EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products – authorisations, EMA

PHARM 608

PHARMACEUTICAL COMMITTEE
22 October 2012

Subject: **Hospital exemption for ATMPs (implementation of Art 28(2) of Regulation 1394/2007): update on feedback received by the Commission**

Agenda item 1. a)

Member States were requested to provide information on the following points regarding Advanced Therapy Medicinal Products:

- How many products are legally on the market of each Member State?
- Which of the products legally on the market are prepared on a routine basis?
- Which of the products legally on the market fall under the hospital exemption?
- Criteria applied for products under the hospital exemption.

Annex 1: Responses from National Authorities on the Status of ATMPs on their territory (September 2012)

Country	How many products legally on the market	Prepared on a routine basis	Which fall under the hospital exemption	Criteria applied for HE

Austria	In Austria three products fall into that group: - IGOR-Institut für Gewebe- und Organkonstruktion seeks a hospital exemption for their chondrocyte product. - Arthro Kinetics Biotechnology GmbH . The company will terminate marketing of their chondrocyte product at the end of the transitional period. - Innovacell is preparing an MAA for their product. The transitional period for the following products has ended: - Cell pro Danube is conducting clinical trials for a dendritic cell product with Life Research Technologies GmbH as sponsor. - CCRI has been restructured and the ATMP is now manufactured by Activartis (formerly Trimed Biotech GmbH). They are in clinical trials for their product.	Has not yet been assessed for the 3 products that remain legally on the market	The Austrian framework for the hospital exemption is currently being developed; no applications have been received so far. No approval under the hospital exemption framework has therefore been granted, which would have included the assessment of "non-routine". Concerned companies need to apply for a "license" (GMP or for cells and tissue) which is issued by the Federal Office for Safety in Health Care.	
Country	**How many products legally on the market**	**Prepared on a routine basis**	**Which fall under the hospital exemption**	**Criteria applied for HE**

Belgium	In Belgium there are no ATMP's legally on the market at the moment. .		As for the products falling under the hospital exemption, 16 cell and tissue banks have been authorized to continue their activities for the products they are allowed to process at this moment. This authorization is temporary until further examination of the exact nature of their activities has been carried out (on the basis of a dossier introduced). The purpose of this examination is to identify products that clearly fall under the exemption and others which would not meet the requirements of the exemption.	Furthermore, the purpose of this examination is to define more specific requirements for the 'hospital exemption'
Croatia	There are no ATMP in the Croatian Medicinal Products Database for 2011, nor in pharmacotherapy manuals nor Croatian pharmacovigilance database. Currently, our Agency is performing PALC (Pre-accession linguistic checking of centrally authorised medicinal products) and we have received an application for the medicinal product ChondroCelect®, so with the EU accession we will definitely have an ATMP approved by EMA.			
Country	**How many products legally on the market**	**Prepared on a routine basis**	**Which fall under the hospital exemption**	**Criteria applied for HE**

Czech Republic	*1) Gene Therapy Medicinal Products:* None. *2) Cell Therapy Medicinal Products:* a) Clinical Trials - 3 medicinal products of anticancer immunotherapy (2 dendritic cells therapy, 1 tumor infiltrating lymphocytes) – will fall under centrally authorized products b) hospital use – 1 medicinal product – extracorporeal phototherapy in indication of graft versus host disease (GVHD), comment – this medicinal product should be re-evaluated, whether it falls under ATMPs (some EU states does not have it as ATMP, re-evaluation should occur in February CAT Meeting) – if considered as ATMP, will fall under scope of hospital exemption, prepared on non-routine basis. *3) Tissue Engineered Medicinal Products:* 2 medicinal products – autologous cultivated chondrocytes for treatment of chondral defects, these will fall under centrally authorized products and can be present on the market only to 30 December 2012 (for this transitional period under scope of article 49 Pharmaceutical Act 378/2007 Coll).			- patient specific (tailored for concrete patient) - the overall numbers of the particular product prepared, - the regularity/frequency of production, and the time period over which the preparation of that product has become established - progression of the rate of manufacturing
Cyprus	There are no ATMP-s legally on the market			
Denmark	In Denmark we have one product on the market under the hospital exemption: Genzymes MACI. They have informed us that they will apply for MA authorisation with EMA before the end of 2011.		1 product	
Estonia	There are no ATMP-s legally in the market.			
Country	**How many products legally on the market**	**Prepared on a routine basis**	**Which fall under the hospital exemption**	**Criteria applied for HE**

Finland	There are no ATM products legally on national markets in Finland. Marketing of the first centrally authorised product, ChondroCelect, is going to start soon in Finland. Still, it is known that Finnish university hospitals, orthopaedic clinics are using autologous chondrocyte preparations, for which patient biopsies are collected in Finland, exported for processing to a Swedish cell laboratory in Gothenburg and imported back to Finland for the clinical use. A license for tissue establishment is required for the procurement and exportation of the chondrocytes. The number of patients treated by using this optional method is approximately 10 to 20/year.	Production of the chondrocyte preparations in Sweden are prepared using a routine process, but the cells and serum in each case are from different donors.	None of the above-mentioned preparations are approved under the hospital exemption. Fimea has given a license for ATMP manufacturing under hospital exemption currently to one applicant producing an oncolytic virus product for cancer therapy and to one applicant producing six different tissue engineering products mainly for bone regeneration. Our interpretation is that the collaboration between the Finnish hospitals and the Swedish production site can continue until the end of the transitional period for TEPs (end of 2012) or until similar, centrally authorised product enters our markets.	The main criterion is an initial phase of drug development before entering into a clinical trial. The oncolytic viruses are used for single patients having different diagnosis of cancer and no option for conventional therapies. The treatment is offered individually in a private hospital under the responsibility of a treating physician. The tissue engineering products are prepared for individual patients in a non-routine basis for experimental treatment of facial defects. The aim of this experimental treatment is to find the most suitable combination of stem cells and biomaterial to be taken into the future clinical trial.
Country	**How many products legally on the market**	**Prepared on a routine basis**	**Which fall under the hospital exemption**	**Criteria applied for HE**

France	In France, for the moment, only one ATMP has a marketing authorization (Chondrocelect).	Chondrocelect which is a preparation of chondrocytes aimed at treating specific joint disorders. This product is prepared on a routine basis by a pharmaceutical company.	We are preparing the decree about the national legal framework describing the requirements to authorise the establishments which will prepare ATMP under HE and to authorize the MTI themselves. This decree will be probably published at the end of April. During the period, before the publication of this text, tissue banks have continued their activities for the products they are allowed to process at this moment.	The criteria applied to define ATMP under hospital exemption are those of the regulation. We have listed in the attached document all these criteria. We shall better know during the examination of the future authorization demands the exact nature of their activities and we could know if they fall under the exemption. We can already say that there are a number of ongoing as well as pending clinical trials using ATMPs in France. We think that very few of them will eventually result in application under article 28 of Reg 1394/2007.
Germany	Besides the product already mentioned which is centrally authorised (ChondroCelect, TiGenix), there are four ATMP legally on the market in Germany due to transitional provisions until December 30, 2012. These products are: Hyalograft C, CartiGro, MACI and CaReS. After the transitional period has expired on December 30, 2012, only ChondroCelect will be legally on the market in Germany. For two of the four products (MACI, Hyalograft) applications for central marketing authorisations are pending. If the procedures are successful, the products could be marketed in Germany as well after December 30, 2012. The procedures will be finished probably in the end of 2012 or the beginning of 2013.	(ChondroCelect, TiGenix),	17 products which are legally on the market are all hospital exemptions. .	In addition to the criteria laid down in Article 3 Nr. 7 of Directive 2001/83/EC (Article 28 of Regulation (EC) Nr. 1394/2007), in Germany for hospital exemptions an authorisation of the product by the higher federal authority is necessary.
Country	**How many products legally on the market**	**Prepared on a routine basis**	**Which fall under the hospital exemption**	**Criteria applied for HE**

Greece	No Advanced Therapy Medicinal Product has been approved in Greece. Concerning new ATMPs, there is one clinical study in process (genetically modified somatic cells).			The implementation of the hospital exemption status is still ongoing. Consequently, at this time point, we cannot specify the products that will fall under this category.
Hungary	There are no ATMPs marketed in Hungary		No "hospital exemption" requests have been received until now.	Their hospital exemption is defined at the level of an Act saying that the human medicines competent national authority has to licence the "manufacturing site" of such products in the in-patient institutions. This is valid since 1 January of 2011. There is an agreement on that some Good Manufacturing Practice rules, specially adjusted to this purpose (not the GMP 'per se'!) will apply, but no details have been issued yet.
Iceland	No Advanced Therapy Medicinal Products are legally on our market or used in hospitals in Iceland.			
Ireland	There is only one product under supplied hospital exemption (article 28) the MACI product which is currently going through the centralized procedure.	None	None	Manufacturer's authorisation required-none yet issued. A guideline has been prepared for interested parties.
Country	**How many products legally on the market**	**Prepared on a routine basis**	**Which fall under the hospital exemption**	**Criteria applied for HE**

Italy	Three advanced therapy products have been granted the status of “legally on the market by the Italian Medicines Agency on November 25th, 2008. The three products are Hyalograft C autograft (cartilage), Hyalograft 3D autograft e Laserskin autograft (skin). The Applicant, Anika Therapeutics (former Fidia Advanced Biopolymers (FAB)) is planning to submit a file for authorization only for Hyalograft C auto graft in March 2012, hence before December 2012 that is the deadline for tissue engineering products.			Concerning the national legislation for “hospital exemption” a draft technical text is available; the verification of legal aspects is currently in progress.
Latvia	In Latvia till this day there were no such products on the market therefore no use in hospitals products are prepared on a routine basis or which fall under the hospital exemption.			
Country	**How many products legally on the market**	**Prepared on a routine basis**	**Which fall under the hospital exemption**	**Criteria applied for HE**

Lithuania	According to the statistic data of the State Medicine Control Agency ATMPs registered centrally have not been supplied to the Lithuanian market.		The Agency has not received any applications to get a permit for manufacture of ATMPs for individual patients yet.	The rules on manufacture of advanced therapy medicinal products for individual patients were approved by the Minister of Health of Lithuania in 2010. An entity is allowed to manufacture ATMPs on non-routine bases for individual patients if it possesses a permit issued by the State Medicine Control Agency at the Ministry of Health of the Republic of Lithuania. ATMPs must be prepared on non-routine bases, when different (modified) manufacturing processes are applied for every MP or when the same ATMP is manufactured with the frequency that may not be attributed to the routine manufacture. An entity is eligible to get a permit if it possesses a health care licence and meets manufacturing and control requirements approved by the Minister of Health.
Luxembourg	2 ATMPs have been centrally authorized, none is in use in Luxembourg	none	none	none
Malta	Until 19 April 2012, no applications for ATMPs had been recieved by the national Competent Authorities.		No hospital exemption request for ATMP have been received until 19 April 2012	
Country	**How many products legally on the market**	**Prepared on a routine basis**	**Which fall under the hospital exemption**	**Criteria applied for HE**

Netherlands			The Inspectorate approved approximately 5 hospital exemptions	In the Netherlands a request for a hospital exemption has to be submitted at the Health Care Inspectorate.
Poland	There are no ATMPs products legally on national market in Poland.			The Article 3 Nr.7 of Directive 2001/83/EC (Art.28 of Reg.1394/2007) is already implemented to the Polish Pharmaceutical law.
Portugal	At present Portugal has no ATMP products legally on the market			
Romania	In Romania there are no ATMP products legally on the market.			
Country	**How many products legally on the market**	**Prepared on a routine basis**	**Which fall under the hospital exemption**	**Criteria applied for HE**

Slovakia	In Slovakia there are no ATMP's legally on the market at the moment	None	The Ministry of Health has not received any applications to get a permit for preparation of ATMPs for individual patients yet. The Article 3 (7) of Directive 2001/83/EC (Art.28 of Reg.1394/2007) is already implemented to the Law on Medicinal Products and Medical Devices (§ 14 of Law 362/2011 Coll.) . Good Manufacturing Practice rules, specially adjusted to this purpose will apply, but no details have been issued yet.	
Slovenia	No advanced therapy medicinal products were approved in Slovenia. Four clinical studies concerning the products have been approved in Slovenia (EudraCT No.: 2010-021867-34; 2009-013042-88, 2009-012389-30, 2008-006710-23) .		There were no applications for manufacturing licences for a "hospital exemption", the implementation of the HE status is ongoing. In this moment we can expect that hospital exemption status will concern eight products considered as hospital exemptions as defined in the Art. 28 of Reg. 1394/2007.	Criteria are in line with art 3(7) of the Dir. 2001/83/EC and Art 28 of the CR 1394/2007.
Country	**How many products legally on the market**	**Prepared on a routine basis**	**Which fall under the hospital exemption**	**Criteria applied for HE**

Spain	We only have ChondroCelect, as it has been centrally authorised. We also have other products in hospital use, belonging to one of the following three categories: corneal limbai stein cells, chondrocytes and skin keratinocytes. These products are manufactured by a non-industrial process and have a "historical", consolidated use previous to the ATMP Reg. 1394/2007, and will be regulated under the HE clause by a project currently under development in Spain.	Only ChondroCelet	For the moment, we only envision to regulate under the hospital exemption the non-industrially produced ATMPs that have been "historically" used in Spain, as described above.	In the future, once that the project of regulation in Spain is approved, we expect other products could apply for authorisation under the HE.
Sweden	In Sweden one can identify two types of products that can be considered legally on the market although no formal decision has been made: These products are: Mesenchymal stem cells for Graft versus Host disease and a Chondrocyte implantation product.	The Chondrocyte implantation product can be considered to be produced on a routine basis.		From May 1st the manufacturers need to apply for a manufacturing licence for “hospital exemption products”. Provisions from the Medical Products Agency sets up the specific requirements for the “hospital exemption products”. So far (Dec. 2011) only one manufacturer has applied for a manufacturing licence for a tissue engineered product.
United Kingdom	18 authorisations to manufacture and supply unlicensed ATMPs under the terms of the exemption provided by Article 5(1) of Directive 2001/83/EC (the UK’s Specials scheme) have been granted.		To date, the UK has not issued any authorisations for ATMPs to be made under the hospital exemption.	The UK has developed guidance for arrangements under the hospital exemption scheme which we notified to the Commission.

Countries which have not sent any information on the status of ATMPs on their territory:
Bulgaria

Chondrocelect is the most frequent ATMP in the countries

N° total countries 27
N° countries with ATMP legally on the market= 10 (37%) range= 1-18
N° countries with ATMP hospital exemption = 6 (22%) range= 1-17