METROLOGY, QUALITY, STANDARDIZATION AND CERTIFICATION

METHODOLOGY FOR ASSESSING THE LIFE CYCLE PROCESSES OF SCAFFOLDS

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Abstract. Due to the increase in diseases in the musculoskeletal system, regenerative medicine is now developing various bone substitutes. Not all scaffolds, due to their shortcomings, are applied for every application. Patients should be provided with basic product information and other warnings about health risks or measures to be taken. From the establishment of the purpose of the biomaterial to apply, several stages of the life cycle can pass. To ensure the biocompatibility of medical devices, there is a legislative framework and standards. They cover the full cycle from testing to market authorization, surveillance, and recall (ISO 15225:2010, ISO/IEC 33001:2015). We have developed the life cycle of bone substitutes and can offer an approach to evaluate operations based on the requirements of the ISO/IEC 33001:2015 series.

Key words. Bone substitute, Life cycle, Risk assessment, Biocompatibility, Process assessment.

1. Introduction

Bone engineering is developing methods to repair damaged bone using a combination of cells, growth factors, and biomaterials [1]. However, not all biomaterials are used for every application [2]. The ideal bone substitute is biocompatible and does not cause an adverse inflammatory reaction. It should be easily fused into the bone defect and should be osteoconductive, osteoinductive, and absorbable [3]. From the establishment of the purpose of the biomaterial to its application can take several stages of the life cycle (Fig. 1) [4].

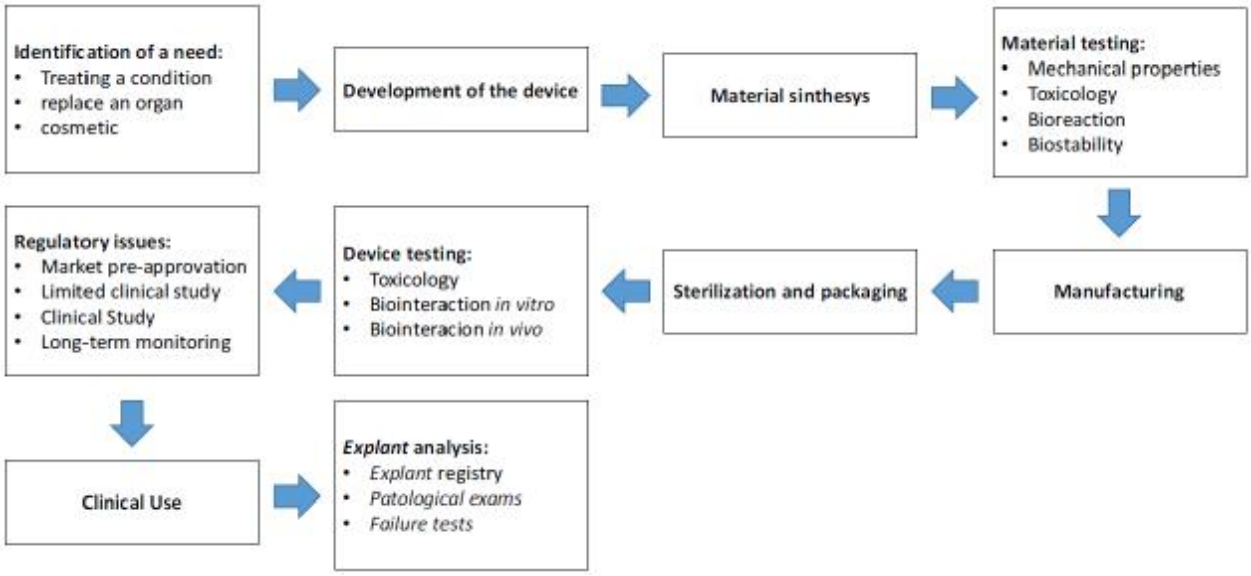


Fig. 1. Stages of the life cycle of a biomaterial, from its need-based concept to its clinical application and subsequent evaluation

Patients implanted with the device must be provided with basic information to identify the device and other health risk warnings or precautions. Such actions should be taken as indications as to whether it is compatible with certain diagnostic devices that are applied for security monitoring [5]. Medical devices are subject to single market rules. There is a legal framework to ensure the safety of these products. It covers the full cycle, from testing and testing to market authorization, surveillance, and recall. To keep up with scientific advances and respond to emerging health threats, legislative measures are subject to regular evaluation and monitoring [6]. ISO 15225:2010 contains

rules for the data structure of a medical product nomenclature to facilitate communication and data exchange. Such data is applied by regulatory authorities at the international level, among the parties involved (regulatory authorities, manufacturers, etc.) [7]. The manufacturer develops and documents in working conditions a system for collecting information about the analyzed medical device. Risks exist throughout the entire life cycle of a medical device. Risks detected at one stage of the life cycle can be managed through actions performed at another stage (through blockchain technology). The manufacturer applies risk management principles to the medical device, from design to disposal. The decision to perform a clinical procedure requires achieving an optimal ratio of residual risks and expected benefits from the procedure. Such decisions should take into account the intended application, the clinical benefit, and the risks associated with the conditions of device usage. Some of these decisions can be made by a qualified healthcare professional. He has information about the patient's health status. [8].

2. Drawbacks

The DSTU 3627:2005 establishes the procedure for the development, testing, acceptance, and relations for the production of samples of new and modernized medical devices, as well as medical devices, the production of which has been mastered by other business entities, and the procedure for issuing a permit for their mass production intended for apply by business entities all forms of ownership. Integration and exchange of information between healthcare organizations and suppliers of medical devices at the stages of their life cycle are considered a problem.

The formation of specifications for ensuring and evaluating interoperability at the stages of the life cycle is carried out based on quality models. They are recommended by the ISO/IEC 2500n series. The specific terminologies and ontologies used, methodologies and frameworks, and the information representations obtained are often quite contradictory for the medical field, requiring a different general harmonized information representation. To achieve interoperability at the stages of the life cycle of medical devices under the requirements [14], it is necessary to form specifications based on the quality assessment models that are considered in this paper.

3. Goal

The purpose of the work is to create a model for assessing processes at the stages of the life cycle of biomaterials according to ISO/IEC 33001:2015 series.

4. Assessment of the processes of the life cycle of biomaterials.

The proposed life cycle of a medical biomaterial consists of 7 stages. First, patient data is collected. Based on these data, an implant is designed. Further, risks are assessed against ISO 14971:2019 and ISO 14040:2006. Step 4 is the production of the material. At the 5th stage, the implant material is tested based on a series of ISO 10993 standards. The next step is the manufacture of the product. The last stage is the implantation of the product (Fig. 2).

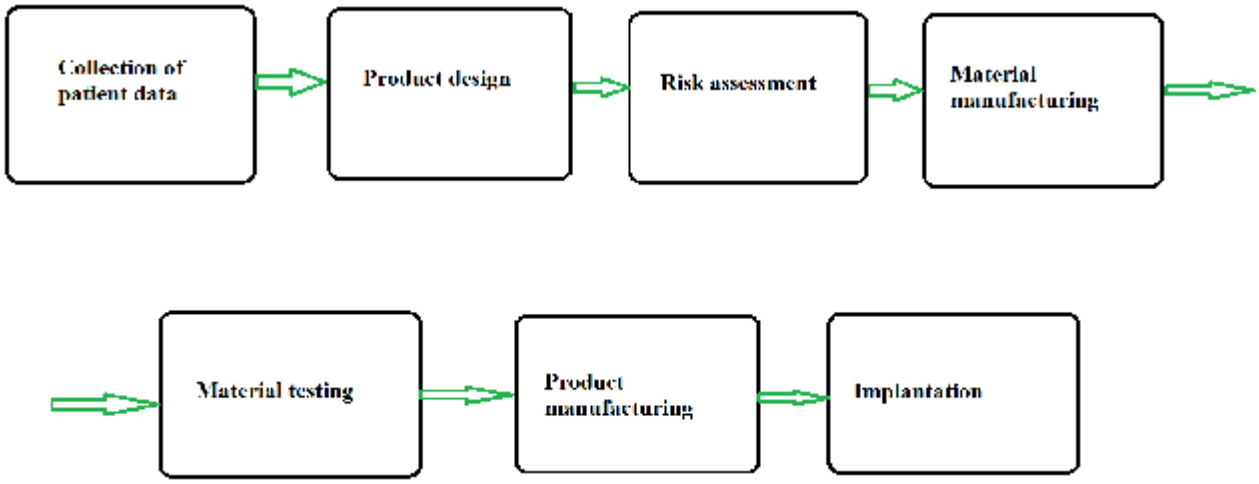


Fig. 2. Life cycle of a medical device

ISO/IEC 33001:2015 provides an overview of the concepts of process assessment, the use of process assessment to assess the achievement of operation quality characteristics and the application of operation assessment results to operation management [9]. According to ISO 33020, process capabilities are evaluated on a six-digit ordinal scale, which allows evaluation from its lower-level - in-progress to the top-level - innovative. The scale reflects the expansion of the possibilities of the operation being implemented, starting from the inconsistency with the purpose of the action, going through the stages of its continuous improvement, and reaching a certain level. At this level, the operation gains the ability to respond to changes occurring in the organization (Table 1) [10].

Table 1

Process capability levels according to ISO 33020

Level "0" is an unfinished process.	The procedure is not implemented or does not achieve its plan.
Level "1" - completed process.	The performed operation achieves the purpose of the procedure.
Level "2" is a controlled process.	The previously described operation is performed in a controlled manner (planned, monitored, and corrected), and the consequences of its operation are established, controlled, and updated properly.
Level "3" is an established process.	The previous procedure described is performed using a specific procedure that is capable of achieving the results of its operation.
Level "4" is the intended process.	The pre-described established procedure works with forecasting within certain limits to achieve the results of the process. Needs for multiple control are identified; measurement materials are accumulated and analyzed. They help to find deviation factors Corrective actions are applied to eliminate deviation factors.
Level "5"- innovation process.	The previously described intended process is continuously improved to respond to organizational change.

ISO/IEC 33004:2015 specifies requirements for process reference models, process assessment models, and maturity models. The requirements form the structure. It defines:

a) relationships between process model classes associated with performing a process assessment;

b) relationships between process reference models and attributive/normative process execution models, as established, for example, in the activities and objectives of ISO/IEC/IEEE 12207:2017 and ISO/IEC 15288:2002;

c) integration of reference models and measurement systems to establish process evaluation models;

d) the applying of common sets of quality process performance indicators in its assessment models;

e) relationships between maturity models, process assessment models, and the extent to which a maturity model can be constructed using elements from different process assessment models (Figure 3) [11].

The purpose of operation evaluation is to understand and evaluate the processes that exist within an organizational unit. The key elements of the process evaluation procedure are shown in Fig. 4 (ISO/IEC 33002:2015) [12].

ISO/IEC 33003:2015 specifies requirements for process measurement systems for applying in process evaluation. The requirements form the structure. This design:

a) establishes requirements for process measurement systems in the context of process assessment,

b) specifies validation requirements for process measurement systems for applying in process assessment;

c) establishes the requirements for any process measurement systems for the development of component indicators by area.

Many quality properties of the process are not subject to control. They can be presented as theoretical concepts - constructions. Complex measurements are provided by conventional proceduras. They must be determined based on a specific model. Such a scheme consists of process properties. The measurement system can be organized into a set of levels. Achieving them is supposed to be managed by the operation. If the quality of the operation is not subject to direct fixation, it can be defined as a construct. A set of process characteristics should be defined by any framework. The design can be informative or formative. Schemes can be used to study the level of operation properties by summarizing measurement values. Such models are presented in Fig.5.

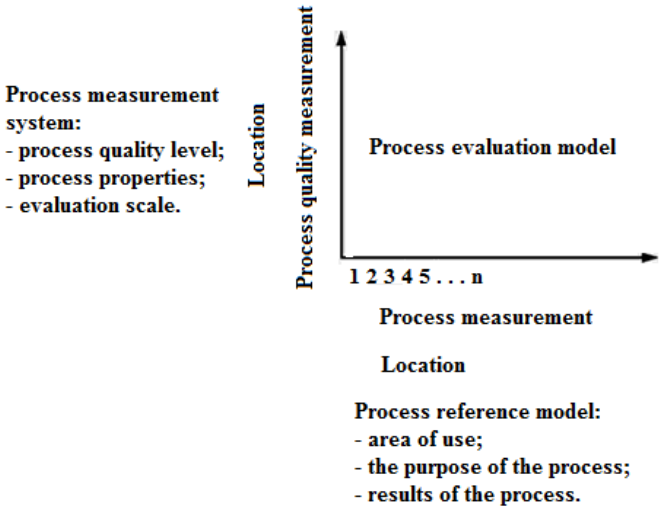


Fig. 3. Relationship of process assessment model according to ISO/IEC 33004:2015

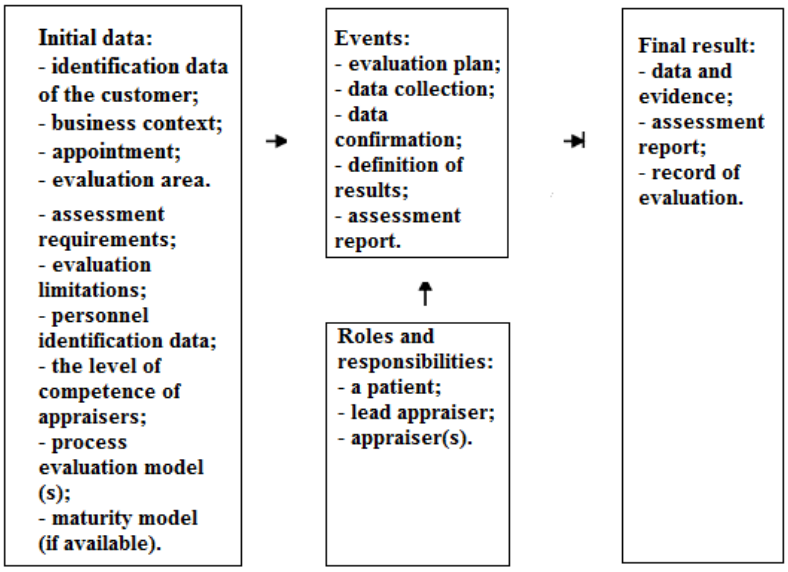
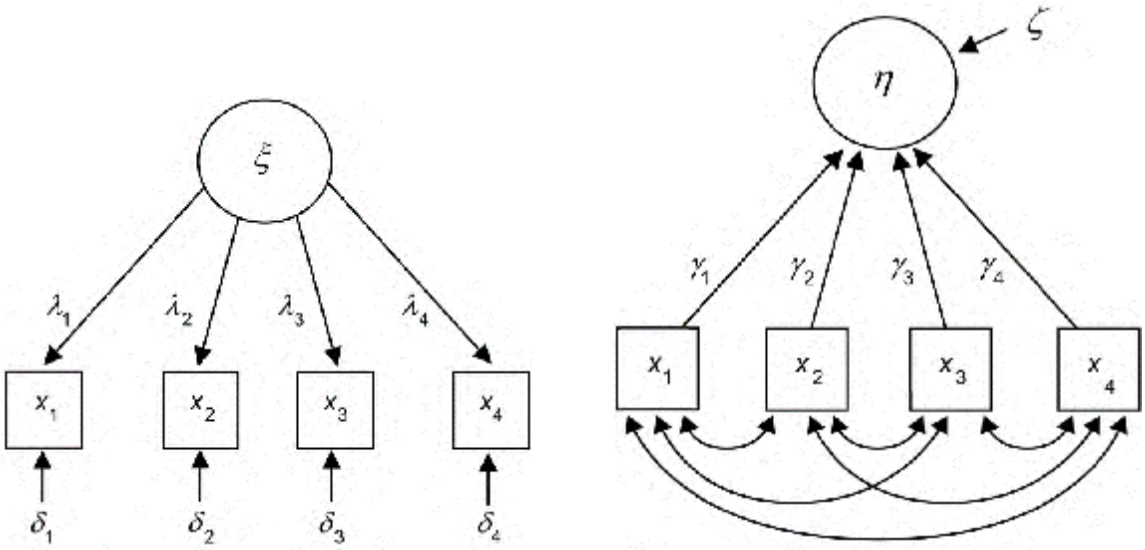


Fig. 4. Key elements of the operation evaluation process [12]



a *b*

Fig.5. The relationship between a structure and its constituent dimensions. Here (a) is an informative specification; (b) is a formative specification

Here λ is the boot parameter (it indicates the relationship between structure ξ and dimension x); δ this is an erroneous condition; g this is the load measurement parameter x; ζ this is the perturbation condition. The relationship between a structure and its dimensions is represented by an equation. Here each dimension depends on the latent variable as follows:

$$x_i = \lambda_i\xi + \delta_i, \quad (1)$$

here x_i is an informative measurement that depends on the latent variable ξ; λ_i is a coefficient representing the expected impact of a change in one unit ξ to x_i; δ_i this is a random condition, which is a measurement error.

The forming structure can be represented as follows:

$$\eta = \gamma_1\gamma_1 + L + \gamma_q\gamma_q, \quad (2)$$

here η is a construct judged by its formative dimension; γ_i is the coefficient indicating the influence of the measurement x_i on a hidden variable η; ς is an excitatory condition indicating the effect of missing measurements in the model on the variable η. The formative structure can be represented in a certain way. Here the perturbing condition is approximately equal to zero. It is marked in Fig. 5 b.

Further, the design works as an MCDM process and indicates a complex dimension. This dimension is defined by a combination of a set of dimensions. They are assigned significant coefficients according to the

degree of importance or priority of such measurements. The relationship can be described as follows:

$$C = \gamma_1\gamma_1 + L + \gamma_q\gamma_q, \quad (3)$$

here C is a composite dimension *xs* with weight coefficients.

Decision rules for controlling an informative or formative measurement scheme are given in Table 2.

Table 3 shows how the ISO 33020 is implemented in the stages of the proposed life cycle.

Table 2

Decision rules for controlling an informative or formative measurement scheme

Decision rule	Informative form of measurement	Formative scheme of measurements
Construction dimension properties.	Dimensions define the properties (aspects) of a structure	Dimensions define the properties (aspects) of a structure
	Measurements have a general direction	Measurements may not have a general direction
	The measurements must be interchangeable	The measurements should not be interchangeable.
	The measurement value must be the same or similar	The measurement value should not be the same or similar.
	The exclusion of a dimension must not change the conceptual scope of the design	Excluding a dimension can change the conceptual scope of a design
	It is assumed that the dimensions change simultaneously.	The dimensions do not have to change at the same time
The direction of the factor relationship between structure and dimensions	The direction of the factor relationship is from structure to complex measurements	The direction of the factor relationship is from measurements to structure
	Amendments that are made to a single dimension should not lead to a change in the structure	Amendments that are made to a single dimension should not lead to a change in the structure.

Table 3

Application of the ISO 33020 at the stages of the life cycle of a medical device

Stage	Process capability level					
	Unfinished	Fulfilled	Managed	Installed	Predictable	Innovative
1	2	3	4	5	6	7
Collection of patient data	There is no required data to start collecting	Data is being collected	The goals of the process, the requirements for the results of the process, and the documentation and control of the results are determined	The awareness and responsibilities required to implement the process are identified as part of a standard process	The previously described established procedure is now implemented predictably within the given framework with the task of acquiring the necessary outcomes	The proposed procedure described earlier is currently being constantly improved to reproduce the changes being made by the goals of the organization
Product design	There is no data to start designing.	The product is being designed	Design under control, and the requirements for the results of the process are determined.	The infrastructure and production environment necessary for the design are determined as part of a standard process	The previously described established procedure is now implemented predictably within the given framework with the task of acquiring the necessary outcomes	The proposed procedure described earlier is currently being constantly improved to reproduce the changes being made by the goals of the organization
Risk assessment	No data to start the evaluation	Risks are assessed.	The process is under control, and the requirements for the results of the process are determined	The resources and information needed for the process are determined and then allocated	The previously described established process is now implemented predictably within the given framework with the task of acquiring the necessary outcomes	The proposed procedure described earlier is currently being constantly improved to reproduce the changes being made by the goals of the organization.

Cont. table 3

1	2	3	4	5	6	7
Material manufac-turing	No data to start design	The material is produced.	The operation is under control, and the requirements for the parameters of the product are determined	The infrastructure and production environment necessary for manufacturing is determined	The previously described estab-lished process is now implemen-ted predictably within the given framework with the task of acqui-ring the neces-sary outcomes	The anticipated process described earlier is currently being continuously improved to reproduce the changes being made by the goals of the organization.
Material testing.	There is no data to start the test.	The material is being tested.	The operation is under control, and the requirements for test results are determined.	The data and sequence of actions and the interaction of the standard operation with other processes are determined.	The previously described estab-lished process is now implemen-ted predictably within the given framework with the task of acqui-ring the neces-sary outcomes.	The anticipated process described earlier is currently being continuously improved to reproduce the changes being made by the goals of the organization.
Product manufac-turing.	There is no data to start manufac-turing.	The product is in the process of production.	The process under control determines the requirements for product parameters.	The infrastructure and production environment necessary for manufacturing is determined.	The previously described estab-lished procedure is now imple-mented predic-tably within the given framework with the task of acquiring the ne-cessary outcomes.	The anticipated process described earlier is currently being continuously improved to repro-duce the changes being made by the goals of the organization.
Implantation.	There is no data to start implantation.	The product is implanted.	The process is under control, and the requirements for the results of the process are determined.	The competencies and responsibilities required to complete the process are determined within the stage.	The previously described estab-lished procedure is now implemented predictably within the given frame-work with the task of acquiring the necessary outcomes.	The anticipated process described earlier is currently being continuously improved to reproduce the changes being made by the goals of the organization.

According to the [12], at each stage, the initial data contains information about the customer (data about the organization that performed the previous stage, at stage 1 the customer is the patient), the purpose of the assessment (the purpose of the tasks at the stage is indicated), the assessment requirements (list necessary equipment, conditions), identification data of the personnel (surnames, names of those participating in the stage), the level of competence of the participants (level of education), the unit in which the process will be carried out; composition of the organizational unit in which the processes will be carried out (number of employees, the scope of the organizational unit), identification of the model (s) applied and the process measurement system:

1) the evaluation method applied (for example, the method of manufacture or testing of the material);

2) the generalizing method (or methods) applied;

g) evaluation constraint, among which the following should be considered:

1) availability of key resources (for example, availability of equipment, reagents),

2) the maximum duration of the assessment,

3) specific processes or organizational units that are excluded from the assessment procedure,

4) owners of the final results of the evaluation and any restrictions on their application,

5) control over the processing of confidential information and its protection;

h) identities and responsibilities of the parties, service personnel assessment teams, specific assessment responsibilities;

i) criteria for determining the competence of the lead assessor.

The article [13] presents a method for controlling the life cycle of scaffolds using blockchain technology (Fig.6).

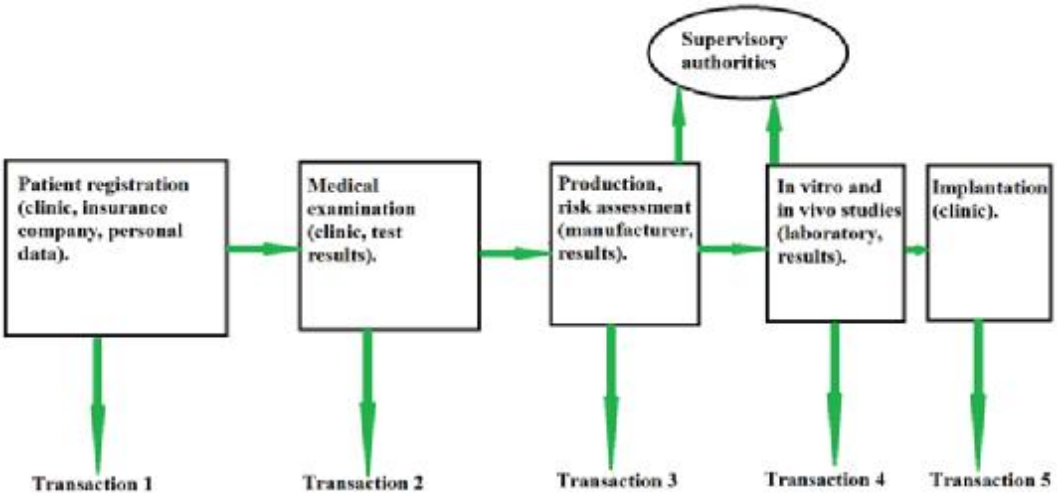


Fig. 6. Blockchain process diagram covering the life cycle of scaffolds

However, this methodology does not provide for how the input and output data are managed, and what are the capabilities of each process at the stages of the life cycle. The requirements for life cycle participants are not taken into account.

Our proposed operation of transferring medical information on the blockchain consists of 5 steps:

1. Registration. The patient (customer) is registered in the clinic, his data is recorded.

2. Survey. A medical examination of the patient is performed, and the results are passed to the manufacturer. The identification data of the personnel (surnames, names of the participants in the stage), and the unit in which the process will be carried out are indicated.

3. Manufacturing. The manufacturer assesses risks according to ISO 14971 and ISO 14040: 2006. The following are recorded:

- data on the organization that performed the survey;
- customer data;
- assignment of tasks at the stage;
- list of necessary equipment, and conditions;
- staff data;
- level of competence of participants (level of education);
- the unit in which this stage will be conducted; composition of the unit;
- method of manufacture and testing.

4. Preclinical studies. The material is subjected to preclinical testing in the laboratory. The following are recorded:

- customer data;
- manufacturer's data;
- staff data;
- the unit where the research will take place;
- research conditions;
- level of education of participants, its composition;
- test methods;
- the maximum duration of the assessment.

5. Implantation. The material is implanted into the patient. Recorded data similar to the previous stage.

Thus, the ISO/IEC 33003:2015 standard is applied to each stage of the life cycle. All stages of the life cycle, except for implantation, are formative specifications, since the removal of one of the components affects information about the patient, the expected material, etc. In the first stage $x_{i,}$ this is patient data (name, age, diagnosis, etc.), on the second $x_{i,}$ these are the parameters of the material (mechanical, chemical properties; composition, dimensions). The implantation process is an informative specification.

5. Conclusions

Based on the ISO/IEC 33001:2015 series of standards, this work has created a model for assessing processes at the stages of the life cycle of medical devices applying biomaterials as an example. To achieve interoperability in the stages of the life cycle of bone substitutes, specifications based on quality assessment models have been created. This allows you to make decisions on assessing the conformity of biocompatibility and analyze possible risks when using matrices based on the requirements of international standards. In turn, this creates a plan for the development, testing, acquisition, and production of samples of new and improved medical products. It also facilitates the realization of advanced collaboration, flexible, scalable, business-driven, adaptive, knowledge-based, intelligent medical and social ecosystems. This approach should be applied to analyze, design, integrate and run systems of any type.

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7. Conflict of interest

There is no conflict of interest during the writing, preparation, and publication of the article and mutual claims of the co-authors.

References

[1] M. Alonzo, F. A. Primo, S. A. Kumar, J. A. Mudloff, E. Dominguez, G. Fregoso, N. Ortiz, Matthew, W. M. Weiss, B. Joddar, "Bone tissue engineering techniques, advances, and scaffolds for treatment of bone defects", Current opinion in biomedical engineering, 2021, Vol. 17: p. 100248, DOI: 10.1016/j.cobme.2020.100248.

[2] G. Fernandez de Grado, L. Keller, Y. Idoux-Gillet, Q. Wagner, A. Musset, N. Benkirane-Jessel, F. Bornert, D. Offner, "Bone substitutes: a review of their characteristics, clinical use, and perspectives for large bone defects management", Journal of tissue engineering, p. 1-18, 2018, DOI: 10.1177/2041731418776819.

[3] V. Campana, G. Milano, E. Pagano, M. Barba, C. Cicione, G. Salonna, V. Lattanzi, G. Lagroscino, "Bone substitutes in orthopedic surgery: from basic science to clinical practice", Journal of Materials Science: Materials in Medicine, no. 10, p. 2445-2461, 2014, DOI: 10.1007/s10856-014-5240-2.

[4] L. R. R. da Silva, W. F. Sales, F. D. A. R. Campos, J. A. G. de Sousa, R. Davis, A. Singh, R. T. Coelho, B. Borgohain, A comprehensive review on additive manufacturing of medical devices, Progress in Additive Manufacturing, no. 3, p. 517-553, 2021, DOI: 10.1007/s40964-021-00188-0.

[5] Regulation (EU) 2017/745 of the European Parliament and the Council, EUR-Lex, 2022. [Online]. Available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745

[6] Medicines and Medical Devices, European parliament, 2022. [Online]. Available: https://www.europarl.europa.eu/factsheets/en/sheet/50/medicines-and-medical-devices

[7] ISO 15225:2010 Medical devices – Quality management – Medical device nomenclature data structure, 2010. [Online]. Available: https://www.iso.org/standard/50728.html

[8] ISO 14971:2007 Medical devices — Application of risk management to medical devices, 2007. [Online]. Available: https://www.iso.org/standard/38193.html

[9] ISO/IEC 33001:2015 Information technology — Process assessment — Concepts and terminology, 2015. [Online]. Available: https://www.iso.org/standard/54175.html

[10] ISO/IEC 33020:2015 Information technology — Process assessment — Process measurement framework for assessment of process capability, 2015. [Online]. Available: https://www.iso.org/standard/54195.html

[11] ISO/IEC 33004:2015 Information technology — Process assessment — Requirements for process reference, process assessment, and maturity models, 2015. [Online]. Available: https://www.iso.org/standard/54178.html

[12] ISO/IEC 33002:2015 Information technology — Process assessment — Requirements for performing process assessment, 2015. [Online]. Available: https://www.iso.org/standard/54176.html

[13] V. Chernobrovchenko, K. Diadiura, A. Panda, "Investigation of the blockchain structure for hydroxyapatite-based scaffolds", Journal of Engineering Sciences, no. 2, p. 30-35, 2021, DOI: 10.21272/jes.2021.8(2).c5.

[14] DSTU 3627:2005 Medical devices — Product development and launching into manufacture — basic principles, 2005. [Online]. Available: http://www.ksv.biz.ua/GOST/ DSTY_ALL/DSTU1/dstu_3627-2005.pdf.