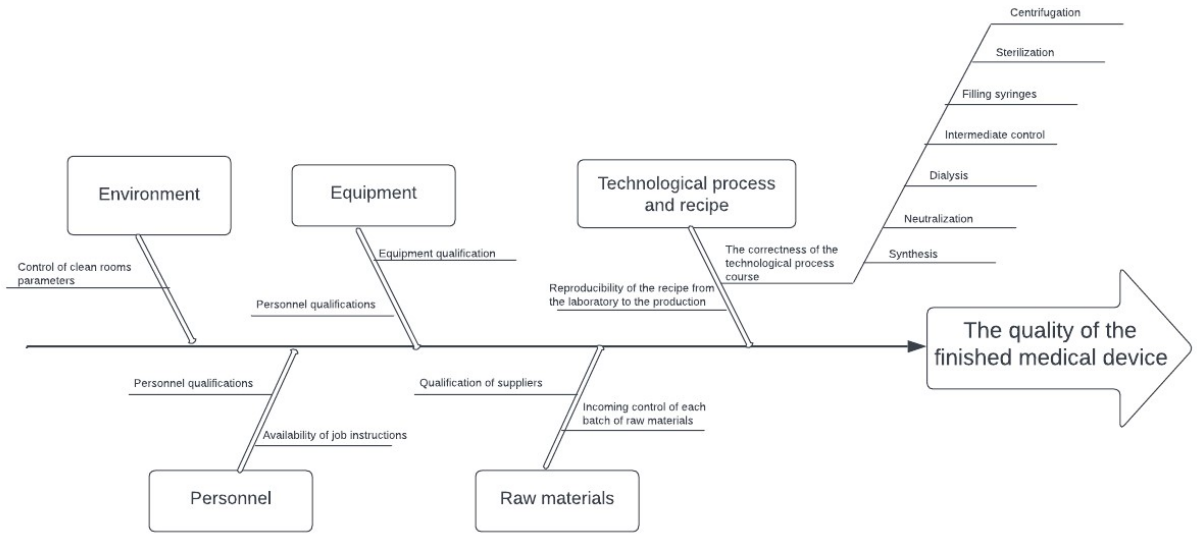


Fig. 3. Ishikawa diagram for displaying critical processes and sub-processes for obtaining a high-quality finished medical device

Table 2

Critical points of the manufacturing process of injectable implants based on cross-linked hyaluronic acid

No	Process	Parameter	Permissible operating range
1	Synthesis	The temperature of the solution in the reactor	45.0±5.0 °C
		Stirring speed	50±5 revolutions per minute
		Mixing time	50±5 minutes
		Synthesis time	12±0.5 hours
		Weighing raw materials for product synthesis	According to the technological instruction and technological route
2	Neutralisation	Intermediate control: pH of sodium hyaluronate gel	6.5–7.5
		Stirring speed	55±5 revolutions per minute
3	Dialysis	Dialysis time	40±1 hours
4	Control of intermediate products	Microbial load	It is carried out according to the monitoring results
		Quantitative content of sodium hyaluronate	Deviation no more than 5 %
5	Filling syringes	Extractable volume	For 1 ml: 1.0–1.1 ml. For 2 ml: 2.0–2.15 ml
		Microbiological purity, bacterial endotoxins	According to the product specification
6	Sterilisation	Sterilisation temperature	121±1 °C
		Sterilisation time	8±1 min
7	Centrifugation	Time	1.5–1.6 min
		Speed	3000 rpm
8	Quantitative content of the main component	Quantitative content of sodium hyaluronate	29.0–32.0 mg/ml

The last option is retrospective validation, i.e. certification of the batch process of the production of the sold product, based on the received data on the production and control of batches of products, analysis of already produced and sold dossiers on the batch (usually at least 5). This approach can be most applicable for medical devices that have extensive experience in industrial production. After all, taking into account the strengthening of regulatory requirements for this type of pharmaceutical product, only during the last 2–3 years has the issue of validation of the technological process of medical devices become more and more relevant. Accordingly, this approach was applied to the previous variations of the Injectable implants based on the hyaluronic acid line, which have been on the market since 2016, and the production has sufficient experience to be able to form a retrospective validation. The approach to determining critical points was applied similarly to the one described above.

In this case, a retrospective validation of the manufacturing technology of injectable implants based on cross-linked hyaluronic acid was carried out. 7 batches produced during 2023 were selected.

Table 3 presents the indicators that were determined above according to the risk assessment according to the Ishikawa diagram and according to which the validation was carried out, respectively. As well as the actual received values for them from each batch.

Most of these indicators are constant, as they are controlled and set by equipment that undergoes regularly scheduled qualification. Accordingly, such indicators have

constant values and are not included in the validation calculation. These are indicators such as temperature and duration of sterilisation – parameters that are controlled by the sterilisation cabinet automatically and do not have variable data.

Indicators that are controlled manually and have the influence of the human factor, as well as those that characterise the quality of the product, have excellent values within the permissible norm and are subject to static calculation. For statistical processing of data, the method of constructing Shewhart control charts was used. For this case, the approach of building control charts for quantitative data, namely control charts for individual values (X), was chosen. The parameters of pH, dialysis time (min), extracted volume (ml) and quantitative content of hyaluronic acid in the finished product (mg/ml) were selected for the construction of maps.

Control limits are calculated based on the data obtained from the sliding scale of two observations to construct control charts for individual values. Control charts are built for each indicator based on the average value and the moving average. Each Shewhart control chart contains two control limits, which are determined statistically: an upper control limit (UCL) and a lower control limit (LCL). An indicator of the statistical quality of the values is a map in which the experimental values are within the limits of UCL and LCL.

4. Results

The control limits are calculated according to the formulas given in ISO 8258:1991. Fig. 4–7 below show the corresponding Shewhart control charts: the individual observation chart (X-chart) to monitor the spread of individual data, taking into account the control limits, and the moving average control chart (R-chart) to monitor the process variability (as the range) at regular intervals from a process. It is important to note that the LCL (R) for n less than 7 is not depicted for individual values.

Table 3

Indicators of 7 batches of medical devices based on hyaluronic acid subject to validation

No.	Process	Parameter	Permissible operating range	batch 0223	batch 0323	batch 0423	batch 0623	batch 0723	batch 0823	batch 1023
1	Synthesis	The temperature of the solution in the reactor	45.0±5.0 °C	45	45	45	45	45	46	45
		Stirring speed	50±5 revolutions per minute	50	50	50	50	50	50	50
		Mixing time	50±5 minutes	51	50	50	51	50	50	50
		Synthesis time	12±0.5 hours	13:00	13:24	13:00	13:11	13:10	13:13	13:00
		Weighing raw materials for product synthesis	According to the technological instruction and technological route	meets the requirements	meets the requirements	meets the requirements	meets the requirements	meets the requirements	meets the requirements	meets the requirements
2	Neutralisation	Intermediate control: pH of sodium hyaluronate gel	6.5–7.5	7.35	7.4	7.4	7.4	7.37	7.35	7.39
		Stirring speed	55±5 revolutions per minute	56:03	56:01	56:02	56:00	55:58	55:59	56:01
3	Dialysis	Dialysis time	Not more 48 hours	45:30	48:00	47:52	47:59	46:43	47:55	47:32
4	Control of intermediate products	Microbial load	It is carried out according to the monitoring results	meets the requirements	meets the requirements	meets the requirements	meets the requirements	meets the requirements	meets the requirements	meets the requirements
		Quantitative content of sodium hyaluronate	Deviation no more than 5 %	meets the requirements	meets the requirements	meets the requirements	meets the requirements	meets the requirements	meets the requirements	meets the requirements
5	Filling syringes	Extractable volume	For 2 ml: 2.0–2.15 ml	2.0	2.0	2.1	2.1	2.0	2.0	2.1
		Microbiological purity, bacterial endotoxins	According to the product specification	meets the requirements	meets the requirements	meets the requirements	meets the requirements	meets the requirements	meets the requirements	meets the requirements
6	Sterilisation	Sterilisation temperature	121±1 °C	121±1 °C	121±1 °C	121±1 °C	121±1 °C	121±1 °C	121±1 °C	121±1 °C
		Sterilisation time	8±1 min	8±1 min	8±1 min	8±1 min	8±1 min	8±1 min	8±1 min	8±1 min
7	Centrifugation	Time	1.5–1.6 min	1.5	1.5	1.5	1.5	1.5	1.5	1.5
		Speed	3000 rpm	3000	3000	3000	3000	3000	3000	3000
8	Quantitative content of the main component	Quantitative content of sodium hyaluronate	29.0–32.0 mg/ml	30.12	30.11	30.11	30.06	30.10	31.08	30.11

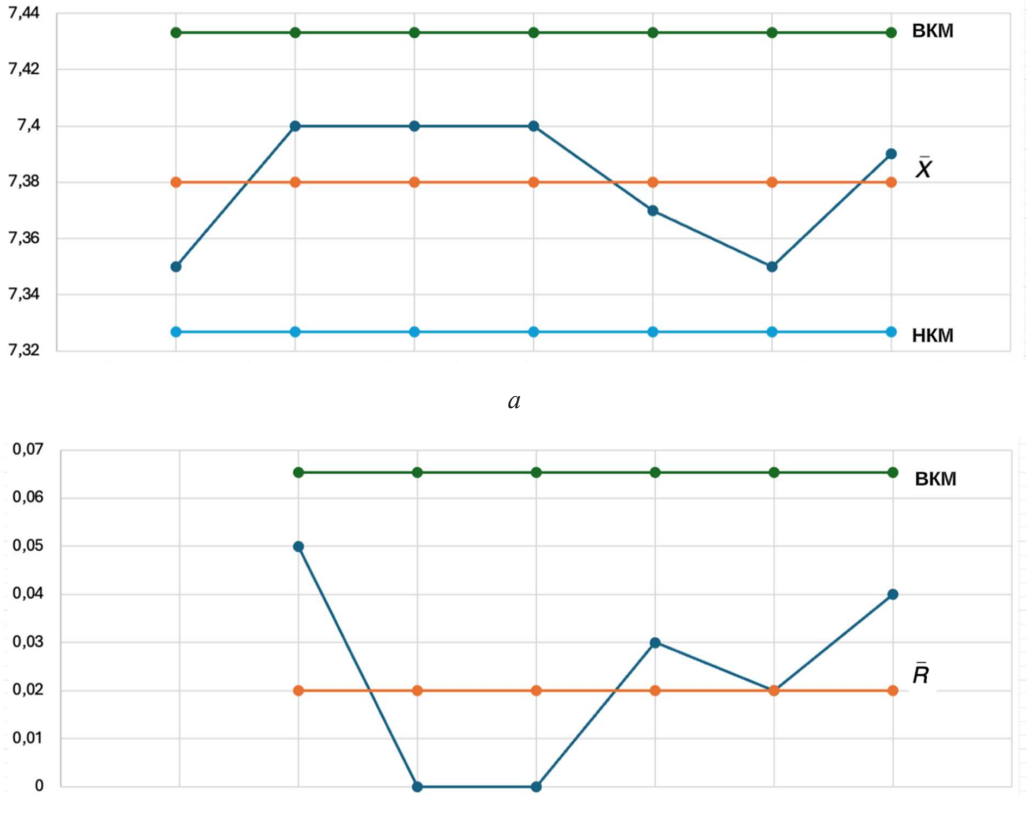


Fig. 4. Shewhart control charts for pH values: *a* – the individual observation chart (X-chart); *b* – the moving average control chart (R-chart)

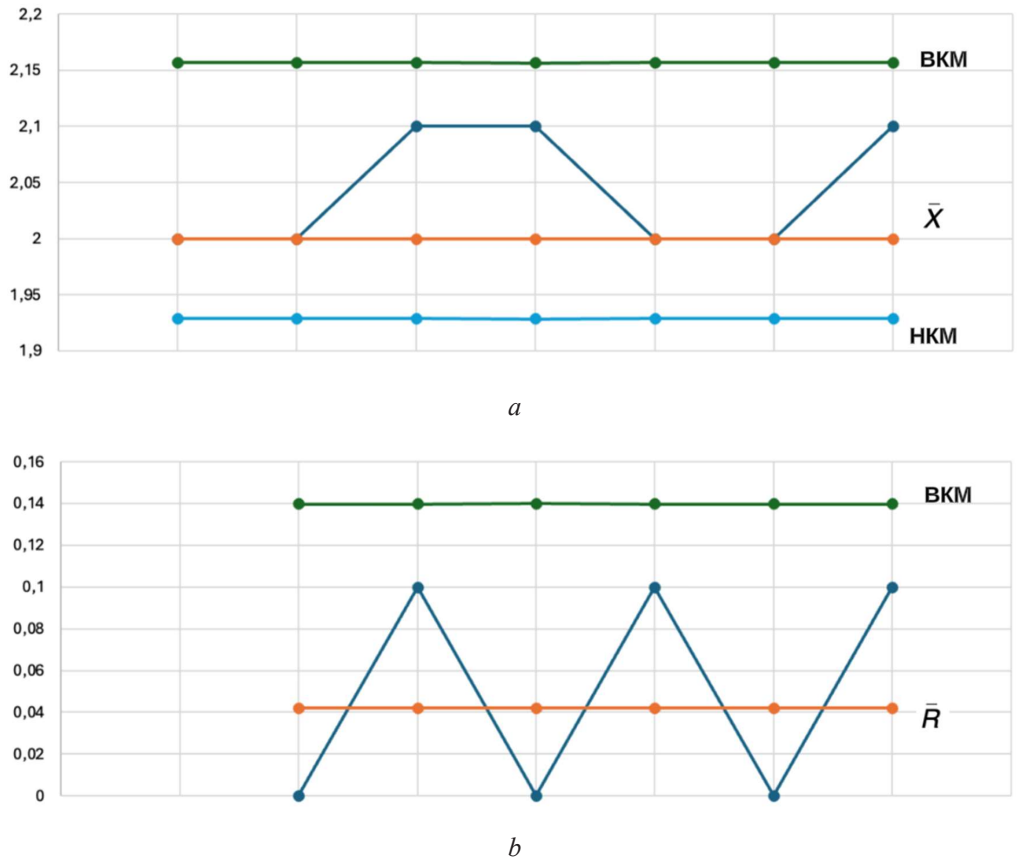
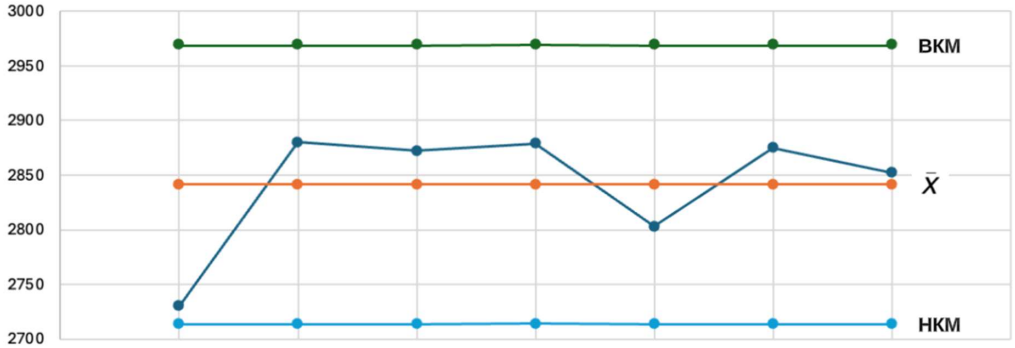


Fig. 5. Shewhart control charts for the extracted volume, ml: *a* – the individual observation chart (X-chart); *b* – the moving average control chart (R-chart)



a

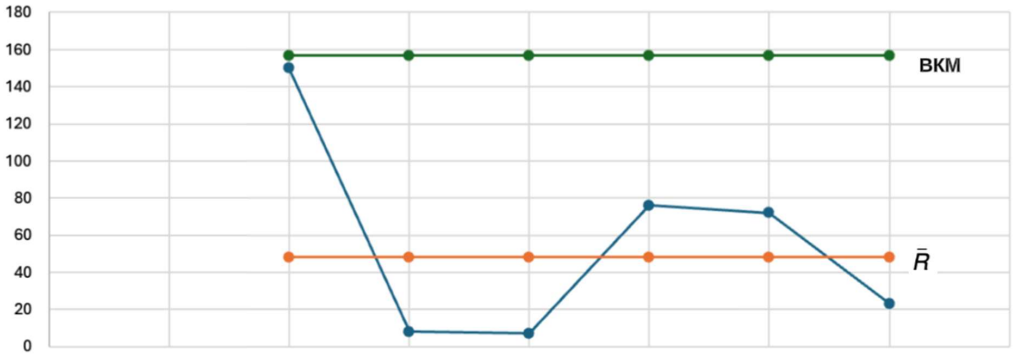


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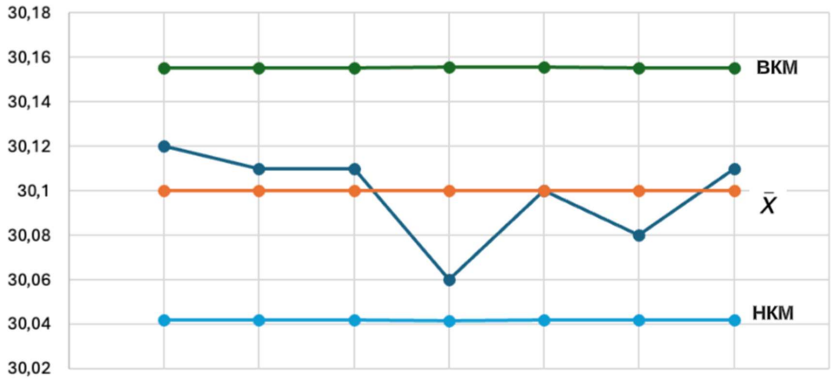
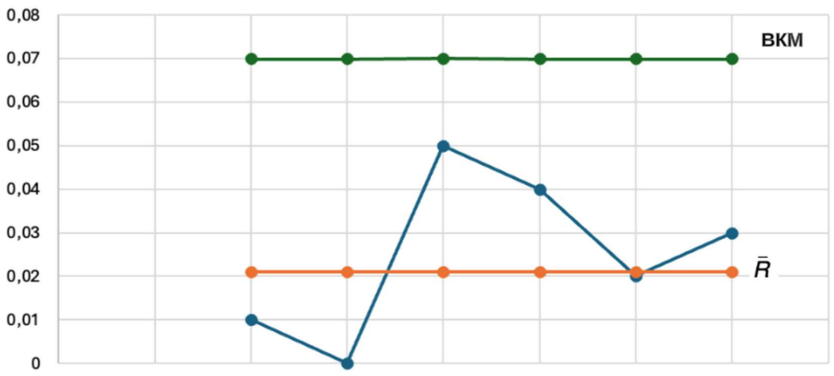
Fig. 6. Shewhart control charts for the dialysis time, min: *a* – the individual observation chart (X-chart); *b* – the moving average control chart (R-chart)



a



b

Fig. 7. Shewhart control charts for the quantitative content of hyaluronic acid, mg/ml: *a* – the individual observation chart (X-chart); *b* – the moving average control chart (R-chart)

5. Discussion

Despite the fact that the regulatory requirements of Ukraine, namely Resolution of October 2, 2013 No. 753 On the approval of the Technical Regulation on medical devices [29], generally do not require the validation of the entire technological process of medical devices (except for the sterilisation regime for sterile medical devices), for manufacturers who plan to introduce their products to the markets of the European Union, the United States of America and a number of other countries, and adapt their regulatory documents to the requirements of Medical Device Regulation 2017/745 (hereinafter MDR) [30] or U.S. Food and Drug Administration [31] validation of the technological process is mandatory.

Currently, the development of the draft law of the resolution of the Cabinet of Ministers of Ukraine on the approval of the Technical Regulation on medical devices with the aim of harmonising the legislation of Ukraine with the updated European regulatory requirements is underway. In addition, the process of preparing for the signing of an agreement between Ukraine and the European Union on the adoption of conformity assessment of medical devices is also ongoing, provided that Ukraine's regulatory requirements are fully adapted to the European Regulation. Thus, all manufacturers of medical devices in Ukraine should be ready to implement the described agreement and introduce stricter requirements for medical devices.

Based on global regulatory requirements and the experience of manufacturing medical devices on an industrial scale, this article describes a general approach to the validation of the technological process of medical devices that can be applied to the Ukrainian market and, as an example, presents a vision for the validation of the technological process of injectable implants.

First of all, it is necessary to evaluate and analyse the requirements for the validation of the medical device manufacturing process described by MDR 2017/745 [30].

As stated in Article 71 of MDR 2017/745 [30], as before, the validation of the sterilisation regime for sterile medical devices remains mandatory. Such a requirement is not new for manufacturers of medical devices of Ukraine, who already have experience in obtaining a conformity assessment. Also, in Appendix II of MDR 2017/745[31)], which regulates the requirements for technical documentation provided to the Conformity Assessment Body, one of the requirements is to provide a detailed description of production processes and information on their full validation. The dossier for a medical device must include information that demonstrates the full extent of assurance of the effectiveness, quality and safety of the product. One of the methods of confirming this is the validation of the design and development of a medical device.

MDR 2017/745 [30] does not give clear instructions on how to directly validate the technological process, except for the requirement regarding the need to carry it out as described above. In general, there are no regulatory requirements for validation for medical devices. However, to build an approach to this process, you can turn to the following sources:

1) DSTU-N GHTF/SG3/N99-10:2015 Quality management systems. Guidance on process validation. The document is harmonised to GHTF/SG3/N99-10:2004 Quality Management Systems – Process Validation Guidance. Edition 2 [32];

2) EMA/CHMP/CVMP/QWP/749073/2016 EMA Guideline he process validation for finished products – information and data that be provided in the regulatory submission, November 10, 2016 [33] ;

3) ICH Q7 Current Step 4 version, dated November 10, 2000 [34] ;

4) EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Volume 4 [35];

5) CT-H MOH of Ukraine 42-4.0:2015 MEDICINAL PRODUCTS Good manufacturing practice [36].

The first document is a guideline that provides clarification of the process verification and validation approach for medical devices and practical advice on conducting validation but it is not a regulatory document. All of the following are regulatory requirements, but primarily, they are used to validate the process of manufacturing medicinal products for medical and veterinary needs. Nevertheless, the principles described in them can be taken as a basis for medical devices as a worse option, especially if the approach to the validation of medical devices of class III with a high degree of risk is considered [37].

According to DSTU-N GHTF/SG3/N99-10:2015 [32], process validation is part of the complex requirements of the quality management system. Validation is performed in the context of a system that includes design and development control and product quality assurance and determines corrective and preventive actions in the event of nonconformities or deviations. Validation of the process for medical devices is carried out in the absence of the possibility of conducting a qualitative evidentiary check (or verification) of the effectiveness, the correctness of the process and its result at the time of completion of design and development, as well as when making any changes.

Validation of a technological process is defined as the collection and evaluation of data, starting from the stage of design and development of a medical device and ending with the establishment of uninterrupted commercial production, in order to establish that the process is capable of consistently producing a quality product [33]. Preparation for validation was divided into three main stages.

– Stage 1 – Design and development of the medical device manufacturing process: determination of the technological route taking into account the characteristics that the final product must meet and the technical capabilities of the corresponding production.

– Stage 2 – Process certification: process testing (production of laboratory samples) to verify the possibility of implementing the process and releasing the product on a production scale. At this stage, a validation plan and protocol were formed based on the acquired knowledge and test results. Also, at this stage, a study of the stability of laboratory samples under conditions of accelerated ageing was carried out to confirm the correctness of the

formulation and the preservation of the usability characteristics of the product during the shelf life.

– Stage 3 – Direct validation of the technological process: carrying out a certain amount of research and confidence in the ability of the process to ensure the release of a quality product on an industrial scale.

When planning the validation, a validation group was formed, which consisted of specialists from various fields. First, technologists are responsible for the course of the production process, its correctness and its results. In addition to technologists, experts in the field of quality management and regulatory requirements, clinical experts, laboratory specialists and sales planning departments, etc., should also be involved in the validation. All experts of the validation group are involved in the formation of the validation plan, which defines the processes that are subject to validation, contains the validation schedule, describes the relationships between the processes that require validation, control parameters that are critical points of the technological process and the time of repeated validation (revalidation). Only after the formation of the plan, the clear establishment of the parameters of validation, and the purpose and scope of work is it possible to start the development of the protocol.

The validation protocol should contain:

– description of the process to be validated;

– list of all equipment involved in the production process;

– a list of critical points, that is, processes that will be subject to inspection;

– process parameters to be monitored, methods of their control and monitoring;

– process success control parameters and their measurement criteria;

– list of operators and qualifications that operators must possess;

– specification for the finished product;

– description of any specific control methods (if available);

– statistical methods of data collection and analysis;

– description of maintenance and repair of production equipment (if applicable);

– duration and repeatability of the inspection;

– re-examination criteria.

The main element of the protocol is the stage of determining the critical points as described above.

Upon completion of the validation activity, a validation report was created, which contains a description of the result of the validation in accordance with the established verification parameters, as well as all documentation confirming the validation, including analytical letters, reports on the operation of the equipment, etc. The report should include conclusions regarding the status of the process verification: the process has been validated and confirmed for the possibility of use on an industrial scale, or deviations have been recorded during the validation process that require additional consideration, corrective actions, or a complete redesign of the process.

In the future, any changes in the process and/or product must be evaluated in terms of the criticality of their impact on product quality and the extent of re-inspection, if necessary.

If several product variations (batch volumes, output volumes, etc.) are expected for the release of industrial batches, according to the regulatory requirements presented above, a bracketing approach is acceptable: a validation scheme designed in such a way that during process validation only batches with extreme values of certain predefined and justified parameters. Such parameters can be the concentration of the main component, the size of the batch, the size of the package, completeness, etc. Bracketing assumes that validation of extreme values guarantees the preservation of quality characteristics for values in the range between them.

In this article, validation was performed retrospectively using Shewhart control charts. Shewhart control charts are a convenient and easy-to-use tool that is a fairly effective indicator of the state of process control. In this article, the calculation was carried out using an individual observation chart – a control chart for evaluating the level of the process based on an individual observation in the sample and a moving average control chart – a control chart for evaluating the level of the process based on the arithmetic average of the latest observations, in which the new observation replaces the older of the latest observations.

Shwehart control chart shows whether the process is in a state of statistical control. If the test process is in a state of statistical controllability, then approximately 99.97 % of the result values will fall within the control limits.

When the value goes beyond one of the control limits, the corresponding stage of the technological process as a whole technological process can no longer be considered a state of statistical controllability of the test process. In this case, it is necessary to investigate and find non-accidental causes, take corrective actions and repeat the validation calculations.

Practical relevance. This article describes an approach to technological process validation of the medical device of the highest risk class using data from real industrial-scale production in accordance with current regulatory requirements of the European market. Applying a similar approach to technological process validation of any other type of medical device guarantees confirmation of compliance with EU regulatory requirements for placing the product on the relevant market, as well as confirmation of the validity and reproducibility of the technology in the manufacture of quality products by the manufacturer.

Research limitations. While this study provides valuable insights into the validation of technological processes for the manufacturing of injectable implants based on hyaluronic acid, certain limitations must be acknowledged:

Scope of validation.

The study focuses primarily on the validation of the manufacturing process itself and does not comprehensively address other critical aspects such as long-term clinical outcomes, patient response variability, or post-market surveillance. The results, therefore, are primarily relevant to the manufacturing phase and may not fully reflect real-world clinical performance or adverse effects.

Regulatory considerations.

While this research aligns with common industry standards, the regulatory landscape for medical devices, especially in different geographical regions, may vary. The validation approaches proposed here may need to be adapted for specific regulatory requirements in various markets (e.g., FDA, EMA).

Technological limitations.

The technological tools and methods used for process validation, such as in-process monitoring, could be limited by the current state of available technology. Some measurement techniques may not be sufficiently sensitive or accurate for detecting all potential sources of variability, especially at microscopic or nanoscale levels.

Prospects for further research. The research presented in this article opens several avenues for further exploration in the field of medical device manufacturing and process validation:

Expanded clinical correlation studies.

Further studies should investigate the correlation between the validated manufacturing processes and the clinical outcomes of patients receiving injectable hyaluronic acid implants. Clinical trials involving long-term follow-ups would help assess the safety, efficacy, and patient-specific responses to different formulations and manufacturing processes.

Process validation in different regulatory environments.

As regulatory requirements for medical devices differ across regions, future studies could assess the adaptability of the validation approach proposed in this study to various regulatory frameworks.

Validation of new production technologies.

Further research could investigate the application of emerging production technologies, to the manufacture of injectable medical devices. These methods could potentially allow for more intricate and personalised implant designs, as well as more efficient manufacturing workflows.

6. Conclusions

Even though the theory of technological process validation is quite simple, medical devices, in addition to a wide spectrum of their diversity, are produced by companies of different sizes, production volumes, management methods, etc. Accordingly, all these factors have a significant impact on the practical application of process validation.

Technological process validation of manufacturing medical devices is primarily not just a regulatory requirement, compliance with which is necessary for the possibility of bringing the product to the desired markets. It is also a manufacturer's guarantee of the ability to continuously manufacture high-quality medical devices, reduce or eliminate the number of defects, improve product quality, etc. Validation for medical devices is somewhat simpler and more flexible than for medicinal device, although it shares the same principles and objectives. As described in the article, the main purpose of the validation of the medical device manufacturing process is to control the validation batches according to the parameters that have been determined to be critical, to confirm the ability of the process to ensure the release of a high-quality and safe product for the end user. An approach for determining critical control points for validation using a graphical method of displaying significant cause-and-effect relationships between the stages of the technological process of manufacturing a medical device is described.

In this article, 4 indicators of the technological process were selected, which were used for retrospective validation: pH, extractable volume, dialysis time, and quantitative content of hyaluronic acid in the finished medical device. 7 consecutive batches of products were selected for the use of their indicators, and two Shewhart charts were constructed for each indicator: the individual observation chart (X-chart) and the moving average control chart (R-chart). As can be seen from Fig. 4–7, all values are within the control limits; no indicator goes beyond the corresponding limits. Accordingly, it can be stated that the investigated technological process of manufacturing a medical device based on hyaluronic acid is in a state of statistical control.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

The manuscript has no associated data.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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