Hospital Exemption in ATMP development

within the Revision of the EU general pharmaceuticals legislation

The signatory organisations jointly call for a strong EU focus

on the societal aim of health equity in rare diseases and

to further support the academic and non profit organisations in their role

in the life-cycle of the Advanced Therapy Medicinal Products (ATMPs).

eahp
european association
of hospital pharmacists

ePTRI®
European Paediatric Translational Research Infrastructure

SIOP Europe
the European Society for Paediatric Oncology

EU|EYE
European Alliance for
Vision Research and Ophthalmology

Executive Summary

The development of advanced therapy medicinal products under Hospital Exemption (HE-ATMPs) is academia-driven innovation achieving timely access to safe therapies and sustainability of healthcare systems. Our organisations jointly welcome the retention and strengthening of Hospital Exemption in the revision of the EU general pharmaceutical legislation. We believe that the introduction of measures for data collection, reporting and regular reviewing will improve transparency whereas the increased responsibility of Member States regarding GMP compliance, traceability, pharmacovigilance and notification of revoked authorisations will ensure harmonisation of HE practices and safety for patients.
We call for the European Commission to maintain a strong focus on the societal aim of health equity and to further support our researchers, clinicians, and hospital pharmacists in their various roles in the ATMP life cycle by:

- defining interests of all stakeholder for a sincere public dialogue and collaborative approach - patients, researchers/developers, healthcare professionals, industry, payers;

- creating a straightforward and affordable authorisation procedure for academic HE-ATMPs drawing from national experiences;

- addressing borderline classification issues to encourage innovation particularly in rare paediatric diseases;

- providing guidelines for reflection as to what non-routine preparation of an ATMP is under hospital exemption as prescribed by the medical needs in each Member State and with clarification on other related terms such as clinical grade;

- defining clearly the legal responsibility across the medical practitioners and the hospital management given the multiple factors involved in ATMP evaluation;

- adopting a comprehensive holistic action plan that recognises the key strategic role of multidisciplinary education and training at all levels (development, manufacturing, delivery) including public awareness on availability of treatments;

- fully assessing the impact of the proposed legislation including cost differences between commercial and academic/non-profit settings; different intellectual property models; and reimbursement sources for HE-ATMPs;

- potentially decoupling cost of development from production according to product characteristics with fine-tuning of relevant regulations related to intellectual property, exclusivity rights, and licensing;

- allowing use of clinical data from observational studies for marketing authorisation;

- support the creation of an industry based on the model of Contract Manufacturing Organizations for selected ATMPs with cost sharing for Good Manufacturing Practice and Good Laboratory Practice wherever appropriate.

We believe that our recommendations will ensure:

- patient autonomy in their right to choose therapy, treating physician and treatment location;

- support for the clinicians' role as stewards of healthcare resources aside their duty to patients;

- support for governmental and non-profit organisations in developing novel therapeutic strategies;

- reduce the risk of abuse of market exclusivity and excessive pricing.

Background - What is Hospital Exemption

The European Union Hospital Exemption (EU-HE) is a nationally regulated exemption from the centralised Marketing Authorisation (MA) requirement for the custom-made and use of ATMPs which fall outside the scope of the Medicinal Product Directive 2001/23. Such products are often intended for small populations (rare diseases) and are regulated at national level according to the Regulation 1394/2007 on the advanced therapies and the amendment of Article 3 of Directive 2001/83/EC which state:

> "*Advanced therapy medicinal products which are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient, should be excluded from the scope of this Regulation whilst at the same time ensuring that relevant Community rules related to quality and safety are not undermined.*"[1]
>
> *"Article 28 Amendments to Directive 2001/83/EC*
> *2. in Article 3, the following point shall be added:*
> *'7. Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.*
>
> *Manufacturing of these products shall be authorised by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency"* [2].

Current implementation and use of Hospital Exemption

Different interpretations of the European provisions of Article 28 (2) of the ATMP regulation precipitated variable implementation of HE across the EU. Conditions for authorisation and manufacturing diverge between states. Eligibility criteria for use differ as the scope and purpose of HE are shaped by or reflect national needs and motives. National policies either impose additional requirements for the HE use or encourage it as a permanent

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[1] (L 324/130; REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL)

[2] OJ L 136, 30.4.2004, p. 1. Regulation as amended by Regulation (EC) No 1901/2006 (OJ L 378, 27.12.2006, p. 1; https://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX%3A32007R1394#ntr17-L_2007324EN.01012101-E0017)

alternative to the central MA. Cross-country differences are inevitable as a result, not only in access to treatment but also in capacity for ATMP production (BOX 1).

BOX 1. Implementation and regulatory framework at national level

France. The MTI-PP (*Médicaments de thérapie innovante préparés ponctuellement*) are ATMPs prepared on an ad hoc basis, a French specificity where the product must be used in a hospital in France for a specific patient and on medical prescription. It is an extemporaneous preparation of MTI carried out by a hospital pharmacist for a given patient in the absence of an alternative treatment. MTI-PP in France contributes to improving patients' access to innovation. Due to the specificity of these medicines, a good quality system requires sufficient staff and appropriate funding to provide the best service to the clinician and the patient.

Germany. A well thought out manufacturing path is offered under the German Medicinal Products Act (Arzneimittelgesetz – AMG) Section 4b Special provisions governing advanced therapy medicinal products very strict standards, pharmacovigilance and quality, and with extra-funding for hospitals managing ATMPs. Temporary HE manufacturing licences are issued by the Paul-Ehrlich Institute, an Agency of the German Federal Ministry of Health with no limit on the number of patients treated with one HE product, neither on the number of HE approved annually. A differential benefit assessment process is applied for reimbursement based on whether the Federal Joint Committee (G-BA) categorizes the ATMP either as a medicine or a medical procedure.

Greece. According to the National Authorities on the Status of ATMPs on their territory, the implementation of the hospital exemption status was ongoing in 2012 and there are no data to today regarding approval of any ATMPs in the country. The only way to proceed with a "in-house made" ATMP is through clinical trials as in the case of adoptive immunotherapy with CoV-2-STs for severe COVID-19.

Italy. The legal transposition of art 28 (2) with the DM of January 16, 2015 created a pathway with insurmountable administrative burden and high uncertainty for success: in fact Section 11.8A2 Overview of the regulatory issue in the Impact Assessment Report of the European Commission reports that 8 out of 9 applications of non-profit organisations failed in 2016 with an impact on the willingness by both commercial and non-commercial settings to invest resources in applying.

Spain. The national regulatory agency encourages and promotes new applications by hospital and research entities according to the "Spanish Model", demonstrated by the ARI-0001 (CART19-BE-01) case, a CAR-T therapy based on patients' own T-cells, developed by the Hospital Clínic Barcelona, Spain and the first candidate in the EMA's pilot on the needs of academic sponsors and non-profit organisations of ATMPs. It involves a thorough evaluation by the Spanish Agency of Medicines and Medical Devices (AEMPS) of preclinical and clinical data, as well as the inspection and accreditation of the GMP Cell Production Facility and a Pharmacovigilance Plan, among other aspects, which are similar to those required for a centralized marketing authorization, in order to ensure the quality, safety and efficacy of the pharmaceutical product.

Clinical efficacy and safety under Hospital Exemption

The Community directives assign responsibility to the national competent authorities of the Member States for the manufacturing of non-routine ATMPs produced in hospitals or other academic settings under Hospital Exemption (referred to further as HE-ATMPs). This includes auditing, the quality standards in the manufacturing process, national traceability and pharmacovigilance equivalent to those provided for at Community level for centrally authorised ATMPs. The HE-ATMPs licensing follow national rules according to the Regulation 1394/2007[3] on the advanced therapies instead of the traditional EMA marketing authorisation process. In that sense HE-ATMPs are not 'unauthorised' as they are often referred to as the HE-ATMPs are not exempt from GMP regulations. A review on the role of academic facilities in the development of cellular therapies in cancer highlights that the successful set-up of an academic GMP unit relies on striking a balance between commercial and academic priorities and that cost, complexity of logistics and risk to product integrity and quality due to transport over long distances are reduced when manufacturing ATMPs in hospitals. However high-profile cases such as the Stamina Foundation - which marketed unproven stem-cell therapy, not authorised by the national technical agencies but by the Italian courts and politicians fearing an electoral backlash - and scepticism regarding the efficiency of national inspections trigger concerns about safety and efficacy of HE-ATMPs. These remain however unfounded: the academic settings have repeatedly demonstrated successfully feasibility of safe ATMP production following a risk-based approach and adhering to the expected quality standards as defined by the Good Manufacturing Practices (GMP) while providing valuable knowledge regarding the investment and the organisational requirements at all levels for such endeavour from staff, premises/equipment, raw/starting materials, and processes (BOX 2).

[3] (L 324/130; REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL)

BOX 2. Shifting to GMP grade at national level

Belgium. University hospitals establish GMP units or upgrade existing clinical-grade manufacturing units to obtain GMP certification for production of investigational ATMPs for early phase clinical trials:
Mesenchymal stromal cell products, Hematology Department, Liège;
Viral vector production, GMP unit Cell Therapy and BVDK Lab, Ghent

Finland. The Finnish Red Cross Blood Service (FRCBS) hosts the Advanced Cell Therapy Centre with GMP facilities for ATMP manufacturing involving GMP materials and material evaluation, QC tests showing identity, purity and safety with defined specifications for release, periodic aseptic process validations, pharmacovigilance (reporting of adverse effects). Investment in the proper infrastructure for cell therapy manufacturing, including clean rooms (grade A isolator and closed systems) and skilful personnel has enabled the HE production under article 15c of the Finnish Medicines Act of bone marrow mesenchymal stromal cell (BM-MSC) product for treating refractory graft versus host disease and autologous keratinocytes for severe burns. It is the only ATMP manufacturer in Finland under national HE licence issued by the Finnish Medicines Agency (Fimea) and which inspects it biennially.

France. The GMP procedure for the production of therapeutic melanoma-specific T lymphocytes has been developed by the Unit of Cell and Gene Therapy, University Hospital (CHU), Nantes and evaluated for adoptive Immunotherapy of Metastatic Melanoma.

Italy. A branch of the Milano Cord Blood Bank starting only at a research and development level in 1998, evolved into the first national hospital-based GMP facility for ATMP production in the 'Ospedale Maggiore' of Milan in 2000

Elsewhere in the EU. Manufacturing of GMP grade Tumor Infiltrating Lymphocytes for clinical trials take place in public hospitals in The Netherlands (Amsterdam and Leiden), Germany (Heidelberg) and Denmark (Herlev).

The added value of the Hospital Exemption

The academic development of novel ATMPs has been gaining overwhelming support by national and European programmes (FP6/7; Horizon 2020; Horizon Europe) requiring clinical trials (CTs), which are under the full application of the regulation. Typical grants are 4-10 million€ over an average funding period of 4-5 years covering up to Phase I-II clinical trials in small populations. Whether perceived as an opportunity for early clinical development prior to CTs; a transition tool from non-routine to routine production and towards a central MA; or a form of experimental clinical treatment outside of CTs[4], Hospital Exemption has carved an undisputed role within the healthcare systems of the EU with its added value in:

- Increasing access to therapies under limited health care resources

  Increased access to novel therapies is enabled at a time of limited resources, reducing thereby cross country health disparities. The most marked savings come from the considerable cost difference between HE-ATMPs and commercial equivalents. Ten-fold differences in cost are often being reported informally between production in academic/ non-profit and commercial settings with data emerging for a variety of conditions: Spain, Hospital Clínic de Barcelona: The ARI-0001 (CART19-BE-01) developed under HE is one third of the cost of the commercial CAR-Ts available in Spain; simple limbal epithelial transplantation (SLET) is one tenth of the costs of cultured limbal epithelial transplantation (CLET) such as Holocar.

  HE-ATMPs offer additional savings in both time and transport costs as manufacturing at close proximity to clinical practice reduces logistical challenges in ATMP delivery and complexity of storage. Moreover cost sharing of the quality system and reinvestment of revenues of traditional activities allow extended ATMP manufacturing as in the case of the Germany, Charité University Medicine Berlin with in-house ATMP manufacturing capacity assigned to the department of transfusion medicine and a GMP license for conventional blood products (e.g. erythrocytes, thrombocytes).

- Maintaining access to therapies under limited reimbursement capacity

  Access to therapies is particularly limited when the capacity of healthcare systems for reimbursement of authorised products cannot meet demand according to the 2022 Impact Assessment Report of the European Commission - a university hospital certified to treat limbal stem cell deficiency (LSCD) for €12 000 reports treating 10-15 patients per year prior to 2015 and no patient post-2015 as they could not afford the authorised product, Holoclar, priced at about €100,000 per eye.

- Providing alternatives at times of market discontinuations/supply chain crises

  The trajectory of the ATMPs in the market is variable as availability and access to commercial ATMPs are often compromised. More often than not, products are withdrawn for commercial reasons rather than safety (Box 3).

[4] pp 32-34 in Schnitger, A. 2014. Master Thesis: The Hospital Exemption, a regulatory option for unauthorised ATMPs

BOX 3. Limitations in availability of and access to commercial ATMPs

- Increasing stress on global supply of clinical grade raw materials; for example, viral vectors for the transduction of T lymphocytes limits the availability of some CAR-T products [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8402758/]
- Business decisions by marketing authorisation holders prescribed among others by:
  - failing regional reimbursement negotiations - e.g. bluebird bio Inc., wounding down operations first in Germany and then across Europe for its gene therapies Zynteglo for beta thalassaemia and Skysona for cerebral adrenoleukodystrophy;
  - organisational reforms and changes in research priorities - e.g. Strimvelis by Orchard, a gammaretroviral vector-based gene therapy for the ultra-rare disease ADA-SCID (adenosine deaminase severe combined immunodeficiency); developed by Fondazione Telethon and Ospedale San Raffaele; sold to GSK; gained marketing authorisation (MA) and licensed to Orchard in 2018, who discontinued its investment in Strimvelis in 2022; sponsorship transferred to Fondazione Telethon Ets, Italy, in June 2023; it is still to be defined how it will be distributed and reimbursed;
  - lack of MA renewal - e.g. Glybera

- Catalysing innovation at all levels while serving the public good

A recent study on the discovery of drugs has concluded that fundamental, curiosity-driven research is “the best route to the generation of powerful new medicines.” Indeed it was the study of the fundamental biology of epithelial cells in 1990 that paved the way for the development of Holoclar, approved by the EMA in 2015 as the first stem cell product in the EU for an ophthalmic indication. Hospital Exemption continues its historical path in triggering innovation at various levels as national authorities increasingly begin to invest considerably having recognised its potential for improving access to novel therapies among political promises for health equity:

- **clinical/therapeutic level**

  The potential of the HE-ATMPs hold particular promise in the field of organ and tissue transplantation for addressing cases of:

  - rejection, treating organ failure and availability of donor organs and tissues
  - post-hematopoietic stem cell transplantation complications e.g. viral infections.

- **manufacturing level**

  Sweden: The pre-GMP facility at Karolinska University Hospital is developed as an intermediate step between early ATMP production in research settings to GMP manufacturing, offering technical/regulatory advice to academics and SMEs and a manufacturing environment that mimics GMP conditions at reduced cost.

  The Netherlands: a number of developments serve the national aspirations to enter the global markets:

- RegMed XB, a national pilot factory for regenerative medicine with further plans to develop cell and gene therapy towards commercial viability;
- NecstGen, a state-of-the-art facility for development/GMP manufacturing;
- Medace, a business-oriented facility for cell and gene therapy offering a GMP compliant, ISO certified research and manufacturing environment.

- **organisational level**

  A review on the changing role of Academia in ATMP development highlighted how network structures at national level and regional centres with expertise in rare diseases and early-phase CTs can implement a decentralized (on-site) ATMP manufacturing concept in regulatory compliance. Cost considerations for the necessary upgrading in manufacturing process for GMP certification have led to collaborations between academics and small or large companies or founded biotechnology start-ups. Market discontinuations for commercial reasons have highlighted how economically inappropriate is the current for-profit model of marketing authorization and commercialization and the need to update it. Numerous organisational structures have indeed emerged across the EU over the years combining academic research with technical and regulatory experience as the following examples show among others:

  - ATMP Sweden, a national ATMP consortium consisting of the national initiatives with common focus, CAMP (Center for Advanced Medical Products) and SWElife-ATMP
  - DARE-NL, the **D**utch platform for cancer-specific **A**TMP **Re**search, with variable activities from setting-up a self-sustaining IT infrastructure; harmonizing procedures for GMP guidelines; developing roadmaps for ATMP regulatory pathways and involving patients;
  - reNEW consortium with global partners strengthening the translational research capacity in cell therapy formed by the University of Copenhagen, Denmark, the Murdoch Children's Research Institute, Australia and the Leiden University Medical Center, Netherlands.
  - AGORA (Access to Gene Therapies for Rare Diseases) comprises clinical academics, scientists and patient organizations and acts as a central body for academic medical centers and not-for-profit organizations, providing regulatory support for ATMPs in rare diseases, working towards the harmonizaton of pan-European national activities

- **regulatory level with new theoretical and conceptual underpinnings**

  The UK has recognised the strategic value of hospital-centred manufacture bestowed by the technical and regulatory experience gained so far by hospitals under the HE and the Specials' designations. Aiming to upscale in-hospital production and to integrate the in-house ATMPs into clinical routines, the UK

continues to recognise the HE regulation after its exit from the EU while it is preparing to launch a tailored framework for the regulation of innovative products manufactured at the point where a patient receives care with requirements being highly dependent on the product's characteristics and associated risks: the Point-Of-Care framework (POC) will regulate personalised therapies requiring rapid manufacture and immediate application due to their short shelf life. The POC will undoubtedly give a competitive advantage to the UK in the healthcare market for a range of ATMPS derived from gene editing, cell manipulation and tissue engineering; 3D printed products; blood products; and medicinal gasses. An analysis of the regulatory rationale and the strategic decisions behind POC discusses the implications and the institutional readiness of the shift from regulatory exemptions (bedside manufacture) to marketing authorizations (point-of-care manufacture) for hospital-produced ATMPs. *Point-of-care manufacturing readiness*[5] is proposed as a new concept to analyse the capacity of a country, a health system or an institution to manufacture therapies in clinical settings (point-of-care manufacture) in terms of three components: the accumulation of expertise (staff and institutional procedures), infrastructure and institutional contacts by an organisation (relations between hospitals and service providers).

Additional considerations

Expanding and strengthening the scope of the "hospital exemption" as proposed in the revision of the pharmaceutical regulation will undoubtedly increase availability of lower cost therapies mostly developed by academia in "centres of excellence" linked to hospitals. Only experience can inform amendments regarding the rules around hospital exemption which will truly deliver access to cost-effective therapies. Therefore we applaud the Commission's intention to explore the suitability of an adapted framework for certain less complex ATMPs that have been developed and used under the HE and the efforts to create a registry for the use of HE across the EU. Monitoring the use of the hospital exemption is critical in providing the evidence base for any future amendments.
We collectively believe that the following deserve to be considered if Hospital Exemption can deliver to its promise for access to novel ATMPs across the EU:

- **Balancing ethics, healthcare system sustainability and markets**

So far on one hand the significantly diverse use of Hospital Exemption HE across the EU under the Medicines Directive 2001/83/EC has raised ethical considerations at both system and patient levels:

[5] The concept of *point-of-care manufacturing readiness* is a broadening of the *technology readiness* concept developed by NASA in 1974. It considers that technologies generate therapeutic products when their developmental level is high within regulatory and institutional environments conducive for safe and effective manufacturing.

- Cross country differences in patient choice and access have precipitated cross country inequities in both health system sustainability and health outcomes undermining thereby the EU commitment to the principle of equal access to therapies for all EU citizens;
- the therapeutic relationship between the patients and the public healthcare providers involved in HE including hospital pharmacists, doctors and other healthcare professionals is continuously undermined as the only alternatives are for profit, not-reimbursed HE products.

On the other hand there are calls for the restriction of HE in the presence of products with centralized marketing authorization triggered by the fear that:

- the Hospital Exemption can be used as a means for bypassing regulatory obligations;
- the HE existence parallel to the central marketing authorisation route creates an unfair competition for commercial medicinal products with the same indication;
- expanding the Hospital Exemption appears to bring into conflict the two key policy goals of the revision of the EU pharmaceutical framework - expanding the availability of medicines and stimulating innovation.

Restricting the use of Hospital Exemption remains a controversial issue with political and economic consequences and it does not serve the group of patients that cannot access the product for variable reasons. Indeed HE must not be used as a means for bypassing regulatory obligations but as a legal instrument that delivers on the political commitment to health equity particularly as for some unmet medical needs, HE is the only pathway. Every effort must be made to ensure that this is the case. Restricting the HE triggers additional ethical, social and economic issues: not only it will effectively restrict access to therapies within a Member State but it will deepen further the health inequities across the EU but it will hold the EU back in the competition for innovation in the light of the emergence of new frameworks outside the EU.
It is however understandable that the HE is considered an increasing threat to the market particularly as ARI-0001 and other HE CAR-Ts against various tumours are, and will increasingly enter in competition with MA holders of similar products. Although no action of a MA holder against an HE product has been recorded yet, legal cases exist of in-hospital production of drugs under orphan drug designation in the presence of an authorised product triggering consideration of EU Competition Law as the case of CDCA, a treatment for cerebrotendinous xanthomatosis manufactured under orphan drug designation at the Academic Medical Centre Amsterdam UMC and also marketed by Leadient Biosciences: in 2021 The Netherlands Authority for Consumers and Markets (ACM) decision on Leadiant Biosciences was to fine Leadiant for abuse of the market exclusivity by its commercial product through excessive pricing (over the years the price rose from €30,000 to over €150,000 per patient per year, which was considered an unacceptable level by the Dutch insurers who refused to cover the CDCA Leadient). Leadiant's actions were considered to be a very serious violation of the Competition Act,

as the medicine is vital for patients and ultimately it is the Dutch society which pays an excessive price.
The continuous increases in price of therapies and the withdrawal of products for commercial reasons create a vicious circle leaving the national health authorities facing the challenge of lack of treatment for rare/ultra-rare diseases amidst extremely high cost/unit of treatment for the few ATMP authorised. Furthermore the current model of drug development is unable to cope with the combination of a small target population and a complex and costly development/production/distribution/follow-up life-cycle of ATMPs particularly when price negotiations are directly between hospitals and payers - for example *Glybera*, a single-administration gene therapy for adults with familial lipoprotein lipase deficiency, was initially assessed as a community product in Germany but due to lack of clinical data it was considered of "unquantifiable additional benefit" by AMNOG (the German Health Technology Assessment process); this repositioned the drug to a hospital-only product allowing price negotiations directly between hospitals and payers; by 2015 only one patient was treated in Germany at an estimated price of €900,000 after an agreement with the health insurance provider DAK (Deutschen Angestellten-Krankenkasse)[6].

- **The solution of the problem is the cause itself - reflecting on definitions and classifications**

The revision of the Directive addresses primarily quality and safety issues through the harmonized requirements on manufacturing practices and pharmacovigilance. It addresses access only partly with the proposed expansions to the exemptions relating to pharmacy compounding and provisions for an expanded regime for hospitals and other health institutions to prepare and use ATMPs. However the practical details of the HE are still to be determined by Member States. Cross country disparities in the use of HE will remain if the reasons for their creation are not acknowledged and addressed. Semantics, ontology and linguistic equivalency are often ignored in policy making and good intentions can be undermined by interpretations which often fall victim to linguistic equivalency challenges:

- The definition of "non-routine" is currently abstract causing confusion as it is not appropriately explained in scientific terms. It even creates challenges for linguistic equivalence e.g. the French law refers to HE-ATMPs as preparations "on an ad hoc basis" ("préparé ponctuellement") instead of "non-routine". However regulators and legislators must be aware that it is neither feasible to delineate the boundary between routine and non routine production in a simple numerical formula nor on the basis of the presence of a product with centralized marketing authorization. 'Non routine' should be primarily prescribed by medical needs of clinical settings within the various health and socioeconomic systems of Member States. Therefore any amendments to the Directive that effectively restrict the HE such as the one proposed currently

[6] Papanikolaou E, Bosio A. The Promise and the Hope of Gene Therapy. Front Genome Ed. 2021 Mar 24;3:618346. doi: 10.3389/fgeed.2021.618346. PMID: 34713249; PMCID: PMC8525363

(Amendment 30 Article 2 – paragraph 1a, pp26-27, Draft Report, Committee on the Environment, Public Health and Food Safety 2023/0132(COD))[7] will have detrimental ethical, social and economic impacts (Box 4).

- Lack of clarity in the delineation between the Blood, Tissue and Cell (BTC) framework and ATMP favours the use of HE approaches although at the same time limits the access to the single "Excellence Center". The low ATMP applications in rare paediatric diseases particularly in eye diseases is often attributed to such classification issues despite timely intervention for inherited diseases with pre- or perinatal onset having is more effective compared to application in adults.
- Other issues stem from differences in understanding regarding clinical vs GMP grade in manufacturing and for which stage of manufacturing.

BOX 4. Ethical, social and economic impact of restricting Hospital Exemption

Overlooking the specific medical needs of Member States in rare diseases;

Undermining the national efforts of Member States with well thought out and rolled out HE process such as Finland, Germany, The Netherlands, France and Sweden;

Restricting access to safe, quality and affordable therapies;

Threatening the sustainability of the healthcare systems.

- **Registry for all ATMPs to increase the evidence base**

It is crucial to have data for the number of people treated, the long-term benefits of the products and the economics involved. According to the 2022 NICE economic apparaisal of commercial ATMPs, the limited data for such therapies create specific methodological needs when addressing the uncertainty of the long-term benefits and which, when factored in pricing and risks taken by healthcare systems, result in preventing reimbursement and market uptake. Moreover lack of transparency around national reimbursement criteria for commercial ATMPs is also a cause for concern: provisional approval by national authorities often involves confidential discount prices with no public data available on numbers of patients treated as in the case of Holoclar in UK

[7] DRAFT REPORT on the proposal for a directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC (COM(2023)0192 – C9-0143/2023 – 2023/0132(COD)) Committee on the Environment, Public Health and Food Safety Rapporteur: Pernille Weiss

Potential improvements

The revision of the EU general pharmaceutical legislation presents an opportunity to address the heterogeneity in HE implementation rules and interpretation of standards. The centralized approval and the Hospital Exemption can function in a complementary than competitive manner. Hospital Exemption represents a unique opportunity of partnership between academia and pharmaceutical industry for the benefit of patients, and the sustainability of our national health systems. Academically-driven research is not always translated in marketed products but historically the development of ATMPs in academic settings followed by engagement in technology transfer with industry partners has produced a number of therapies based on data derived entirely from academic clinical research such as Holoclar, and Strimvelis. Partnerships between academia/non-profit organizations and industry have tested successfully various models for intellectual property rights, monitoring, etc. Moreover GMP manufacturing in the academic setting is feasible at small scale, but moving to large-scale production necessary for phase III trials would require the involvement of industrial partners.

The implementation of Hospital Exemption can benefit from the following:

Definitions

Standardising the term ‘non-routine’ may not be practical — for example the French term ‘ad hoc’ may work well within the French regulations which provide for a strict separation of drug production and their use. However the implementation challenges faced by Member States are partly due to abstract definitions in the Regulation (EU) 1394/2007. We envisage a role for the EU by triggering regulatory and legislative reflection on the definitions involved with input by all stakeholders including patient organisations and payers as end users. Empowering clinicians, researchers and end users in understanding how 'non routine’ term fits within the socioeconomic reality of their own Member State, will shape the hospital exemption to serve the public good in as many Member States as possible. Defining medical needs will effectively guide to the type of process and scale of production required and whether other factors such as shelf life of products or multi-site manufacturing should be taken into consideration. GMP standards should be followed as they are currently at national level but additional clarifications may prove beneficial regarding other essential terms used such as clinical grade, GMP grade and for which manufacturing stage (raw materials, end product, etc). Different grades do not necessarily imply different standards.

- Regulatory Considerations

We welcome the retention and strengthening of HE[8]: the introduction of measures for data collection, reporting and regular reviewing including a data repository maintained by the

[8] COM(2023) 192 final 2023/0132(COD. Document 52023PC0192. Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC. (18)

EMA will improve transparency. Increased responsibility of Member States regarding compliance with GMP, traceability, pharmacovigilance and notification of revoked authorisations of ATMPs under HE will strengthen the EU-wide harmonisation of HE practices and contribute decisively to a higher level of protection for patients. At the same time it will address concerns regarding the potential of the HE in enabling gaming of the system - bypassing clinical trials and MA process. In particular, the use of HE cases as supporting safety information for the entrance into the formal clinical trial pipeline should be formalised in the legislation. Currently clinical data obtained from the use of HE products are not accepted for MA applications. However, duplicating the clinical trial structure without clarifying the scope and objective of the single patient treatment may cause a risk of frustrating its original purpose, i.e., of allowing physicians to treat a single patient outside a standardized drug system. The promotion of the use of regenerative medicine as a national policy in Japan[9] and the UK guidelines on HE may provide useful insights for the EU (BOX 4).

BOX 4. Hospital exemption elsewhere

JAPAN. The Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act) and the Act on the Safety of Regenerative Medicine (RM Act) came into effect in 2014. The Act on the Safety of Regenerative Medicine is an approach similar to the HE in EU and it lays out the regulations that doctors, review committees, and cell culture/ processing facilities must adhere to when providing regenerative medicine in medical care, not only in clinical research but also in private practice. The PMD Act created a new category for regenerative medicine products, and established the process for obtaining approval for cell therapy and other regenerative therapies through the implementation of clinical trials. The two Acts work synergistically with the use of similar data sources being allowed for the authorization of CTs especially in the absence of useful or valid animal models.

UK. Although the UK is not an EU member, it continues to recognise the HE which, together with the UK's Specials Scheme, oversees bedside manufacturing of ATMPs in or for hospitals. The Guidance on the UK's arrangements under HE Scheme recognises that a simple numerical formula can not distinguish between routine and non routine production and the UK Guidance on "non routine" issues pointers as to the factors that should be considered when developing HE-ATMPs: the set of criteria provided include the mode of action, the intended use, the manufacturing processes applied and the scale and frequency of the preparation of the specific product; both regulatory exemptions are based on the specificities of hospitals and clinical needs.

[9] Kuroiwa K. 2018. Regulatory frameworks of regenerative medicines and products review in Japan; [Online]. Accessed 3.07.2023; https://www.pmda.go.jp/files/000226121.pdf; Tobita M, Konomi K, Torashima Y, Kimura K, Taoka M, Kaminota M. Japan's challenges of translational regenerative medicine: Act on the safety of regenerative medicine. Regen Ther. 2016 May 31;4:78-81. doi: 10.1016/j.reth.2016.04.001. PMID: 31245489; PMCID: PMC6581824; Fujita, M., Hatta, T., & Ide, K. (2022). Current status of cell-based interventions in Japan. *Cell Stem Cell*, *29*(9), 1294–1297. https://doi.org/10.1016/j.stem.2022.08.003

HE may also represent a first step toward a non-profit pathway for the development of therapies when the size limitation of the target population makes the current drug development pathway unfeasible. An adapted framework expanding a homogeneous HE use across the EU will potentially reduce "health tourism" to non-EU countries and address the ethical issues involved ensuring common high quality, safety, and efficacy standards with continuous evaluation of the outcomes for academic ATMPs. It is however important to define stakeholder interests in such exercise and fully evaluate the risks and benefits of any regulatory change.

- Workforce considerations

Multi-professional teams are essential in achieving integrated management of ATMPs and ensuring treatment quality and safety. A clear and more homogenous definition of the legal responsibility across the medical practitioners and the hospital management is needed given the multiple factors involved in ATMP evaluation including logistics (process and order management), contract management, compounding or production, reconstitution, quality control, medication management, pharmacovigilance, and clinical follow-up are. Hospital pharmacists in particularly play a pivotal role as the handling of ATMPs as licensed medicines, falls under their responsibility and their knowledge of pharmacoeconomics and clinical evaluations is essential in assessing the added value of an ATMP.

- Education and training

A comprehensive holistic action plan is essential to facilitate the required paradigm shift needed for all ATMPs - the treating physicians must start reasoning in terms of ‘cells', and not ‘tissues or organs’. Education and training are key strategic areas including public awareness among both physicians and patients on availability of treatments for informed decisions. Identifying multidisciplinary training needs at development (research), manufacturing (hospital pharmacy) and delivery (clinical and hospital pharmacy) levels is crucial for outcomes particularly when surgery or complex processes are involved. Harmonised education and training of healthcare professionals is pivotal for harmonised practices of HE including the development of European education and training materials with the integration of ATMP training in pharmacy[10] and medicine schools. The collaboration of scientific societies involved across the entire ATMP spectrum is essential as well as of professional bodies offering continuing education programmes.

- Cost considerations

The cost differences between public and commercial settings in the ATMP development and production are potentially due to the financing of ATMP development in academic and non-profit settings by public research grants and fund raising activities rather than

[10] Segura, J. M. G. (2014). Advancing Hospital Pharmacy Practice Through New Competences in Advanced Therapy Medicinal Products. American Journal of Pharmaceutical Education, 78(1); available at: https://www.ajpe.org/content/78/1/22, accessed 8.06.2023

private investment. Moreover it is expected that academic and non-profit settings, as purpose-driven entities dedicated to scientific benefits, do not generate income for individuals and/or the organization itself whereas the safety and quality of academic and non-profit setting ATMPs should be comparable to commercial settings as both ATMP production and their clinical application are verified and authorized by the respective national regulatory authority. A full impact assessment of the effects of the proposed legislation should therefore be performed taking into account the various aspects involved such the reasons behind the lower costing of HE-ATMPs; the source of reimbursements for the HE; the link with the intellectual property (IP) for commercial products and the non-profit application of HE.

Future possibilities

The central role of academic institutions as drivers of both the development and the manufacture of ATMP is often overlooked rendering the ATMP manufacture in academic settings being "caught in the gap"[11]. It has long been proposed that perhaps the most effective transition out of such 'gap' is by local practice under hospital exemption with the integration of the academic organisations and hospitals in the value creation. The changing role of academia in ATMP development has been recently reviewed regarding the contributing logistical, financial, and regulatory factors in reshaping the academic environment[12].

Currently the research funding model allows academia to reach phase II with preliminary proof of efficacy. Decentralized point-of-care models and decentralized or 'redistributed manufacturing' have already been highlighted in view of "*democratising supply, creating jobs without geographical restriction to the central hub and allowing a more flexible response to external pressures and demands*"[13].

Therefore, an alternative approach to hospital exemption for rare and ultra-rare pathologies may increase ATMP availability by adopting the principles below:

a. Decoupling cost of development from production with fine-tuning of regulations related to IP, exclusivity rights, and licensing policies, according to relevant product characteristics:

- ownership of IP derived from public funding could be limited by patents being licensed at cost recovery rather than sold for profit;

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[11] Sethe S, Hildebrandt M. Caught in the gap: ATMP manufacture in academia. *Telegraft.* 2012;19((1)):1–10; https://mediatum.ub.tum.de/doc/1100606/1100606.pdf

[12] Priesner C, Hildebrandt M. Advanced Therapy Medicinal Products and the Changing Role of Academia. Transfus Med Hemother. 2022 May 16;49(3):158-162. doi: 10.1159/000524392. PMID: 35813600; PMCID: PMC9209977.

[13] Arnaudo L. On CAR-Ts, decentralized in-house models, and the hospital exception. Routes for sustainable access to innovative therapies. J Law Biosci. 2022 Sep 23;9(2):lsac027. doi: 10.1093/jlb/lsac027. PMID: 36168389; PMCID: PMC9507023.

- reimbursement for products under such licenses being capped at the cost of manufacturing;

b. Use of clinical data from observational studies for MA by:

- defining clearly the conditions under which data obtained from a "non profit" development can be used for MA;
- potentially expanding conditional MA by prescribing an increased pharmacovigilance/registry model for post-marketing data collection;

c. Supporting the creation of an industry based on a Contract Manufacturing Organizations (CMO) model for selected ATMPs where the cost of GMP/GLP plants are shared across multiple medicinal products with similar manufacturing process by:

- supporting smaller, niche manufacturing units specialised by type of product and process;
- clear specifications of the "close system" manufacturing;
- the risk evaluation taking into account that many products would be administered to individual patients.

Our signatory organisations stand ready to assist the EU Institutions and agencies in their efforts to optimise the regulatory strategy for the field of ATMPs and achieve a more healthy and productive European society.

Our collective experience can offer valuable insights regarding the needs and scientific and development challenges that academic and non profit ATMP developers face in the European Union.

EAHP The European Association of Hospital Pharmacists represents more than 27.000 hospital pharmacists in 36 European countries and is the only association of national organisations representing hospital pharmacists at European and international levels.

EPTRI The European Paediatric Translational Research Infrastructure is a distributed Research Infrastructure (RI) composed of several research units grouped both within Thematic Research Platforms – TRPs (according to the field of expertise) and National Nodes (according to their location).

EU EYE European Alliance for Vision Research and Ophthalmology is a non-profit pan European group comprising of ophthalmological societies representing over 9,000 medical specialists active in clinical medicine, research, education and training in 100 countries.

SIOPEurope The European Society for Paediatric Oncology is the only pan-European organisation representing all professionals working in the field of childhood cancers. With more than 2,500 members across 35 European countries, SIOPE is leading the way to ensure the best possible care and outcomes for all children and adolescents with cancer in Europe.