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).

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of hospital pharmacists

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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;

- 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 (CMO) for selected ATMPs with cost sharing for Good Manufacturing Practice and Good Laboratory Practice wherever appropriate.

We believe that our recommendations will:

- ensure autonomy of patient in their rights to choose therapy, treating physician and treatment location;

- support clinicians in their role as stewards of healthcare resources in addition to their responsibility to the patients;

- strengthen the contribution of governmental and non-profit organisations in the development of 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 provision for the custom-made and use of ATMPs which fall outside the scope of the Medicinal Product Directive 2001/23. The Regulation 1394/2007[1] on the advanced therapies states:

> "*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*."

Such products are often intended for small populations (rare diseases) and are regulated at national level:

> *"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

- The amending of Article 3 of Directive 2001/83/EC has effectively rendered HE as a nationally regulated exemption from the centralised Marketing Authorisation (MA) requirement. Different interpretations of the European provisions of Article 28 (2) of the ATMP regulation precipitated variable implementation of HE by Member States. Conditions for authorisation and manufacturing diverge between states and eligibility criteria for use differ as the scope and purpose of HE are shaped by or reflect national

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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)

needs and motives. National policies either impose additional requirements for the HE use or encourage it as a permanent 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

Spain. The regulatory agency encourage and promote new applications by hospital and research entities as 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.

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.

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.

- Hospital Exemption has an undisputed role in innovation and advancing the ATMP field whether it is 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[3].
- Academic development of novel ATMPs gains 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.
- Although academically-driven research is not always translated in marketed products, partnerships between academia/non-profit organizations and industry have demonstrated potential for success under various models for intellectual property rights, monitoring, etc such as the cases of Holoclar, a limbal stem cell deficiency treatment,

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

and Strimvelis, a gammaretroviral vector-based gene therapy for the ultra-rare disease ADA-SCID (adenosine deaminase severe combined immunodeficiency).

- The existence of HE parallel to the central marketing authorisation route is often perceived as unfair competition to commercial medicinal products with the same indication. Ten-fold differences in cost are often reported informally between the two pathways.
- The current model of drug development is however unable to cope with the combination of a small target population and a complex development/production/distribution/follow-up life-cycle of ATMPs. The trajectory of the ATMPs in the market is variable: availability and access to commercial ATMPs are often compromised (Box 2). Moreover lack of transparency around national reimbursement criteria for commercial ATMPs is 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 the Holoclar and the UK NICE[4].

BOX 2. 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, developed by Fondazione Telethon and Ospedale San Raffaele; sold to GSK; gained marketing authorisation (MA) and licensed to Orchard in 2018, discontinued in 2022;
  - lack of MA renewal - e.g. Glybera;
- Price increases of commercial therapies may not always be acceptable by payers - e.g., Dutch insurers refused cover for the CDCA Lediant product when over the years the price was raised from €30,000 to over €150,000 per patient per year.

- In the last few years the use of HE has been linked with competition considerations: a number of cases examined at EU and national levels within the EU Competition Law focussed on either the abuse of the market exclusivity by commercial products through excessive pricing - such as the 2021 Netherlands: ACM decision - or on anti-competitive agreements between industry and hospitals (for a list of cases see Dominant position and HE-ATMPs). No action of a MA holder against an HE product has been recorded yet. The current EMA pilot based on the Spanish experience with ARI-0001 (CART19-BE-01) aims to optimise development of ATMPs by academic and non-profit developers

[4] https://bjo.bmj.com/content/106/7/923

within the EU. However, this and other HE CAR-T against various tumours are, and will increasingly enter in competition with MA holders of similar products.

- The national health authorities are faced with the challenge of lack of treatment for rare/ ultra-rare diseases amidst extremely high cost/unit of treatment for the few ATMP authorised. Access to therapies is particularly limited when the capacity of healthcare systems for reimbursement of authorised products cannot meet demand or price negotiations are directly between hospitals and payers - a university hospital certified to treat limbal stem cell deficiency (LSCD) for €12 000 has reported to treat roughly 10-15 patients per year prior to 2015 and not being able to treat anyone post-2015 as they could not afford the authorised product, Holoclar, priced at about €100,000 per eye)[5]; in 2015 only one single patient was treated in Germany with Glybera, a single-administration gene therapy for adults with familial lipoprotein lipase deficiency at an estimated price of €900,000 after an agreement with the health insurance provider DAK (Deutschen Angestellten-Krankenkasse)[6].

- Enlarging the scope of the "hospital exemption" will increase availability of lower cost therapies mostly developed by academia in "centres of excellence" linked to hospitals. Manufacturing of ATMPs in close proximity to patients addresses also logistical challenges in ATMP delivery.

- 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.

- The diverse HE implementation across the EU raises ethical considerations at both system and patient levels. It undermines the principle of equal access to therapies for all EU citizens as it precipitates cross country inequities in both health system sustainability and health outcomes due to cross country differences in patient choice and access. It also undermines the alliance between the patients and the multidisciplinary teams involved in HE including hospital pharmacists, doctors and other healthcare professionals: the only alternatives are for profit, not-reimbursed HE products.

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[5] 11.8A2 Overview of the regulatory issue in: Proposal for a Regulation of the European Parliament and of the Council on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC, SWD(2022) 190, final. [Online]. [Accessed 26 June 2023]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52022SC0190&from=EN

[6] Glybera 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. 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

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.

- Regulatory Considerations

We welcome the retention and strengthening of HE[7]: the introduction of measures for data collection, reporting and regular reviewing including a data repository maintained by the 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 may provide useful insights for the EU (BOX 3)[8].

BOX 3. Hospital exemption in 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.

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[7] 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)

[8] 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 where 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[9] 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

Data comparing production in academic and non-profit settings to commercial settings has shown ATMPs produced under HE to be significantly less expensive than commercial ones for a variety of conditions - CDCA Lediant vs CDCA under HE at Academic Medical Centre

[9] 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

Amsterdam UMC; SLET vs Holoclar. The cost differences between the settings 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 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; 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"[10]. 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[11].

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*"[12].

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

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[10] 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

[11] 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.

[12] 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.

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;
- 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.