Cell and Organ Transplantology. 2023; 11(1): 26-33.
https://doi.org/10.22494/cot.v11i1.147

# Features of technological regulation for cardiac bioimplants

Shchotkina N.[1,3], Palamarchuk Y.[1], Skorokhod I.[3], Dolinchuk L.[2], Sokol A.[1], Motronenko V.[1], Besarab A.[1], Gorchakova N.[2], Frohme M.[3], Herzog M.[3]

[1]*National Technical University of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute", Ministry of Education and Science of Ukraine, Kyiv, Ukraine*
[2]*O. O. Bogomolets National Medical University, Kyiv, Ukraine*
[3]*Technical University of Applied Sciences Wildau, Wildau, Germany*

*Corresponding author's e-mail: cardiotissue@gmail.com

## ABSTRACT

*Patients with congenital heart defects and cardiovascular diseases require new approaches to surgical intervention. The use of biological cardiac implants, which are made from the extracellular matrix, is a promising trend in modern regenerative medicine. These bioimplants can completely replace defective tissue or organs, and when manufactured with strict protocols and quality control measures, can be safe and effective for therapeutic applications. The process of manufacturing bioimplants involves various risks that need to be assessed and mitigated with ongoing monitoring and evaluation necessary to ensure the highest standards of quality. Overall, this study successfully evaluated the requirements for introducing a new medical device into practice and created a technical file that meets all necessary documentation for certification.*

***KEY WORDS:*** *cardiac bioimplant; quality system; manufacturing risk management; technical regulation; medical devices*

The rapid increase in the incidence of cardiovascular diseases and high mortality rates among patients with congenital heart defects requiring surgical intervention have made the search for new modern approaches to the treatment of such patient groups urgent. Among the main trends of today, the use of synthetic and biological cardiac implants can be noted. Transplants, which are made on the basis of purified extracellular matrix and are functionally and structurally similar to native pericardium, are of particular interest. In contrast to synthetic analogs, such constructions can fully replace the defective part of tissue or organ, after which they are integrated and function properly.

Modern regenerative medicine successfully combines fundamental research data and clinical practice, providing great potential for therapeutic applications. It is based on the restoration or replacement of tissues and organs that have a structural or functional deficit, using synthetic, biological, and extracorporeal matrices [1, 2]. Synthetic frameworks provide opportunities for manipulation and control of structural properties, but do not guarantee the same functionality as native tissue [3]. The advantage of using biomaterials in tissue engineering is their property of resorption in the body with subsequent replacement by the body's own tissues. However, there is an increasing interest in frameworks based on natural extracellular matrix (ECM), which is reproduced by the microarchitecture of native tissue [4]. An alternative is bioimplants, created from xenogeneic tissues (e.g. horses, pigs, cattles), which are similar to human tissues in their mechanical and biological properties [5]. Bioimplants based on decellularized ECM, purified from cells via decellularization (bioengineering transformation) of tissue, are increasingly used in reconstructive and regenerative medicine, as they provide repopulation by the recipient's own cells, rapid growth and restoration. In addition, such bioimplants are considered less prone to calcification and provide ideal hemodynamic parameters. Due to its biomechanical properties, ECM are a little different from pericardial tissue and, therefore, suitable for the use in the replacement of heart valves in adults and correction of congenital heart defects in children [6].

Thus, in view of the urgent need for high-quality biological material in medicine, Ukrainian scientists have developed a unique technique for decellularization of tissue-modified matrix of bovine pericardium, which has already successfully passed the stage of preclinical trials. Five different decellularization schemes were investigated by the authors, and the one that involved the use of sodium dodecyl sulfate (SDS) ionic detergent was chosen, which demonstrated the most effective method of cleaning from cellular components with the maximum degree of preservation of tissue architecture [7, 8, 13]. Subsequently, the proposed biotechnological scheme was improved by optimizing the temperature regime and duration of decellularization, as well as the lyophilization stage [9, 10, 12].

The bioimplant developed by domestic researchers has no cytotoxic effect *in vitro* and high biocompatibility, demonstrated on experimental models *in vivo* (absence of immunogenic reactions, replacement of the scaffold by growing immature connective tissue, enhanced vascularization) [11].

However, the guarantee that the bioimplant in its finished form will function in accordance with its purpose and its use will be safe for humans is the assessment of its biological effect based on information about the advantages and disadvantages of various materials and research methods. So, for further certification of the product, there arose the task to substantiate the bioengineering parameters of production in accordance with national and international regulatory requirements.

**THE AIM** of this review was to explain in detail the features of the bioimplant manufacturing technology using the example of a bioengineering scheme for the production of a tissue-modified biocompatible matrix for use in cardiac surgery developed by domestic scientists. This technology can predict the safety, effectiveness, and quality of a medical device. The ultimate goal of this short review was to assess the technological regulation of the manufacture of cardiosurgical bioimplants. The review included researching regulatory requirements and standards for medical devices, as well as conducting a risk assessment and developing a plan to address any potential risks. This plan can then be used to facilitate the certification of the device for the use in medical practice.

## REVIEW OF TECHNOLOGICAL PROCESS OF MANUFACTURING BIOIMPLANTS

A review of the literature on the technology for producing xenogeneic bioimplants was allowed for the development of a general process scheme (**Fig. 1**) [14-16]. Thus, the creation of a unique technological map of production enabled the certification of the medical device and accelerated the process of its application in cardiac-surgical practice.

Regardless of the methods used, the main biotechnological stages are:

1. Sample collection.
2. Processing (mechanical processing/cleansing of tissue, decellularization, scaffold fixation/stabilization).
3. Sterilization.
4. Conducting tests to meet the requirements for application (preclinical testing).
5. Using the bioimplant in clinical practice.

Despite similarities in the first two stages among most technologies, the remaining processes can differ significantly and be modernized, affecting the quality and speed of product manufacturing (**Fig. 2**).

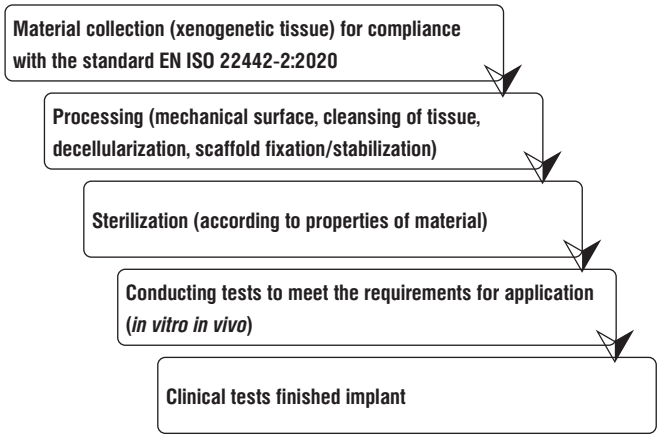


**Fig. 1.** Biotechnological scheme of obtaining of xenogeneic bioimplants

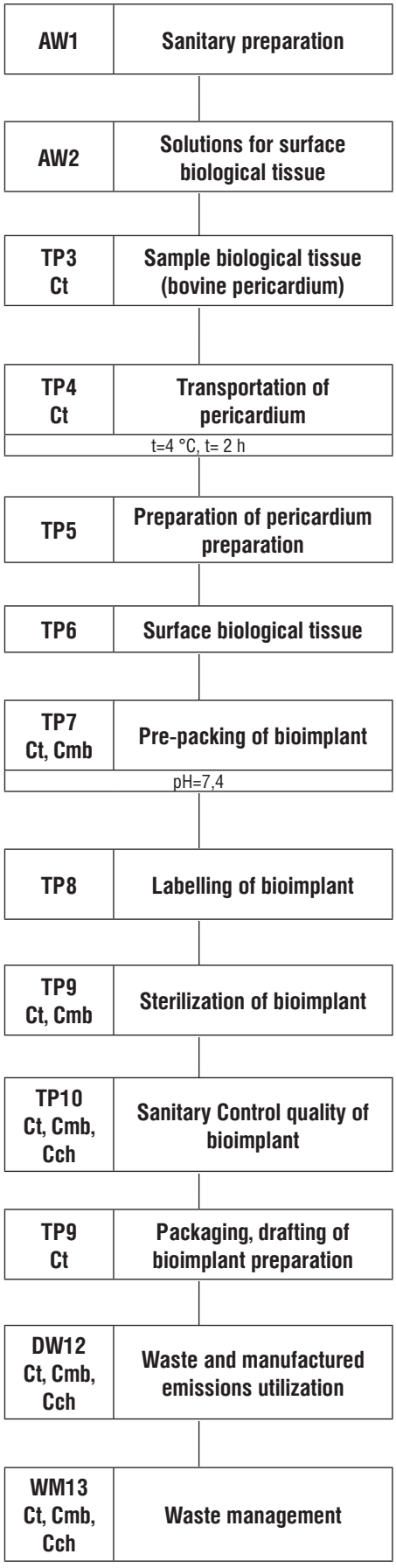


**Fig. 2.** Basic technological scheme of xenogeneic pericardium bioimplant obtaining.

*Notes: AW – additional work; TP – technological process; Ct – control technological; Cmb – control microbiological; Cch – control chemical; DW – disposal waste; WM – waste management*.

However, each of these stages has its peculiarities and requirements that must be followed to achieve a high-quality and safe bioimplant. When working with xenogeneic tissues, it is also necessary to adhere to the ISO 22442-1:2020 standard, which applies to medical devices, excluding *in vitro* diagnostic medical devices, manufactured using materials of animal origin that are non-viable or rendered non-viable. The purpose of this standard is to provide requirements and recommendations for the risk control associated with hazards inherent in medical devices produced using animal tissues or their derivatives, such as: a) contamination with bacteria, molds, or yeasts; b) contamination with viruses; c) contamination with agents causing transmissible spongiform encephalopathies; d) materials causing undesirable pyrogenic, immunological, or toxicological reactions. For example, tissue sampling should be carried out taking into account the biological properties of the tissue and reducing the risk of contamination by microflora of animals. Processing includes decellularization and fixation steps necessary to ensure mechanical stability and reduce the immunological reaction to the implant. Physical, enzymatic and chemical methods can be used to purify xenogeneic tissues from cellular components [17].

Therefore, sterilization of transplants can be performed using various methods, but it must be carried out in such a way to ensure the absence of living microorganisms and not to damage the structure of the material (final product), especially of biological origin with high sensitivity to outer factors [18]. During the collection, processing and engineering of tissues intended for transplantation, the obtained tissue transplants can become contaminated with bacteria, fungi, and other organisms. Therefore, it is necessary to sterilize these transplants before implantation. Sterilization is mainly achieved through aggressive processing methods using physical agents (temperature and pressure, ionizing radiation, ultraviolet and infrared radiation), chemical agents (formaldehyde, hydrogen peroxide, ethylene oxide, nitric oxide, ozone, peracetic acid, chlorine compounds, glutaraldehyde, phthalaldehyde, silver, etc.) and mechanical methods, including sterilizing filtration of solutions.

***The following items are subject to sterilization:***

- All medical and veterinary products that penetrate tissues, come into contact with mucous membranes, fluids, and pathological areas of the skin.
- Pharmaceutical products, injection solutions, tablets, and inhalation forms.
- Artificial transplants and implants.

Several sterilization methods have been widely implemented on an industrial scale, such as chemical sterilization, steam sterilization, hot air sterilization, incineration, gas and plasma sterilization, infrared and ultraviolet sterilization, gamma irradiation, and electron beam sterilization [19, 20]. The choice of a particular method is determined by the resistance of different microorganisms to various means of influence, the physicochemical properties of the sterilized products, environmental safety, economic feasibility, technological capabilities of the sterilization equipment and other factors. Each of these sterilization methods has its advantages and disadvantages and can only be applied to specific types of objects requiring sterilization.

For example, it has been proven that gamma irradiation alters the ultrastructure of decellularized valves during *in vitro* testing [21]. The changes include stitching, molecular fragmentation and degradation of protein materials due to the breakage of peptide chains, resulting in significant changes in mechanical properties [22]. This unfavorable structural change leads to the adhesion of lower cells [23]. It has been found that decellularized tissue treated with peracetic acid was sterilized but lost 44 % of glycosaminoglycans [24]. However, most sterilization methods have not demonstrated sufficient effectiveness when it comes to sterilizing tissues, as evidenced by damage or structural changes in the matrix.

Testing before implantation into the patient's body is necessary to evaluate the effectiveness and safety of the application and monitoring after implantation will help to determine the duration and quality of the bioimplant's performance in the body. In Ukraine, the creation of a new medical product requires manufacturers to comply with the legislative standards, in particular EN ISO 10993-5:2014 Biological evaluation of medical devices. According to this document, the procedure for studying the medical product is defined. Section 5.2.2 of this document specifies that when studying cytotoxicity, methods using cell cultures should be chosen to determine their lysis and other types of cellular effects caused by the medical device, material or their extracts. The methods for cytotoxicity testing are outlined in ISO 10993-5.

Section 5.2.9 defines the basic provisions for prosthesis implantation. These investigations determine the local pathological effect on living tissue (at macroscopic and microscopic levels) when examining a sample of the material or the implanted end product, either through surgical means or placement in specific tissue according to the intended use. The selected investigation methods typically correspond to the type and duration of contact. The methods for studying local effects after implantation are chosen in accordance with ISO 10993-6.

So, the development of a technology for producing biocompatible matrixes is involved studying the technological parameters and processing modes of xenogeneic tissues. A bioimplant is intended to correct defects in cardiovascular surgery by implanting it into the donor's body. Patches based on xenogeneic tissues are used in the cardiovascular surgery departments of medical institutions of various applications [25, 26]. Thus, the technological process of manufacturing a bioimplant for use in cardiothoracic surgery belongs to biotechnological production, which is based on a standard scheme of conducting auxiliary processes and main stages of manufacturing.

The technological requirements were developed by the regulatory body State Enterprise "Ukrainian Research Center for Standardization, Certification and Quality Problems" based on Ukrainian regulatory documentation, which is currently maximally harmonized with the requirements of the European Union (**Table 1**) [27].

**Table 1.** The regulatory documents that were used to create technical specifications of xenogeneic bioimplant manufacturing

| The regulatory document enabling | The regulatory document full title | Ref. |
|---|---|---|
| EN ISO 22442-1:2020 | Medical devices utilizing animal tissues and their derivatives — Part 1: Application of risk management | [31] |
| EN ISO 22442-2:2020 | Medical devices utilizing animal tissues and their derivatives — Part 2: Controls on sourcing, collection and handling | [32] |
| ISO 15223-1:2021 | Medical devices — Symbols to be used with information to be supplied by the manufacturer — Part 1: General requirement | [33] |
| ISO 14971:2019 | Medical devices — Application of risk management to medical devices | [34] |
| ISO 13485:2016 | Medical devices Quality management systems - Requirements for regulatory purposes | [35] |
| ISO 9001:2015 | Quality management systems — Requirements | [36] |
| ISO 14644-1:2015 | Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness by particle concentration | [37] |
| ISO 14644-2:2015 | Cleanrooms and associated controlled environments — Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration | [38] |
| ISO 14644-4:2022 | Cleanrooms and associated controlled environments — Part 4: Design, construction and start-up | [39] |
| EN ISO 11137-1:2006 | Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices | [40] |
| EN ISO 11607-1:2019 | Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems | [41] |
| EN ISO 11607-2:2019 | Packaging for terminally sterilized medical devices — Part 2: Validation requirements for forming, sealing and assembly processes | [42] |
| EN ISO 10993-3:2014 | Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity | [43] |
| EN ISO 10993-5:2009 | Biological evaluation of medical devices — Part 5: Tests for in vitro cytotoxicity | [44] |
| EN ISO 10993-6:2016 | Biological evaluation of medical devices — Part 6: Tests for local effects after implantation | [45] |
| EN ISO 10993-9:2019 | Biological evaluation of medical devices — Part 9: Framework for identification and quantification of potential degradation products | [46] |

| | | |
|---|---|---|
| EN ISO 10993-11:2017 | Biological evaluation of medical devices — Part 11: Tests for systemic toxicity | [47] |
| EN ISO 10993-16:2017 | Biological evaluation of medical devices — Part 16: Toxicokinetic study design for degradation products and leachables | [48] |
| ISO 14001:2015 | Environmental management systems — Requirements with guidance for use | [49] |
| ISO 534:2011 | Paper and board — Determination of thickness, density and specific volume | [50] |
| ISO 15394:2017 | Packaging — Barcode and two-dimensional symbols for shipping, transport and receiving labels | [51] |
| ISO 22742:2010 | Packaging — Linear bar code and two-dimensional symbols for product packaging | [52] |

## ORGANIZATION OF THE MANUFACTURING OF BIOIMPLANTS

The manufacturing of bioimplants requires strict adherence to cleanliness and quality control standards to ensure that the final product is safe and effective for use in medical applications [28]. In this case, the main principles for ensuring the quality of sterile medical products are identified during the manufacturing process and involve minimizing the potential for contamination of bioimplants with hazardous substances.

As described in the previous chapter the manufacturing of bioimplants consists of several main technological stages, such as material preparation, processing of biological tissue, packaging, labeling and sterilization as well as a packaging workshop for the finished product. To obtain a bioimplant of the proper quality with appropriate characteristics, the manufacturing process must be distributed by cleanliness classes. To obtain bioimplants, it is sufficient to have a cleanliness class 7 or 8. According to the technological process (**Fig. 2**), TP 5 (Preparation of pericardium), TP 7 (Pre-packing), TP 8 (Labeling), and TP 9 (Sterilization of bioimplant) take place in a Class 8 facility. Class 7 cleanliness is necessary during the TP 6 (Surface biological tissue) stage. TP 11 (Packaging, drafting of bioimplant) is carried out in non-clean areas. After this stage, the finished bioimplants are transferred to a storage area for further storage or shipment to the end-user.

Auxiliary work, such as preparation of solutions, treatment of working surfaces, and others, is performed as part of the overall process but is not carried out in controlled clean areas or specific stages, meaning that the presence of a cleanliness class is not a mandatory condition. In addition to the main production rooms, there are also general rooms such as a changing room, a non-food storage room, a refrigerator and an office.

In order to comply with GMP (Good Manufacturing Practices) standards, it is advisable to have the changing room located directly at the entrance to the biotechnology laboratory and clean production areas. This room is designated for personnel to change into and out of special clothing required for working in those areas. The changing room serves multiple purposes, including providing a space for personnel to change into clean technical clothing. It should also have a small stock of packaged clean technical clothing, which is monitored and restocked by a designated responsible person. The changing room which is conveniently located at the entrance ensures easy change of the personnel from their regular clothing into the required clean technical clothing before entering the laboratory or clean production areas. This helps to maintain the cleanliness and integrity of the working environment, reducing the risk of contamination and ensuring compliance with GMP standards.

The refrigerator is used for storing certain materials, reagents and products that require low-temperature storage. The temperature of the refrigerator should be monitored and recorded regularly to make sure that it remains within the required range.

The non-food storage room is used for storing raw materials, packaging materials and other supplies that are used in the production process. The room should be kept clean and well-organized to prevent contamination and to facilitate inventory control.

Technological and microbiological control is carried out by an accredited laboratory at every stage of production. The methods used include assessment of the total microbial count and sterility. This control is necessary to prevent cross-contamination, ensure compliance with quality standards and verify the absence of microorganisms in the clean room environment.

Overall, the office is an important part of the bioimplant manufacturing process as it is responsible for the documentation of the production process, including batch records, quality control data and other important information. The office should be kept clean and free of any potential contaminants to ensure the accuracy and completeness of the documentation. This applies particularly to the documentation related to the processing of raw materials and reagents.

## ASSESSMENT OF THE RISKS OF THE MANUFACTURING PROCESS OF OBTAINING BIOIMPLANTS

In order to ensure the safety and quality of bioimplants during their manufacturing process, a thorough analysis and evaluation of potential risks must be conducted using ISO 14971:2019 “Medical devices — Application of risk management to medical devices” guidelines. That is why the planning of the manufacturing of devices and the development of the technological process involves analyzing and evaluating the risks that may arise in production.

The risk assessment process involves considering both the likelihood and severity of harm that could result from the production process. The Hazard Analysis Critical Control Point (HACCP) method is often used to control risks and involves identifying critical control points, monitoring them and implementing corrective actions as needed. By implementing such risk management measures, all stages of the production process can be monitored and any potential risks can be addressed before they become major issues [29].

***Therefore, using the example of the technological process of producing bioimplants, the following control points and expected risks were identified:***

- Production preparation: training of personnel, preparation disinfectant and cleaning solutions, laboratory equipment, utensils, production premises, water and air are considered to be the main auxiliary stages of production. Therefore, poor initial preparation, i.e. failure to comply with preparation rules, may be lead to microbial and/or chemical contamination.
- Preparation of solutions for processing biological tissue: at this stage risks may be associated with incorrect dosing of necessary substances, failure to follow instructions for preparing particular solution, which may cause microbial and/or chemical contamination.
- Collection of material and its transportation: at this stage risks may be associated with incorrect collection of material and failure to comply with conditions for transporting the material, which may cause microbial and/or chemical contamination as well as impractical use of the material in further work.
- Preparation of material for work: at this stage risks may be associated with failure to comply with technology rules when preparing the material and the emergence of microbial and/or chemical contamination.
- Processing of biological tissue: the risks of this stage may be caused by incorrect preparation of tissue processing solutions at the auxiliary work stage, failure to comply with the prescribed conditions for processing and the emergence of microbial and/or chemical contamination.
- Packaging and labeling of the finished bioimplant: at this stage risks may be related to non-compliance with labeling or confusion of samples in blisters.
- Sterilization: the risk may be caused by the delivery of an increased dose of radiation that is not prescribed in the instructions.
- Packaging and shipping of finished products: risks at this stage are associated with incomplete assembly of the finished product and confusion of labels.

To reduce the likelihood of risks occurring, appropriate preventive measures need to be taken, such as detecting and controlling parameters of the technological process that lead to production risks [29].

### A SYSTEM FOR EVALUATING THE QUALITY OF BIOIMPLANT MANUFACTURING

According to ISO 13485:2016 "Medical devices — Quality management systems — Requirements for regulatory purposes" and ISO 9001:2015 "Quality management systems — Requirements", quality control is a mandatory requirement during the manufacturing process of medical devices and the aim is to ensure that the product complies with regulatory requirements. The quality control process involves monitoring and verifying that the product meets its intended requirements and specifications.

In addition, ISO 13485:2016 emphasizes the importance of maintaining consistence and stable manufacturing processes to ensure the quality of the final product. This is achieved through the use of validation procedures, which involve conducting experiments and tests to confirm that the manufacturing process is capable to consistently produce products that meet the desired quality standards.

Validation is an essential element of the quality management system for medical devices and it is used to demonstrate that the manufacturing process is capable of producing products that meet the regulatory requirements and intended use of the device. The results of validation are used to establish acceptance criteria, specifications, and process controls that ensure the consistent quality of the manufactured products.

Therefore, quality control and validation has a critical role in ensuring the quality of medical devices and complying with regulatory requirements.

So, for example, during the stages of the technological scheme of production, the production of a bioimplant for cardio-surgical use is controlled by specific methods. Traceability is an essential aspect of quality control in the production of any product, including bioimplants. The mandatory checks are:

- presence and amount of nucleic acids;
- determination of product sterility;
- testing for bacterial endotoxins;
- testing for biomechanical properties;
- testing of the level of purification of the bioimplant from cells and their components.

It's also important for the checks to be performed at the end of the entire processing of the biotissue. This ensures that any changes or modifications made to the bioimplant during the processing are accounted for and can be traced back to the source.

Finally, selecting no more than 5 % of samples from the total number of produced bioimplants is a common practice in quality control. This allows for a representative sample of the batch to be tested without incurring excessive costs or delays in production.

In the production process, the used materials and raw materials are the factors that most significantly affect the quality of finished products. It's essential to select carefully raw materials that meet regulatory requirements and have easily traceable control mechanisms in place to ensure their quality [29].

In addition to raw materials, all stages of the production process must be closely monitored and controlled, including the quality of incoming materials, the work of personnel, and the correctness of each stage according to work process instructions. This ensures that any potential issues or defects are identified and addressed promptly, minimizing the risk of economic or reputational losses and ensuring the safety of the finished product for human use.

According to ISO 9001:2015 "Quality management systems. Requirements" personnel is one of the main links of the production process. Therefore, to ensure cleanliness and safe use of the finished bioimplant as well as protection during the work process, it is mandatory to follow certain rules and requirements for employees. For this reason, control of personnel, room air and equipment is essential to ensure the quality of the finished implant and obtain sterile products.

Samples should be periodically taken in the production premises to control the microbiological parameters of the air supplied to the work area. This happens when monodisperse aerosol (test culture of *B. subtilis* spore microorganisms) is used.

Laboratory equipment and utensils are in direct contact with the products of the manufacturer and must be washed and disinfected regularly to avoid contamination or transfer of material that could adversely affect the quality of the intermediate product.

Documentation is also an important aspect of quality control [30]. All processes and procedures should be documented and controlled to ensure that they are consistently followed. This includes documenting the results of testing and inspections, as well as any corrective actions taken to address the issues that arise during the production process.

In summary, ensuring the quality of bioimplants requires a comprehensive approach that includes controlling personnel, room air and equipment as well as controlling all aspects of the production process. Regular testing and inspections, documentation of processes and procedures and corrective actions are all important elements of ensuring quality control in bioimplant manufacturing.

## CONCLUSION

***In conclusion, the manufacturing of bioimplants is a complex process that involves various risks that need to be assessed and mitigated to ensure the safety and effectiveness of the implants. Manufacturers must adhere to strict protocols and quality control measures to minimize risks and ensure the highest standards of quality. Ongoing monitoring and evaluation are also necessary to address any potential issues that may arise during the manufacturing process.***

## FINANCIAL SUPPORT AND SPONSORSHIP

This research is supported by the Volkswagen Foundation, VolkswagenStiftung.

## REFERENCES:


1. Hacker MC, Krieghoff J, Mikos AG. Synthetic polymers. In: Atala A, editor. Principles of regenerative medicine. 3rd edition. Academic Press; 2018. p. 1428.
2. Sultanova AS, Bespalova OYa, Galkin OYu. Stromal-vascular fraction of adipose tissue as an alternative source of cellular material for regenerative medicine. Ukr Biochem J. 2021; 93(1): 40-50. Available from: https://doi.org/10.15407/ubj93.01.040
3. Hench LL, Polak JM. Third-generation biomedical materials. Science. 2002 8; 295(5557):1014-7. Available from: https://doi.org/10.1126/science.1067404
4. Gilbert TW, Sellaro TL, Badylak SF. Decellularization of tissues and organs. Biomaterials. 2006; 27(19):3675-83. Available from: https://doi.org/10.1016/j.biomaterials.2006.02.014
5. Grebenik EA, Gafarova ER, Istranov LP, Istranova E V, Ma X, Xu J, et al. Mammalian Pericardium-Based Bioprosthetic Materials in Xenotransplantation and Tissue Engineering. Biotechnol J. 2020; 15:1900334. Available from: https://doi.org/10.1002/biot.201900334
6. Ayala P, Dai E, Hawes M, Liu L, Chaudhuri O, Haller CA. Evaluation of a bioengineered construct for tissue engineering applications. J Biomed Mater Res B Appl Biomater. 2018; 106(6):2345-54. Available from: https://doi.org/10.1002/biot.20190033410.1002/jbm.b.34042
7. Shchotkina NV, Sokol AA, Yemets GI, Galkin OY, Dolinchuk LV, Dovghaliuk AA, et al. Microarchitectonic of Decellularized Bovine Pericardium Matrix Proceedings of the World Congress on New Technologies, 2021. Available from: https://doi.org/10.11159/icbb21.167
8. Sokol AA, Grekov DA, Yemets GI, Galkin AYu, Shchotkina NV, Dovghaliuk AA, et al. Comparison of bovine pericardium decellularization protocols for production of biomaterial for cardiac surgery. Biopolymers Cell. 2020; 36(5):392-403.
9. Shchotkina NV, Sokol AA, Galkin OYu, Yemets GI, Dolinchuk LV, Rudenko NM, et al. Optimized method of bovine pericardium decellularization for tissue engineering. Wiadomości Lekarskie. 2021; 74(4):815-20. Available from: https://10.36740/WLek202104101
10. Shchotkina NV, Sokol AA, Dolinchuk LV, Galkin OYu, Yemets GI, Grekov DA, et al. The Effect of sterilization on the bovine pericardium scaffold decellularized by the glutaraldehyde-free technology. J Biomed Eng Biosci. 2021; 8:28-35. Available from: https://doi.org/10.11159/jbeb.2021.004
11. Sokol AA, Grekov DA, Yemets GI, Galkin OYu, Shchotkina NV, Yemets IM. Biocompatibility analysis of the decellularized bovine pericardium. Cell Organ Transpl. 2020; 8(2):112–116. Available from: https://doi.org/10.22494/cot.v8i2.110
12. Shchotkina N. Aspects of Lyophilization of Cardiac Bioimplant. Innovative Biosystems and Bioengineering. 2021; 5(4):200-206. Available from: https://doi.org/10.20535/ibb.2021.5.4.239725
13. Sokol A, Grekov D, Yemets G, Galkin A, Shchotkina N, Dovghaliuk A, et al. The Efficiency of Decellularization of Bovine Pericardium by Different Concentrations of Sodium Dodecyl Sulfate. IBB. 2020; 4(4):189-198. Available from: https://doi.org/10.20535/ibb.2020.4.4.214765
14. Lam NT, Lam H, Sturdivant NM, Balachandran K. Fabrication of a matrigel–collagen semi-interpenetrating scaffold for use in dynamic valve interstitial cell culture. Biomed Mater. 2017; 12(4):045013. Available from: https://doi.org/10.1088/1748-605X/aa71be
15. Available from: https://clinicaltrials.gov/ct2/show/NCT03669042
16. L, Palmosi T, Dal Sasso E, Gerosa G. Bioengineered tissue solutions for repair, correction and reconstruction in cardiovascular surgery. J Thorac Dis. 2018; 10 (Suppl 20):S2390-411. Available from: https://doi.org/10.21037/jtd.2018.04.27
17. Gilpin A, Yang Y. Decellularization strategies for regenerative medicine: from processing techniques to applications. Biomed Res Int. 2017; 2017:9831534. Available from: https://doi.org/10.1155/2017/9831534
18. Farago D, Kozma B, Kiss RM. Different sterilization and disinfection methods used for human tendons – a systematic review using mechanical properties to evaluate tendon allografts. BMC Musculoskelet Disord. 2021; 22:404. Available from: https://doi.org/10.1186/s12891-021-04296-4
19. Holy CE, Cheng C, Davies JE, Shoichet MS. Optimizing the sterilization of PLGA scaffolds for use in tissue engineering. Biomaterials. 2001; 22(1):25-31. Available from: https://doi.org/10.1016/s0142-9612(00)00136-8
20. de Sousa Iwamoto LA, Duailibi MT, Iwamoto GY, et al. Evaluation of ethylene oxide, gamma radiation, dry heat and autoclave sterilization processes on extracellular matrix of biomaterial dental scaffolds. Sci Rep. 2022; 12:4299. Available from: https://doi.org/10.1038/s41598-022-08258-1
21. Harrell CR, Djonov V, Fellabaum C, Volarevic V. Risks of Using Sterilization by Gamma Radiation: The Other Side of the Coin. Int J Med Sci. 2018; 15(3):274-279. Available from: https://doi.org/ 10.7150/ijms.22644
22. Zhang H-r, Xu M-y, Zhang L, Zhang H, Yang L, Liu J, et al. Effects of Chemical Sterilization and Gamma Irradiation on the Biochemical and Biomechanical Properties of Human Tendon Allografts In Vitro Study. Orthop Surg. 2022; 14:2657-2668. Available from: https://doi.org/10.1111/os.13465
23. Matuska AM, McFetridge PS. The effect of terminal sterilization on structural and biophysical properties of a decellularized collagen-based scaffold: implications for stem cell adhesion. J Biomed Mater Res B Appl Biomater. 2015; 103(2):397-406. Available from: https://doi.org/10.1002/jbm.b.33213
24. Hussein KH, Park KM, Teotia PK, Hong SH, Yang SR, Park SM, et al. Sterilization using electrolyzed water highly retains the biological properties in tissue-engineered porcine liver scaffold. Int J Artif Organs. 2013; 36(11):781-92. Available from: https://doi.org/10.5301/ijao.5000246
25. Lam MT, Wu JC. Biomaterial applications in cardiovascular tissue repair and regeneration. Expert Rev Cardiovasc Ther. 2012; 10(8):1039-49. Available from: https://doi.org/10.1586/erc.12.99
26. Durko AP, Yacoub MH, Kluin J. Tissue Engineered Materials in Cardiovascular Surgery: The Surgeon's Perspective. Front Cardiovasc Med. 2020; 7:55. Available from: https://doi.org/10.3389/fcvm.2020.00055
27. Pashkov V, Kotvitska A, Harkusha A. Legal regulation of the production and trade of medical devices and medical equipment in the EU and US: experience for Ukraine. Wiad Lek. 2017; 70(3 pt 2):614-618. PMID: 28713093
28. Prat-Vidal C, Rodríguez-Gómez L, Aylagas M, Nieto-Nicolau N, Gastelurrutia P, Agustí E, et al. First-in-human PeriCord cardiac bioimplant: Scalability and GMP manufacturing of an allogeneic engineered tissue graft. EBioMedicine. 2020. Available from: https://doi.org/10.1016/j.ebiom.2020.102729
29. Kheir O, Jacoby A, Verwulgen S. Risk Identification and Analysis in the Development of Medical Devices Among Start-Ups: Towards a Broader Risk Management Framework. Med Devices (Auckl). 2022; 15:349-363. Available from: https://doi.org/10.2147/MDER.S375977
30. Lebedynets VO, Kovalenko SM, Takhtaulova NO. Regulation of document flow in the quality management system of a pharmaceutical enterprise. Management, economics and quality assurance in pharmacy. 2011; 5:15-21.

31. ISO 22442-1:2020 Medical devices utilizing animal tissues and their derivatives. Part 1: Application of risk management. Available from: https://www.iso.org/standard/74280.html
32. ISO 22442-2:2020 Medical devices utilizing animal tissues and their derivatives. Part 2: Controls on sourcing, collection and handling. Available from: https://www.iso.org/standard/74281.html
33. ISO 15223-1:2021 Medical devices — Symbols to be used with information to be supplied by the manufacturer. Part 1: General requirements. Available from: https://www.iso.org/standard/77326.html
34. ISO 31000:2009(en) Risk management Principles and guidelines. Available from: https://www.iso.org/obp/ui/#iso:std:iso:31000:ed-1:v1:en
35. ISO 13485:2016 Medical devices — Quality management systems — Requirements for regulatory purposes. Available from: https://www.iso.org/standard/59752.html
36. ISO 9000:2015 Quality management systems. Fundamentals and vocabulary. Available from: https://www.iso.org/standard/45481.html
37. ISO 14644-1:2015 Cleanrooms and associated controlled environments. Part 1: Classification of air cleanliness by particle concentration. Available from: https://www.iso.org/standard/53394.html
38. ISO 14644-2:2015 Cleanrooms and associated controlled environments. Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration. Available from: https://www.iso.org/standard/53393.html
39. ISO 14644-4:2022 Cleanrooms and associated controlled environments. Part 4: Design, construction and start-up. Available from: https://www.iso.org/standard/72379.html
40. ISO 11137-1:2006 Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices. Available from: https://www.iso.org/standard/33952.html
41. ISO 11607-1:2019 Packaging for terminally sterilized medical devices. Part 1: Requirements for materials, sterile barrier systems and packaging systems. Available from: https://www.iso.org/standard/70799.html
42. ISO 11607-2:2019 Packaging for terminally sterilized medical devices. Part 2: Validation requirements for forming, sealing and assembly processes. Available from: https://www.iso.org/standard/70800.html
43. ISO 10993-3:2014 Biological evaluation of medical devices. Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity. Available from: https://www.iso.org/standard/55614.html
44. ISO 10993-5:2009 Biological evaluation of medical devices. Part 5: Tests for in vitro cytotoxicity. Available from: https://www.iso.org/standard/36406.html
45. ISO 10993-6:2016 Biological evaluation of medical devices. Part 6: Tests for local effects after implantation. Available from: https://www.iso.org/standard/61089.html
46. ISO 10993-9:2019 Biological evaluation of medical devices. Part 9: Framework for identification and quantification of potential degradation products. Available from: https://www.iso.org/standard/64580.html
47. ISO 10993-11:2017 Biological evaluation of medical devices. Part 11: Tests for systemic toxicity. Available from: https://www.iso.org/standard/68426.html
48. ISO 10993-16:2017 Biological evaluation of medical devices. Part 16: Toxicokinetic study design for degradation products and leachables. Available from: https://www.iso.org/standard/64582.html
49. ISO 14001:2015 Environmental management systems — Requirements with guidance for use. Available from: https://www.iso.org/standard/60857.html
50. ISO 534:2011 Paper and board — Determination of thickness, density and specific volume. Available from: https://www.iso.org/standard/53060.html
51. ISO 15394:2017(en) Packaging — Bar code and two-dimensional symbols for shipping, transport and receiving labels. Available from: https://www.iso.org/obp/ui/#iso:std:iso:15394:ed-3:v1:en
52. ISO 22742:2010 Packaging — Linear bar code and two-dimensional symbols for product packaging. Available from: https://www.iso.org/standard/53004.html




*The authors declare that the research was conducted in the absence of any commercial or fi-nancial relationships that could be construed as a potential conflict of interest.*

УДК 606:576:616.12-89.843

# Особливості технологічного регулювання серцевих біоімплантів

Щоткіна Н. В.[1,3], Паламарчук Ю. В.[1], Скороход І. М.[3], Долінчук Л. В.[2], Сокол А. А.[1], Мотроненко В. В.[1], Бесараб О. Б.[1], Горчакова Н. О.[2], Фроме М.[3], Герцог М.[3]

*[1]Національний університет України «Київський політехнічний інститут імені Ігоря Сікорського», Київ, Україна*
*[2]Національний медичний університет імені О. О. Богомольця, Київ, Україна*
*[3]Технічний університет прикладних наук Вільдау, Вільдау, Німеччина*

## РЕЗЮМЕ

*Пацієнти з вродженими вадами серця та серцево-судинними захворюваннями потребують нових підходів до оперативного втручання. Використання біологічних серцевих імплантів, виготовлених із позаклітинного матриксу, є перспективним напрямком у сучасній регенеративній медицині. Такі біоімпланти здатні практично повністю замінити дефектні тканини або органи, і якщо вони виготовлені з дотриманням суворих протоколів і заходів контролю якості, можуть бути безпечними та ефективними для терапевтичного застосування. Процес виготовлення біоімплантів включає різні ризики, які потребують оцінки та їх зменшення шляхом постійного моніторингу для забезпечення найвищих стандартів якості. Загалом, це дослідження аналізує вимоги до впровадження в клінічну практику нових медичних виробів для серцево-судинної хірургії та створення технічних файлів, які відповідають усій необхідній документації для сертифікації.*

***КЛЮЧОВІ СЛОВА**: серцевий біоімплант; контроль якості; управління виробничими ризиками; технічне регулювання; медичні вироби*