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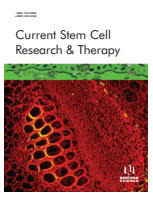
REVIEW ARTICLE

Hospital Exemption for Advanced Therapy Medicinal Products: Issue in Application in the European Union Member States



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Abstract: Regulation (EC) 1394/2007 of the European Parliament and the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 allowed the use of non - authorized advanced therapy medicinal products under the certain circumstances. This so-called hospital exemption rule needs to be applied in the each Member State of the European Union individually and for this purpose Member States should provide national procedures and control measures. The aim of this article is to clear up the criteria for hospital exemption listed in Regulation (EC) 1394/2007 and to contrast the difference in implementing hospital exemption rule into national legal regimes on examples of the United Kingdom, Lithuania and Poland.

Keywords: Advanced therapy medicinal product, hospital exemption, regulation.

INTRODUCTION

Regulation (EC) 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (hereafter "ATMP Regulation") was adopted in 2007. The scope of ATMP Regulation is to regulate advanced therapy medicinal products (hereafter "ATMP"), which are intended to be introduced on the market of the European Union (hereafter EU) Member States and either prepared industrially or manufactured by a method involving an industrial process [1].

According to ATMP Regulation ATMPs include:

- Somatic cell therapy medicinal products (CTMP). These products "contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases" [1].
- Gene therapy medicinal products (GTMP). These products "contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, 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" [1].
- Tissue engineered product (TEP). These products "contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue" [1].
- Combined advanced therapy medicinal products. These products "contain one or more medical devices as an integral part of the medicine. An example of this is cells embedded in a biodegradable matrix or scaffold" [1].

It is worth mentioning that ATMP is a new legal category of regenerative medicine products, which is typical to the EU law only and does not exist as a legal category somewhere else in the world [2].

The centralized European marketing authorization is obligatory for all the ATMPs, which are intended to be placed on the market of the European Union. The application for marketing authorization must be made to the European Medicines Agency and to be passed through its Scientific Committee, the Commitee of Advanced Therapies [1]. Committee for Medicinal Products for Human Use (CHMP) adopts an opinion, which is based on the CAT opinion, to recommend the authorization of ATMP or not. The European Commission takes the final decision based on the assessment of the CHMP opinion due to risk of benefit ratio [1].

The subject of this article is the hospital exemption rule. The hospital exemption rule was introduced in the EU ATMP Regulation and is exceptionally specific to the

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European law and does not exist elsewhere in the world. No other country has exactly the same regulation. It empowered the EU Member States to allow the use of ATMP in hospitals for individual patients in the absence of a marketing authorization [3]. It means that the EU Member States had to prepare and adopt specially tailored legislation implementing this rule according to the ATMP Regulation.

The criteria listed in ATMP Regulation and submitted below are obligatory for ATMP, which are going to be used under the hospital exemption rule:

- Preparation on a non - routine basis;
- Preparation according to specific quality standards;
- Use within the same EU Member State;
- Use in a hospital;
- Use under the exclusive responsibility of a medical practitioner;
- Compliance with an individual medical prescription for a custom-made product for an individual patient [4].

It is worth to stress that criteria for hospital exemption application were set in ATMP Regulation, but not opened out enough, this *a priori* presumes miscellaneous interpretation. Now the article turns to consider the differences in implementing hospital exemption rule into the national legislation regimes of the United Kingdom, Lithuania and Poland.

REGULATORY FRAMEWORK FOR THE HOSPITAL EXEMPTION IN THE EU MEMBER STATES

ATMP Regulation stipulates that manufacture and use of ATMPs under the hospital exemption must be authorized by the Member State and to be administred by National Competent Authority. As it was mentioned before the Member States must have to incorporate adequate provisions into national legislation. On 22 October 2012 Pharmaceutical Committee of European Commission Health and Consumers Directorate-General carried out the survey on the hospital exemption for ATMPs and it was found out that the most European countries had no appropriate regulatory framework on that day [5]. The EU Member States, which legislative framework is going to be discussed in this article, have already implemented hospital exemption clause into national legislation on the date of the survey and it was the main reason we have chosen them.

The UK's legislation implementing the ATMP Regulation including the requirements that apply under hospital exemption scheme was laid in Parliament on 26 July 2010 and came into force on 19 August 2010 [6, 7]. The Medicines for Human Use (Advanced Therapy Medicinal Products and Miscellaneous Amendments) Regulations 2010 sets out requirements for manufacturer's licences, wholesale dealer's licences and traceability. The UK's competent authority responsible for manufacture licence of ATMP is the Medicines and Healthcare products Regulatory Agency (hereafter MHRA), who developed "Guidance on the UK's arrangements under the hospital exemption scheme" and "Guidance on "non – routine" [8-10].

In Lithuania the Pharmaceutical Law was supplemented by provisions regarding the implementation of Article 28 of ATMP Regulation into national legislation [11]. On 28 July 2010 the Minister of Health of Lithuania approved special rules on manufacture of advanced therapy medicinal products for individual patients, which includes requirements for quality, safety, traceability and pharmacovigilance [4]. The competent authority, which is responsible for authorization of exempted ATMP in Lithuania is the State Medicines Control Agency of Lithuania [12].

Poland incorporated Article 28 of Regulation 1394/2007 into the Polish Pharmaceutical Law [13]. On 29 June 2011 Minister of Health of Poland adopted regulation, which confirmed the application form with requirements for an authorization to the production of advanced therapy medicinal products [14]. On 12 April 2013 Main Pharmaceutical Inspector and Director of the National Center for Tissue and Cell Banking approved Bulletin No. 1/2013 on the rules for obtaining approval for the production of advanced therapy medicinal products [15]. The competent Authority in Poland, which is responsible for hospital exemption application - is the Main Pharmaceutical Inspectorate [15, 16].

CRITERIA FOR THE APLICATION OF HOSPITAL EXEMPTION

Preparation on a Non - Routine Basis

Only those ATMP, which have been created in accordance with "non-routine" basis fall under the hospital exemption definition. But, it is rather unclear, how to evaluate whether ATMP is prepared on a non-routine basis. The EU Member States have interpreted this definition in various ways, because European Regulatory Authorities have never detailed what particular number of ATMP constitute "non-routine" preparation [17].

In Lithuanian legislation "non-routine basis" defined as preparation, when the modified manufacturing processes are applied for every medicinal product or when the frequency may not be attributed to routine manufacture [4]. The first condition is quite clear, but the second one is rather questionable and returns the manufacturer exactly to Regulation 1394/2007 definition, which did not give the answer what number of ATMP or ATMP batches will suit „non-routine" definition [18].

The Polish Pharmaceutical Law does not provide the legal definition of "non-routine basis", there is only one sentence that ATMP must be prepared on "unsystematic" basis [19]. Bulletin No. 1/2013 text repeats that product should be prepared on "unsystematic" way, but spreading does not follow [15]. It is worth mentioning that there is the provision in Bulletin No. 1/2013, which states that the permission for the manufacture ATMP under the hospital exemption is unlimited in time [15]. This leads to the conclusion that process would be not controlled and evaluated after the permission issued to distinguish "routine" and "non-routine". It seems that the meaning of a "non-routine" clause would be lost in translation.

UK's MHRA issued "Guidance on "non – routine" and highlighted that "it is not feasible to provide a simple numerical formula that would delineate the boundary between routine and non-routine production" [10]. Guidance on "non – routine" cleared up the steps MHRA would take to evalu-

ate and decide on whether the product falls into hospital exemption definition. MHRA identified two areas, which are the main in decision making process: the first one is "whether it is the same product under consideration" and the second "the scale and frequency of preparation of specific product". Also it is worth mentioning that the manufacturer of ATMP can take advice from MHRA at the early stages. This is very important and helpful tool to have early dialogue with regulators to avoid unnecessary endeavours to get the manufacturer's licence.

Comparing the legal provisions concerning "non – routine" definition in three EU countries we can definitely say that divergence is not only in the definition used, but also in explanation consistency. None of the countries chose quantitative definition of a "non – routine" as, for example, in the Netherlands [21]. In the UK and Lithuania's legislation some flexibility is allowed for the case- by- case evaluation. Poland failed to establish ctiretia for a "non – routine". In our opinion, the UK's approach is the clearest, but also not all inclusive.

Preparation According to Specific Quality Standards

Regulation states that ATMP under the hospital exemption should be prepared according to specific quality standards, which are not detailed, but at the same time there is a requirement that relevant Community rules related to quality and safety should not be undermined. Member States should also ensure national traceability and pharmacovigilance requirements, which should be provided by National Competent Authorities and have to be equivalent to those provided for at Community level [1].

Special rules adopted by Minister of Health of Lithuania foresee that manufacture of ATMP under the hospital exemption must be carried out in accordance with GMP and related to EU institutions documents to the extent that they can be applied [4]. Practically, the GMP rules may be applied not in the full scope and some exemptions may take place.

In the UK, the ATMP made and used under the Hospital Exemption scheme, must comply with the principles of GMP. But the compliance with GMP "will be applied appropriately to the nature of the products involved", some flexibility is also foreseen [21].

Poland's Pharmaceutical Law states that the manufacture of ATMP under the hospital exemption must satisfy the requirements of Good Manufacturing Practice [22].

There is some divergence regarding the implementation of this criterion into the national legislation of the Member States. The UK's and Lithuania's requirements are similar on particular point regarding GMP for the hospital exemption and allow some degree of flexibility, Poland has chosen the strictest way and require compliance with GMP.

It should be mentioned that Annex 2 of the GMP Guide has been revised and one of the reasons was the "increased breath of biological medicinal products" which included advanced therapy medical products [23], but the final agreement is not reached yet and recently European Commission announced that the survey on the topic "Targeted stakeholder consultation on the development of Good Manufacturing Practice for Advanced Therapy Medicinal Products pursuant to Article 5 of Regulation 1394/2007" is being carried until 15 November 2015 [24].

Regarding traceability and pharmacovigilance requirements Articles 14 and 15 of Regulation 1394/2007/EC set additional requirements for ATMP and products under the hospital exemption must comply with them. There are no striking differences between implementation of these requirements at national levels in the UK, Lithuania and Poland.

Use Within the Same EU Member State

National provisions concerning the use of ATMP under the hospital exemption in the same Member State are equal in the UK, Lithuania and Poland. ATMP Regulation does not provide any opportunity to interpret on this topic.

Use in a Hospital

At first sight this condition is quite transparent and does not provide for additional discussion, but there are slight differences in its implementation.

There is a provision in the Lithuanian legislation which states that the prescription and the use of ATMP under the hospital exemption must take place in the same hospital.

In Guidance on the UK's arrangements under the hospital exemption there are no requirements concerning the prescription and the use in the same hospital, but Human Tissue Authority highlighted that when ATMP formulation has been tailored to the individual patient, ATMP should be prepared within the same hospital [21, 25].

The Polish Pharmaceutical Law does not distinguish any specific requirements to those set in Regulation 1394/2007/EC. Bulletin No. 1/2013 repeats that ATMP, which are prepared under the hospital exemption, are used in hospitals. There are no requirements concerning the prescription and use in the same hospital or manufacture in the same hospital.

This issue posed a question if the legislator has in mind that prescription and use of ATMP under the hospital exemption have to be in the same hospital? Of course, in many cases, manufacture and use should be performed in the same hospital, cause it is the only way to use it, this status was fixed by the UK Human Tissue Authority. But, if the manufacture process is separated and performed not in a hospital, is it a problem if manufactured ATMP in the same Member State might be used in several hospitals?

Compliance with an Individual Medical Prescription for a Custom-Made Product for an Individual Patient

ATMP regulation does not provide the meaning of a "custom-made product", this issue is left to the competence of the EU Member States [26].

In the UK, the Human Tissue Authority has defined "custom-made" as "using a one-off formulation or a formulation that has been tailored to the individual patient and prepared within the same hospital" [25].

Poland has no legal definition of a "custom – made product", this condition is delineated as an individual designed product prescription for an individual patient [15].

There is no legal definition of a "custom - made product" in Lithuanian legislation, but this concept was defined as product for which the tailored prescription is required. The special form of prescription called "Medical Practitioneer prescription for advanced therapy medicinal product" was approved by Minister of Health of Lithuania [4].

The UK's, Lithuania's and Poland's approaches specify that ATMP under the hospital exemption should be tailored for individual patient, but there is still a lot of space for interpretation. First, there is no clarity on the issue who constitute the individual patient group, second - there are no detailed requirements for medical prescription and the "custom-made" definitions remains rather vague in national legislations. Some authors maintain that individual patient group is composed of patients for whom there are no treatment alternatives or in case of last hope, but this condition is not mentioned in ATMP Regulation and leaves the question open [27]. During the Public Consulation on ATMP most representatives from the industry sector suggested that „the hospital exemption should not be permitted when there is an authorized product available" [3]. These statements confirmed the hypothesis that the use of ATMP under the hospital exemption is allowed when there is authorized alternative ATMP. It would be beneficial to put definite conditions for the individual patient group in a legal framework.

Use Under the Exclusive Responsibility of a Medical Practitioner

This condition causes debates by its definition. Treatment process involves particular number of medical personnel and it is quite difficult to distinguish one concrete person, who may be responsible for the whole process. It is more acceptable to determine ranges of responsibility or even it would be more correct to talk about the responsibility of a hospital as legal unit and a manufacturer's responsibility if they are not the same person.

The Lithuanian Pharmaceutical Law and relevant orders of Minister of Health define this condition as "under the prescription of medical practitioner". There are no additional conditions for medical practitioner responsibility, which could differ from the regular procedure [4, 28].

In the UK ATMP must be commissioned by a medical practitioner in accordance with a medical prescription. There are no special conditions for medical practitioner responsibility [21].

The Polish Pharmaceutical Law states that ATMP should be used under the exclusive professional responsibility of a medical practitioner, Bulletin No. 1/2013 ascertaines the same, no additional provisions concerning that point were made in relevant documents.

Here we insert one more issue regarding the hospital exemption. The hospital exemption permits treating patients outside clinical trials or when performance of clinical trials is not available [29]. Rhetorical question is - who will take a risk and exclusive professional responsibility for the treatment, which is unauthorized, did not pass or even did not start to perform clinical trials? We suppose that condition of exclusive responsibility is an excess, because the responsibility for personal health care services is well defined in details in national legislations.

Other Issues Regarding the Application of the Hospital Exemption

Despite the main issues discussed above, we presume that classification of ATMP under the hospital exemption by National Competent Authorities might be a problem. We have a group of experts at European level and even in this case opinions sometimes are disseminated. An example of good practice is the UK's regulation. HTA and MHRA developed "Joint statement from the Human Tissue Authority (HTA) and the Medicines and Healthcare products Regulatory Agency (MHRA)", which states that "in cases where the regulatory status of a manufactured product derived from human tissues or cells is unclear, the MHRA should be asked to determine if the product is a medicinal product. The decision of whether a given treatment falls within the scope of the European definition of medicinal product (MP) and ATMP, as opposed to a tissue or cell graft, will eventually be determined by the EMEA working in conjunction with the MHRA". We did not find similar provisions in Lithuania's and Poland's documents, but in our opinion the consultations with EMEA on classification topic should be mandatory to National Competent Authority until the absence of appropriate experience will be replenished.

Critical question is when the hospital exemption rule might be applied? There is no direct requirement in ATMP Regulation that the hospital exemption rule might be applied only when there are no treatments available or in situation of high unmet medical need. Such a situation might lead to misuse of this clause and creates conditions to avoid application for marketing authorization.

Another issue, which requires more detailed regulation on national level, is the possibility to get ATMP, which are authorized in another EU Member State as hospital exemption. Criteria set in ATMP Regulation do not forbid patients movement to another EU Member State to get life-saving treatment. Example is DCVaz – L products, which received approval from the Paul Ehrlich Institute and is covered by the hospital exemption status in Germany. It is manufactured in Germany, but it „can be administered to patient from anywhere [30]. It would be useful to develop unified recipe or direction for ATMP under the hospital exemption treatment form, which would be authorized in all EU Member States. It would help patients to avoid unnecessary long bureaucratic procedures and reduce differences among the EU Member States in implementing this part of ATMP Regulation.

ATMP Under the Hospital Exemption in the EU Member States

The first permission for ATMP under the hospital exemption in Poland was issued in 2013 by Main Pharmaceutical Inspector. For this day 8 permissions have been issued by the Polish Competent Authority. There were no approvals issued for the hospital exemption in Lithuania so far. In the

UK 18 authorizations to manufacture and supply unlicensed ATMP under the terms of the exemption provided by Article 5 (1) of Directive 2001/83/EC (the UK's specials scheme) were granted, but no authorizations for ATMPs under the hospital exemption were provided.

There are some difference regarding the number of authorized hospital exemptions products in these three EU Member States regarding the number of authorized hospital exemption differs, but it is clear that the hospital exemption clause has not been very attractive as it supposed to be at first sight and one of the reason was unregulated national legal frameworks [3].

Examples of ATMP Regulations in Different Countries

As it was mentioned before the ATMPs and the hospital exemtion rule concepts are specific only to the European Union law. There are different approaches in regulating regenerative medicine products around the world. In the United States regenerative medicine products are regulated in a category of biologics as Human Cells, Tisues and Cellular and Tissue based Products. These products should be passed through the US Food and Drug Administration (FDA) evaluation before they get Biologics License Application. The medicinal products based on the use of stem cells in Japan are regulated as „regenerative medicine products" and it has the similar regulatory pathway to the USA [31]. Clinical trial phases in Japan are also similar to the US and the EU. Japan is developing guidance based on regulatory science to simplify revision of innovative drugs. The new system "would move approval from the end of clinical trials to a stage intermediate between the confirmation of efficacy and safety to follow" [32]. India is developing cell/tissue therapy regulatory framework. Drug Controller General of India (DCGI) regulates clinical trials based on human stem cells and tissues without specific regulation [33]. Mexico also has no specific regulation on that point. Federal Commission for the Protection Against Sanitary Risk of Mexico (COFERPRIS) registers clinical trials based on cell therapy treatment, but doesn't have regulatory documents for evaluation, authorization or monitoring treatment involving human cells and tissues [32]. China has adopted several guidelines regarding somatic cell therapy, human gene therapy and product quality control. The ethical guidelines and regulation concerning human embryonic stem cell research have been also recently adopted in China [33]. To summarize this abstract, we can definitely say that in the US, the EU and Japan regenerative medicine products are regulated as drugs and reguire marketing authorization. Mexico, India and China approaches in regulation regnerative medicine products need future development.

Another Access to Unauthorized ATMP

As far as the unauthorized regenerative medicine products is concerned, there is another important tool to get unathorized medicines for severely ill patients with no therapeutic alternative in the EU and the USA. The provisions of Article 5 (1) of Directive 2001/83/EC says that "a Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health-care professional and for use by an individual patient under his direct personal responsibility" [34]. The United States has the similar access to drugs unapproved by the Food and Drug Administration (FDA). The is a provision in the US Code regarding the use of unapproves therapies says, that "any person, acting through a physician licensed in accordance with State law, may request from a manufacturer or distributor, and any manufacturer or distributor may, after complying with the provisions of this subsection, provide to such physician an investigational drug or investigational device for the diagnosis, monitoring, or treatment of a serious disease" [35].

SUMMARY

The ATMP development is still at the early stage and the hospital exemption which is very important tool for patients to get possible life-saving treatment [36]. Criteria for the application of the hospital exemption rule has been set in ATMP Regulation, but hasn't opened out enough, which *a priori* presumes miscellaneous interpretation.

We have analysed national legislation of the UK, Lithuania and Poland, which implemented the hospital exemption clause and found out that the Member States have taken the different approaches to regulate it. The divergence is indentified not only in the interpretation of the criteria listed in ATMP Regulation, but also in explanation consistency. In our opinion most the regulatories gaps, which have been left for interpretation by the Member States, still remained unclear and need to be clarified in further guidelines. Despite this, we have missed transparency concerning the classification procedure for advanced therapy of medicinal product under the hospital exemption by National Competent Authorities.

To the date no authorizations were provided for ATMPs under the hospital exemption in the UK and Lithuania. Poland issued 8 permissions for the hospital exemption clause during the last two years. It leads to the conclusion that the hospital exemption clause is not very attractive as was expected in the beginning and one of the reason was unclear legal provisions, which deters the development of ATMP to use it in full scope.

Whereas the application for the hospital exemption is limited for the internal country use, it would be useful to regulate patient's movement across the EU. Nowadays patient's possibilities to survive getting the hospital exemption are significantly higher in the EU Member States where the regenerative medicine sector is high active and efficient.

FUTURE PROVISIONS FOR HOSPITAL EXEMPTION REGULATION

One of the main problem, which we noticed during our study, is that all criteria applied for hospital exemption in the EU Member States are written in national languages. The criteria for the hospital exemption are hidden in the local documents of the health authorities and it is rather difficult to get them without special request. There is no publicly available information about what the kind of products are used under the hospital exemption rule in the EU Member States

without the written request to the national competent authorities. In our point of view, this situation restricts information, which is valuable to medical practitioners and complicates patient's access to available treatments across the EU and it has to be changed.

The miscellaneous interpretation of the hospital exemption rule has to be harmonized across the EU, cause the differences have negative effect on the future developments of ATMP.

The situation when there are no written conditions when the hospital exemption clause might be applied, it creates the conditions to misuse. Situation must be changed by regulators by inserting respective provisions into ATMP Regulation.

CONFLICT OF INTEREST

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the IMC, VU or one of its working parties.

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