Advanced Therapy Medicinal Products for human use – a new multidisciplinary technical and educational challenge in engineering and quality assurance

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Abstract

Advanced therapy medicinal products (ATMP) are a wide range of highly sophisticated modern therapeutical tools such as: gene therapy medicinal products, cell therapy medicinal products, tissue engineered products, preparation of which involves a multidisciplinary cooperation - clean-room designers and clean-room service engineers, biotechnologists and quality assurance supervisors. European Commission has issued regulations and directives defining the products and setting legal, formal and technical requirements for any entity wanting to prepare this type of products. ATMP Regulation has set a transition period to allow member states industry to adjust to these new high standards. Worldwide preparation of that kind of therapeutical tools has been similarly regulated. The new law, especially in the range of engineered tissue and cell products changes significantly the requirements to be met and can be considered to be a milestone in biotechnology. A dynamic expansion and development of this type of products is already taking place. Hence the products are devoted for human use, safety and quality assurance is of highest importance. There is a strong need for education in this arising field for engineering staff, their employers as well as for including this knowledge and skills in the university curricula.

Keywords: *ATMP, tissue engineered products, clean rooms, tissue establishments.*

1. Introduction

Until 1900 human knowledge doubled approximately every century. By the end of World War II knowledge was doubling every 25 years. Today the ratio is different depending on what knowledge branch is considered. Clinical knowledge every 18 months. [1] Especially if the influence on human health is to be considered in the first place, the development of knowledge, technology and their applicative potential, is followed by legal and regulatory actions that set down not only formal but also often technical conditions and requirements to be met while translating the new technology into practice and offering new products for general use. Employers, while defining the attributes of an entry-level employee, will point out the skills and capacities enabling the employee to work the way and under the conditions specified by the current law and international standards, expecting the skills to have been acquired at the university or vocational school. It usually takes time to adopt vocational schools and university curricula to the changed work market. On the other hand, employers are also faced with the fact that already experienced and highly qualified personnel has to be thoroughly and anew trained as a result of the legal change. The field of tissue-engineering and the introduction of regulatory laws concerning tissue engineered products and classifying them as advanced therapy medicinal products in the European Union is a very good example of the aforementioned situation. Advanced therapy products are products of high novelty, complexity and technical specificity. They are designed to be applied for treating or preventing diseases in human beings, so the regulators took actions to safeguard public health and specified rules governing their production, distribution and use. The products have been precisely

defined in legal terms. Specially tailored and harmonized rules are also needed to ensure the free movement of those products within the community, while guaranteeing the highest level of health protection for patients. The major changes for institutions involved in research, development, distribution and marketing of materials falling now into the category of ATMPs were: the necessity to adopt their production facilities – cleanrooms, following new registration and legalization paths, redesigning operating procedures and running a quality assurance and secure themselves to have an appropriately trained staff .Similar regulatory actions with all the consequences have taken place in other parts of the world.

2. Objectives

The aim of the study is to present: the specificity of Advanced Therapy Medicinal Products (ATMPs), especially tissue engineered products; the current state of education in the area of tissue engineered products, including various target groups; proposals of training models and contents to be included in courses devoted to prepare employees for working in applied tissue engineering.

3. Advanced Therapy Medicinal Products – what is so specific about them

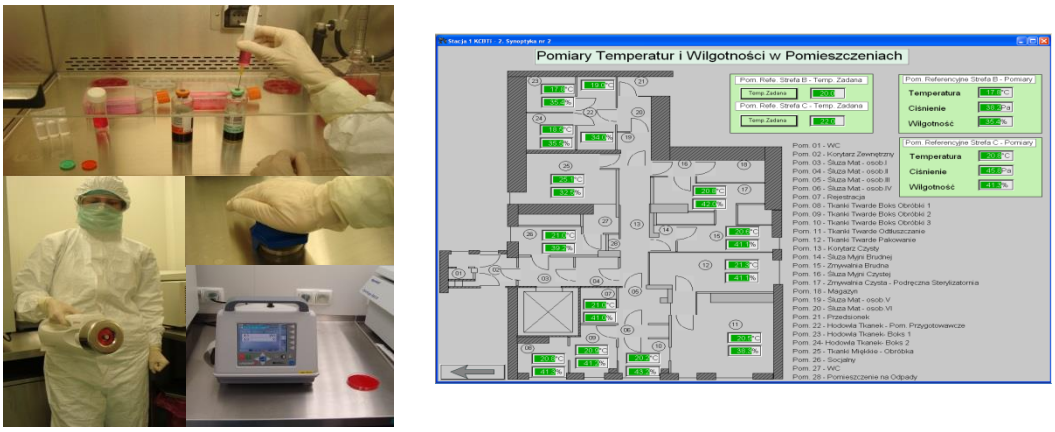
Advanced Therapy Medicinal Products are different from conventional medicines, which are made from chemicals or proteins. There are four main groups:
1) gene-therapy medicines: these contain genes that lead to a therapeutic effect. They work by inserting 'recombinant' genes into cells, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources;
2) somatic-cell therapy medicines: these contain cells or tissues that have been manipulated to change their biological characteristics. They can be used to cure, diagnose or prevent diseases;
3) tissue-engineered medicines: these contain cells or tissues that have been modified so they can be used to repair, regenerate or replace tissue;
4) combined advanced-therapy medicines: these are medicines that contain one or more medical devices as an integral part of the medicine (eg: a biodegradable matrix or scaffold).

Examples of tissue-engineered medicines are: autologous human keratinocytes (patient's own skin epithelial cells, propagated in cell culture) – for treatment of superficial, partial and full thickness burns; allogenic (from a donor) bone-marrow derived osteoblastic cells – for treatment of non-union, delayed union or other bone fractures; allogenic cultured corneal epithelial cell sheet in amniotic membrane – for treatment of ocular diseases.
Examples of combined advanced-therapy medicines are: autologous cultured chondrocytes (patient's own cartilage cells, propagated in cell culture) in a scaffold – for repair of symptomatic joint cartilage defects such as knee and ankle; frozen, cultured allogenic keratinocytes on a silicon dressing material - for treatment of acute burn wounds. [2]

The general regulatory framework for advanced therapy medicinal products (ATMPs) is established by Regulation (EC) No 1394/2007 on advanced therapy medicinal products. This Regulation introduces additional provisions to those laid down in Directive 2001/83/EC on the Community code relating to medicinal products for human use. The scope of this Regulation is to regulate advanced therapy medicinal products which are intended to be placed on the market in EU Member States and either prepared industrially or manufactured by a method involving an industrial process. As a regulation it is to be automatically implemented by the legal system of each EU Member State. A transition period lasting was set down to enable legal and structural changes. [3]-[4]

The nature of ATMPs and their application requires sterility. Therefore their preparation has to be carried out in a controlled environment as defined in Good Manufacturing Practices as set down by the Commission Directive 2003/94/EC laying down the principles and guidelines of good manufacturing

practice in respect of medicinal products for human use and investigational medicinal products for human use, EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use and a set of ISO Standards 14644 – "Cleanrooms and associated controlled environments". Cleanrooms class A and B conditions must be assured. Monitoring and limitation of air-borne particles and observing of recommended microbiological contamination limits are compulsory. Monitoring of temperature, humidity and pressure cascade shall be carried out. Appropriate clothing shall be used. [5]-[6]



A B

Figure 1. Monitoring the environment of clean rooms: A. taking samples for microbiological tests and measurement of air-born particles; B. A print-screen from an electronic Building Monitoring Systems – temperature and humidity measured in particular rooms.

Table 1. and 2. Clean room classification according to GMP. Cfu – colony forming unit. [6]

	Maximum permitted number per m^3 to or greater than the tabulated size			
	At rest		In operation	
Grade	0,5 µm	5,0 µm	0,5 µm	5,0 µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

	Recommended limits for microbiological contaminations			
Grade	air sample cfu/ m^3	settle plates diameter 90 mm cfu/4hrs	contact plates diameter 55 mm cfu/plate	glove print five fingers cfu/gloves
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

If advanced therapy medicinal product contains human cells or tissues, Directive 2004/23/EC should apply as far as donation, procurement and testing are concerned. The donation of human cells or tissues, shall be based on principles such as the anonymity of both donor and recipient, altruism of the donor should be respected. Detailed aspects technical aspects regarding donation, procurement and testing of human tissues and cells are presented and set down by implementing Directives: 2006/17/EC and 2006/86/EC. [7]-[10]

All advanced-therapy medicines are authorized centrally via the European Medicines Agency. The Agency monitors the safety and effectiveness of advanced therapies once they are on the market. The Agency's Committee for Advanced Therapies (CAT) plays a central role in the scientific assessment of advanced-therapy medicines. It provides the expertise that is needed to evaluate advanced-therapy medicines. The European Commission may grant or refuse a marketing authorization on the basis of the Agency's recommendation. ATMPs have drawn considerable attention in academia due to their therapeutic potential. But clean room technology is complex and requires significant financial investment in the manufacturing process. Nevertheless, for the time being, this is the academia that is the major investor in research and development of ATMPs across Europe while in the USA, Canada and Israel the prevailing cost participation is performed by commercial entities. Charity foundation generally play a minor role. [11]

4. Current state of education in the area of ATMPs and tissue engineered products

ATMPs preparation requires in the first place involvement of specialists with background in biotechnology, biology, pharmacy, bioengineering, biomaterials engineering and medicine. Because of the formal and technical requirements concerning production environment, the clean rooms, also the following professions are involved: architectures and designers, construction engineers, clean room maintenance engineers, quality assurance specialists. To analyze the current state of education in all these areas would exceed the possible range of this paper. Therefore we focus on specializations directly involved in tissue engineered product/ATMP preparation and its management. Academia has been very much involved in research and development of human cells and tissues engineered tools for disease treatment. A well-known example are the mesenchymal cells that can be derive from bone marrow or adipose tissue and then propagated and differentiated in culture into various types of human cells for transplantation purposes. However, the focus was basically on the scientific side and the thorough understanding of the biological mechanisms behind observed processes and not the practical application on an industrial scale, which would require a range of additional procedures not science-related, taking administrative steps to obtain legalization from a competent authority and investment in clean rooms [12]. After years of research it has turned out that there has not really much been transferred into therapeutical practice. This phenomenon was described as a "translation problem" in tissue engineering and regenerative medicine. As a result, students had barely if any practice in proper clean rooms and were not prepared for the requirements of the work market. The tremendous gap between ever-day laboratory practice and clean room reality is visualized to some extent by the following pictures made at the authors' university, in regular laboratories and clean rooms located within the same building (Figure 2).

A B C D

Figure 2. A. Every-day work and reality in university labs; B. Working in clean rooms; C. Interiors of regular labs at the university; D Interiors of clean-rooms, specific design elements – glassed doors, internal windows, windows for material flow, ventilation system, special material for wall and floor surfaces, merging of floor and wall surface.

Basing on accessible curricula review four faculties type: biology, biotechnology, pharmacy, biomaterial engineering at 35 Universities has been carried out (10 faculties of each type). The curricula have been checked on presence of the following topics: clean room practical operation as a separate course, regulatory framework of ATMP-related fields, tissue engineering/ATMPs as a separate course. General observation was: most pharmacy faculties included in the research provide courses in all aforementioned aspects. Biomaterial engineering faculties usually provide courses and practical training in clean rooms, but mainly not as provided in GMP for ATMPs. Biology and biotechnology very often lack devoted courses in any of the aforementioned.

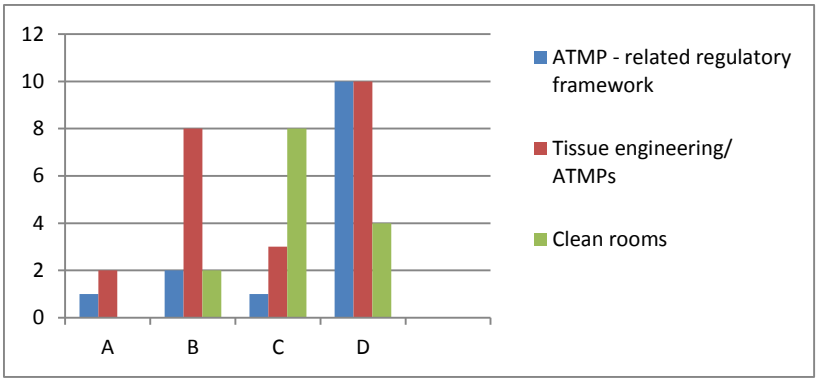


Figure 3. Presence of ATMP-related issues in university curricula. Faculties: A Biology, B Biotechnology, C Biomaterial engineering, D Pharmacy.

The most often practiced method of personnel introduction into ATMPs field and cleanroom operations are internal courses carried out at work place. The law obliges the employers to provide the personnel with the opportunity to update their qualifications. So far, this is the most cost-effective method. A new commercial or fee-based training branch has arisen offering courses in ATMP-related issues. These are offered first of all by organizations close to pharmaceutical sector, like the established non-profit organization The Parenteral Drug Association, the leading global provider of science, technology and regulatory information and education for the pharmaceutical and biopharmaceutical community. Examples of such services are few – this is a developing branch. Participation costs tend to be high. [13]

5. Target groups, training deliverers, contents, systemic solutions

A universal way of training for the area of ATMPs and tissue engineered products cannot be recommended. Even if limited to a particular group of employees who use and work in cleanrooms for ATMP and tissue engineering purposes, a range of models shall be developed and proposed.

Taking the point of view of an investor/employer seeking for qualified personnel, the following target groups can be distinguished, at whom the training shall be addressed to:

1) Students/technicians within their training program at school – potential future employees
2) Students/technicians starting their work in the field
3) New employers with no previous experience - scientific, engineering and technical staff
4) Experienced employers needing learning new skills - scientific, engineering and technical staff
5) Managers, administrators and decision-makers not directly involved in cleanroom operation

Development of curricula/course programs and realization of training can be realized by the following institutions:

1) Universities, vocational schools by including the subject into their curricula for biotechnology, bioengineering, biology, pharmacology faculties – for undergraduate and graduate students
2) Employer himself – for new employees and for raising qualification of experienced staff
3) Public institutions appointed and financed by government to offer low-cost o free courses to support this emerging economy and services branch
4) Non-public, for-profit institutions offering courses as a part of their business activity.

Irrespectively of the provider – university, employer, outside provider - the character of the training can be as followed eg.: compulsory or facultative, modular or continuous or at regular intervals, devoted to a special topic or general, theoretical or practical, basic or advanced, addressed to special groups or uniform, commercial or free of charge. The content of the courses shall have a basic core that can be expanded according to the specific needs of the target group (Table 3).

Table 3. Proposals concerning training contents for personnel in tissue-engineered field.

Basic content Students Unexperienced employees	**Expanded content** Experienced employees Introduction of new procedures	**Contents for managers, quality assurance specialists, decision-makers, marketers**
Cleanrooms: idea and basic technical information	**Cleanrooms:** classification, validation, monitoring of the environment, managing function disorder, building monitoring system, function of the central ventilation unit	**Cleanrooms:** general background, technical outline, classification, validation, monitoring of the environment, building monitoring system, meaning of the central ventilation unit
Operations – theory and practice: Clean room clothing Clean room cleaning Entry and Exit procedures Personnel, material, equipment flow Behavior in cleanrooms Monitoring and sampling of air-borne particles and microbial contamination	**Operations** – theory and practice: Managing non-routine situations Detailed rules of clean room cleaning Advanced course in environment monitoring Material approval and disqualification Validation of equipment and materials Managing equipment defects Aseptic, antiseptic, disinfection sterilization	**Operations** – can be limited to theory: Clean room clothing Clean room cleaning Entry and Exit procedures Personnel, material, equipment flow Behavior in cleanrooms Monitoring and sampling of air-borne particles and microbial contamination Validation of equipment and materials
Emergency procedures **Quality Assurance System:** Basic information Learning and practicing current Operating Procedures Coding system	**Emergency procedures** – repetition **Quality Assurance System:** Creating documents of the Quality Assurance Systems Training if any change in existing procedure appears and if any new procedure is to be introduced Risk management	**Emergency** procedures **Quality Assurance System:** Legal framework and requirements Documents flow Tasks and responsibilities according to QAS Creating documents for QAS Oversight and approval of QAS documents
Legal framework: Basic information GMP - production of sterile products ISO-14644-5 Operations	**Legal framework:** Extended course on current regulations	**Legal framework:** International and local legal regulations concerning ATMPs and related areas Specifically issues concerning: Registration and controlling rules for the producing entities Registration and marketing of the product **Other:** Cost assessment in ATMP s area

A single country or economy, with no previous base in a given area, is not able to train and meet the demand for personnel in a short period of time, which imposes the risk of vanishing of whole services branches. This could have been the fate of Polish and other Eastern European specialized laboratories, tissue banks, that retrieve and process the tissues and cells for tissue engineered products. The shut-down was prevented thanks to international co-operation, and public funding. The first training program outline was created in co-operation with the Institute for Life Long Learning at University of Barcelona in 2006. These initial training courses were financially supported by EU Transition Facility Program 2004. Starting from 2006, advanced training program was financially supported by the National Program for the Development of Transplantation Medicine 2006-2009 funded by Polish Ministry of Health. Between 2006 and 2009, courses were organized for over 350 persons [14]. Since several years the National Centre of Tissue and Cell Banking in Warsaw organizes courses on behalf of The Polish Ministry of Health. Tissue banking and ATMPs products areas overlap and similar qualifications are required from the personnel, so the courses also prepare employees for work as set down by the ATMP Regulation.

Table 4. Training agenda - a course for tissue and cell bank employees devoted to work in cleanrooms class A and B, developed and realized by the Polish National Centre for Tissue and Cell Banking.

Day 1	
11^{30} - 11^{45}	Asepsis, antisepsis, sanitization, disinfection, sterilization
11^{45} - 12^{00}	Classification of cleanrooms – rules, environmental requirements: microbiological cleanness, air-borne particles, humidity, pressure cascade
12^{00} - 12^{45}	Measurement of microbiological contamination in cleanrooms: rules, methodology, equipment
12^{45} - 13^{30}	Measurement of air-borne particles in cleanrooms: range, rules, methodology, equipment
14^{30} - 15^{15}	Disinfection in cleanrooms
15^{15} - 16^{00}	Validation of equipment applied in cleanrooms class A and B: range, rules, methodology, equipment
16^{15} - 17^{00}	Proceeding in case of contact with potentially infectious material (HIV, HCV, HBV)
17^{00} - 17^{45}	Microbiological evaluation of tissue and cell grafts prepared in cleanrooms
Day 2	
8^{30} - 9^{15}	Operations in cleanrooms and associated controlled environments according to ISO 14644-5
9^{15} - 11^{00}	Simulation of procedures in cleanrooms at the National Centre for Tissue and Cell Banking
Entry procedures – introduction; Cleanroom clothing changing; Washing hands; Transporting material; Equipment flow	
11^{15} - 13^{15}	Simulation of procedures in cleanrooms of the National Centre for Tissue and Cell Banking
General and critical cleanroom surfaces; Cleaning of working area in a clean-bench; Preparing for work and arranging working area; Methodology of work in various cleanroom classes; Cleaning after work; Exit procedures: carrying out of grafts/ATMPs; carrying out of wastes	

6. Discussion and conclusions

The field of ATMPs and as one of them - tissue engineered products is a rapidly growing economy branch. The need for qualified personnel will increase as a result. At the moment, in general, university curricula are not properly adopted to prepare students to perform work in ATMPs field. An exemption is pharmacy faculties that have had a long tradition of training medicine industry which overlap in many areas ATMPs training. Academia invests a lot in scientific research on tissue engineered products but usually does not possess facilities enabling them to transfer the technology developed into industry and to teach skills required in high class clean rooms as set down by ATMP and GMP regulations. Public and non-public enterprises have had to make enormous financial effort to adopt their facilities to new law requirements. [15] The demand for appropriately qualified personnel is high and will be growing. The market is reacting relatively slowly: in Europe commercial courses are not common in this field. It is at the moment an emerging niche. International co-operation, financial support by governmental authorities is of great importance to achieve international standards in running ATMPs-related establishments, including organization of training courses. State administration and relevant authorities can play a positive and proactive role in stimulating and supporting universities and vocational schools to extend their curricula. During the transition period, public and non-public entities, especially small and medium enterprises, involved in ATMPs preparation shall be also given an opportunity to take advantage of governmental programs and of a pro-development approach of the state in form of product registration fee lowering, access to free training courses for personnel.

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References

[1] R. Buckminster Fuller, „*Critical Path",* St Martins Press, New York 1981, at: http://epoq.wikia.com/wiki/Knowledge_doubling, Last accessed 17 March 2014

[2] European Medicines Agency, at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_ topics/general/general_content_000504.jsp&mid=WC0b01ac058050f347, Last accessed 16 March 2014

[3] Regulation (EC) No 1394/2007, at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri= OJ:L:2007:324:0121:0137:EN:PDF, Last accessed 15 March 2014

[4] Directive 2001/83/EC, at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L: 2001:311:0067:0067:EN:PDF, Last accessed 15 March 2014

[5] Directive 2003/94/EC, at: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2003_94/dir_2003_94_en.pdf, Last accessed 17 March 2014

[6] Good manufacturing practice (GMP) Guidelines at: http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm, Last accessed at 16 March 2014

[7] Directive 2004/23/EC, at: http://eur- lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L: 2004:102:0048:0058:en:PDF, Last accessed 17 March 2014

[8] Directive 2006/17/EC, at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L: 2006:038:0040:0052:EN:PDF, Last accessed 17 March 2014

[9] Directive 2006/86/EC, at: http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_294/l_29420061025 en00320050.pdf, Last accessed 17 March 2014

[10] E. Olender, I. Uhrynowska-Tyszkiewicz, A. Kaminski, „Revitalization of biostatic tissue allografts: new perspectives in tissue transplantology", Transplant Proc., Vol. 43, No. 8, pp. 3137-41, October 2011

[11] R. Maciulaitis, L. D'Apote, A. Buchanan, L. Pioppo, Ch. Schneider, „Clinical Development of Advanced Therapy Medicinal Products in Europe: Evidence That Regulators Must Be Proactive", Molecular Therapy, Vol. 20 No. 3, pp.479-482, March 2012

[12] M. Abou-El-Enein, A. Römhild, D. Kaiser, C. Beier, G. Bauer, HD. Volk, P. Reinke, „Good Manufacturing Practices (GMP) manufacturing of advanced therapy medicinal products: a novel tailored model for optimizing performance and estimating costs", Cytotherapy, Vol, 15, No. 3, pp.362-83, March 2013

[13] Parenteral Drug Association, at:https://europe.pda.org/index.php?n1=665&n2=689&id=1512&content=Overview

[14] A. Kaminski, G. Gut, I. Uhrynowska-Tyszkiewicz, E. Olender, „Tissue banking training courses: Polish experience"Cell Tissue Bank Vol. 14: pp,141–145, March 2013

[15] J. Cibis, in: „Building renovation and modernization of built-up area,", „New functions in post-industrial environment – adaptation potential for production purposes", in Polish, Zielona Góra, 2006, pp. 61-70

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