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# Resource-Based View of Laboratory Management: Tissue Bank ATMP Production as a Model

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## Abstract

Modern health care organizations, e.g., tissue banks, require a resource-based view (RBV) for an efficient stimulation of innovation, productivity, and performance, especially in the context of laboratory management and new product development. High quality advanced therapy medicinal products (ATMPs) are expected to bring important health benefits; therefore, their production has to be performed in accordance with good manufacturing practice (GMP). Although there are no precisely defined criteria for quality control/evaluation methods of obtained ATMPs, all aspects of pharmaceutical quality of ATMPs' development, manufacturing, distribution, inspection, and review processes ought to be strictly fulfilled. Explicit performance management and production regimes in accordance with pharmacopeia and RBV philosophy have been proposed in this chapter.

**Keywords:** resource-based view, advanced therapy medicinal products, tissue bank, good manufacturing practice, lean management

## 1. The change of paradigm

An innovative way of hospital management appeared in the 1990s. Methods originating from the industry and known as lean management and Theory of Constraints (TOC) have proven surprisingly adequate in health care environment. These helped to overcome the problems of many hospitals facing severe issues and as a result requiring turnaround.

Effective management of the organization has to be holistic in nature and focus exclusively on the point of view of client/patient instead of unit managers. The effectiveness and process synchronization have to be also looked upon from the same perspective. Management approach aiming at local optimizations traps the managers ultimately leading to underperformance of the organization as a whole, with hunt and frustration from the very bottom to the top of the organizational ladder. Moreover, most of the employees including top managers are not fully aware of the structure of processes in their company. These processes do not fit the most commonly applied management practices. In their nature, these are horizontal and not vertical like the structures of most of the organizations [1].

The term “lean management” has been first formulated by the American researcher John Krafcik who has been investigating the reasons behind competitive advantage of Japanese automobile industry over its American counterpart. Krafcik has been particularly impressed by the Toyota Production System (TPS), which has been developing in Japan from mid-1940s.

Essentially, lean system could be defined as an elimination of waste and respect to all of the employees organization-wide. The goal of the organization is to deliver added value to the patient/client/payer. Added value is generated when any activity that delivers tangible results in the process is performed correctly the first time and for which the patient/client/payer is ready to pay. All the rest is regarded as waste. There are seven types of waste defined by the TPS originator—Taiichi Ohno. Detailed description is outside the scope of this book, but an interested reader will easily find it outlined in many available resources [2].

The set of tools and techniques applied in lean is usually presented as the so-called Toyota House or Lean House. The fundamentals of the house comprise 5S—the system of creating and maintaining a neat and clean work environment, continuous improvement, standard work, balanced distribution of the job, and visual controls. All of these elements are crucial; nevertheless, 5S and standardized work require closer explanation.

The majority of organizations do not realize how much waste is hidden in their current processes. There is an abundance of unnecessary tools, equipment, excess inventory, documentation, etc., in any hospital. All these obscure the real problems. Any attempt to optimize the processes without launching 5S at the very beginning is doomed to fail as the main issues will stay hidden behind the visible surface.

Standard work in lean is different from what is usually meant by the notion. Standardization is the best presently known way of performing a certain task. If the employees develop a better, safer way, the standard work can be changed almost immediately. This is different from the traditional approach relying on rigid rules, which are almost impossible to change. Actually, lean is a scientific method based on continuous experiments, which make it extremely flexible, and ensures involvement of the employees on all the levels.

Two walls of the Toyota House can be distinguished. The first one is continuous flow, which concentrates on elimination of delays as well as right care in the right time in the right place. The second one is a quality approach, focusing on error detection, preventing errors at the very source, and involving the employees in problem-solving. The most important rule is to ensure that no witch hunt takes place. Instead, employees providing information about the existing and possible issues and implementations of related solutions should be rewarded.

Finally, the roof comprises the ultimate goals: health, safety, staff morale, and patient satisfaction.

Unfortunately, the term “lean” has been misinterpreted, mainly in the USA, and used in the form of practices involving layoffs and increased work burden. As a result, it has led to pathologies that are in no way connected to the Japanese ideas. The authors would like to stress that the aforementioned mismanagement has nothing in common with genuine lean, which is based directly on TPS.

Theory of Constraints emerged at the beginning of the 1980s, when the Israeli physicist, Dr. Eliyahu Goldratt who became interested in the production planning processes, published his first book on the subject in the form of a bestselling business novel *The Goal* [3]. Goldratt claimed that every organization has its own main constraint, either internal or external, and proposed a set of five steps called the Process of Ongoing Improvement (POOGI) to handle these issues accordingly. The aforementioned steps are:

- Identify the constraint,
- Exploit the constraint—ensure that the constraint is operational all the available time,
- Subordinate all the resources within the organization to the requirements of the constraint,
- Elevate the constraint, i.e., widen it, and
- If the constraint has been broken, identify the new one and start the process all over again, but be aware of the inertia.

Over the following years, Goldratt developed the applications of the TOC in various areas like project management, sales, marketing, and people management. In the 1990s, he introduced the TOC thinking processes—a set of tools aimed at enhancing the analysis of the problems and building solid, logical, time-proven solutions. Today, TOC has found its applications in many different areas both in manufacturing and in services like logistics, strategy, health care, education, and resocialization [4].

It has to be stressed that both lean and TOC—if they are to be implemented the proper way—have to be a company-wide effort closely supervised and led by the top management. Both clinical and nonclinical departments must be taken into account. Obviously, the positive cultural change of the organization will follow as an ultimate result of the implementation. The task is by no means easy, but the payoffs are well worth it. Potential benefits include 20–80% of productivity improvement, reduction of unnecessary length of stay, and significant reduction in inventory and space, and savings counted in millions of local currency are not uncommon if the methods are applied properly and given sufficient time [5]. One has to remember that both methods advocate continuous and growing improvement and are therefore not a one-time initiative.

Neither lean nor TOC is meant to replace the golden medical standards or the standards of pharmaceutical production like GMP. They are rather complementary tools and techniques, paving the way for the existing standards to rise to new levels.

Dr. Stanislaw Sakiel Burn Treatment Centre (CLO) based in Siemianowice Śląskie, Poland, is a top hospital specializing primarily in the treatment of burns and chronic wounds. CLO has been a pioneer in application of TOC and lean in hospital management since early 2016. According to the knowledge of the authors, it is the only hospital in Poland where the system not only is still functioning but also delivers constantly better results. The Bank of Tissues has been among the first units where the approach has been applied. The project was initiated in 2016. Despite the fact that GMP was already in place, it soon became apparent that there is still a huge room for improvement. The decision to implement 5S quickly delivered results. Process mapping followed, together with visible changes in the flow in local production site. Today, the flow is faster, job is better organized, and the breaks are sporadic instead of being a norm. Improved communication with the operating theater resulted in more on-time deliveries and less unnecessary additional transports. This in turn contributed to shorter surgical procedures and better overall conditions for patients and medical personnel alike.



## 2. Resource-based view (RBV) approach in health care organizations and tissue bank laboratory management

### 2.1 Resource-based view framework for health care organizations

The resource-based view (RBV) is a theoretical framework used to study and explain the competitive behavior of organizations [6, 7] that emerged in 1980s and 1990s, after the major works published by Barney, J. *Firm Resources and Sustained Competitive Advantage*, Prahalad and Hamel *The Core Competence of the Corporation*, and Wernerfelt, B. *The Resource-Based View of the Firm*. Since then, RBV approach has been widely used and appreciated in the management of private organizations. However, it may also bring a promising framework to implement in the context of large-scale quality improvement within the public health care entities. Although these theories may be novel for the health management field, including models of strategic management originally developed for private sector firms, their application within publicly funded settings may be problematic or require customization, but nevertheless provide interesting insights [8]. It may provide a sustainable solution to manage quality driven, highly complex, and environmentally turbulenced settings such as tissue bank laboratories. RBV approach may be the answer to maximize growth, quality, and performance in a way to cope with modern, rapid technological changes and competitive medical environments.

The tissue banking sector quality improvement efforts take place in inter-organizational networks rather than in a large, vertically integrated organization. Therefore, tissue bank managers encounter significant difficulties in understanding high organizational complexity that cannot be reduced to simple cause-effect relations or one variable [8]. The challenge is not only to be in compliance with applicable codes and quality regulations of good manufacturing practice (GMP), state regulatory agency, or pharmaceutical regulatory requirements, but also at the same time to optimize your business operations and standardize workflows in processing laboratories. Navigating through this complicated regulatory milieu and at the same ensuring efficient manufacturing process along with sensible business cost balance may require a RBV theoretical framework. Resource-based view and regulatory compliance are not mutually exclusive but should be combined to deliver excellent performance improvements and complex approach to stimulate organization's competitiveness, productivity, and innovation.

### 2.2 RBV model

The RBV resource approach assumes that the success of the organization lies within the organization itself, or to be exact, in its valuable, intangible, and not perfectly imitable resources (VRIO condition) allowing it to achieve a sustainable competitive advantage [9]. Resource-based view (RBV) analyzes and interprets resources of the organizations to understand how organizations achieve sustainable competitive advantage. The RBV focuses on the concept of difficult-to-imitate attributes of the firm as sources of superior performance and competitive advantage [10, 11]. It takes an 'inside-out' view of firm-specific perspective on why organizations succeed or fail in the market place [12]. According to this approach, resources are given the superior role in achieving higher organizational performance. The RBV model presents some critical assumptions regarding resources, which are about to be met, in order to obtain efficient manufacturing process in line with regulatory compliance. The first stage of the RBV model categorizes resources within the organization into two basic types: tangible and intangible resources. The literature categorizes

| Types of Tissue Bank Tangible and Intangible Resources and Capabilities                           |  |
|---|--|
| Tangible resources and capabilities   | Examples   |
| Financial   | <ul style="list-style-type: none"><li>• Ability to generate internal funds</li><li>• Ability to raise external capital (i.a., EU funding)</li></ul>  |
| Physical  | <ul style="list-style-type: none"><li>• Location of the tissue bank</li><li>• Location of offices and laboratories</li><li>• Location of machines, equipment, and systems</li><li>• Access to distribution channels (hospitals)</li><li>• Access to starting materials (hospitals and forensic medicine labs)</li></ul>  |
| Technological   | <ul style="list-style-type: none"><li>• Possession of patents, trademarks, and trade secrets,</li><li>• R&amp;D labs</li></ul>   |
| Organizational  | <ul style="list-style-type: none"><li>• Quality, planning, and command and control systems</li><li>• Integrated lab management information systems</li></ul>   |
| Intangible resources and capabilities   | Examples   |
| Human   | <ul style="list-style-type: none"><li>• Managerial and operational talents (employees)</li><li>• Organizational culture</li></ul>  |
| Innovation  | <ul style="list-style-type: none"><li>• R&amp;D capabilities to innovate new grafts, products, medical procedures, and services</li><li>• Capabilities for organizational innovation and change</li></ul>  |
| Reputational  | <ul style="list-style-type: none"><li>• Perception of product quality and reliability among medical staff</li><li>• Reliability among patients</li><li>• Successful product positioning among hospitals and medical staff</li><li>• Domestic and international recognizability of the tissue bank</li><li>• Reputation as a good employer</li><li>• Reputation as an innovative unit</li></ul> |
| Adapted from P. M. Madhani, 2010, Resource Based View (RBV) of Competitive Advantage: An Overview |  |

**Table 1.**  
*Examples of tissue bank tangible and intangible resources and capabilities.*

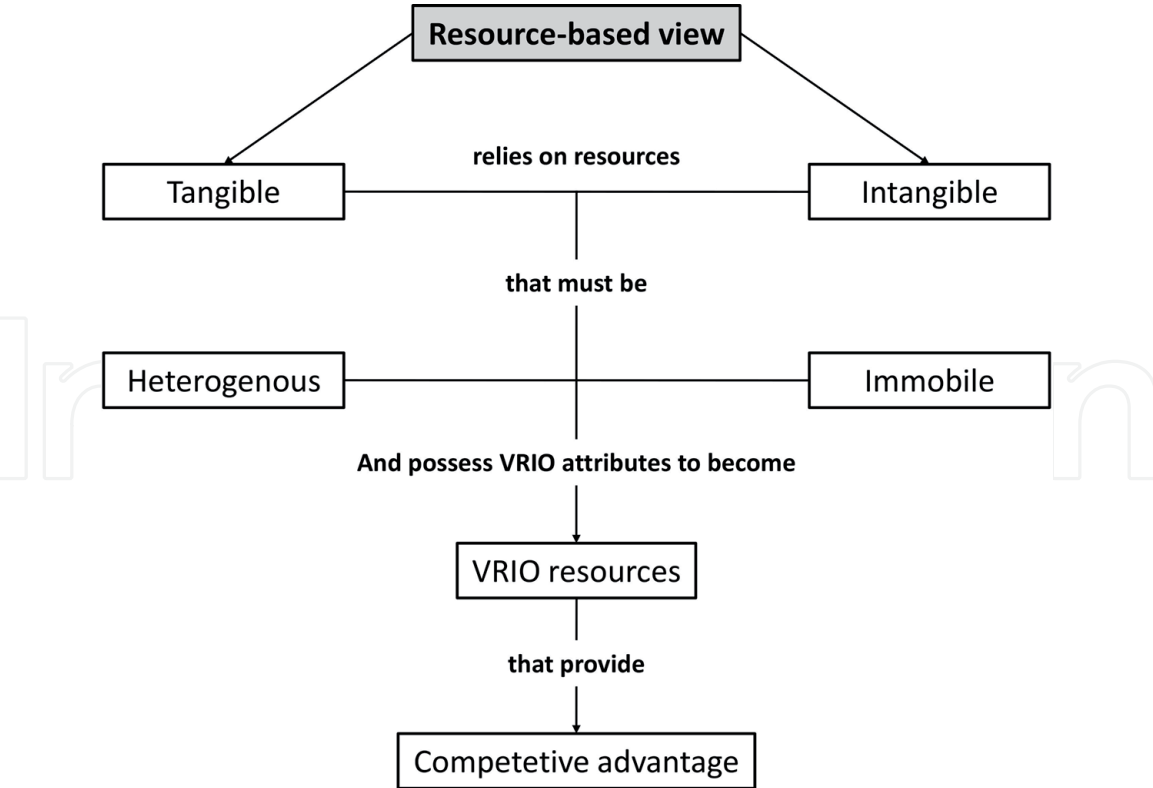
resources also into three main categories: tangible resources, intangible resources, and capabilities [13]. Capabilities refer to the skills organization possesses to coordinate the resources (i.a., teamwork, organizational culture, and trust); however, they are not clearly owned and difficult to measure. For the purpose of the RBV model in this paper, the author included capabilities into tangible and intangible resource category (**Table 1**).

Tangible resources belong to the organization and can be divided into fixed assets (i.e., tissue bank facilities, land, laboratory machinery, clean room systems, and furniture) and current assets including, i.a., capital equipment, laboratory equipment, inventory, and financial means. Such assets are also referred to as property-based resources [6]. Other divisions of tangible resources include also categories of physical and financial assets [14].

Intangible resources, also referred to as knowledge-based resources [15], consist of intellectual property and include, i.a., operational knowledge of the laboratory employees, process knowledge, procedures, accumulated experience, patents, tissue bank brand recognition, community relationship, trademark, and legal agreements. They can be further divided into infinite and finite intangible assets (**Figure 1**).

Tangible and intangible resources can be further grouped into various sub-categories. One of them was first presented by Barney [13] and included physical resources (physical, technological, plant, and equipment), human capital resources (training, experience, and insights), and organizational capital resources (formal structure). An example of broader classification of resources and capabilities of a tissue bank can be found in **Table 1**.

According to RBV, not all resources of the firm will be strategic and, hence, sources of competitive advantage. Competitive advantage occurs only when there is a situation of resource heterogeneity and immobility [16]. The resource heterogeneity implies that organizations have varying capabilities and possess unique bunch of resources allowing them to design different strategies to obtain competitive advantage. Resource immobility may be understood as inability of competing firms to obtain resources from other firms. If the resource is not perfectly mobile



**Figure 1.**  
RBV model.

(i.e., the resource is not free to move between firms, or if a firm without a resource faces a considerable cost burden in developing, acquiring, or using it that a firm already using it does not), then the resource is likely to be a source of sustained competitive advantage [16].

In order for the resource to provide sustainable and desirable performance, VRIO framework criteria must be fulfilled. The original tool VRIN was described by Barney [10] in his work *Firm Resources and Sustained Competitive Advantage* and was later improved by Barney to VRIO in *Looking Inside for Competitive Advantage* (1995).

1. **Valuable (V):** a resource is considered valuable when it provides strategic value to organization, enabling it to exploit opportunities or defend against threats. The resource that is unable to meet this criterion leads to competitive disadvantage.
2. **Rare (R):** rare resources, hard to obtain by competitors, grant temporary competitive advantage. The resource must be rare enough to design and execute unique business strategy in comparison with other organizations on the market.
3. **Imperfect imitability (I):** the resource leading to competitive advantage must be costly to imitate for other organizations that do not have it. The resource may also be hard to imitate not only because of financial reasons but also because of difficulties in acquiring it, its complexity, causal ambiguity, or even historical conditions.
4. **Non-Substitutability (N):** it is impossible for a competitor to substitute or replace a certain resource by other or alternative resource/**Organized to Capture Value (O):** it is the task of the organization to be able to organize its management systems, processes, and procedures in a way to fully realize the



| Tissue Bank VRIO resource analysis example   |  |  |   |
|--|--|--|---|
| Patent:<br>Production of Acellular Dermal Matrix (ADM) inhabited by in vitro culture cells   |  |  |   |
| Valuable?  | Rare?  | Costly to imitate?   | Is the organization organized to exploit it?  |
| Yes  | Yes  | Yes  | Yes   |
| The resource adds value to the organization by allowing it to perform and refund innovative and efficient ADM skin graft procedures. | The patent is controlled by the tissue bank and protected by patent regulations. | The research process of developing the production method is costly and time-consuming, and it requires specialized knowledge, equipment and workforce. | The tissue bank underwent general redecoration of the laboratories and equipment allowing it to produce ADM on a large scale. The organization possesses appropriate quality, production and management systems, and procedures to prepare and distribute the grafts in compliance with GMP and state regulatory agency requirements. The tissue bank employs qualified and experienced staff able to run the production process. |
| Result: sustained competitive advantage  |  |  |   |

Table 2.  
Examples of VRIO analysis: ADM patent.

potential of its unique resources. Therefore, the resource itself does not confer any value to the company; it is crucial to organize the company allowing it to achieve not only temporary but also sustained competitive advantage.

The VRIO framework may therefore be a crucial strategic analysis tool uncovering resources and capabilities that give organizations a long-term competitive advantage. An example of VRIO analysis for tissue bank can be found in **Table 2**.

2.3 Summary

Internal resources and capabilities determine strategic choices made by firms while competing in their external business environment [15]. As resource requirements in health care organizations must be carefully managed due to cost constraints, RBV approach along with VRIO resource analysis adaptation to tissue bank not-for-profit settings seems intuitively sound. Resource-based view can ensure sensible balance between complying quality regulations that govern tissue banks and optimizing processing practices. Examining and identifying unique (valuable, rare, and costly to imitate) organizational resources through RBV and VRIO framework may deliver simple but excellent performance improvements. Finding out if the entity is organized to exploit the resources and protecting them may lead to better financial results as control of superior and unique resources is necessary to establish a cost advantage, which leads to profitability [14]. Finally, constant review of VRIO resources and capabilities enables organizations to establish clear-cut sustainable competitive advantage and growth.

3. Activity and documentation of a tissue bank

The activity of a tissue bank may be limited to the preparation of biostatic (radiation sterilized) and biovital (living) grafts using documented and proven procedures. In this regard, a tissue bank operates under a Ministry of Health License and must demonstrate the implementation of a quality assurance system that meets the requirements of the Law of July 1, 2005, on the collection, storage, and transplantation of cells, tissues, and organs as amended (*Journal of Laws 2017 item 1000*). The regulation



contains the basic documents that a tissue bank quality system must include; however, some of the mentioned documents seem to be obsolete. The basic documents used in a tissue bank are standard operating procedures (SOPs). SOPs must describe the requirements regarding primarily the processes and activities related to the collection of cells or tissues, their acceptance, processing, storage, distribution, transport, as well as monitoring the condition of cells or tissues on their way from the donor to the recipient. Standard operating procedures should specify the medical devices and materials that have direct contact with cells or tissues. The criteria for the qualification and selection of the cell or tissue donor and the criteria for excluding the deceased donor, including the objection against the collection of tissues, must be clearly defined. Standard operating procedures should describe the method of cell or tissue collection, detailing the data necessary for the identification of the entity arranging the tissue collection and the data regarding the collection itself so as to ensure full traceability of the collected cells or tissues. The procedures must specify the means of transporting the collected cells or tissues and their acceptance into the tissue and cell bank. The quality system procedures in a tissue bank must specify how to identify and secure cells or tissues during transport, and describe the stage of acceptance of tissue and cellular material into the bank, specifying the information on:

The way in which cells or tissues are accepted into a tissue and cell bank, taking the following into account:

- a. The common understanding of the purpose of the collected cells or tissues
- b. Results of medical examinations, specialist examinations, and laboratory tests
- c. Documented criteria of donor selection performed by an authorized person
- d. Documented transport, packaging, and labeling conditions
- e. The assessment of the quality of the cells or tissues accepted into the tissue and cell bank
- f. The method of dealing with cell or tissue transplants that do not conform with the specification and have incomplete test results and unacceptable quality or defects
- g. The course of quarantine from the time of acceptance of cells or tissues into the tissue and cell bank until they are released for processing or withdrawn

The next step, which must be included in standard operating procedures, is the processing of cells or tissues. These procedures must take into account the requirements regarding the following elements of all cell or tissue type processing: labeling, processing conditions, and ongoing evaluation of the processing operations in order to ensure the safety and quality of the cells or tissues being processed. The SOPs must describe the manner of approval and documentation of the changes in the processing operations. A cell or tissue identification system must be developed and described at every stage of the processing to distinguish between authorized products and unauthorized products. The infected cell or tissue removal or withdrawal procedures must be developed and described to prevent infection of other processed cells or tissues, the processing products, environment, or personnel.

The SOPs must include the following:

- The grace period conditions after the processing of cells or tissues
- The method of cell or tissue sterilization
- The grace period conditions after the sterilization of cells or tissues
- The manner of storing the processed cells or tissues and releasing them for distribution after the grace period

Another stage that must be included in the quality system is the storage of cells or tissues after processing. Procedures in this regard must specify the requirements for the following:

- Separate storage conditions and maximum storage time for each cell or tissue type, taking into account the possibility of deterioration of the cell or tissue properties in the course of storage
- Separate storage conditions and maximum storage time for each type of product derived from the processed cells or tissues, taking into account the possibility of deterioration of the product properties
- The development of a cell or tissue inventory and identification system at each storage stage

Standard operating procedures for the distribution of cells or tissues determine the requirements regarding labeling of materials intended for distribution as well as transport criteria and conditions. The scope of standard operating procedures must also include the monitoring of the quality of cells or tissues on their way from the donor to the recipient.

A very important aspect is to define the manner of recording significant adverse events and significant adverse reactions associated with the collection, testing, processing, storage, distribution and transplantation of cells or tissues, their reporting, and elimination of the reasons for their occurrence.

The documentation of the quality system must also contain the operating manuals specifying the applicable documentation, including types of documents, their keeping and circulation in the tissue and cell bank, and the manner of keeping records of specific activities performed in a tissue bank. The documentation must also contain reporting forms and donor cards.

The described quality system concerns procedures regarding tissue and cell banking. If a tissue bank additionally produces advanced therapy medicinal products (ATMPs) using the hospital-exemption advanced therapy medicinal product (HE-ATMP) production procedure, two complementary systems must be developed. Becoming a producer of hospital-exemption advanced therapy medicinal products, the tissue bank must additionally implement the good manufacturing practice (GMP) quality system certified by the Main Pharmaceutical Inspectorate.

The system requires the development of documentation necessary to meet the requirements of the GMP quality system. The basic document containing the producer's characteristics is the site master file describing the activities of the production authorization holder related to the good manufacturing practice.

The GMP documentation must also include the following manuals:

- Specifications describing in detail the requirements for a medicinal product or material used or obtained in the production process. They constitute the basis for quality assessment.
- Production recipes, processing and packaging instructions, and testing manuals. This documentation must provide details of all the output materials, devices, and computer systems used. All instructions regarding the processing, packaging, sampling, and sample testing must also be specified in detail.

In-process control and process control in real time (PAT—process analytical technologies) that are used in the process must be specified along with the acceptance criteria:

- Procedures: standard operating procedures (SOP) determining the manner of operation execution
- Protocols presenting the manuals and records of the concerned operation execution
- Contractual agreements referring to arrangements between the client and the contractor for commissioned activities

The GMP system defines the types of records and reports:

- The records provide evidence of actions taken to demonstrate compliance with the manual, e.g., activities, events, tests, and, in the case of batch production, the history of each batch of a medicinal product, including its distribution. Records contain raw data that are used to create other entries. All data used as the basis for quality activities should be defined as raw data.
- The analytical certificates provide a summary of the medicinal product sample or material test results including the assessment of compliance with a given specification. Alternatively, the certification can be based entirely or in part on real-time process control (summaries and deviation reports) for a batch associated with real-time batch control (PAT—process analytical technologies), with parameters and measurements that must comply with the approved documentation attached to the marketing authorization.
- The reports document the execution of individual tests, projects, or studies as well as results, conclusions, and recommendations.

In the GMP quality system, it is necessary to develop and supervise the documentation, which is defined in the good documentation practice.

It includes the following recommendations:

- The manually entered data must be clear, legible, and impossible to delete.
- The records must be made or supplemented in the course of execution of each activity in such a way that all important activities related to the production of medicinal products are reproducible.

- Every change of a record in a document should be signed and dated, and the means of introducing the change must enable the original information to be read. The reason for the change must be provided in justified cases.

In order to properly archive documents, the relationship between the record and the production activity should be clearly defined as well as the place where the record has been entered.

It is also necessary to have the properly approved and dated specifications of starting and packaging materials as well as the finished products.

The following documents should also be developed:

- Production recipes and production manuals
- Packaging instructions
- Batch production records
- Batch packaging records

The acceptance of each delivery of any starting material (including bulk products, intermediate products, and finished products) of any direct, external, and printed packaging material requires written procedures and records. It is necessary to develop written procedures for material and product testing at various stages of production, describing the methods and equipment used. The executed tests should be documented.

As part of the GMP system, written procedures for releasing or rejecting materials and products, including the certification of the finished products by the qualified person, must be developed. All entries must be available to the qualified person. The developed system must immediately identify deviations and any changes implemented in the critical data.

The distribution records of each manufactured batch of medicinal product must be kept and stored in order to withdraw a series from the market if necessary.

The system also requires the development of written procedures, programs, protocols, reports, and related records regarding undertaken actions or final conclusions. These procedures should include the following:

- Process, equipment, and system validation and qualification
- Device assembly and calibration
- Technology
- Maintenance, cleaning, and disinfection
- Personnel issues, including a list of specimen signatures, and training in respect to the requirements
- Technical issues, protective clothing and hygiene, as well as the verification of the effectiveness of the training sessions conducted
- Environmental monitoring
- Pest control



- Complaints
- Withdrawal from the market
- Returns
- Change control
- Explanatory proceedings regarding deviations and nonconformities
- Internal audits regarding the quality and observing the good manufacturing practice
- Record summaries
- Audits at suppliers

The producers must provide clear and understandable operating instructions for the main production and control equipment. They must keep logs of the master and critical control equipment, production equipment, and areas in which production processes take place. There must be records regarding each area, device, method, calibration, maintenance, cleaning, or repair introduced in chronological order, dated and signed by the personnel performing these activities. A list of quality management system documents should be kept.

#### **4. Quality and risk management in compliance with GMP and with reference to RBV**

As described above, the cells were qualified by the European Medicines Agency as advanced therapy medicinal products (ATMPs), so their production is subject to good manufacturing practice (GMP) [17]. The ATMP implementation is therefore not only technologically complex but also strictly regulated by national and European laws. GMP, although it is the legal basis, is only a part of quality management at tissue banks [18]. By definition, resource-based view contains all the principles of good manufacturing practice. If the quality of the delivered product is defined by us as meeting the requirements and expectations of patients, simple observation of the GMP does not guarantee that these requirements will be met [18]. It seems that only the combination of GMP with the ISO 9001 standard, the RBV approach, and lean management enables a comprehensive approach to management, including quality and risk management. ATMP production is special and requires a rigorous and carefully monitored bioprocess to control the intrinsically complex and variable nature of the substance, especially since some ATMPs can be combined with medical devices, such as biodegradable matrices or scaffolds [19]. It should also be mentioned that material collection from a patient takes place in a hospital that is not a GMP-controlled environment, which additionally contributes to the increased variability of this stage [20] and leaves room for other management techniques, such as RBV and lean. A better understanding of graft production management requires risk analysis, including its identification, assessment, and control. The risk is determined by the likelihood of damage and the consequences of this damage. The risk associated with the quality of the advanced therapy medicinal product/tissue is one of the components of the total risk arising from the production and use of the graft. This indicates the need to extend quality management

with a resource approach. Product quality must be maintained throughout the entire production cycle and must allow identification and control of potential risks associated with development, production, and transplantation. The quality risk management principles include development, production, distribution, process reviews, and validations. An important element of the quality system resulting from GMP is the process of corrective and preventive actions (CAPA), which refers to deviations, i.e., events departing from the approved procedures or instructions. An example would be a change of the culture incubator during the process or allowing the tissue to be packaged without obtaining the results of quality control analyses. These types of activities are sometimes undertaken to rescue the medicinal product (graft) or to maintain the continuity of cell culture; however, the area of their application ends at the stage of production of the medicinal product. The initial stage in the CAPA process is to clearly define the problem, i.e., register the deviation and provide its short description containing the scope and area of the occurrence of the irregularity and to indicate the leader of the explanatory actions, who will be responsible for carrying out the entire explanatory procedure. At this stage, it must be added that the idea of corrective and preventive action implementation is not to blame anyone but to continuously improve the production process and the quality of grafts. In determining the actual or most probable cause of an adverse event, the following elements should be taken into account: the equipment and materials used, validity, feasibility and comprehensibility of procedures, the design of the entire process (including its bottlenecks), the level employee qualifications, software, and external factors. Any additional resources that may potentially have an impact on the adverse event that has occurred are also identified and documented. After preparing a list of probable causes, the information and data collection must ensue to be used to draw conclusions about the possible cause of the event. Then, the explanatory actions are implemented and the reasons for the deviation are identified. Repair/corrective actions and their implementation are also specified, and all these actions should be described in order to later verify the effectiveness of the steps taken. Then, there is risk communication, which is a process of sharing risk information and risk management methods between decision-makers and other parties. The parties exchange information at each stage of the risk management process. If the explanatory actions do not show the reason for the deviation, a quality risk assessment should be performed. A number of commonly accepted and well-defined methods and processes of risk analysis and quality risk management have been developed. Risk control in turn involves actions that introduce decisions in the area of risk management. The purpose of risk control is to make decisions, which lead to risk reduction to an acceptable level. The contribution of work devoted to risk management should be proportional to the risk weight. Preliminary hazard analysis (PHA) is an analytic tool based on the application of previous experience or knowledge about the threat or failure to identify future threats (Annex 20 GMP). One of the PHA variations is brainstorming, during which the expert group asks “what if” questions to identify the impact of individual elements on the production process and formulate recommendations for the actions to be taken. The quality of the results obtained using this method depends to a large extent on the experience and knowledge of the participants [20]. The hazard and operability studies (HAZOP) method of analysis was developed in the 1960s. Like the PHA, it is a systematic method; however, it requires more detailed information. The HAZOP method uses a predefined set of guiding words to describe the parameters, which leads to the creation of a pair of words that is referenced to a point in the process that can potentially fail. As a result of using this method, a table is created that includes situations, which can cause a failure, together with its consequences and specific causes. However, this is a

time-consuming and labor-intensive method and as such it generates considerable costs [20]. The process map is a technique based on a graphical representation of the functioning of a set of processes and their mutual relationships. The fault tree analysis (FTA) has been developed for the aviation industry and is a deductive method that assumes the occurrence of a defect in process functionality and can link multiple causes to identify the cause-and-effect chain. Failure mode and effects analysis (FMEA) is mainly focused on the optimization of the product and is particularly recommended in the situation of new product introduction because it allows for the recognition of the potential interfering factors. As a result of this quantitative method, we obtain the so-called risk priority number (RPN) and information about strong and weak points of production. The criticality of the defect is calculated, and the higher the calculated parameter, the greater the risk associated with the defect. After identifying the risks and weaknesses of the process and their characterization, decisions should be made on which risks should be reduced and which should be observed or eliminated. Controlling risks is a technological and economic challenge. Before making any changes, an assessment must be performed to ensure that the proposed change will not cause any new or unexpected risks. The fact that a change is inevitable makes it a critical factor, especially in GMP and ISO environments, where inappropriate or “uncontrolled” changes can affect patient safety and public health. For this reason, the concept of change control is closely related to compliance with GMP and ISO, where any changes in production and processes must be controlled. Change control procedures must be recorded in order to standardize the workflow, especially at key stages such as collecting material outside the production environment. The “uncontrolled” change refers to modifications made without verification and approval by the quality control manager and in special cases also the hospital management. In GMP and ISO environments, strict adherence to approved policies and procedures is a key factor in maintaining production efficiency in a controlled state, and change control is critical. Changes are subject to review and approval by the quality control unit. To summarize, GMP is a formalized procedure and imposes a heavy burden on the producer of transplants, and while compliance is a required minimum, it is not enough to ensure the right quality of using the manufactured products [18]. The specificity of risk management in the aspect of GMP consists in focusing on potential failures in the production of transplants and their safety for the patient. RBV refers to a broader management area including risk management at the time of collecting cellular material and its transplantation as well as the patient's fate. However, some authors point to limitations in the application of resource management in the public health service [8] due to the complex nature of such entities. Lean management possesses tools that are able to systematize it [21].

## **5. Production management**

The tissue bank is the place for graft preparation for the treatment of patients with severe burns and chronic wounds. As already mentioned, the preparations produced in our bank are biostatic grafts, which are subject to radiation sterilization and live cell transplants, produced under sterile conditions. Due to the specificity of the products manufactured in the laboratories, appropriate, supervised environmental conditions must be ensured. For this purpose, we use “clean rooms,” in which, thanks to the use of special HEPA filters and laminar air vents, it is possible to obtain the appropriate class of air purity. The highest class achieved in our bank is air purity class A achieved under the laminar chamber, where the amount of particles and microorganisms generated during operation should be zero. In order



to provide such sterile and dust-free conditions in air purity class A, the rooms located on the way to a class A clean room must meet a series of criteria. The main one is the maintenance of a pressure cascade, which means that in order to get to a class A clean room, you have to go through several airlocks separating neighboring rooms of the following purity class: gray (of the least air purity) D, C, and B. Positive pressure is maintained in each airlock in relation to the previous lock, employees wear dust-free and sterile clothes and gloves, and, finally, in the class B air purity room, they put on a sterile dust-free clean room suit covering their entire body. All these precautions are necessary because we want to protect the product we manufacture, i.e., the advanced therapy medicinal product in the form of cultured skin cells. The cultures that we prepare are supervised by the Main Pharmaceutical Inspector; therefore, as mentioned above, they must be prepared in accordance with good manufacturing practice (GMP). The requirements that we must meet in order to culture cells for a burn patient make all the preparations leading to the process initiation strategic. It should be noted that employees and resources (reagents and consumables) in the laboratory are in a constant state of readiness. At the same time, we are not able to estimate with 100% certainty whether, at a given time, we are going to culture cells at all and, if so, for how many patients. The unpredictability of the production process (cell culture) in the face of the risk of expiry of reagents necessary for maintaining production continuity means that a compromise must be found consisting in the continuous maintenance of small-scale stock of culture materials. The greater part of consumables used in the preparation of medicinal products is highly specialized and is not widely available, and the delivery of a larger quantity often takes a long time. Therefore, ensuring constant availability of materials seems to be one of the solutions enabling continuity of production. However, lean management requires keeping losses to a minimum, which is, in a way, contrary to the GMP assumptions making production halt risk minimization a priority. A common-sense approach should therefore be applied translating into ensuring the minimum amount of reagents that is sufficient to maintain the continuity of production, even in the case of mass events, such as an explosion in a coal mine, when mass production of cellular grafts must be available immediately.

In the case of maintaining sterile environmental conditions, it is also important to systematically and periodically perform cleaning and disinfection of rooms according to the adopted schedule. It is also necessary to permanently perform environmental monitoring: continuous monitoring of the amount of particles in class B rooms, as well as microbiological tests of air and clean room surfaces, carried out according to schedule. Control and supervision are also applied to devices used for cell culture and the conditions prevailing in them, e.g., the devices that are critical in the production process—incubators. A monitoring system is installed in the rooms. It monitors the environment and notifies employees supervising cell cultures about the occurrence of errors in the culture process. Such monitoring is necessary because it allows for quick response and taking action in the event of a risk of culture loss.

Highly specialized persons who have acquired appropriate skills in numerous training sessions are assigned to work in the clean rooms. Their professional experience and the ability to organize and manage their working time are also important. Due to the specifics of the work—a sterile, monitored and supervised environment in a clean room—each entrance to such rooms generates additional costs. That is why, employees working with cell cultures must carefully consider, plan, and organize all elements of their work in the laboratory before it begins. Employees involved in the preparation of cell cultures follow the applicable, written procedures and validated processes. Most processes should be validated based on reference reagents; however, the tissue material from which the cells are isolated

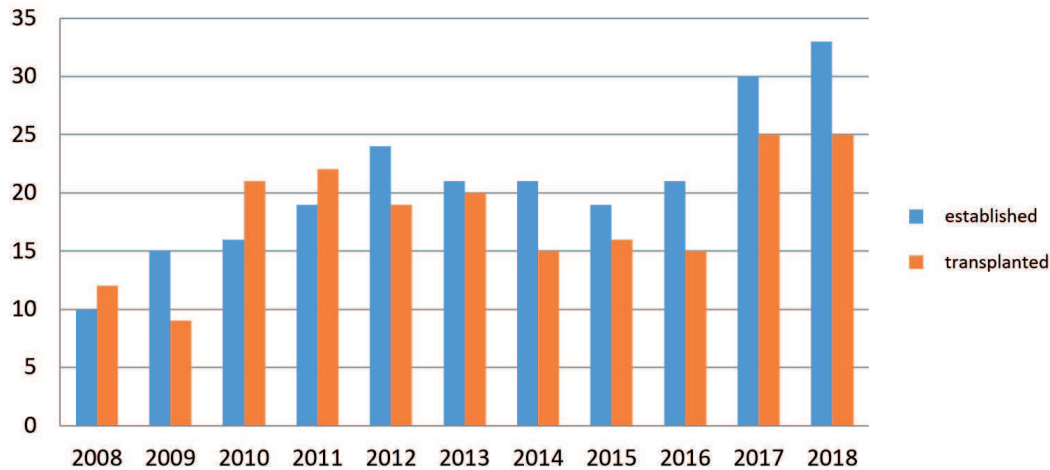


and the culture is established is so unique that it is not possible to replace it with the reference material. Therefore, all employees must comply with specific requirements. In standard work, it is important not only to maintain the purity and sterility of the cell culture and the rooms but also to ensure that all necessary reagents and materials are available in the laboratory. The duty of employees leaving the laboratory is to supplement, prepare, or provide information on missing items to all persons involved in the cell culture process. Each employee entering the laboratory studio must be sure that he or she will be able to perform all the tasks without any problems. Due to the need to monitor and maintain room sterility, any unnecessary entering and exiting the clean room creates a risk of pollution and generates costs of, among other things, used protective clothing and cleaning agents. All these activities are aimed at ensuring the sterility of the advanced therapy medicinal product manufactured in the tissue bank. **Figure 2** shows the increase in the number of cultures and autologous skin cell transplantations. This increase has been possible thanks to the standardization of production processes that has been achieved by minimizing material losses. The lean and TOC management methods contributed to the increase in the number of cultures, which made better management of laboratory resources possible.

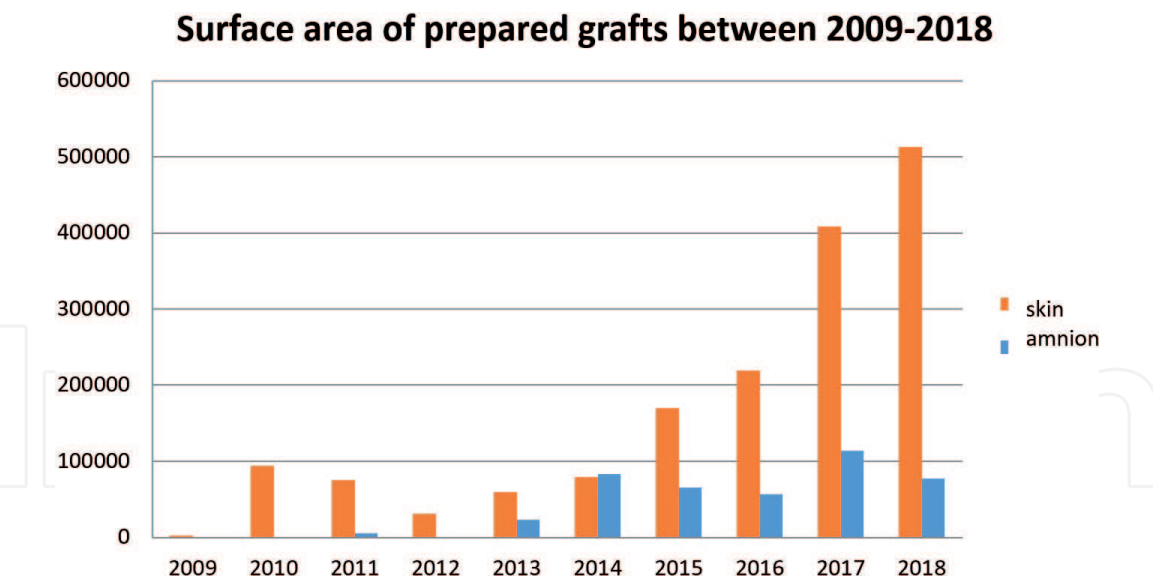
As mentioned above, cell cultures can be established after the occurrence of a mass event, e.g., an explosion in a coal mine or a large fire, in which more people suffer burns. In such a situation, our only safeguard that makes it possible to take appropriate action is to keep reagents and consumables in the laboratory. In such cases, the experience of employees and cooperation with other hospital departments are very important. This allows for the planning of a strategic approach to the problem, which goes beyond the GMP management area, and still requires management and control. Establishing a cell culture is conditioned not only by securing the necessary reagents and materials but also by providing care for the most disadvantaged patients, which results from the efficient operation of the hospital, reinforced by the management system. In such cases, it is also important to adopt the right approach and plan the work of all personnel to avoid unwanted cross-infection or contamination, which could result in the loss of valuable cell culture. The resource-based view (RBV) approach seems to be necessary to manage the aspects that are not covered by the GMP procedures.

The preparation of biostatic skin and human amnion grafts is much less restrictive. These are grafts, in which the final stage of preparation is radiation

**Number of autologous skin cell cultures during 10 years**



**Figure 2.**  
*Number of cultured and transplanted autologous skin cell cultures in years 2008–2018.*



**Figure 3.**  
*The surface area of prepared skin and amniotic grafts in years 2009–2018.*

sterilization. This means that these transplants are not live and constitute only a temporary dressing. Due to the fact of sterilization, the grafts are also prepared in clean rooms, under the laminar chamber of class A air purity, but in the class C environment. When preparing tissue transplants, employees also use their experience in managing their working time, maintaining cleanliness and order in the laboratory and good manufacturing practice. These skills are very useful and promote continuous improvement of the produced grafts and production efficiency. The chart in **Figure 3** shows the increase in the surface area of biostatic amniotic and dermal grafts prepared in particular years. The use of a resource management approach, among others, has enabled the increase in productivity, which translates into the surface area (cm<sup>2</sup>) of the prepared tissue and cellular grafts. The increasing number of donors, and hence the amount of documentation to complete, makes it necessary to adopt a strategic approach to the work so that as much work as possible can be performed at the same time, thus generating added value.

## 6. Strategic potential of a tissue bank in terms of validation of processes and qualification of equipment and rooms

Tissue bank management requires well-established, thorough knowledge of the processes occurring in the area of clean room production. In this respect, the key issue for a tissue bank, as mentioned above, is to have adequately qualified personnel and therefore human resources possessing the required education, experience, competences, and abilities. The second important element in the process of managing a tissue bank is the possession of appropriate devices and rooms, i.e., the hardware and accommodation resources. User requirements for hardware and accommodation resources should be characterized and defined in detail. These elements, in the RBV approach, can be collectively referred to as strategic potential. In general terms, the strategic potential is a factor influencing the tissue bank's achievement of the expected results. The key effects include the ability to use resources to achieve the intended targets and, therefore, obtain the highest quality product according to the tested, repeatable, and effective production methodology using adequately verified equipment and rooms.

The expected effects are, therefore, the result of the tissue bank's implementation of adequately planned tasks. These tasks are directly related to the achievement of the intended objective. In this respect, the achieved production effects are the so-called determinants of a tissue bank success. We use this expression to appropriately define the ranges and criteria of acceptance that a given tissue bank product must meet before a batch is released to distribution. These criteria must be strictly defined in the production specification. Moreover, in addition to the so-called determinants of success, so-called success factors must also be defined. These factors result from adequately defined and purposefully adopted strategic potentials of the tissue bank. The strategic potentials include in particular the professional experience of human resources. Based on specific experience and "know-how," appropriate operational procedures should be created for all activities performed in the tissue bank. However, the final adoption of all the proposed solutions (e.g., methodological, analytical, and technological) requires evaluation that is very carefully planned and analyzed in terms of the correctness of the adopted assumptions. This means that each parameter that constitutes a specific stage or the whole of a given process must be subject to control in terms of meeting the expected assumptions. In case of changes in the specified parameter or parameters, a whole evaluation of the process must be repeated.

Procedures related to the evaluation of processes executed in the tissue bank are called validation procedures. In this respect, special consideration should be given to the validation of the manufacturing process of the hospital-exemption advanced therapy medicinal product (HE-ATMP), the process of manufacturing medical devices, tissue transplants, transport of these products, cleaning, and disinfection, including employee clothing. However, by contrast, the evaluation procedures related to the correct functioning of devices and rooms are called qualification procedures. In this respect, it should be clearly emphasized that the qualification of devices and rooms covers the entirety of undertakings related to the purchase, installation, and operation of a given device or room, starting from specifying the user's specific requirements to determining the conformity of the proposed preliminary design with the requirements, to subsequent processes confirming the compliance regarding the installation and proper functioning.

## **6.1 Main validation plan**

The main validation plan (MVP) defines the approach to the qualification/validation of GMP areas for all validation activities carried out in the existing or newly designed premises of a tissue bank. It is aimed at ensuring that the expectations have been clearly communicated to all participants implementing the validation program. The MVP clearly and comprehensively defines the requirements and scope of responsibility in the validation process. The main objectives and tasks of the MVP are as follows:

1. Presentation of policy, requirements, and expectations regarding the validation activities in laboratory rooms where the tasks related to the production of advanced therapy medicinal products, HE-ATMP, analysis and quality control, as well as research and development work are performed
2. Defining the organizational structure of validation activities
3. A brief description of the installations, systems, and devices that will be validated with reference to the existing documents
4. Specification of the format of the validation documentation used in the protocols and reports

5. Outlining the validation strategy and indicating the documents defining the task and scope of responsibility for the tissue bank, contractors and suppliers of particular systems, installations, and process equipment
6. Presentation of the approach to change control
7. Drawing up a plan and scheduling validation activities
8. Ensuring consistent application of the terms in accordance with their established definitions (in documents such as the standard operating procedures (SOPs), validation protocols, etc.)

The MPV contains general guidelines for the preparation of other validation documents. Rational principles and a rational approach when using the MPV are recommended. In the event of circumstances unforeseen in the plan, the rationale and assessment of the deviation must be documented.

Validation/qualification activities will be carried out depending on the subject of validation/qualification and on the nature of the activities performed by the validation team appointed by the qualified/competent/responsible person to perform specific tasks. The validation team may consist of representatives of quality assurance, tissue bank user/manager, technical and technological experts, and quality control.

This approach to validation and carrying out validation work fulfills the regulations and guidelines specified in the European Commission Directive 2003/94/EC and the Regulation of the Minister of Health of October 1, 2008, on the requirements of good manufacturing practice (Journal of Laws 2008.184.1143) as amended. Validation is an action aimed at confirming, in a documented manner and in accordance with the principles of RBV and good manufacturing practice, those procedures, processes, devices, materials, activities, systems, and installations truly lead to planned results. This is achieved through the development of test plans, protocols, and procedures, as well as the implementation of the records made in the protocols and the documentation of the results obtained in the intermediate and final reports. The report is an approved written plan of the measurement, control, and methodology of testing and result documentation. The verification and validation of the qualification and validation documentation are performed in accordance with the internal procedure prior to the initiation of the qualification/validation activities. In any case, the validation activities performed by external companies must be supervised by an appropriate employee of the tissue bank and are subject to acceptance and approval by tissue bank employees. The same persons and the persons performing the tests (other than those included in the validation team) also check and approve the reports from a given qualification/validation phase following the tests, in order to confirm that the production environment, devices, and the process are indeed suitable for the production of HE-ATMP, medical devices, tissue grafts, etc., in the tissue bank and that they meet the requirements of good manufacturing practice. The full set of qualification and validation documents consists of protocols and test cards.

The installation qualification (IQ) protocols pertaining to the equipment, installations, and clean rooms, similar to the operational qualification (OQ) protocols of these systems, are developed for all critical modules of systems, installations, and devices.

The process qualification (PQ) protocols are developed only for those systems, installations, or devices for which their operation data are necessary to verify the correctness of the process and for which long-term monitoring of their performance is recommended (e.g., laminar chamber, CO<sub>2</sub> incubator, bioreactor, and



refrigerator-freezer). Systems, installations, or devices for which PQ activities are necessary will be selected at the risk analysis (RA) stage. Any noncompliance with the conditions set out in the protocols encountered during the validation process will be recorded and evaluated. The registered nonconformities will be analyzed, and then the actions regarding the manner of further dealing with the nonconformities (e.g., the development of justification/explanation, making corrections, and then carrying out reclassification tests) will be defined. All such data will be documented and saved. The obtained results will be collected and presented in relevant reports after the completion of each qualification stage.

## **6.2 Approach to validation**

Validation of rooms, devices, systems, and installations used in production carried out in the tissue bank constitutes a part of the quality assurance policy of the entire enterprise (tissue bank, hospital, and biotechnological or pharmaceutical company). Qualification/validation activities and the creation of appropriate documentation must be carried out in accordance with the qualification/validation schedule by tissue bank representatives, suppliers of installations, systems, process equipment, and/or contractors providing validation services. Supervision and coordination of qualification/validation activities should be carried out by a tissue bank representative. Validation teams and validation contractors are required to develop a series of protocols to check all critical parameters of rooms, systems, installations, and devices in the tissue bank. The protocols will be implemented in accordance with the test methods presented in the protocols. Each protocol will be used to obtain documentation that will confirm the compliance of the system, installation, or device with the GMP guidelines. To qualify equipment, rooms, and installations, the documents obtained after carrying out the service activities can be used. All protocols and reports will be archived after their final approval.

It should be emphasized that conducting validation cannot negatively affect the production process. In addition, special attention should be paid to the timely performance of validation work, and subsequent planned validation activities related to a given device, room, etc., should be carried out within the prescribed time limit. However, it is possible that the deadline of the next validation is not met. This disadvantageous situation may occur due to a number of possible occurrences that may affect the feasibility of performing validation work. The factors affecting the performed validation work time shift include, among others, production, sickness of the person performing the validation, mechanical failure, etc. The information about the validation time shift must be included in the validation protocol.

In order to summarize and approve the completion of individual stages of qualification/validation activities, appropriate reports are prepared, which are checked and approved by appropriate persons. The report must include a summary of the qualification/validation course, a description of test results, and documented, explained, and evaluated nonconformities. After the approval of the report, if no critical nonconformities were found or all critical nonconformities were resolved, you are allowed to proceed to the next qualification/validation phase.

## **6.3 Summary**

The activities related to the performance of validation/qualification activities are aimed at ensuring the highest quality of the tissue bank products being developed. They take place in accordance with RBV and with the optimal use of the strategic potential of the laboratory. The approach to validation is part of the broadly understood RBV, which results from the conscious management of the unit using

knowledge and science. The validation and qualification activities are necessary to verify the adopted methods and the continuous improvement of processes. This, in turn, fits into modern management systems using the PDCA or DMAIC approach, based on a thorough analysis of a given process and a thorough problem solution. It should also be emphasized that the validation activities require the involvement of appropriately qualified personnel, which will contribute to ensuring high quality and safety of the obtained products.

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