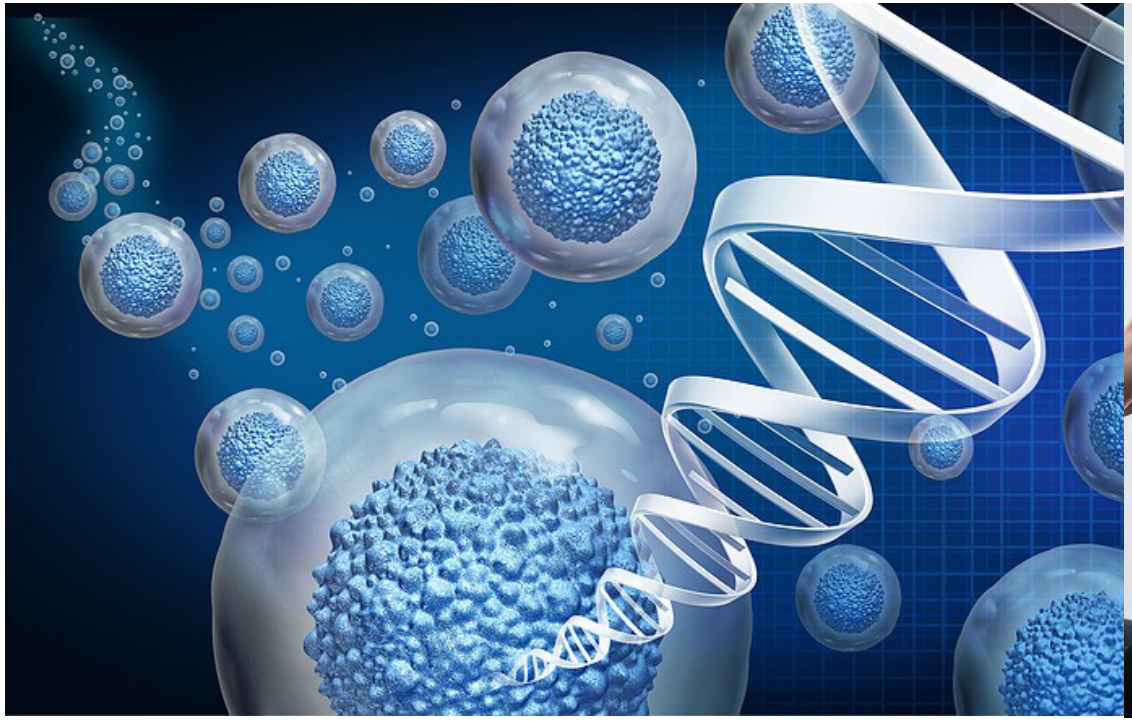
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ACADEMIC DEVELOPMENT OF ATMPS IN BELGIUM

AN EXPLORATORY STUDY OF THE LEGAL & STRATEGIC OPTIONS

SUPPLEMENT





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CÉLINE POUPPEZ, JOLYCE BOURGEOIS, FRANK HULSTAERT, IMGARD VINCK

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1. SCOPE OF THE EU PHARMACEUTICAL LEGISLATION

CÉLINE POUPPEZ (KCE), FRANK HULSTAERT (KCE), JOLYCE BOURGEOIS (KCE), IMGARD VINCK (KCE)

The general scope of the EU Directive 2001/83/EC[1] (article 2) as well as the scope of the ATMP Regulation[2] are currently applicable to medicinal products for human use that are intended to be placed on the market in Member States and are either prepared industrially or manufactured by a method involving an industrial process. Medicinal products that are usually prepared or compounded on a small scale, locally fall outside the scope of the harmonised EU legislation and are mainly regulated at national level.[3] Nevertheless, the definitions of these two concepts are not straightforward:

The intention to be placed on the market

1. The intention to be "placed on the market" is a general concept used in the context of the general products rules in Europe (covering all sort of products, including drugs and medicinal products but also toys, food, cosmetics etc). As developed in the Blue Guide of the European Commission[4], a product is placed on the market when it is "*made available for the first time on the Union market*". Each individual product can only be placed once on the Union market. The Guide specifies that "*placing a product on the market requires an offer or an agreement (written or verbal) between two or more legal or natural persons for the transfer of ownership, possession or any other property right concerning the product in question; it requires that the manufacturing stage has been completed. This transfer could be for payment or free of charge. It does not require the physical handover of the product*".

   However, this does not mean that clinical collaboration agreements between hospitals within in the same Member State for the treatment of certain patients, for instance in the context hospital networks would automatically be regarded as a "transfer".

2. Regarding products that are manufactured following the placing of an order, the Guide states that "*an offer or agreement concluded before the stage of manufacture has been finalised cannot be considered as placing on the market (e.g., an offer to manufacture a product according to certain specifications agreed by the parties to the contract, where the product will only be manufactured and delivered at a later stage*)".

3. The Blue Guide does not specifically address the situation of medicinal products. It only states that there is ***no*** placing on the market when *"a product is (…) manufactured for one's own use unless Union harmonisation legislation covers products manufactured for own use in its scope*". Occasional manufacture for personal use by a private individual in a non-commercial context is not considered equivalent to placing on the market.

4. EU guidelines or EU case-law do not provide further interpretation regarding this concept. Therefore, it must be interpreted in each Member State, based on the circumstances of the specific case (first

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1 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, O.J.E.U., L 311, 28 November 2001, pages 67-128 (hereafter referred to as "the Directive 2001/83/EC").

2 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, O.J.E.U., L 324, 10 December 2007, pages 121-1371. (hereafter referred to as "the ATMP Regulation").

3 This currently covers the following preparations: magistral formulas, officinal formulas, IMPs (for clinical trials), intermediate products, radionuclides in the form of sealed sources, blood, plasma or blood cells of human origin, except for plasma which is prepared by a method involving an industrial process and ATMPs prepared under hospital exemption.

4 European Commission *Blue Guide on the implementation of EU product rules,* 2022, O.J.E.U (2022/C 247/01), EUR-Lex - C:2022:247:TOC - EN - EUR-Lex (europa.eu).

under the control of the national courts and ultimately under the control of the Court of Justice of the European Union).

The industrial character of the production

1. The definition of what constitutes an industrial production is also a grey zone in the EU legislation. There is some relatively recent and important EU case law regarding the difference between industrial products and preparation of magistral and officinal formulas by (hospital) pharmacies[5].
2. In this regard, the Court of Justice of the European Union recalls that interpretations of all exceptions to the general scope of the pharmaceutical legislation should have regard to the objective of protection of public health pursued by the EU rules on medicinal products for human use. Taking into account those objectives, the terms 'prepared industrially' and 'manufactured by a method involving an industrial process' cannot be interpreted narrowly.
3. Regarding the preparations as such, the Court of Justice of the European Union defined an industrial process as a process "*characterised in general by a succession of operations, which may, in particular, be mechanical or chemical, in order to obtain a significant quantity of a standardised product*". Consequently, the Court held that "*the standardised production of significant quantities of a medicinal product to be stocked and sold wholesale and the large-scale or serial production of magistral formulae in batches are characteristic of industrial preparation or manufacture by a method involving an industrial process*". However, given the fact that the manufacturing of ATMPs present some particularities and that they are often personalised, the application of this case law to ATMPs is uncertain.
4. In the context of the adoption of the ATMPs Regulation in 2007, the European Commission defined the industrial production or process of an ATMP as (*inter alia*):
   - any 'mass production' of advanced therapy products for allogeneic use (batch production, 'on the shelf' products etc.).
   - any advanced therapy product for autologous use which, although being patient specific by definition, is manufactured in accordance with a standardised and industrial process.[6]
5. Almost 20 year later, in the view of the difficulty of interpreting the concept of industrial production, not only in the ATMPs sector, but the European Commission proposes to abolish this concept[7].

In summary, European legislation gives Member States some discretion in defining what constitutes industrial production and placing on the market. Each case requires careful analysis by national courts and may ultimately be reviewed by the Court of Justice of the European Union. National interpretations should always be guided by the overriding objective of protecting public health as pursued by EU pharmaceutical legislation. In addition, national rules must not undermine the effectiveness of EU law[8].

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5 CJEU, Joined cases C-544/13 and C-545/13*, Abcur AB v Apoteket Farmaci AB and Apoteket AB (Abcur*), ECLI:EU:C:2015:481, para. 51. See also: CJEU, C-29/17, Judgment of 21.11.2018, para. 56; CJEU, Judgment of 16.07.2020, C-544/13 & 545/13, para. 39.*;* CJUE, C-512/12, EU:C:2014:149, para. 38, 29 & 30.

6 Council of the European Union, Impact assessment report annexed to the Proposal for a Regulation on ATMPs, 2005/0227 https://data.consilium.europa.eu/doc/document/ST-15023-2005-ADD-1/en/pdf

7 See in particular article 1 of the European Commission's 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.

8 See for instance CJUE – Judgement of 21.11.2018, C-29/17.

2. CLINCIAL TRIALS WITH ATMPS IN EUROPE

QUINZ

2.1. Introduction

According to the EU Regulation on Clinical Trials, a clinical trial is any investigation in relation to humans that goes beyond the normal clinical practice and is intended to (i) discover or verify the clinical, pharmacological or other pharmacodynamic effects, (ii) to identify any adverse reactions or (iii) to study the absorption, distribution, metabolism and excretion of one or more medicinal products, in each case, with the objective of ascertaining the safety and/or efficacy of those medicinal products. An investigation goes beyond the normal clinical practice if either (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice; (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.[9]

The sponsor, meaning the individual, company, institution or organisation that takes responsibility for the initiation, management and the (establishment of) financing of the clinical trial, can be an industry sponsor, or the clinical trial can be initiated within a research site and/or led by Academia. Note also that the entity that finances a clinical trial is not always equivalent to the entity taking up the role as sponsor.

Clinical trials are often categorised in four temporal phases: 'Phase I' or first-in-human studies are generally focused on safety, tolerability, pharmacokinetics and/or pharmacodynamics in healthy volunteers or a small population of patients; later exploratory and confirmatory studies ('Phase II' and 'III') further evaluate safety and efficacy of a medicinal product in a patient population, with data from Phase III studies being considered pivotal to support a marketing authorisation application.[10] For some medicinal products, 'Phase IV' studies are initiated after marketing authorisation to provide more evidence on a medicinal product's use, which could be the result of a regulatory requirement and/or may inform health economics or health technology assessments. However, categorising clinical studies in phases is a description and not a requirement, as the phases of drug development may overlap or be combined.[11] Notably, this is often the case for clinical studies involving ATMPs, where products are often not tested on healthy volunteers and where smaller, open-label, non-randomised and single arm studies are more prevalent, either without control or by using historical controls.[12]

The data generated from clinical trials and included in clinical study reports are an essential part of the evaluation of application dossiers for a centralised marketing authorisation by the EMA's Committee for Medicinal Products for Human Use (CHMP).

This section describes the regulatory framework applicable to the conduct of clinical trials in the European Union, specifically focusing on clinical trials related to ATMPs and, more in particular, the hurdles that arise in relation thereto.

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9 Art. 2.2(1) and (2) of Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC;

10 G. Detela and A. Lodge, "EU Regulatory Pathways for ATMPs: Standard, Accelerated and Adaptive Pathways to Marketing Authorisation", Molecular Methods & Clinical Development 2019, Volume 13, 28 January 2019, 212.

11 EMA, ICH guideline E8 (R1) on general considerations for clinical studies, Step 5, version 1 December 2022, 11-14 p., ICH E8 General considerations for clinical studies - Scientific guideline | European Medicines Agency (EMA) (europa.eu)

12 Iglesias-Lopez C, Agustí A, Vallano A, Obach M. Current landscape of clinical development and approval of advanced therapies. Mol Ther Methods Clin Dev. 2021 Nov 11;23:606-618. doi: 10.1016/j.omtm.2021.11.003. PMID: 34901306; PMCID: PMC8626628.

2.2. General regulatory framework for clinical trials with ATMPs

2.2.1. Competent authorities

Clinical trials taking place in Belgium are authorised and supervised by the FAMHP and the relevant Ethics Committees in Belgium.[13] The College for Clinical Trials coordinates and supervises the quality of the work of the Ethics Committees and is a unique point of contact for any communication with the FAMHP and the Ethics Committees.[14] The EU, on the other hand, drives innovation, harmonisation and competitiveness of the clinical trial landscape at the community level. As such, the EMA and the HMA (i.e. the network of the heads of the national regulatory authorities) are steering the Accelerating Clinical Trials in the EU (ACT EU) program. The EMA further manages the clinical trial databases (EudraCT under the Clinical Trial Directive and the Clinical Trials Information System under the Clinical Trial Regulation, each as explained below).

2.2.2. Legislative framework

Clinical trials have been regulated by the European Union since 2004 under the Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (the "**Clinical Trials Directive**" or "**CTD**"). Although the aim of the Clinical Trials Directive was to harmonise and simplify the conduct of clinical trials in the EU, the implementation remained relatively fragmented, with sponsors wishing to conduct multi-country trials having to submit application dossiers to the competent authorities of each relevant Member State. Since 31 January 2022, clinical trials conducted in the EU/EEA are governed by Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (the "**Clinical Trials Regulation**" or "**CTR**"). Clinical trials conducted outside the EU/EEA, which are included in the application for a marketing authorisation in the EU must comply with ethical principles equivalent to those set out in the EEA, including adhering to international good clinical practice (GCP) and the Declaration of Helsinki.[15] The law on clinical trials with medicinal products for human use of 7 May 2017 describes the responsibilities and procedures on a national level, as further implemented by the Royal Decree of 9 October 2017.[16]

The CTR aims to establish the EU as an attractive environment for large-scale clinical research with high standards of transparency and safety for clinical trial participants. It further intends to ensure the reliability and the robustness of data generated in clinical trials.[17]

One of the major innovations introduced by the CTR is the harmonization of the processes for assessment and supervision of clinical trials throughout the EU. Under the previous regime (CTD) , sponsors were required to submit clinical trial applications to each of the national competent authorities (NCAs) and ethics committees of the countries where they intended to conduct a clinical trial. The CTR allows sponsors to submit a single online application through the Clinical Trials Information System (CTIS) platform for approval to conduct a clinical trial in multiple European countries, enhancing efficiency for multinational trials.[18] The CTIS further increases

13 Art. 4 and 6 of the law of 7 May 2017 on clinical trials of drugs for human use, B.S./ M.B. 22 May 2017.

14 Art. 9 § 3,1° of the law of 7 May 2017 on clinical trials of drugs for human use.

15 World Medical Association, Declaration of Helsinki: www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/ (consultation 23 December 2023).

16 Royal Decree of 9 October 2017 implementing the Law of May 7, 2017, on clinical trials of medicinal products for human use, B.S./M.B. 10 November 2017.

17 Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, p. 1–76.

18 Art. 5 of Regulation (EU) No 536/2014.

transparency through a searchable public website for information on clinical trials conducted in the European Economic Area.[19]

The CTR also introduces new timelines, i.e. for responses to requests for information, authorised clinical trials for which no patient is recruited within two years, serious breaches and the archiving of the Trial Master File (TMF) after 25 years.[20]

Further, a simplified safety reporting system is implemented, requiring sponsors to submit all safety reports through EudraVigilance.[21]

Finally, the CTR enhances patient protection for vulnerable subjects by substantively changing provisions for informed consent. It provides more detailed EU-level guidelines on broad consent, simplified consent for cluster trials, consent for minors or incapacitated individuals, consent for pregnant or breastfeeding women, consent for other vulnerable populations, and consent during trials in emergency settings.[22]

The CTR provides for a three-year transition period from 2022 to 2025. By January 31, 2025, all ongoing trials approved under the Clinical Trials Directive must transition to the new Regulation and come under the jurisdiction of CTIS.[23]

Good Clinical Practices

The principles of Good Clinical Practice (GCP) as set out in ICH Guidelines ("**GCP Guidelines**") are internationally accepted standards for designing, conducting, recording and reporting clinical trials, consistent with principles that have their origin in the abovementioned Declaration of Helsinki. The GCP Guidelines aim to ensure that the safety and wellbeing of clinical trial subjects are safeguarded and that the data generated out of clinical trials are robust and reliable and can be accepted by regulatory authorities.[24] The GCP Guidelines are applicable to clinical trials with ATMPs, however, given the complexity and specific characteristics of ATMPs, a specific set of guidelines has also been issued by EMA, namely the Guidelines on Good Clinical Practice specific for Advanced Therapy Medicinal Products ("**ATMP GCP Guidelines**"). As such, it will not always be possible to abide by the general principles of the GCP Guidelines. For instance, due to the scarcity of the starting materials for the relevant ATMP, it might not always be possible to retain sufficient quantities of the investigational medicinal product, as is required by the GCP Guidelines. The ATMP GCP Guidelines therefore provide for some leniency.[25]

The ATMP GCP guidelines emphasise that the unique characteristics of ATMPs and the potential risks to participants, the investigator team and other stakeholders should be considered when planning clinical trials with ATMPs. In particular, elements such as the study population, cohorts, comparator products, etc. should be considered, as also set forth below.[26] Study participant should also be comprehensively informed about the risks involved with ATMPs and require long-term follow-up.[27]

Additionally, investigational ATMPs must be traceable from delivery to the clinical trial site to administration to the trial subject. Bidirectional traceability should be ensured and data should be retained for at least 30 years after the expiry date of the product.[28]

Good Manufacturing Practice

To ensure the safety of clinical trial subjects and to warrant that the data generated from clinical trials are not affected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture, the investigational

19 Art. 81 of Regulation (EU) No 536/2014.
20 Art. 6(8), 8(9), 52 and 58 of Regulation (EU) No 536/2014.
21 Art. 40 of Regulation (EU) No 536/2014.
22 Chapter V of Regulation (EU) No 536/2014.
23 Art. 98 of Regulation (EU) No 536/2014.
24 EMA, Good Clinical Practice, https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/compliance-research-and-development/good-clinical-practice (consultation on 18 February 2024).
25 EMA, Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products, C(2019) 7140, 11-12.
26 EMA, Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products, C(2019) 7140, 4.
27 EMA, Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products, C(2019) 7140, 12-14.
28 EMA, Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products, C(2019) 7140, 11.

medicinal products administered in clinical trials should be subject to a robust quality management system and Good Manufacturing Practice.[29] Specific requirements apply to accommodate for the specific situation of a clinical trial (for instance, double blinded clinical trials) and the nature of investigational medicinal products.[30]

2.3. General challenges for setting up clinical trials with ATMPs

The nature of ATMPs and the diseases that they often aim to treat bring specific challenges to drug developers (both industry as well as Academia), concerning the clinical trial application requirements, as well as study design issues and data collection difficulties.

2.3.1. Clinical trial application

Each clinical trial application that is submitted under the CTR must include a number of forms (e.g. cover letter, proof of payment of fee…), Part I consisting of clinical trial details (e.g. protocol, investigator's brochure, GMP documentation and labels for the investigational medicinal product (IMP), IMP dossier on quality and on safety and efficacy) and Part II consisting of clinical trial site details (e.g. recruitment arrangements, patient information, proof of insurance…).[31] The assessment of Part I will be led by the reporting Member State and conducted jointly by all Member States concerned, Part II will be individually assessed by each Member State concerned.[32]

Comprehensive quality documentation must be submitted as part of the clinical trial application (which may bring about similar hurdles as those set out in 5.2).[33] In addition, adequate preclinical data must be presented in the section regarding non-clinical pharmacology and toxicology data. The latter presents several challenges when it comes to ATMPs, due to the limitations of animal and other non-clinical models. Finally, the dossier needs to include an overall risk-benefit assessment of the investigational medicinal product, which should review any favourable and unfavourable effects the medicinal product is expected to have. Although the benefits of an ATMP may be considerable, as the product may target an unmet medical need, information regarding the risks may be difficult to assess, considering that conventional safety testing may not always be at hand in non-clinical models, literature may be scarce and ATMPs generally present notable risk differentiation from product to product.[34]

2.3.2. Study designs

The specific nature of ATMPs and the type of target diseases (including orphan indications, paediatric patient populations and unmet needs) pose specific challenges in the study design[35]:

- Small clinical trial sample sizes

Clinical trial sample sizes are often relatively small for ATMPs, where it is no exception that as little as less than 25 patients are enrolled.[36]

29 Art. 63(1) of Regulation (EU) No 536/2014.

30 Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014, C(2017) 8179 final; EMA, Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice, EMA/INS/GMP/258937/2022.

31 Annex I of Regulation (EU) No 536/2014.

32 Art. 5-8 of Regulation (EU) No 536/2014.

33 See EMA, *Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials*, EMA/CHMP/BWP/534898/2008 Rev. 2, 31 January 2022.

34 E. OLESTI, Y. NUEVO, E. GUILLEN, J. BASCUAS, S. VAREA, J. SAEZ-PENATARO, G. CALVO, "Academic challenges on ATMPs' development: a regulatory perspective", 2023, 5-7.

35 Iglesias-Lopez C, Agustí A, Vallano A, Obach M., *Current landscape of clinical development and approval of advanced therapies*, Molecular Therapy Methods & Clinical Development 2021, Nov 11, 606.

36 E. Hanna, C. Rémuzat, P. Auquier and M. Toumi, "Advanced therapy medicinal products: current and future perspectives", Journal of Market

- Uncertain representativeness

Identifying very rare conditions and (re)defining a subpopulation within a larger patient population lead to difficulties in recruiting enough patients, thus complicating successful implementation of the clinical trials. Moreover, it is reported that very small study populations lead to statistical bottlenecks (underpowered trials) and negatively affect the robustness of the clinical evidence.[37]

- Single arm clinical trials

Whereas randomised controlled trials may be the most rigorous and robust research method, such trials may not always be possible .It should of course be acknowledged that for some of the ultrarare diseases it may be impossible to recruit a minimum number of patients in an RCT[38] However, the single arm design should not be misused to evaluate treatments for which a sufficient number of eligible patients are available to conduct a well powered RCT. Even in patients who have exhausted the existing treatment options, a randomised comparison versus best supportive treatment is possible.

- Inappropriate endpoints

Efficacy conclusions for ATMPs are sometimes based on changing or novel and non-validated primary endpoints, which may result in overestimation of patient relevant effects.[39]

- Inappropriate or no comparator

Finding an appropriate comparator for ATMPs can be difficult, especially when the therapy targets an unmet need or leads to practical changes in clinical practice.[40]

- Long-term risks and benefits

The short-term effects observed in relatively short clinical trials are sometimes extrapolated to the long term, which may result in uncertainty regarding magnitude of benefits and risks in the long term for the assessment of marketing authorisations or health economics analyses.[41]

Access and Health Policy 2016, 4(1), 31036; Gort J, Van Hattem CC, Bloem LT, Ten Ham RMT. Geneesmiddelen voor Geavanceerde Therapie (ATMP's) in Nederland: Veldverkenning, Knelpuntanalyse en Activiteitenkaart. 2023. Geneesmiddelen voor Geavanceerde Therapie (ATMP's) in Nederland: Veldverkenning, Knelpuntanalyse en Activiteitenkaart, 54.

37 Gort J, Van Hattem CC, Bloem LT, Ten Ham RMT. Geneesmiddelen voor Geavanceerde Therapie (ATMP's) in Nederland: Veldverkenning, Knelpuntanalyse en Activiteitenkaart. 2023. Geneesmiddelen voor Geavanceerde Therapie (ATMP's) in Nederland: Veldverkenning, Knelpuntanalyse en Activiteitenkaart, 53.

38 IGLESIAS-LOPEZ C, AGUSTÍ A, VALLANO A, OBACH M., Current landscape of clinical development and approval of advanced therapies, Molecular Therapy Methods & Clinical Development 2021, Nov 11, 606-608;; VAN OVERBEKE, E., MICHELSEN, S, "Market access of gene therapies across Europe, USA, and Canada: challenges, trends and solutions", *Drug Discovery Today* 2021, Volume 26, no. 2, 403.

39 Gort J, Van Hattem CC, Bloem LT, Ten Ham RMT. Geneesmiddelen voor Geavanceerde Therapie (ATMP's) in Nederland: Veldverkenning, Knelpuntanalyse en Activiteitenkaart. 2023. Geneesmiddelen voor Geavanceerde Therapie (ATMP's) in Nederland: Veldverkenning, Knelpuntanalyse en Activiteitenkaart, 53; IGLESIAS-LOPEZ C, AGUSTÍ A, VALLANO A, OBACH M., Current landscape of clinical development and approval of advanced therapies, Molecular Therapy Methods & Clinical Development 2021, Nov 11, 606-608; VAN OVERBEKE, E., MICHELSEN, S., "Market access of gene therapies across Europe, USA, and Canada: challenges, trends and solutions", Drug Discovery Today 2021, Volume 26, no. 2, 403.

40 HAMPSON, G., "Gene therapy: evidence, value and affordability in the US health care system", *J. Comp. Eff. Res.* 7, 15-28 p; Gort J, Van Hattem CC, Bloem LT, Ten Ham RMT. Geneesmiddelen voor Geavanceerde Therapie (ATMP's) in Nederland: Veldverkenning, Knelpuntanalyse en Activiteitenkaart. 2023. Geneesmiddelen voor Geavanceerde Therapie (ATMP's) in Nederland: Veldverkenning, Knelpuntanalyse en Activiteitenkaart, 53

41 BARLOW, J., BENS, C. (et all), "AMCP Partnership Forum: designing benefits and payment models for innovative high-investment medications", J. Manag. Care Spec. Pharm. 25, 156-162 p.

2.3.3. Clinical evidence

The aforementioned difficulties in the study design contribute to the fact that sometimes only limited efficacy and safety data can be collected in clinical trials for ATMPs. As mentioned, trial sample sizes for rare or ultrarare diseases can be small and lack of appropriate comparators may lead to uncertainty in the magnitude of benefits of the ATMP.[42] Additionally, long-term benefits may be unknown following relatively short-term clinical trials.[43]

Such limited clinical evidence has a direct impact on the level to which a marketing authorisation or reimbursement application can be substantiated.

2.3.4. Regulatory barriers

2.3.4.1. Introduction

Regulatory uncertainty regarding country specific requirements is often identified as the culprit for delays or difficulties in conducting clinical trials in the EU[44]. As set out above, the CTR has partially tried to remedy such different requirements by imposing a joint review of Part I of the clinical trial application and by imposing strict timelines. However, timelines may be extended by the reporting Member State to allow for expert consultation on ATMPs[45]. It remains to be seen whether the innovations brought by the CTR result in fewer country-specific constraints in the European Union.

In addition, the implications of the GMO legislation may sometimes be the basis of national delays, as set out further below.

2.3.4.2. GMO legislation

Drug developers of ATMPs should also take into account the legislation on genetically modified organisms ("**GMOs**"). The CTR regulates the general set-up of clinical trials, however, is not addressing the environmental risk associated with clinical trials with GMOs. GMOs are strictly regulated within the European Union, under Directive 2001/18 (the "**GMO-Directive**"). According to article 2 (2) of the GMO-Directive, a GMO means: *"[a]n organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination*"[46]. The GMO-Directive gives examples of (1) techniques that are considered to be a GMO, (2) techniques that are not considered to be a GMO and (3) techniques that are considered to be a GMO but are exempt from the obligations in the Directive.[47]

If an ATMP qualifies as a GMO under EU law, additional requirements must be met before the ATMP may be used or released in the environment (e.g. via a clinical trial) and may be subsequently placed on the market. The handling of ATMPs containing or consisting of GMOs may pose a risk for the environment, requiring the implementation of additional control measures.

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42 ATILLA, E., "Cellular therapies: Day by day, all the way", Transfus. Apher. Sci. 57, 187-196 p.; VAN OVERBEKE, E., MICHELSEN, S, "Market access of gene therapies across Europe, USA, and Canada: challenges, trends and solutions", *Drug Discovery Today* 2021, Volume 26, no. 2, 399-415 p.; CARVALHO, M., "Hurdles in gene therapy regulatory approval: a retrospective analysis of European Marketing Authorisation Applications", *Drug Discov. Today* 24, 823-828 p.

43 VAN OVERBEKE, E., MICHELSEN, S, "Market access of gene therapies across Europe, USA, and Canada: challenges, trends and solutions", Drug Discovery Today 2021, Volume 26, no. 2, 399-415 p.

44 R.M.T. ten Ham, J. Hoekman, A. M. Hövels, A. W. Broekmans, H.G.M. Leufkens, O.H. Klungel, Challenges in Advanced Therapy Medicinal Product Development: A survey among Companies in Europe, *Molecular Therapy: Methods & Clinical Development*, 2018, Volume 11, 121-123.

45 Art. 6(7) of Regulation (EU) No 536/2014.

46 Article 2 (2) Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (consolidated version), OJ.L. 17 April 2001, nr. 106, 1.

47 G. FERNÁNDEZ ALBÚJAR and B. VAN DER MEULEN, "The EU's GMO Concept: Analysis of the GMO Definition in EU Law in the Light of New Breeding Techniques (NBTs)", EFFL 2018, (14) 15; H. SCHEBESTA, "Confédération paysanne case (C-528/16): Legal Perspective on the GMO Judgment of the European Court of Justice", REDC 2020, (369) 369.

The GMO-Directive establishes an authorisation procedure for products containing or consisting of GMOs: one for the release of a GMO in the environment, one for placing a GMO on the market. A third procedure for contained use of a GMO is included in Directive 2009/41/EC (together with the GMO-Directive, "**GMO-legislation**").

Since the GMO-legislation is laid down in a Directive, variability between the Member States is still possible since Member States have some freedom in how to transpose the GMO-Directive into national laws.[48] Member states differ in timing of both authorisation procedures, for example in some countries, the GMO-authorisation must be submitted before the clinical trial application.[49] In Belgium, each of these procedures can be initiated in parallel with the general CTR procedure.[50] Furthermore, in some countries the competent authority to examine the GMO and clinical trial requirements is the same (e.g. Germany, Italy, Sweden), while in other Member States, including Belgium, the competent authority differs.[51] Moreover, the documentation to be submitted, as well as related administrative fees, differ.[52]

Consequently, at present, while the CTR has streamlined the application process for clinical trials, specific challenges still exist for ATMPs that qualify as GMOs.

Authorisation procedures for GMOs

Before any authorisation procedure can be initiated, an environmental risk-assessment is required, taking into account the risk of the isolated ATMP, as well as the risk in case of expansion inside a permissive cell host. The risk assessment should result in a categorization of the products as having a negligible, low, moderate or high risk for the environment.[53]

Depending on the set-up of the trial, either the contained use procedure, the deliberate release procedure or both shall apply. The FAMHP offers the possibility to request a scientific and technical advice to determine which procedure is applicable.[54] This can cause significant delays, since the GMO requirements must be met before a clinical trial can be initiated.[55] In case the clinical trial concerns an ATMP that already has marketing authorisation and is used in accordance with the summary of product characteristics, no GMO-specific authorisation is needed, on the condition that the environmental risks are covered by the ERA from the MA (see 3.3.3).[56] After

48 TAJIMA, G., HUH, S., SCHIMIDT, N. A., MACDONALD, J. C., FLEISCHMANN, T., WONNACOTT, K. M., "Impact of genetically modified organism requirements on gene therapy development in the EU, Japan and the US", *Molecular Therapy: Methods & Clinical Development* 2022, 74 – 83.

49 IGLESIAS-LOPEZ, C., CORTADELLAS, M., VALLANO, A., AGUSTÍ, A. and MONTANÉ MOGAS, "Hurdles of environmental risk assessment procedures for advanced therapy medicinal products: comparison between the European Union and the United States, *Critical Reviews in Toxicology* 2019, 1 – 17.

50 Belgian Regulatory guidance on the use of genetically modified organisms in a clinical trial, Federal Agency for Medicines and Health Products and Sciensano, October 2023.

51 TAJIMA, G., HUH, S., SCHIMIDT, N. A., MACDONALD, J. C., FLEISCHMANN, T., WONNACOTT, K. M., "Impact of genetically modified organism requirements on gene therapy development in the EU, Japan and the US", *Molecular Therapy: Methods & Clinical Development* 2022, 74 – 83.

52 IGLESIAS-LOPEZ, C., CORTADELLAS, M., VALLANO, A., AGUSTÍ, A. and MONTANÉ MOGAS, "Hurdles of environmental risk assessment procedures for advanced therapy medicinal products: comparison between the European Union and the United States, *Critical Reviews in Toxicology* 2019, 1 – 17.

53 Scientific Guideline – Environmental risk assessment for medicinal products containing, or consisting of, genetically modified organisms (GMOs), Environmental risk assessments for medicinal products containing, or consisting of, genetically modified organisms (GMOs) - Scientific guideline | European Medicines Agency (europa.eu) (consulted on 23 December 2023).

54 Belgian Regulatory guidance on the use of genetically modified organisms in a clinical trial, Federal Agency for Medicines and Health Products and Sciensano, October 2023.

55 TAJIMA, G., HUH, S., SCHIMIDT, N. A., MACDONALD, J. C., FLEISCHMANN, T., WONNACOTT, K. M., "Impact of genetically modified organism requirements on gene therapy development in the EU, Japan and the US", *Molecular Therapy: Methods & Clinical Development* 2022, 74 – 83.

56 Belgian Regulatory guidance on the use of genetically modified organisms in a clinical trial, Federal Agency for Medicines and Health Products and Sciensano, October 2023.

authorisation, additional rules on labelling and traceability must be followed.[57]

According to the Service Biosafety and Biotechnology of Sciensano a total of 288 clinical trials with GMOs have been notified between 1996 and 2022, of which 94% targeted humans. Of those 288 trials, 54% were notified under the "contained use" procedure only and 44% were notified under both the "contained use" and "deliberate release" procedures. Merely 2% were notified under the "deliberate release" procedure only since this procedure only applies separately if the GMO is used only outside of a controlled environment like a hospital. The investigational medicinal product most often (64% of the cases) involved a recombinant viral vector. A total of 55% of the trials related to the treatment of cancer.

Contained use procedure

In Belgium, "contained use" is defined as "any activity in which organisms are genetically modified or in which genetically modified and/or pathogenic organisms are cultured, stored, transported, destroyed, disposed of or used in any other way, and for which specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment".[58]

The applicant needs to evaluate if there is a probability of release into the environment of the GMO, for example as the result of shedding (i.e. when the GMO is released into the environment via the patients' secretions/excreta). If there is no risk for shedding or spreading of the GMO in the environment or the release is prevented because of proper management procedures or working practices are followed, the contained use procedure is sufficient.[59] If the activities related to a clinical trial are performed in a "contained use" facility only, for example in laboratories or hospital rooms, the contained use procedure will generally suffice.

The contained use procedure is subject to regional legislation and timelines differ between Flanders, Brussels and Wallonia.[60] The type of procedure will vary depending on the risks of the contained use. The risk class of the involved organism, the clinical trial and the required containment level need to be assessed.[61] Each facility participating in the clinical trial must submit a separate notification.

Under the contained use procedure, the following steps must be followed:

- Collection of scientific and technical information and a risk assessment
- Submission of a biosafety dossier via a notification form
- Possibly: (extension of or addition to) an environmental permit

Deliberate release procedure

Deliberate release is defined as "any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment".[62]

If there is a risk of shedding or spreading during a clinical trial and there are no sufficient measures to avoid exposure to the environment, the deliberate release procedure will need to be followed. This will, for example, be the

57 R. O'ROURKE, European Food Law, London, Sweet & Maxwell, 2005, 176-185.

58 Belgian decrees on the contained use GMOs and/or pathogens transposing European Directive 2009/41/EC.

59 Belgian Regulatory guidance on the use of genetically modified organisms in a clinical trial, Federal Agency for Medicines and Health Products and Sciensano, October 2023.

60 Belgian Regulatory guidance on the use of genetically modified organisms in a clinical trial, Federal Agency for Medicines and Health Products and Sciensano, October 2023.

61 Belgian Regulatory guidance on the use of genetically modified organisms in a clinical trial, Federal Agency for Medicines and Health Products and Sciensano, October 2023.

62 Directive 2001/18/EC transposed in the Belgian Royal Decree of 21 February 2005.

case if the study subject leaves the clinical center while there is still a risk for spreading or shedding or if the GMO-containing ATMP is administered at home. Since the deliberate release application does not exempt the applicant from the contained release procedure, in most cases a contained release procedure should be followed as well. An application for deliberate release needs to contain a complete dossier which is submitted to the FAMHP. The Biosafety Advisory Council (BAC) evaluates the application and transmits their advice to the FAMHP.[63]

At the time of the writing of the report (October 2024), the Belgian database for the deliberate release of GM medicinal products contains 122 entries, most of which have been submitted by the industry, including spin-offs.[64] The number of applications by hospitals and other non-profit organisations is limited, especially when compared to the Netherlands. One application has been submitted by Wageningen Bioveterinary Research as part of the Larissa Consortium. Additionally, the University of Antwerp submitted two notifications, both for genetically modified vaccines against the poliovirus:

Phase 1 clinical trial evaluation of two genetically modified vaccines against poliovirus (only notified under the "contained use procedure")[65]

A phase 2 vaccine study in healthy adults and adolescents to evaluate the safety and immunogenicity of two oral polio type 2 vaccine candidates[66]

Furthermore, a notification under the "contained use" procedure was made by the International AIDS Vaccine Initiative.

Criticisms on GMO-legislation and remediations

The current GMO-legislation has been criticised by the industry. In 2019 the Alliance for Regenerative Medicine (ARM) published a report on recent trends in ATMP development. The ARM found that between 2014 – 2019 three times as many new interventional clinical trials were initiated in North America compared to Europe.[67] The ARM concludes that national discrepancies in GMO-legislative frameworks constitute an additional hurdle in the approval of clinical trials in the EU for ATMPs, for example by desynchronizing clinical trial approval throughout the EU, rendering the organisation thereof challenging.[68]

In addition to national discrepancies, the legislation in Belgium is further fragmented, with the different GMO procedures being subject to both regional and federal legislation. In its 2022 recommendations, Pharma.be therefore recommends streamlining the requirements for contained use and

63 Belgian Regulatory guidance on the use of genetically modified organisms in a clinical trial, Federal Agency for Medicines and Health Products and Sciensano, October 2023.

64 E.g. Actogenix (spin-off Vlaams Instituut voor Biotechnologie en UGent, overgenomen door Intrexon Corporation), T-Knife (spin-off Max Delbruck Centre for Molecular Medicine together with Charité University Hospital in Berlin); Vaccitech Limited / Barinthus Biotherapeutics (spin-off University of Oxford)

65 Genetic modifications of the nOPV2 vaccine candidates aimed at stabilizing the genetic sequence against reversion compared to the Sabin-2 strain, nOPV2 candidate 1 (S2/cre5/S15domV/rec1/hifi3), nOPV2 candidate 2 (S2/S15domV/CpG40)

66 The nOPV2 candidate strains include different combinations of 5 distinct modified regions of the Sabin-2 genome, including changes to the RNA sequence in the 5' untranslated region of polio genome (5' UTR), the capsid protein coding region (P1), the non-structural protein 2C, and the polymerase 3D. Of these modifications, only the changes to polymerase 3D result in a change in the amino acid sequence. The rest of the modifications aim to stabilise the genetic sequence against reversion in either the 5' UTR or capsid regions.

67 Clinical trials in Europe: Recent Trends in ATMP Development, Alliance for Regenerative Medicine (ARM), 2019, p. 1.

68 Clinical trials in Europe: Recent Trends in ATMP Development, Alliance for Regenerative Medicine (ARM), 2019, p. 7; TAJIMA, G., HUH, S., SCHIMIDT, N. A., MACDONALD, J. C., FLEISCHMANN, T., WONNACOTT, K. M., "Impact of genetically modified organism requirements on gene therapy development in the EU, Japan and the US", Molecular Therapy: Methods & Clinical Development 2022, 74 – 83.

deliberate release procedures not only with the CTR, but to also harmonise the contained use requirements across regions.[69]

In the past decade, several initiatives were launched to reduce national discrepancies and facilitate the authorisation process. However, the current framework in the EU still causes delays in the development of ATMPs.[70] This has been specifically acknowledged regarding the COVID-19 pandemic, during which a temporary exception was made from some provisions of the GMO requirements for potential COVID-19 treatments and vaccines.

On a national level, the FAMHP has drawn up specific guidelines on the use of GMOs in clinical trials, attempting to simplify the procedural requirements For example, CAR-T cells meet the legal definition of GMO but are subject to less stringent requirement due to these new practical guidelines.[71]

In the European Commission's proposed reform of the European pharmaceutical legislation, the submission and review of risk assessment of GMOs would be harmonised with the clinical trial application procedure.[72] Timelines would be streamlined with the clinical trial application, and separate national procedures would no longer be required.

However, the proposal still includes the obligation for Member States to "*implement appropriate measures to minimize foreseeable negative environmental impact resulting from the intended or unintended release of medicinal products containing or consisting of GMOs*".[73] This seems to implicate that some variation between Member States might continue exist.

69 Pharma.be, "Advanced Therapeutic Medicinal Products (ATMPs) in Belgium: a roadmap for the future Recommendations of pharma.be following multistakeholder consultation" (2022).

70 Call for more effective EU regulation of clinical trials with Advanced Therapy Medicinal Products consisting of or containing Genetically Modified Organisms, EFPIA, 2020.

71 Belgian Regulatory guidance on the use of genetically modified organisms in a clinical trial, Federal Agency for Medicines and Health Products and Sciensano, October 2023.

72 Article 177 Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency; TAJIMA, G., HUH, S., SCHIMIDT, N. A., MACDONALD, J. C., FLEISCHMANN, T., WONNACOTT, K. M., "Impact of genetically modified organism requirements on gene therapy development in the EU, Japan and the US", *Molecular Therapy: Methods & Clinical Development* 2022, 74 – 83.

73 Article 7 Proposal for a Regulation of the European Parliament and the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency.

3. MARKETING AUTHORISATION FOR ATMPS IN EUROPE

QUINZ

3.1. General requirements

Insofar as ATMPs are presented as having properties for treating or preventing diseases in human beings, or that they may be used in or administered to human beings with a view to restoring, correcting or modifying physiological functions by exerting principally a pharmacological, immunological or metabolic action, they are medicinal products within the meaning of Article 1(2) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (the "**Medicines Directive**"). This is confirmed in the preamble of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and ATMP Regulation No 726/2004, *lex specialis* for ATMPs. The *lex specialis* status means that the general pharma legislation applies unless specified differently in ATMP Regulation.

In the interest of public health protection, no medicinal product may be placed on the market of an EU Member State unless a marketing authorisation ("**MA**") valid in that Member State has been issued by the competent authorities. The Medicines Directive (transposed into Belgian law by the Belgian Medicines Act of 25 March 1964, the "**Medicines Act**") and ATMP Regulation No 726/2004 lay down the main requirements and procedures for marketing authorisation, as well as the rules for monitoring authorised products. The general requirement to obtain a marketing authorisation can be found in Article 6(1) of the Medicines Directive and Article 6§1 of the Medicines Act.

The MA is a product specific license held by the legal entity that actually places the medicinal product on the market in the EU. This entity, called the marketing authorisation holder ("**MAH**"), should be established in the EU. The purpose of the MA is to ensure that the safety, efficacy, and quality of the medicines made available to EU citizens are up to standard.[74]

The MA is renewed after five years of granting on the basis of a re-evaluation of the benefit-risk balance by the competent authority who issued it. Once renewed, the MA is valid for an unlimited period. Note, however, that under the proposal adopted by the European Commission to revise and replace the existing pharmaceutical legislation MAs will be valid for an unlimited period (instead of a five-year period, which can be renewed), unless there are grounds relating to the safety of the medicinal product concerned that justify a limitation of the initial validity of the MA to five years, after which renewal must be sought.

The MA is not required for intermediate products intended for further processing, nor for investigational medicinal products to be used in clinical trials or other products currently falling outside the scope of the Directive 2001/83.

74 https://health.ec.europa.eu/medicinal-products/legal-framework-governing-medicinal-products-human-use-eu_en.

3.2. MA Procedure

Centralised procedure

Four different procedures for obtaining a marketing authorisation exist in the EU: the (EU) centralised procedure, the decentralised procedure, the mutual recognition procedure and the national procedure. While in principle, a medicine developer is free to decide which procedure to use, the centralised procedure is compulsory for ATMPs.[75]

The centralised procedure involves the submission of a single application to the EMA, leading to a single evaluation and authorisation procedure. If the medicine is approved, a license for marketing the medicine is granted for all EU countries as well as for Iceland, Norway and Liechtenstein.

3.3. Regulatory dossier

3.3.1. General

Applications for MA require the submission of a dossier of documents in a standardised electronic format (the so-called Common Technical Document or "CTD"). The format of the CTD is harmonised across the EU, Canada, Japan, Switzerland, the US, and other countries and across all types of procedures and products. Annex 1 to the Medicines Directive lays down detailed requirements regarding the content of the CTD. The CTD contains 5 modules:

- Module 1 includes specific administrative information (cover letter, application form, product leaflet, environmental risk assessment, PV information, clinical trial information);
- Module 2 should show summaries and overviews of the information submitted for the other Modules;
- Module 3 includes all quality related (chemical, pharmaceutical and biological) information;
- Module 4 provides non-clinical study reports (i.e. the reports of toxicological and pharmacological tests designed to show the activity and effects of the medicine in the laboratory); and
- Module 5 provides clinical study reports (i.e. studies of the medicine in patients or healthy volunteers, to show the benefits and side effects observed in humans).

The application should also include a draft package leaflet, a summary of product characteristics, and an outline of the primary and outer packaging. The submission of samples is not required, but they must be provided upon request by the authority.

3.3.2. Demonstration of Quality, Safety and Efficacy

The three key criteria on which the grant of the MA is based, are quality, safety and efficacy. Taken together, these criteria give an idea of overall benefit-risk balance provided by a medicinal product.

Applicants must provide extensive documentation showing that the product is of suitable quality, and are required to demonstrate safety and efficacy through the results of clinical trials. For established compounds, reference can be made to data from already authorised medicines (generic marketing authorisation) or to published literature (well-established medicinal use).[76]

Annex 1 of the Medicines Directive lays down in detail the data to be provided (mainly in Modules 3, 4 and 5 of the application dossier) to demonstrate the quality, safety and efficacy of the product, and scientific guidelines prepared by the EMA in consultation with the competent authorities of the EU Member States help applicants prepare their MA applications in a manner that will be recognised as valid by the EMA. The EMA's pre-authorisation procedural advice for users of the centralised

75 https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview

76 https://health.ec.europa.eu/medicinal-products/legal-framework-governing-medicinal-products-human-use-eu_en.

procedure[77] may also provide assistance with early planning, method development and evaluation.[78]

CMC Information

An important part of the regulatory dossier in relation to quality is the so-called "CMC" information included in Module 3. CMC is short for Chemistry, Manufacturing and Controls and covers the following topics:

- Chemistry – product characterization and specifications, formulation development, release, stability testing, storage conditions, and shelf-life
- Manufacturing – facilities, equipment, utilities, raw materials, suppliers, production of API, and process (development)
- Controls – analytical test methods (SOPs), process validation, batch records, training, auditing, and batch release

For this part of the application, the applicant will need the input of the manufacturer of the medicine, usually a third-party contract manufacturing organisation ("CMO") which has already been involved in the research & development phase (e.g. to manufacture the investigational product for use in clinical trials).

For advanced therapies, it's essential to meticulously monitor the manufacturing process to ensure the final product is consistent and reproducible. This is particularly challenging when using autologous cells or tissues and other biological materials, as they are more difficult to standardise due to inherent variability.[79]

The definition and implementation of relevant controls for testing safety (particularly genetic stability) and efficacy, is challenging.[80]

3.3.3. Environmental risk assessment

Information pertaining to the potential harm that the use and/or disposal of the medicinal product may cause to the environment and human health, the so-called environmental risk assessment ("ERA"), should be included as an appendix to Module 1 of the regulatory dossier. If required based on the identified hazards and level of risk involved, the ERA should also put forward proposed strategies for risk management and risk minimization, including a post-market monitoring plan and information to appear in the summary of product characteristics, labelling and package leaflet.

As outlined above, the ERA is particularly relevant for medicines containing or consisting of GMOs, for which the requirements of Directive 2001/18/EC should be taken into account as well. A specific guideline on the scientific requirements for the ERA of GTMPs has been issued by the EMA.[81] This ERA will also be reviewed by the national competent authorities responsible for GMOs in each Member State.[82]

Although the GMO-legislation complicates the initiation of a clinical trial in the EU, the effect on the marketing of the product is smaller since the application of the marketing authorisation for an ATMP consisting of a GMO

77 https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-pre-authorisation-procedural-advice-users-centralised-procedure_en.pdf.

78 Whomsley, R., Palmi Reig, V., Hidalgo-Simon, A. Environmental risk assessment of advanced therapies containing genetically modified organisms in the EU, Br J Clin Pharmacol 2021 Vol. 87 Issue 6 Pages 2450-2458.

79 https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview

80 Sensebé L, Gadelorge M, Fleury-Cappellesso S. Production of mesenchymal stromal/stem cells according to good manufacturing practices: a review. Stem Cell Res Ther. 2013 Jun 7;4(3):66

81 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-requirements-environmental-risk-assessment-gene-therapy-medicinal-products_en.pdf.

82 Whomsley, R., Palmi Reig, V., Hidalgo-Simon, A. Environmental risk assessment of advanced therapies containing genetically modified organisms in the EU, Br J Clin Pharmacol 2021 Vol. 87 Issue 6 Pages 2450-2458.

is centralised.[83] The ERA should be submitted in accordance with the principles of deliberate release (see section 2.3.4 supra).[84] In addition, a monitoring plan should be prepared and performed post marketing authorisation.[85]

Note that an ERA is also required for the purpose of the clinical trial application, and that similar requirements apply as regards the content of the ERA in clinical and MA applications. The results of any investigations already performed at the R&D stage can thus be incorporated directly in the MA application dossier.[86] However, the EC Pharma Proposal provides for additional requirements on the ERA in applications for marketing authorisation, including far-reaching sanctions (such as refusal of the marketing authorisation) in case the ERA is incomplete or the mitigation measures proposed by the MA holder are insufficient. After authorisation, the MA holder must continuously update the ERA if important new information becomes available.

3.3.4. Specific requirements for ATMPs

Specific dossier requirements exist for ATMPs. These are included in Part IV of Annex 1 to the Medicines Directive and contain, on the one hand, explanations as to how the general requirements should be applied in relation to ATMPs and, on the other hand, a few additional requirements. The specific requirements are intended to take into account the unique and diverse structural and biological properties of ATMPs and the fact that ATMPs often do not have a clear "identity" and are rather defined by their manufacturing process.[87]

Important to note is the principle that, due to the specific nature of advanced therapy medicinal products, a risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorisation application.

In summary, the risk-based approach for ATMPs is more dynamic and tailored, focusing on the unique challenges and risks associated with these advanced therapies. This contrasts with the more standardised approach used for classical medicines. While the risk-based approach offers greater flexibility to accommodate the unique nature of ATMPs, it also demands more effort and resources to ensure safety and efficacy (see also 5.9 of this Supplement).

The risk analysis, as well as the scientific justification for any deviation from the dossier requirements, shall be included in Module 2. Examples of risk factors to consider include the origin of the cells (autologous, allogeneic, xenogeneic), the ability to proliferate and/or differentiate and to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the nature of the ATMP, the extent of replication competence of viruses or micro-organisms used in vivo, the level of integration of nucleic acids sequences or genes into the genome, the longtime functionality, the risk of oncogenicity and the mode of administration or use.

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83 IGLESIAS-LOPEZ, C., CORTADELLAS, M., VALLANO, A., AGUSTÍ, A. and MONTANÉ MOGAS, "Hurdles of environmental risk assessment procedures for advanced therapy medicinal products: comparison between the European Union and the United States, *Critical Reviews in Toxicology* 2019, 1 – 17.

84 IGLESIAS-LOPEZ, C., CORTADELLAS, M., VALLANO, A., AGUSTÍ, A. and MONTANÉ MOGAS, "Hurdles of environmental risk assessment procedures for advanced therapy medicinal products: comparison between the European Union and the United States, *Critical Reviews in Toxicology* 2019, 1 – 17.

85 IGLESIAS-LOPEZ, C., CORTADELLAS, M., VALLANO, A., AGUSTÍ, A. and MONTANÉ MOGAS, "Hurdles of environmental risk assessment procedures for advanced therapy medicinal products: comparison between the European Union and the United States, *Critical Reviews in Toxicology* 2019, 1 – 17.

86 Whomsley, R., Palmi Reig, V., Hidalgo-Simon, A. Environmental risk assessment of advanced therapies containing genetically modified organisms in the EU, Br J Clin Pharmacol 2021 Vol. 87 Issue 6 Pages 2450-2458.

87 Morrow D, Ussi A and Migliaccio G (2017) Addressing Pressing Needs in the Development of Advanced Therapies. Front. Bioeng. Biotechnol. 5:55, p. 3

Additional requirements worth mentioning include:

- Module 3 should provide a description of the traceability system that the applicant intends to establish to ensure that the product and its raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the entire manufacturing and distribution process;
- summary information on donation, procurement and testing of the human tissue and cells used as starting materials should be included in Module 3. If non-healthy cells or tissues (e.g. cancer tissue) are used as starting materials, their use shall be justified;
- additional studies to demonstrate comparability may be required for Module 5, given that, due to the nature of advanced therapy medicinal products, their manufacturing process may change during clinical development;
- in Module 5, the (long-term) efficacy of the proposed indications should be supported by results of clinical studies using clinically meaningful endpoints for the intended use; and
- Module 5 should address risks arising from potential infectious agents or the use of material derived from animal sources and measures taken to reduce such risk.

3.3.5. Review / Evaluation

Competent authority

In the centralised procedure, the authorising body is the European Commission but the scientific assessment is done by the European Medicines Agency (EMA).[88] Three of EMA's scientific committees are involved in the evaluation of marketing authorisation applications for ATMPs: the Committee on Advanced Therapies (CAT), the Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC).

The CAT (a multidisciplinary committee) currently plays a central role in the scientific assessment, providing the expertise needed to evaluate ATMPs. Note, however, that the EC Pharma Proposal provides for simplification by reducing the number of EMA scientific committees, leaving only the CHMP and the PRAC responsible for the scientific assessment of all types of medicinal products.[89] The other committees, including the CAT, will take the form of scientific working parties playing a supportive and/or advisory role.

For medicines containing a GMO, the national competent authorities of each Member State must be consulted to review the assessment on the ERA and provide their input.[90]

Duration

In principle, each assessment procedure takes maximum 210 days of active evaluation time. However, there are clock-stops during which the applicant is given time to answer the questions raised by the evaluators, which may take several months.

Decision

During the assessment procedure, the CAT prepares a draft opinion on the quality, safety and efficacy of the advanced therapy medicine. The assessment is led by two CAT members from different countries (the rapporteur and co-rapporteur), but all CAT members can provide comments and propose questions to be asked to the applicant. The opinion of the CAT is sent to the CHMP, which consists of one member appointed by each of

88 https://health.ec.europa.eu/medicinal-products/legal-framework-governing-medicinal-products-human-use-eu_en.

89 Covington, "EU Pharma Legislation Review Series: Marketing Authorisations", https://www.insideeulifesciences.com/2023/05/02/eu-pharma-legislation-review-series-marketing-authorisations/

90 Whomsley, R., Palmi Reig, V., Hidalgo-Simon, A. Environmental risk assessment of advanced therapies containing genetically modified organisms in the EU, Br J Clin Pharmacol 2021 Vol. 87 Issue 6 Pages 2450-2458.

the EU countries as well as for Iceland, Norway and Liechtenstein and five expert scientists, as well as to the PRAC.

Based on the CAT opinion, the CHMP adopts an opinion recommending or not the authorisation of the medicine by the European Commission. The European Commission makes its final decision on the basis of the CHMP opinion and issues the MA.[91] The European Commission shall, based on the recommendations of the CHMP, specify in its decision the conditions or restrictions regarding the supply and use of the product, such as whether or not the medicinal product is subject to prescription.[92]

A MA will be refused, in cases where:

- The benefit-risk balance is not considered to be favourable;
- the therapeutic efficacy is insufficiently substantiated by the applicant; or
- the qualitative and quantitative composition of the medicine is not as declared.
- Uncertainty on the (long-term) efficacy, have proven to be an important hurdle for the approval of ATMPs.

Fees

The EMA charges fees for applications for marketing authorisation, and for variations and other changes to marketing authorisations, as well as annual fees for authorised medicines.

Example of basic fees (until 1 January 2025)

Fee type	Human medicines
Marketing-authorisation application (single strength, one pharmaceutical form, one presentation)	From €357,600
Extension of marketing authorisation (level I)	€107,300
Type-II variation (major variation)	€107,300
Variations requiring assessment	-
Scientific advice	From €53,600 to €107,300
Annual fee (level I)	€123,900
Establishment of MRLs	**-**

91 https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview

92 European Commission, The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A: Procedures for marketing authorisation, Chapter 1, p. 15, https://health.ec.europa.eu/system/files/2019-07/vol2a_chap1_en_0.pdf.

Fees are adjusted every year for inflation.

Fee reductions and incentives are available for micro, small and medium-sized enterprises (SMEs), and for designated orphan medicines, including a 90% reduction of fees for obtaining scientific advice, and a conditional fee exemption if scientific advice is obtained and followed, but the MAA isn't successful. In addition, there is the opportunity to obtain a fee deferral until after the outcome of the MA procedure Academia under the Academic Pilot benefit from the same reductions.

It should be noted that as of 1 January 2025, a new fee structure will apply. Pursuant to Regulation (Eu) 2024/568 of the European Parliament and of the Council of 7 February 2024 on fees and charges payable to the European Medicines Agency, amending Regulations (EU) 2017/745 and (EU) 2022/123 of the European Parliament and of the Council and repealing Regulation (EU) No 658/2014 of the European Parliament and of the Council and Council Regulation (EC) No 297/95, the EMA fees will no longer be a flat-fee, but shall be cost-based. For instance, costs for a marketing authorisation application for a new active substance start at 865 200 EUR.[93] The fee structure reflects the average time the EMA expects to spend on the application process based on the complexity of the product for which an application is submitted. It should be noted that the new Regulation specifically recognises that fees can present a significant obstacle for those entities that are not engaged in an economic activity, such as Academia and non-profit entities. For that reason, they should equally benefit from fee reductions, provided that they are not owned or controlled by a commercial undertaking and that they have not concluded agreements with any commercial undertaking concerning sponsorship or participation in the development of the medicinal product which would give the commercial undertaking any rights to the final medicinal product.[94]

3.3.6. Extraordinary procedures

There are several flexibilities in the current regulatory framework for the centralised MA procedure which enable early patient access to new medicines, particularly those that target an unmet medical need or are of major public health interest.[95]

3.3.6.1. Accelerated assessment

When a MA application is submitted for a product which is of major public health interest, in particular from the viewpoint of therapeutic innovation (unmet medical need), the applicant may request an accelerated assessment procedure in accordance with Article 14(9) of Regulation (EC) 726/2004. This regulatory tool reduces assessment time for MA applications to 150 days or less (compared to standard 210 days). The request for accelerated assessment should be made at least two to three months before submitting the MA application and should include justification for the claim that the product concerned is of major public health interest.[96]

3.3.6.2. Conditional MA

In the interest of public health, applicants may be granted a conditional marketing authorisation on the basis of less comprehensive clinical data than normally required (Article 14-a of Regulation (EC) No 726/2004). Medicines for human use are eligible if they are intended for treating,

93 https://www.consilium.europa.eu/en/press/press-releases/2024/01/23/european-medicines-agency-council-gives-final-green-light-to-the-overhaul-of-its-fee-system/

94 See Recital 20 Regulation (Eu) 2024/568 of the European Parliament and of the Council of 7 February 2024 on fees and charges payable to the European Medicines Agency, amending Regulations (EU) 2017/745 and (EU) 2022/123 of the European Parliament and of the Council and repealing Regulation (EU) No 658/2014 of the European Parliament and of the Council and Council Regulation (EC) No 297/95, *OJ L, 2024/568, 14.2.2024*

95 https://www.ema.europa.eu/en/human-regulatory-overview/support-early-access

96 https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/accelerated-assessment.

preventing or diagnosing seriously debilitating or life-threatening diseases, and provided that all of the following criteria are met:

- the existing data points to a positive benefit-risk balance of the medicine;
- it is likely that the applicant will be able to provide comprehensive data post-authorisation;
- the medicine fulfils an unmet medical need; and
- the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.

Conditional MAs are valid for one year and can be renewed annually. Once a conditional MA has been granted, the holder must comply with the post-authorisation obligations imposed by the EMA, e.g. complete ongoing or conduct new studies or collect additional data to confirm, within the agreed timeframe, that the medicine's benefit-risk balance remains favorable. The conditional MA will be converted into a standard MA (no longer subject to specific obligations) once the holder fulfils all such obligations and the complete data confirm that the medicine's benefits continue to outweigh its risks. As for any medicine, if new data show that the medicine's benefits no longer outweigh its risks, or if the holder does not comply with the conditions, the EMA can take regulatory action, such as suspending or revoking the MA.[97]

Many ATMPs have their MA granted conditionally on the basis of small, open-label, single arm trials. As those are unable to address long-term safety and efficacy, post-authorisation obligations usually include the carrying out of additional studies on the long-term effects.[98]

The only ATMP approved in 2023, Hemgenix®, received a conditional MA. In December 2023, the CHMP recommended conditional approval for Casgevy®, with a decision expected in Q1 2024. The other ATMPs which have received conditional MA in the past are:

2022 - Carvykti® and Roctavian®;

2021 - Abecma®;

2020 - Tecartus® and Zolgensma®;

2019 - Zynteglo® (withdrawn);

2016 - Zalmoxis® (withdrawn); and

2015 - Holoclar®.

For Zolgensma®, the company has supplied the additional information necessary and hence the authorisation has been switched from conditional to full authorisation.

3.3.6.3. MA under exceptional circumstances

EMA may also grant a MA in absence of comprehensive data under exceptional circumstances. Unlike conditional MA, which is granted in the likelihood that the requestor will provide such data within an agreed timeframe, EMA can grant a MA under exceptional circumstances when comprehensive data on the efficacy and safety cannot be obtained even after authorisation for objective and verifiable reasons (i.e. because the condition to be treated is too rare, the present state of scientific knowledge is insufficient to provide full information, or it would be unethical to collect this information) (Article 14(8) of Regulation (EC) No 726/2004).[99] Continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions and other post-authorisation obligations may be imposed, such as additional safety and efficacy studies and notification of incidents. This regulatory route is relevant for ATMPs as the

97 https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/conditional-marketing-authorisation.

98 E. VAN OVERBEEKE et. al., "Market access of gene therapies across Europe, USA, and Canada: challenges, trends, and solutions", *Drug Discovery Today* 2021, 26(2), 404.

99 https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/conditional-marketing-authorisation.

eligibility criteria reflect some of the most important barriers to obtaining a standard MA for ATMPs (e.g. limited efficacy and safety data not meeting evidence requirements). To date, 3 ATMPs were granted a MA under exceptional circumstances in the European Union: Glybera® (2012), Upstaza® (2022), and Ebvallo® (2022). The MA for Glybera® was not renewed after 2017.

3.3.7. Regulatory support and interaction

To assist ATMP developers, several EMA guidance documents have been published (*Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products*,(European Medicines Agency 2014)) or being updated or drafted (*Draft guideline for investigational advanced therapy medicinal products in clinical trials*(European Medicines Agency 2024)). In addition to the abovementioned flexibilities in the regulatory procedure and requirements, the EU framework provides for different support programs focused on early interaction with regulators to help developers navigate the regulatory framework and as such facilitate market access for ATMPs and other promising treatments.[100] Optimal dialogue between regulators and ATMP developers is important to guide the development process and reduce uncertainty on the level of evidence required for a successful MA application.[101] Some of the support tools provided by EMA are specifically focused on SMEs and Academia.[102]

3.3.7.1. Scientific advice

EMA offers scientific advice on the quality, non-clinical and clinical aspects of medicine development, in the form of, for example, protocol assistance for orphan medicines, the qualification of novel development methodologies, advice on medicine repurposing, quality by design, etc. Scientific advice helps to ensure that developers perform the appropriate tests and studies, so that no major objections regarding the design of the tests are likely to be raised during the evaluation of the MA application.[103] This also helps avoid patients taking part in studies that will not produce useful evidence. Scientific advice is however not a pre-assessment of the benefits and risks of a medicine, nor does it guarantee that a medicine will receive a MA. It is also not binding, neither on EMA regarding future assessment nor on the developer.[104]

In principle, applicants pay an administrative fee for scientific advice. Total or partial exemptions apply for ATMPs for human use, as laid down in Article 16(2) of Regulation (EC) No 1394/2007: there is a general 65% fee reduction for ATMPs compared to the standard fees, but micro and SMEs benefit from a 90% fee reduction for non-orphan ATMPs and a 100% reduction for orphan ATMPS. EMA is also waiving fees for Academia when they apply for protocol assistance for orphan medicines.

EMA offers the possibility of joint scientific advice with EU HTA bodies to help generate optimal and robust evidence that satisfies the needs of both regulators and HTA bodies. The EMA and the US Food and Drug Administration (FDA) of the US Department of Health and Human Services have a program to provide parallel scientific advice (PSA) to sponsors.[105]

3.3.7.2. ATMP classification and certification

Developers can also consult the EMA to determine whether a medicine they are developing is classified as an ATMP. The procedure allows them to receive confirmation that a medicine, which is based on genes, cells or tissues, meets the scientific criteria for defining an ATMP prior to submitting

100 E. VAN OVERBEEKE et. al., “Market access of gene therapies across Europe, USA, and Canada: challenges, trends, and solutions”, *Drug Discovery Today* 2021, 26(2), 410.

101 D. MORROW et. al., “Addressing Pressing Needs in the Development of Advanced Therapies”, *Frontiers in Bioengineering and Biotechnology* 2017, 5, Article 55, p. 5.

102 An overview of the tools available to medicine developers from the academic sector can be found at https://www.ema.europa.eu/en/documents/leaflet/ema-tools-available-medicines-developers-academic-sector_en.pdf.

103 www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance

104 https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-advice-and-protocol-assistance

105 https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-advice-and-protocol-assistance

any application.[106] This is an optional procedure which involves the CAT. In addition to such classification advice, SMEs may also receive scientific feedback (a "pre-evaluation", if you will) on the experimental data already generated on the ATMP through a process called certification. This may be useful to attract investors or interested parties to license out the product.

Note that under the current version of the reform of the EU Pharma Proposal (see Box 1 of the scientific report), the CAT as separate scientific committee of the EMA will be abolished. However, their expertise will be retained and reorganised in the form of working groups, working parties and a pool of experts.

3.3.7.3. PRIME scheme

EMA has launched the PRIME scheme to enhance support for the development of medicines that target unmet medical needs ("PRIority MEdicines").

PRIME is a voluntary program designed to promote early dialogue between the various stakeholders on a.o. clinical trial design, with the aim of optimizing evidence-generation and expediting the regulatory review process so that these priority medicines can reach patients earlier. Developers of medicines that benefit from PRIME get additional advice and support at the development stage and their products can expect to be eligible for accelerated assessment (see above).

The scheme builds on other regulatory tools in place within the EU legal framework, essentially helping medicine developers to make the best use of EMA's early dialogue and early access routes, for example by offering expedited follow-up on requests for scientific advice. To be accepted for PRIME, a medicine must demonstrate the potential to address an unmet medical need to a significant extent.

The majority of the ATMPs authorised in recent years have benefited from PRIME status: Casgevy(2023), Breyanzi(2022), Carvykti(2022), Ebvallo(2022), Hemgenix(2022), Roctavion(2022), Abecma(2021), Skysona(2021), Tecartus(2020), Zolgensma(2020), Zynteglo(2019).

Small and medium-sized enterprises (SMEs) and applicants from the academic sector may be granted *Early Entry PRIME status* if they demonstrate proof of principle, in which case they are offered even more benefits:

- advice from the EMA product team on plans to generate the proof-of-concept data required to transition to full PRIME status;
- introductory meeting to raise awareness of regulatory requirements and to provide scientific and regulatory advice on the overall development plan;
- and total fee exemption for scientific advice.p

3.3.7.4. Innovation task force

The EMA's Innovation Task Force (ITF) is a multidisciplinary group that includes subject-matter experts from EMA's working parties and committees with scientific, regulatory and legal competences. One of its main objectives is to establish a discussion platform for early dialogue with applicants, in particular SMEs, academics and researchers, to proactively identify scientific, legal and regulatory issues arising from innovative medicines development, emerging therapies, new technologies and borderline products. These discussions take place earlier than applicants would normally seek scientific advice but may be followed by an EMA scientific opinion on the eligibility for access to EMA procedures where applicable (e.g. for borderline products). ITF briefing meetings facilitate informal exchange of information, brainstorming, and guidance in the development process, complementing and reinforcing existing formal procedures.

106 https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/advanced-therapies-marketing-authorisation/advanced-therapy-classification

Developers of innovative medicines, technologies and methods may apply for a briefing meeting with the ITF at any time by sending their request to ITFsecretariat@ema.europa.eu. Meetings are free of charge.

3.3.7.5. Orphan designation

While not specifically targeted to SMEs or academic drug developers, there exist important incentives facilitating the development and authorisation of medicines for rare diseases (i.e. a condition affecting not more than five in 10 thousand persons in the EU at time of the marketing authorisation application) through the grant of orphan designation by the EMA (so-called "orphan medicine").[107] Many ATMPs seek to treat rare diseases and could benefit from such orphan medicine status.

Orphan designation is a specific designation awarded by the EMA to a medicinal product intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating rare disease ('prevalence criterion'), or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the medicinal product in the EU would generate sufficient return to justify the necessary investment ('ROI criterion'). This ROI criterion is almost never used.[108] In addition, no satisfactory method of diagnosis, prevention or treatment of the condition concerned is authorised, or the medicine provides a significant benefit for such condition ("significant benefit criterion").

Particular benefits of receiving a designation as 'orphan medicine' include protocol assistance in the form of a broadened possibility to request scientific advice from the EMA regarding the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy, at a reduced fee, reduced fees for regulatory activities, and market exclusivity for a 10-year period (with the potential to prolong to 12 years in case of pediatric medicines if certain conditions have been met). It should be noted that the EU Pharma Reform will amend the above, including for example the market exclusivity period (increasing such period to 11 years if the orphan medicine addresses a high unmet medical need).

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107 Regulation (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on orphan medicinal products; COMMISSION REGULATION (EC) No 847/2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority'; Commission Regulation (EU) 2018/781 of 29 May 2018 amending Regulation (EC) No 847/2000 as regards the definition of the concept 'similar medicinal product'; Guideline on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000 of the European Parliament and of the Council: Review of the period of market exclusivity of orphan medicinal products (2008/C 242/07).

108 Denis Alain, Simoens Steven, Fostier Christel, Mergaert Lut, Cleemput Irina. Policies for Rare Diseases and Orphan Drugs. Health Technology Assessment (HTA). Brussels. Belgian Health Care Knowledge Centre (KCE). 2009. KCE Reports 112C. DOI: 10.57598/R112C.

4. THE POSSIBILITY FOR ACADEMIA TO HOLD MARKETING AUTHORISATIONS FOR ATMPS

QUINZ

4.1. Introduction

Holding a marketing authorisation in principle means that the safety, quality and efficacy of the relevant ATMP has been sufficiently demonstrated and is authorised (in case of a centralised procedure, throughout the EU). It also facilitates a possible reimbursement, is not subject to strict eligibility criteria (as is the case under the clinical trial pathways) and enhances transparency (through the availability of an approved SmPC). It is sometimes argued that a marketing authorisation therefore should be the preferred method of providing access to patients, since it ensures control on the safety and efficacy of the product and allows for a more equitable access. That being said, specifically for ATMPs, considering the often limited clinical evidence caused by the flexibilities and the constraints discussed under the previous sections, a marketing authorisation also entails limitations. Moreover, patient access is often limited, considering that ATMPs are often not effectively commercialised and reimbursed throughout all of the EU.

The EU legislation does not prohibit academic institutions to apply for and hold MAs. Moreover, current regulatory support measures and interaction initiatives affirm the right of academic institutions to apply for and hold MAs, particularly in the context of ATMPs.

However, as further discussed in this section, additional national legal provisions may restrict certain academic institutions from engaging in the commercial activities associated with such MAs.

In addition, this (theoretical possibility) for Academia to hold MAs for ATMPs appears limited in practice due to state aid restrictions outlined in section 8 of the scientific report.

An alternative route could be to provide public support to academic ATMP development with the aim to out-license such developed ATMPs to industry partners or independent spin-offs at a more mature stage of clinical development (when safety and efficacy is more clearly demonstrated and potential commercialisation may appear more “attractive”), possibly under pre-defined licensing conditions (see section 8.1.2. of the scientific report).

Some (but definitely not all) concerns that Academia (and notably academic hospitals) may have in working towards an academic MA pathway could be overcome by creating a “special purpose vehicle” (“SPV”) to specifically manage all developed IP, own the relevant MA, and take responsibility for the commercialisation of the applicable ATMP. This spin-out route is currently generally used to enable further development of academically developed products without out licensing to industry. However, currently, such spin-out SPV is usually operating as a commercial company, ultimately seeking to commercialise and/or maximise profits. External investors expect returns on their investment, which risks driving prices. Alternatively, one could imagine non-profit SPVs, which remain fully controlled by the original Academic drug developer. Such an SPV would, theoretically, have less of a commercial objective, which may lead to lower prices and investment into less commercially viable diseases.

Regardless of the nature of the SPV, the advantages of such SPV are straightforward. It would enable hospitals to compose a dedicated workforce to manage an ATMP launch, it allows hospitals to carve out potential (product) liability risks and financial flows from its day-to-day activities, it facilitates compliance with pharmaceutical legislation, etc.

4.2. Hospitals acting as MA holder and/or commercial actor: compatibility, feasibility and risks

4.2.1. Introduction

It is striking to note that with a single exception (Telethon Italy is since 19 September 2023 the marketing authorisation holder of Strimvelis) *all* marketing authorisations for ATMPs approved in the EU are held by commercial actors. For less complex medicinal products (and API), however, examples of Academia or publicly-funded organisations as marketing authorisation holders do exist throughout the EU: for example, in the United Kingdom, until end of 2023, Torbay Pharmaceuticals Ltd. was an NHS owned pharmaceutical manufacturer. In Denmark, Amgros I/S, a publicly owned organisation, holds several marketing authorisations for local self-administered drugs (SAD) pharmaceuticals.

4.2.2. Compatibility with classic hospital activities

Considering the increased attention for the potential for Academia as drivers in ATMP development, one could consider Academia progressing the full development in house up to marketing authorisation. As discussed in the scientific report (see section 8 of the scientific report), such effort would necessitate support and partnerships on multiple levels, including financial support. Although there is no express prohibition for Academia to obtain marketing authorisations (see also 4.1 above), in addition to state aid considerations, other legal hurdles under Belgian laws may restrict the potential for Academia to establish commercial activities, such as progressing to marketing authorisation.

4.2.3. Hospital legislation

4.2.3.1. Restricted statutory purpose

The central legal instrument governing hospitals in Belgium is the Hospital Act of 10 July 2008 ("**Hospital Act**").[109] The Hospital Act lays down the general authorisation requirements for hospitals in Belgium, in addition to regulations on the organisational structure of the hospital and general funding conditions.

Hospitals' primary purpose is the provision of care and treatment of patients. Academic hospitals, since they are connected to universities, also have an educational role, and are engaged in scientific research, development of new technologies and evaluating medical activities.[110] Generally, the focus of hospitals is not geared towards developing commercial activities. However, it is understood that hospitals despite their medical focus can be regarded as enterprises within the scope of the Belgian Code of Economic Law and have the capacity to engage in economic activities (see also Section 8.2.3 of the scientific report).[111]

Research and development activities are an essential and funded activity in an academic hospital setting.[112] Indeed, performing clinical trials and testing new technologies or in vitro diagnostics are frequent activities in which academic hospitals play a crucial role, often in collaboration with research centers at the affiliated university.

Interestingly, the Hospital Act does not prescribe a legal form for the exploitation of a hospital. Both non-profit as well as for-profit entities can exploit a hospital. However, Article 63 Hospital Act specifies that only hospitals organised in the form of governmental organisations, non-profits or universities are eligible to benefit from the general structural funding

109 Coordinated Act of 10 July 2008 on hospitals and other care facilities, *BS 07 November 2008 ("Hospital Act")*

110 Article 4 Hospital Act.

111 Aanvullend Verslag Namens De Commissie Voor Het Bedrijfsleven, Het Wetenschapsbeleid, Het Onderwijs, De Nationale Wetenschappelijke En Culturele Instellingen, De Middenstand En De Landbouw Uitgebracht Door De Heer Peter DEDECKER of 13 March 2014 at https://www.lachambre.be/FLWB/pdf/53/3300/53K3300006.pdf, p. 7 ; See in addition the guidance of the FPS Economy on https://economie.fgov.be/nl/file/152338/download?token=xxS4qlam#:~:text=Deze%20nieuwe%20definitie%20van%20%E2%80%9Conderneming,iedere%20andere%20organisatie%20zonder%20rechtspersoonlijkheid.

112 Article 4 Hospital Act.

under the Hospital Act. Consequently, in reality, no hospitals are organised as a for-profit entity, and most of them are organised as a not-for profit entity as association (*vzw*) or have a *sui generis* legal form (organised or recognised pursuant to a Decree).[113]

In the past, it was debated whether non-profit private organisations such as associations were allowed to engage in commercial activities. Non-profit organisations were not allowed to establish commercial activities other than activities that were subsidiary to their non-profit goal. The Belgian Code of Companies and Associations has abolished any such restriction, and in general non-profit organisations are allowed to engage in all legitimate commercial activities, provided that they do not provide (in)direct monetary advantages to their members or directors. Hence, there are no restrictions under general company law that would prohibit a hospital to engage in activities with a view to marketing an ATMP.

However, despite the foregoing broad potential for establishing commercial activities, non-profit associations are bound and limited by their statutory object. The statutory object of a legal entity defines the scope of activities that that entity specifically may establish.[114]

Specifically for hospitals, additional restrictions in relation to the statutory object have been imposed by Article 15 Hospital Act, which prescribes that hospitals should be operated by a legal entity whose sole statutory object is the operation of one or more hospitals or health facilities or medical-social facilities. Activities that do not fall within the scope of the operations of a hospital are, in theory, restricted and cannot be established by a legal entity which is also exploiting a hospital. Unfortunately, the Belgian legislator has not expressly defined which activities fall within the operation of a hospital, and which activities fall outside of such scope.

Importantly, if a legal entity's statutory object is not permitted by law, the legal entity can be terminated; this also includes the case where the statutory object as written in the bylaws is permitted, but where the entity in reality acts as if its statutory object was different and unpermitted.[115] In addition, the entity should be careful not to act outside of its statutory object: activities which fall outside of the scope are precarious and if substantial may jeopardise the whole organisation. Any member, any interested party or the public prosecutor may demand the dissolution of an entity that seriously disregards its statutory object, e.g. by carrying out an activity outside its statutory object.[116] Furthermore, the directors of the entity could incur liability for any such activities.[117]

For the purpose of this study, it will hence be important to analyze whether researching, developing, manufacturing and marketing a treatment, including ATMPs, falls within the scope of the operations of a hospital.

113 For example: UZ Gent is part of the broader University of Ghent, decreet d.d. 3.2.2017 betreffende de re-integratie van het Universitair Ziekenhuis Gent in de Universiteit Gent (BS 27.2.2017) en het Bijzonder decreet d.d. 3.2.2017 tot wijziging van diverse bepalingen van het bijzonder decreet van 26 juni 1991 betreffende de Universiteit Gent en het Universitair Centrum Antwerpen (BS 15.3.2017).

114 Note, however, that in accordance with Article 9:11 of the Belgian Code of Companies and Associations, such legal entity remains bound by any action in the context of such activities, unless the party participating to such activity knows or should have known that the action was not within the scope of the statutory object of the entity.

115 Art. 9:4, 4° Belgian Code of Companies and Associations; D. VAN GERVEN, Verenigingen, vennootschappen en stichtingen. Deel 1. Rechtspersoonlijkheid. Verenigingen, stichtingen & publiekrechtelijke rechtspersonen, in Reeks 'Beginselen van Belgisch Privaatrecht', nr. 4, Wolters Kluwer Belgium, Mechelen, 2022, 371.

116 Art. 2:113, § 1, 3° BCCA

117 D. VAN GERVEN, Verenigingen, vennootschappen en stichtingen. Deel 1. Rechtspersoonlijkheid. Verenigingen, stichtingen & publiekrechtelijke rechtspersonen, in Reeks 'Beginselen van Belgisch Privaatrecht', nr. 4, Wolters Kluwer Belgium, Mechelen, 2022, 158

Operation of a hospital

Hospitals are defined as follows:

"[Ziekenhuizen zijn] de instellingen voor gezondheidszorg waarin op ieder ogenblik geëigende medisch-specialistische onderzoeken en/of behandelingen in het domein van de geneeskunde, de heelkunde en eventueel de verloskunde in pluridisciplinair verband kunnen verstrekt worden, binnen het nodige en aangepaste medisch, medisch-technisch, verpleegkundig, paramedisch en logistiek kader, aan patiënten die er worden opgenomen en kunnen verblijven, omdat hun gezondheidstoestand dit geheel van zorgen vereist om op een zo kort mogelijke tijd de ziekte te bestrijden of te verlichten, de gezondheidstoestand te herstellen of te verbeteren of de letsels te stabiliseren. Deze ziekenhuizen vervullen een opdracht van algemeen belang."

The operations of a hospital are divided into services and functions.[118]

Services of a hospital are structured around the diagnosis and treatment needs of the patient and are characterised by allocated letters per type of service (e.g. C= Service for diagnosis of a surgical condition and surgical treatment, D = Paediatrics service, M = maternity service, etc.). For each service, requirements for recognition have been established, e.g. in relation to minimum bed capacity and occupancy rate, the technical equipment, the medical, paramedical and nursing staff, the activity level etc.

Functions of a hospital capture hospital activities which are not specific to a (type of) patient but benefit the care organisation to a patient and are transversal to the hospital services[119]. These functions include the hospital pharmacy[120], hospital blood bank[121], surgical day hospitalization[122], first aid emergency care[123], specialised emergency care[124], intensive care[125], local neonatal care[126], mobile emergency group (MUG)[127], palliative care, psychiatric care, family nursing[128], regional perinatal care[129], non-chirurgical day hospitalization, etc.

Finally, hospitals can also establish care programs ("*zorgprogramma's"),* which are reproductive medicine, cardiac pathology, oncology, the care program for children, the care program for the geriatric patient and stroke care.[130]

118 Art. 1 and 2 of the Royal Decree of 23 October 1964 for the determination of the requirements for hospitals and their services (BSG 7 November 1964).

119 Art. 79 Hospital Act

120 Royal Decree of 4 March 1991 laying down standards with which a hospital pharmacy must comply in order to be recognised

121 Royal Decree of 17 February 2005 laying down the standards with which a hospital blood bank must comply in order to be recognised

122 Royal Decree of 25 November 1997 setting the standards that the 'surgical day hospitalisation' function must meet to be recognised

123 Royal Decree of 25 November 1997 decree declaring applicable to the function "first reception of emergency cases, and Royal Decree of 27 April 1998 laying down the standards that a function "first reception of emergency cases" must satisfy in order to be recognised.

124 Royal Decree of 27 April 1998 declaring certain provisions of the law on hospitals, coordinated on 7 August 1987, applicable to the function "specialised emergency care" and Royal Decree of 27 April 1998 establishing the standards which a "specialised emergency care" function must meet in order to be recognised

125 Royal Decree of 27 April 1998 declaring certain provisions of the law on hospitals, coordinated on 7 August 1987, applicable to the standards that an 'intensive care function' must meet to be recognised

126 Royal Decree of 10 August 1996 establishing the standards that a local neonatal care function (N* function) must meet in order to be recognised

127 Royal Decree of 10 August 1998 laying down the standards that a "mobile emergency group" (MUG) function must meet in order to be recognised and Royal Decree of 20 September 2002 laying down the details of the maximum number and the programming criteria applicable to the "mobile urgency group" function

128 Royal Decree of 10 April 1991 laying down the standards that a psychiatric family nursing function must meet in order to be recognised

129 Royal Decree of 20 August 1996 establishing the standards which a function of regional perinatal care (P* function) must meet in order to be recognised

130 Royal Decree of 15 February 1999.establishing the list of care programmes as referred to in article 12 of the coordinated Act of 10 July 2008 on hospitals and other care facilities and designating the articles of the

Specifically for university hospitals, the Hospital Act also recognises that scientific research, development of new technologies and evaluating medical activities is part of the hospital activity.[131] Specific funding for research is part of university hospital funding in Belgium.[132]

Based on the above, it seems that the scope of hospital operations are defined with a focus on patient care. Hospital activities comprise organising different care modalities, but generally do not include commercially driven activities which are not focused on this element of patient care, i.e. the primary aim of hospital operations should be the provision of care to patients. As such, also the research and development and manufacturing of an ATMP under the hospital exemption falls within such scope, taking into account that the hospital exemption can only be used to manufacture ATMPs for own patient care; it is not intended to allow for broader distribution and marketing of ATMPs.

The scope of potential activities that fall within the permitted hospital operations is broader for academic hospitals, and, in addition to the activities focused on patient care also allow for academic activities such as the research and development of new technologies, including new therapeutic medicinal products such as ATMPs, also outside of the hospital exemption.[133]

It is doubtful, however, that this scope extends to the commercialisation of such medicinal products, including commercial manufacturing and distribution.

A. Flexibility of statutory purpose

Nevertheless, many hospitals, including general hospitals, have a broadly defined statutory object, comprising a purpose of patient care as well as ancillary commercial or industrial activities that directly or indirectly relate to its purpose, or that can help progress such purpose.[134] These references to ancillary activities are reminiscent of the (abolished) limitation under non-profit legislation that commercial activities were only allowable insofar the commercial activity is subsidiary to the non-profit goals of the association. Instead, for Belgian hospitals, these references stretch the scope of a hospital's allowed statutory object to include activities which are not strictly needed for their core purpose of patient care. An argument could be made

coordinated Act of 10 July 2008 on hospitals and other care facilities applicable to them

[131] Article 4 Hospital Act.

[132] Article 77 of the Royal Decree of 25 April 2002 on the determination and disbursement of financial resources for hospitals.

[133] Article 4 Hospital Act.

[134] Notwithstanding that Article 15 of the Hospital Act prescribes that the sole statutory object of the entity should be the operation of one or more hospitals (or health facilities or medical-social facilities), the bylaws expand such scope in most instances. For example, the bylaws of Emmaus VZW provide the following: "De vereniging mag a*lle initiatieven nemen, alle activiteiten uitoefenen of laten uitoefenen, kortom alle rechtshandelingen verrichten die rechtstreeks of onrechtstreeks met de verwezenlijking van haar doel te maken hebben en/of dit doel kunnen bevorderen. De vereniging kan in dit kader handelsactiviteiten voeren waarvan de opbrengsten zullen worden bestemd voor de verwezenlijking van het belangeloos doel"; the bylaws of AZ Delta VZW provide the following: "de vereniging heeft tot doel het oprichten, inrichten, beheren, en exploiteren, of het bijdragen hiertoe, van één of meerdere ziekenhuizen/of ziekenhuisdiensten het bijdragen hiertoe, van één of eerdere ziekenhuizen en/of ziekenhuisdiensten, alsmede van instellingen en diensten voor het verstrekken van welzijnszorg, ouderenzorg en gezondheidszorg in de breedste betekenis van het woord met inbegrip van alle andere activiteiten, zoals het verstrekken van vorming en opleiding, wetenschappelijk onderzoek, enz., die rechtstreeks of onrechtstreeks tot het verwezenlijken ervan kunnen bijdragen en dit met uitsluiting van enig winstoogmerk [...] De vereniging zal tevens activiteiten van commerciële, industriële of financiële aard mogen verrichten voor zover deze bijdragen tot het verwezenlijken van het doel van de vereniging en kaderen in de wettelijke mogelijkheden."* It is common for associations (as for corporations) to word their statutory objects in a broad way, to create flexibility and allow evolution in the entity's activities. These 2 examples (Emmaus VZW and AZ Delta VZW) may be part of that practice. Obviously, no practice of such wording can override the restriction of Article 15 Hospital Act. The self-imposed limitation in the bylaws of AZ Delta (*"in de wettelijke mogelijkheden"*) is worth to note; it may reflect awareness of the limitation of Article 15 Hospital Act.

that the marketing of a medicinal product at least indirectly supports patient care, and hence should be permitted as ancillary commercial activity of the hospital. Moreover, it is clear that the niche in which Academia would most likely operate is driven by the lack of interest of primarily commercial actors: indications for which there is an unmet clinical need and a small patient population; fulfilling the full development and marketing trajectory produces better safety and efficacy information and has a broader potential to obtain reimbursement, improving care that can be provided to patients. In addition, it can be envisaged that the commercial freedom of Academia would be restricted in the interest of patient access and care, by government involvement in supporting this commercial pathway.

Moreover, at least one Belgian university hospital (UZ Leuven) has obtained a (national) marketing authorisation for a (radiopharmaceutical) medicinal product (Glucogast 1850 MBq/ml inj. opl. i.v. flac., which is reimbursed and on the market.

B. Separating commercial activity from hospital operations in a special purpose vehicle (SPV)

A solution to the abovementioned incompatibility may exist in separating the commercial activity from the activities that relate to the hospital operations, functionally, but also legally, by establishing a separate legal entity which takes on the development activities, in cooperation with the hospital, and which takes on the further commercialisation of the resulting ATMP.

For Academia that fall within the scope of the Codex Hoger Onderwijs, conditions under chapter 2 of such Codex need to be taken into account, which include restrictions on taking on founder's responsibility.[135] KULeuven, for example, restricts spin-out participations to two thirds of the share capital.[136]

This approach would have several benefits:

- It avoids contamination of hospital operations by commercially focused activities;
- It allows for risk containment, since the risks of operating a hospital differ from the risks and responsibilities connected to the commercialisation of a medicinal product (see below);
- It allows the separate legal entity to better define its own strategy.
- The demarcation between the non-economic activity and economic activity from a competition law perspective would also be reflected in the legal structure of the development.

The goal to ensure accessibility and affordability could be ensured through the inclusion of social responsibility commitments towards the founding institution. This can be achieved through the inclusion of socially responsible licensing clauses in the relevant contractual documentation between the parties. Alternatively, these commitments could be enshrined in the statutory purpose of the legal entity.

In a 'standard' spinoff, a new commercial legal entity is created in which the commercial activities are further developed and external investments can be attracted. Another paradigm could entail organising such SPV as a drug developer that is not seeking to maximise profits. For example, the new legal entity could be established as a non-profit association or foundation (since there are no specific limitations that exist in relation to their economic activities, see above). Other legal forms that could be considered are social profit entities, such as a cooperation recognised as a social enterprise. The latter are companies that incorporate a social purpose into their statutory object, which it must consider in its operational model. Consequently, it allows these entities to prioritise social benefits over shareholder value.[137]

135 https://data-onderwijs.vlaanderen.be/edulex/document.aspx?docid=14650

136 https://lrd.kuleuven.be/spinoff/faq-spinoff

137 MARA DEL BALDO, "Acting as a benefit corporation and a BCorp to responsibly pursue private and public benefits. The case of Paradisi Srl (Italy)", International Journal of Corporate Social Responsibility (2019), 4:4; ALAIN FISCHER, MATHIAS DEWATRIPONT and MICHEL GOLDMAN,

C. Conclusion

Notwithstanding the limited example of UZ Leuven, the scope of activities that are legally permitted for hospitals under the Hospital Act is too unclear for a hospital to reliably follow a commercially focused development process up to and including the marketing of a medicinal product. The limitation of Article 15 of the Hospital Act could be seen as an obstacle to opening Belgian hospitals' activities to the actual marketing of ATMPs. Indeed, to fit within the provision, marketing ATMPs would need to qualify as an activity of a hospital, a health facility or a medical-social activity (ziekenhuis, gezondheidsvoorziening, medisch-sociale inrichting). None of those seems to be an evident basis for developing the activity of marketing ATMPs. The risk exists for hospitals that the development of commercial activities such as obtaining a marketing authorisation for medicinal products is considered incompatible with their restricted legal purpose.

Interestingly, the law itself gives the Belgian government a role in further shaping the restriction of Article 15, as the Belgian government is authorised to allow deviations to the restriction[138]. Consequently, if the government seeks to incentive the development of ATMPs by Academia, it should consider creating certainty for Academia in relation to such activities as regards their status as hospital under Article 15 of the Hospital Act, for example by elaborating specific deviations for specific development programs of Academia, confirming these programs and potential marketing authorisations resulting therefrom do not conflict with these restrictions.

4.2.3.2. Legislation on medicinal products

Incompatibility for pharmacies

Other statutory restrictions exist in the Law of 25 March 1964 on medicinal products for human use, which seemingly prohibit hospitals to commercialise a medicinal product.

The manufacturing of medicinal products requires a license, to be obtained with the ministry upon advice of the FAMHP.[139]

Art. 12*ter* of the Law of 25 March 1964 specifies that a manufacturing license includes a wholesaler license for the products under the manufacturing license. Without such wholesaler license, the manufacturer would be unable to hold and ship its products.[140] However, the same Art. *12ter* also contains a strict incompatibility between a wholesaler and a pharmacy (or a doctor or dentist).[141]

As set out above, the hospital pharmacy is a core function of a hospital, which is operated within the same legal entity as the hospital. The strict incompatibility between wholesalers and pharmacy limits the hospital's ability to market a medicinal product. While such wholesaler's license is not required to supply the hospital itself, further distribution of the product would necessitate such license, but would not be possible under the present legal framework.

Interestingly, the establishment of an SPV to proceed to the commercial stage for the product (as described above) would alleviate this

"Benefit Corporation: a path to affordable gene therapies?", Nat Med. 2019 Dec;25(12),1813-1814; M. D'HERDE, "Van VSO naar CV erkend als SO : geslaagde restyling, of doorgeslagen striptease?", TRV 2018, (817) 830.

138 *"De Koning kan, bij een besluit vastgesteld na overleg in de Ministerraad, in afwijkingen voorzien ten aanzien van de bepaling bedoeld in het eerste lid."* (Article 15 paragraph 1, second sentence Hospital Act)

139 Art. 12bis, paragraph 1 of the Law of 25 March 1964.

140 Note that such wholesaler license is needed to enable the manufacturer to keep the product in stock after production, and supply it further down the supply chain. The definition of wholesale distribution of medicinal products under Art 1 §1, 17) was taken from Directive 2001/83/EC, and includes any activity consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public. Such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorised or entitled to supply medicinal products to the public in the Member State concerned.

141 Art. 12ter, § 1, paragraph 8, while specifying also that these persons do not need a wholesaler license to dispense medicines to the public. Interestingly, no wholesaler's license was granted to UZLeuven.

incompatibility. Indeed, such separation would ensure the pharmacy function of the hospital and the exploitation of the product are not intertwined.

That being said, the current legal framework seems in any case to some extent incompatible with a hospital taking on a fully in-house development pathway for ATMPs, including the final marketing thereof. Formal deviations to this incompatibility should be established, for example by allowing specific exceptions under Art. 12*ter* of the Medicines Act.

Healthcare compliance

Entities that bring a pharmaceutical product to the market are subject to stringent regulations regarding healthcare compliance, i.e. how they can interact with healthcare organisations, healthcare practitioners and patients, without unduly influencing the decisions of these actors.

In Belgium, Article 10 of the Medicines Act includes a broad prohibition, in the context of supplying, prescribing, dispensing or administering medicines, to promise, offer or allocate, directly or indirectly, premiums or benefits in cash or in kind to wholesalers, to mediators, persons authorised to prescribe, supply or administer medicines, as well as to institutions where the prescription, delivery or administration of the medicines takes place.

Article 10 of the Medicines Act starts from the traditional set-up of a pharmaceutical company that might influence the prescribing behaviour of healthcare practitioners and the purchasing decisions of healthcare organisations to enhance its sales. It is clear that the legislator did not consider the possibility of Academia, and in particular healthcare organisations themselves as marketing authorisation holders.

In the event the healthcare organisation would be the marketing authorisation holder, the classic dichotomy pharmaceutical company and healthcare organisation becomes vague. Healthcare practitioners are closely connected to the healthcare organisation: they sit in the governance bodies of the healthcare organisation and are paid by the healthcare organisation.[142]

One could question whether a healthcare organisation holding a marketing authorisation for a medicinal product is not inherently providing benefits to institutions where the prescription, delivery or administration of the medicines takes place if it is purchasing the medicinal product for which it is the marketing authorisation holder. In addition, it is not inconceivable that healthcare practitioners might be incentivised to prescribe the medicinal product marketed by the hospital for which they are working. Of course, if such marketing authorisation is held for an ATMPs that aim to treat patients with previously clinical unmet needs, and hence the only valid treatment option would be the product for which the healthcare organisation is the marketing authorisation holder, such incentive might be less present.

Pharmaceutical companies traditionally are very well aware of the implications of Article 10 of the Medicines Act and have dedicated regulatory and compliance functions within their organisation to ensure the company stays within the boundaries of the law. Academia are not familiar with the role that generally is under scrutiny and will need to put in place the rigorous processes and standards of operations to ensure that Article 10 is complied with.

An additional complexity in this regard could be the clinical practice of off-label prescriptions. Healthcare practitioners enjoy a broad therapeutic freedom under Article 73, § 1, of the Act on compulsory insurance for medical care and benefits coordinated on 14 July 1994, Art. 31 of the coordinated law of 11 May 2015 on the exercise of healthcare professions and Art. 4 of the law of 22 April 2019 on quality practice in healthcare. This freedom includes that practitioner may (or even have to if there is no alternative) prescribe an off-label treatment to its patients, if they determine that such treatment is justified for the patient's well-being.

However, under Article 9 of the Medicines Act, it is not allowable to promote the use of unauthorised medicinal products, including the use of medicinal products outside of their authorised indication. A conflict hence may arise

142 For example, the governance of every hospital must include a head-doctor and a medical council (Art. 18 and 132 Hospital Act).

between the prohibition of off-label promotion, and the prescribing behaviour of healthcare practitioners working at the marketing authorisation holding healthcare organisation, taking into account the relationship between healthcare practitioners (which can be an employment, a service, or a statutory engagement,) and the healthcare organisation.

The risk of infringement of Art. 9 and 10 of the Medicines Act by a healthcare organisation-marketing authorisation holder hence would become an issue that may impede adoption of healthcare organisations of initiatives to progress the full commercialisation pathway of a medicinal product.

A separation of the quality of marketing authorisation holder and healthcare organisation through the incorporation of an SPV might help resolve the inconsistency between both. However, depending on the involvement of Academia in the governance (and compensation received) of the SPV, such issues may still persist.

To enable Academia to pursue a development trajectory for ATMPs up to marketing of the final product, the legal compliance framework under articles 9 and 10 of the Medicines Act will need to be streamlined, to take into account cases in which the classic dichotomy between pharmaceutical manufacturer and healthcare organisations no longer apply, for example through the issuance of specific guidelines by the FAMHP to help guide Academia in their compliance programs.

4.2.4. Feasibility of commercialisation by Academia

In addition to the legal restrictions identified above (including also state aid considerations), Academia should consider additional legal requirements that may impact the feasibility of the development of commercial activities in ATMP development (i.e. pursuing marketing authorisation). Manufacturers and marketing authorisation holders of medicinal products are subject to specific legal obligations and responsibilities in relation to the product they market, which may be difficult to reconcile with the organisational model of Academia.

In this section, the risks associated with the strict product liability regime will be discussed, especially in relation to Academia, which might not have correct insurance arrangements in place to cover these liabilities. In addition, this will explore the difficulties for Academia to comply with the different responsibilities that apply to marketing authorisation holders.

4.2.4.1. Product liability

Academia, in particular hospitals, are well-versed and prepared for handling traditional liability associated with correctly diagnosing and choosing the right treatment method for a particular patient.[143]

However, “marketing” medicinal products expands potential liability of the hospital to the (strict) liability in relation to the therapy itself. This section explores the rules of product liability in Belgium and more specifically how these would be applied to complex therapies such as ATMPs developed, manufactured and “brought to market” by Academia. I

143 On that subject, see also S. LIEVENS, “De centrale aansprakelijkheid van het ziekenhuis voor zelfstandige artsen: een kwalificatievraagstuk inzake arbeidsrelaties”, *T.Gez*. 2022-23, afl. 2, 170-175; N. EL YATTOUTI, “Centrale aansprakelijkheid van het ziekenhuis: de relevantie van het bestaan van een zorgovereenkomst”, *T.Gez.* 2021-22, afl. 3, 236-239.

The legal framework

The current legal framework

The Belgian product liability framework is laid down in the Product Liability Act of 25 February 1991 (the "**Product Liability Act**") and is a national implementation of the Directive no. 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products. In essence, the framework establishes a strict liability regime whereby manufacturers are held responsible for the safety of their products.

Several actors can be considered manufacturers under the act, i.e. manufacturer of a finished product, the manufacturer of a component of a finished product, the manufacturer or producer of a raw material, as well as any person who presents himself as a manufacturer or producer by affixing his name, trademark or other identifying mark to the product.[144] If [145]under the Product Liability Act, a manufacturer will generally be held liable for damages caused if its product is faulty, which is assessed based on the general safety expectations a user of the product can have. These general safety expectations are assessed on a case-by-case basis, but are influenced by, *inter alia* the information on adverse effects in the package insert, the general presentation of the product to the public and the time at which the product was put on the market. [146].

Article 8 of the Act describes several situations in which the manufacturer can escape liability. Particularly relevant for cell and gene therapy is the defence that the state of scientific and technical knowledge at the time the product was put into circulation made it impossible to detect the existence of the defect.[147]

Liability claims can be initiated for material damage and physical damage. This may, inter alia be medical costs, loss of income, funeral costs and moral damage. Although the European legislator offered the possibility to introduce a product liability cap, the Belgian implementation does not provide for such cap. The amount of the compensation is therefore in principle unlimited. It must however be noted that Belgian law does not allow for punitive damages. The maximum amount of damages to be paid will therefore be the real suffered losses by the plaintiff. In case of damages which are hard to quantify, judges generally use a table of compensation to estimate the amount of personal suffering.

The Product Liability Act does not set up a specific burden of proof regime, so that the general rule applies. In this general regime, the plaintiff typically carries a high burden of proof which renders pharmaceutical liability cases rare in Belgium. The plaintiff will have to (i) prove a fault in the product, (ii) their own damage, and (iii) causality between the fault in the product and the damage. However, the bearer of the loss will not have to prove any fault on the part of the producer (such as negligence), a cause of the fault in the product, or the existence of the fault upon delivery of the product. In a case before the court of Liège in 2014, the judge decided that the causal link between the use of a product (a hepatitis B vaccine) and damages (a neurological disease) needs not be an absolutely certain one. A reasonable presumption by the judge suffices[148].

A plaintiff cannot bring a claim under the Product Liability Act after more than 10 years, starting from the day the product was brought into commerce[149].

[144] Article 3 of the Product Liability Act.
[145] Article 9 of the Product Liability Act.
[146] Article 5 of the Product Liability Act.
[147] Article 8, e) of the Product Liability Act.
[148] Court of Appeal Liège 9 October 2014, *RGAR* 2015, no. 15153.
[149] Article 12 of the Product Liability Act.

The revision of the Product Liability Directive

The current EU rules on product liability, based on strict liability of manufacturers have been written almost half a decade ago and are not necessarily fit for new and complex (healthcare) technologies. At the end of 2022, the European Commission has published a proposal for the revision of the product liability directive.[150]

The proposal seeks to modernise the European Union's product liability regulations to better accommodate the digital era, circular economy business models and the complexities of global value chains. It aims to ensure that consumers are adequately compensated for defective products, even if they are manufactured outside the EU. The proposal introduces new provisions to address liability concerning new technologies, including artificial intelligence systems, and digital services that impact product functionality. Remarkably, no attention is paid to evolving and complex health technologies, such as ATMPs. Additionally, the new directive aims to ease the burden of proof for victims in specific situations.[151]

The proposed directive on liability for defective products implements various elements, such as firstly the extension of the 'product' definition to digital manufacturing files and software. Secondly, in case of a product's substantial modification, the person making the substantial modification shall be held liable as the manufacturer of the modified product. Thirdly, equal protection must be afforded to defective products originating from non-EU manufacturers, mirroring the level of protection offered to products from EU manufacturers. Fourthly, the Council has simplified the presumptions applied in cases where claimants encounter significant challenges, especially those arising from the technical or scientific complexity of the case. Lastly, in situations where the symptoms of personal injury gradually manifest, the expiration period is prolonged to 20 years.[152]

ATMPs challenge traditional product liability concepts

The highly specialised, complex and individual nature of ATMPs puts the traditional concepts of current product liability legislation and its application under pressure on a number of fronts.

Chain of actors and definition of manufacturer

The management of the supply chain for Advanced Therapy Medicinal Products (ATMPs) involves several unique challenges: the presence of numerous stakeholders, the increased personalisation, and consequently, the absence of standardised manufacturing procedures for these products[153]. These features put tension on the traditional concept of manufacturer used in the present product liability legislation.

Defining the role of a "manufacturer" within the legal framework, along with the regulatory responsibilities it entails, presents a complex challenge for companies operating in Europe, particularly in the realm of ATMPs. Specifically, for medicinal products utilizing autologous cells, the manufacturing process involves a series of intricate steps. These include the initial extraction of cells from patient tissue, their isolation, transportation to the clinic, removal from carrier containers, site preparation for implantation, final preparation such as trimming, and ultimately, implantation itself. Consequently, a thorough legal risk analysis for any ATMP-focused company necessitates a detailed examination of which of these steps truly constitute "manufacturing". While the role of the "manufacturer" is central to

150 Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on liability for defective products, https://eur-lex.europa.eu/resource.html?uri=cellar:b9a6a6fe-3ff4-11ed-92ed-01aa75ed71a1.0001.02/DOC_1&format=PDF

151 The European Parliament, New Product Liability Directive, www.europarl.europa.eu/RegData/etudes/BRIE/2023/739341/EPRS_BRI(2023)739341_EN.pdf (consulted on 19/02/2024).

152 The Council of the EU, The Council adopts its negotiating mandate for a new EU law on liability for defective products, www.consilium.europa.eu/en/press/press-releases/2023/06/14/the-council-adopts-its-negotiating-mandate-for-a-new-eu-law-on-liability-for-defective-products/pdf (consulted on 19/02/2024).

153 C. Di Mauro and C-H. Caron, Gene therapy development in Europe brings layers of liability risks, available at: Gene therapy development in Europe brings layers of liability risks - Lexology.

the administration of ATMPs, it's essential to recognise the significant contributions of healthcare practitioners and hospital teams, who also carry new legal risks in this evolving landscape. At each stage of an ATMP procedure, the outcome can be compromised by factors like contamination, or incorrect manipulation by healthcare practitioners. Consequently, legal liability may be distributed among the legal manufacturer of the ATMP, contract manufacturers, or other involved service providers, as well as those responsible for tissue extraction and implantation.[154]

Individualised Nature of Therapies:

By their very nature, ATMPs are highly individualised treatments which pose unique and inherent risks. Unlike traditional pharmaceuticals, these therapies involve manipulating a patient's (own) biological material. Determining the safety expected by a patient becomes intricate when the product itself is tailored to an individual's unique genetic makeup. In addition, the utilization of human biological material and the possibility of triggering immune responses generate unique risks for patients[155].

The concept used in traditional product liability legislation of "safety expected by the patient" assumes a level of predictability in product outcomes. However, each patient's response to these therapies is inherently unique, making it challenging to establish a universal safety threshold that aligns with individual expectations.

The highly specialised, complex and individual nature of ATMPs puts the traditional concepts of current product liability legislation and its application under pressure on a number of fronts.

These are concerns which become critical in terms of liability if it means that the benefits and risks of the respective therapies may not be able to be universally translated in the presentation of the product (i.e. the package leaflet or product information)[156]

Evolving understanding of risks and benefits

ATMP developers often operate at the frontier of medical knowledge, with evolving understandings of both risks and benefits. ATMPs are often indicated for serious, life-threatening diseases and often harbour different, new and higher risks than conventional drugs. The more severe the disease, the more inadequate the available treatment alternatives and the higher the probability of a successful therapy with a novel active substance, the more patients are generally willing to accept serious side effects. The question of what risk a patient is willing to accept when the drug is their only hope of survival is difficult to assess and makes the application of the current product liability framework a challenge.

In addition, adverse events may manifest over an extended period, requiring a nuanced understanding of temporal dynamics that may not align with the prescription limitation set by traditional liability frameworks, such as the ten year limitation in the Belgian Product Liability Act. In this regard, the proposal to extent this period to twenty years in some cases under the novel product liability legislation are probably welcome for patient, while at the same time extending and increasing the exposure for ATMPs developers.

In conclusion, the rise of ATMPs presents a significant challenge to traditional product liability legislation. The complexity of the ATMP supply chain and individualised manufacturing processes strains conventional legal definitions of a "manufacturer," while the personalised nature of these therapies complicates the establishment of universal safety thresholds. Additionally, evolving understandings of risks and benefits, particularly in the context of life-threatening diseases with limited treatment options, challenge the temporal constraints of current liability frameworks. To address these

154 C. Di Mauro and C-H. Caron, Gene therapy development in Europe brings layers of liability risks, available at: Gene therapy development in Europe brings layers of liability risks - Lexology

155 C. Di Mauro and C-H. Caron, Gene therapy development in Europe brings layers of liability risks, available at: Gene therapy development in Europe brings layers of liability risks - Lexology.

156 Av Alexander Klatt, Cell and Gene Therapies: An Overview of Liability Risks. Consulted on 22 October 2024, https://qbe.se/nyheter-och-rapporter/bloggartiklar/cell-and-gene-therapies-an-overview-of-the-liability-risks/

challenges, regulatory bodies, legal experts, and industry stakeholders must collaborate to adapt liability frameworks to accommodate the unique characteristics of ATMPs. The European revision of the product liability legislation and the lack of attention paid therein to new health technologies appears to be a missed opportunity in this respect.

4.2.4.2. Responsibilities for marketing authorisation holders

Obtaining a marketing authorisation for an academically developed ATMP could yield various benefits for patient access (see section 6.3 of the scientific report). However, it should be considered that holding a marketing authorisation and marketing a product also comes with certain commitments in relation to the product, commitments for which Academia may not be adequately equipped in their current organisational model.

- ***Obligation to market:*** Marketing authorisation holders not only have the right to market their product, but also have an obligation to do so. This includes ensuring no out-of-stock of marketed product occurs. Under the EC Pharma Proposal, these continuity of supply obligations are set to be further strengthened, including the establishment of shortage prevention and mitigation plans.
- ***Pharmacovigilance***: once placed on the market, medicines must continue to be monitored (pharmacovigilance) to assure that any event or adverse side effect that could impact the safety profile of a medicine is detected and assessed and that necessary measures are taken. Also lack of efficacy should be evaluated long term. The EMA also gives scientific support to developers to help them design pharmacovigilance and risk management systems used to monitor the safety of these medicines.[157] According to the EMA, a prolonged post-marketing follow-up might be required for ATMPs, depending on the intended therapeutic effect, to assess the long-term safety and unique risks associated with them.[158] In case of quality concerns, the marketing authorisation for the product may be suspended or even withdrawn.
- ***Information:*** Whilst on the market, new data or information on the products' efficacy, safety, or production may become available or changes may occur. In this case, it is the responsibility of the marketing authorisation holder to send a 'variation' application to the health authorities. After marketing authorisation has been granted, any change to the data in the dossier must be submitted to the competent authorities. The underlying principle is that changes in the information that was decisive for the granting of marketing authorisation require a change in the marketing authorisation and therefore the approval of the competent authority, while other changes (that are less important in terms of, e.g. safety and efficacy considerations) only need to be notified (in advance, or sometimes only after implementation of the change).[159]

4.2.4.3. Conclusions

Many legal hurdles exist for Academia to bring an ATMP to the market. Some of these hurdles, such as the incompatibilities regarding their activities relate to their operations as a hospital and could to some extent be mitigated by the creation of an SPV.

Other hurdles exist in the additional exposure activities as a marketing authorisation holder would generate, including product liability for the marketed ATMP, as well as responsibilities in relation to their marketing authorisation.

157 https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview

158 https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-stem-cell-based-medicinal-products_en.pdf

159 See in particular Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02008R1234-20210513&qid=1657204000089.

Aforementioned incompatibilities could generally be solved by allowing for specific deviations to the legal framework applicable to hospitals in Belgium in case of specific government supported development programs. In this regard, specific authorisation requirements could be envisioned, ensuring that these deviations are only granted in exceptional circumstances, where the government has identified the need for academic drug development. Broader, more structural deviations should be embedded in a more thorough reform of hospital and medicines legislation and resulting incompatibilities.

Direct support measures in relation to marketing authorisation risks and responsibilities, (e.g. government guarantees for product liability, administrative support measures) will need to be assessed under state aid considerations (see section 8.2.3 of the scientific report).

5. MANUFACTURING REQUIRMENTS FOR ATMPS

QUINZ

The European Union upholds stringent quality standards for the manufacture of pharmaceutical products. A framework of manufacturing authorisations guarantees that all medicinal products that are approved for commercialisation on the European market have exclusively been manufactured by authorised producers subject to scrutiny by competent authorities overseeing their operations. Such manufacturing authorisations are required by all pharmaceutical manufacturers in the EU.[160]

Pursuant to the Medicines Act manufacturers of pharmaceutical products should equally obtain a manufacturing authorisation.[161] There are however exceptions to this rule, *e.g.*, such a manufacturing authorisation is not required for magistral preparations of medicinal products, *i.e.,* products that are prepared in the pharmacy according to a prescription for a specific patient.[162]

In order to obtain a manufacturing authorisation, the applicant needs to meet at least the following requirements:

- specify the medicinal products and pharmaceutical forms which are to be manufactured or imported and also the place where they are to be manufactured and/or controlled;
- have at its disposal suitable and sufficient premises, technical equipment and control facilities complying with the specific legal requirements;
- have at its disposal the services of at least one qualified person.[163]

160 Article 40 EU Directive 2001/83/EC; EudraLex – Volume 4 – Good Manufacturing Practice (GMP) guidelines, Introduction, European Union, Brussels, Feb 2011, 2 [Online]. URL: https://health.ec.europa.eu/system/files/2016-11/2011_intro_en_0.pdf.

161 Article 6, § 1 Medicines Act of 25 March 1964.
162 Article 6quater, § 3 Medicines Act of 25 March 1964.
163 Article 41 EU Directive 2001/83/EC

- In addition, a manufacturing authorisation holder is, amongst others, required to:
- have at its disposal the services of qualified staff who comply with the relevant legal requirements;
- be committed to only deliver pharmaceutical products to other license holders as per the Medicines Act;
- comply with GMP;
- notify the FAMHP of any variation to the information provided by it to obtain the manufacturing authorisation.

Specifically, for ATMPs containing GMOs, manufacturing also requires specific environmental authorisations, generally under the framework of contained use (see also 2.3.4.2 of this Supplement).

5.1. GMP Requirements

Adherence to GMP is obligatory for all pharmaceutical products that are commercialised in the European Union (and thus have received a marketing authorisation).[164] Similarly, the manufacturing of investigational medicinal products must also align with GMP requirements.[165] ATMPs that are administered to patients pursuant to the hospital exemption equally need to be manufactured under equivalent standards as apply for the manufacturing of products for commercialisation in the European Union.[166]

Pursuant to Article 47, § 1 of the EU Directive 2001/83/EC the Commission is authorised to specify the principles and guidelines of good manufacturing practices for medicinal products. Consequently, the EU Directive 2017/1572 and Commission Delegated Regulation 1252/2014[167] lay down such general GMP principles.[168]

In addition, Article 5 of the ATMP Regulation No 1394/2007 has mandated the Commission to draw up specific guidelines on good manufacturing practices that are specific to ATMPs.

These detailed guidelines are set out in Part IV of Volume 4 of the rules governing medicinal products in the European Union (hereinafter "**ATMP GMP Guidelines**")[169] and thus elaborate on the GMP requirements to be implemented for the manufacturing of both authorised ATMPs and investigational ATMPs. These ATMP GMP Guidelines are relevant only for ATMPs.[170]

The following paragraphs set out a summary of the GMP requirements applicable to ATMPs and the potential impact thereof on, or difficulties to be expected to be encountered by, Academia.

164 Article 46(f) EU Directive 2001/83/EC

165 Article 63(1) EU Regulation 536/2014

166 Article 40 EU Directive 2001/83/EC; EudraLex – Volume 4 – Good Manufacturing Practice (GMP) guidelines, Introduction, European Union, Brussels, Feb 2011, 2. URL: https://health.ec.europa.eu/system/files/2016-11/2011_intro_en_0.pdf.

167 This Commission Delegated Regulation specifically has regard to principles and guidelines of good manufacturing practice for active substances. ATMPs can also contain active substances (https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf)

168 The exclusion referred to in Section 1.12 of the [Detailed Guidelines] refers to second subparagraph of Article 47 Directive 2001/83. Consequently, the (general) principles referred to in subparagraph 1 and 3 of Article 47 Directive 2001/83 are applicable. These subparagraphs serve as legal basis for EU Commission Directive 2017/1572 and EU Commission Delegated Regulation 1252/2014

169 EudraLex – Volume 4 – Good Manufacturing Practice (GMP) guidelines, Part IV – GMP requirements for Advanced Therapy Medicinal Products, European Union, Brussels, Oct 2017. URL: https://health.ec.europa.eu/system/files/2017-11/2017_11_22_guidelines_gmp_for_atmps_0.pdf.

170 Article 40 EU Directive 2001/83/EC; EudraLex – Volume 4 – Good Manufacturing Practice (GMP) guidelines, Introduction, European Union, Brussels, Feb 2011, 2. URL: https://health.ec.europa.eu/system/files/2016-11/2011_intro_en_0.pdf.

5.2. Quality Assurance

Quality plays a major role in the safety and efficacy profile of ATMPs. The ATMP GMP Guidelines identify that the manufacturer of an ATMP – whether that be for commercial or investigational purposes – is responsible for the implementation of appropriate measures to safeguard the quality of these ATMPs. This quality system should be designed with the objective to ensure that pharmaceutical products are of the quality required for their intended use.

When setting up a quality system, the size of the company and the complexity of the activities should be taken into account.[171]

Ensuring compliance with GMP is an essential part of the quality system. A continuous assessment of that quality assurance system, and its effectiveness, is thus very important. The quality system should ensure, at minimum, the following:

- personnel is adequately trained and has a clear understanding on the allocation of responsibilities;
- premises and equipment are suitable and are appropriately maintained;
- an adequate documentation system is in place ensuring that the appropriate specifications are laid down, the production process is clearly understood and the appropriate records are kept;
- an adequate manufacturing process to ensure consistency;
- the quality control system operates independent from manufacturing;
- a system for prospective evaluation of planned changes, approval process before their implementation and evaluation of implemented changes;
- timely identification of quality defects and process deviations;
- adequate systems to ensure traceability of ATMPs.

In addition, specifically for ATMPs having obtained a marketing authorisation, quality review should be performed to review the functioning of the process, highlight trends and to identify opportunities for improvements. The frequency for these reviews should be determined on a case by case basis taking into consideration the specific risks of the underlying process and product, as well as the volume of such product being manufactured.

The entire manufacturing process and quality assurance strategy will have to be designed in such a way, leveraging a risk-based approach (cfr. *infra*), to guarantee the quality and safety of the ATMPs that are manufactured at the institution.[172]

This quality assurance requirements may pose difficulties for institutions considering that the main aim of hospital Academia is to simply ensure the best performance of care services for patients. Hence, they may not be accustomed to obtaining a pharmaceutical product with predefined quality characteristics.[173] Essentially, a change in the mindset of Academia, and especially in the quality assurance staff, may be needed in anticipation of ATMP manufacturing in order to ensure GMP compliance (see also in that regard section 6.2.1.2 and 8.3 of the scientific report), in which the mindset of Academia in relation to ATMP development at the stage of clinical trials

171 Article 40 EU Directive 2001/83/EC; EudraLex – Volume 4 – Good Manufacturing Practice (GMP) guidelines, Introduction, European Union, Brussels, Feb 2011, 2. URL: https://health.ec.europa.eu/system/files/2016-11/2011_intro_en_0.pdf.

172 Lancu M. E., Kandalaft E. L., Challenges and advantages of cell therapy manufacturing under Good Manufacturing Practices within the hospital setting, Current Opinion in Biotechnology (2020), 65, 233-241.

173 Vigano M., Giordano R., & Lazzari L., Challenges of running a GMP facility for regenerative medicine in a public hospital, Regen.Med (2017), 12(7), 803-813.

has been identified as an important consideration for later upscaling of ATMP treatment).[174]

The ATMP GMP Guidelines are fit for industrial manufacturing of ATMPs and have been developed keeping in mind the biological specificities of ATMPs. They do not take into consideration the specificities of an environment within Academia. Nevertheless, the ATMP GMP Guidelines do appreciate that ATMPs are often developed in such an environment, in which different quality systems are in place than the ones usually encountered in an industrial setting. Consequently, the ATMP GMP Guidelines find it necessary to recognise the need for flexibility in respect of how the various GMP measures can be implemented, while still safeguarding the quality, efficacy and safety of a product. The ATMP GMP Guidelines, therefore allow, basis the risk-based approach (see *supra*), manufacturers to implement alternative approaches to achieve the required standards. In doing so, these manufacturers will have to show, and properly document, that these alternative approaches are capable of meeting the same objectives.

That said, irrespective of where an ATMP is manufactured, the quality, safety and efficacy should at all times be ensured. Manufacturers thus remain responsible for the quality of ATMPs that they have manufactured, whether that manufacturer is operating in an industry setting or rather qualifies as Academia. While the application of a risk-based approach may thus facilitate compliance for certain Academia it will not release the obligation to comply with regulatory requirements and the content of the marketing authorisation (in case of an ATMP having obtained marketing authorisation).

5.3. Personnel, Premises & Equipment

Manufacturers of ATMPs should have an adequate number of qualified personnel having adequate practical experience relevant to the intended operations. Section 3 of the ATMP GMP Guidelines sets out multiple GMP requirements regarding personnel working in a GMP manufacturing facility. More specifically, the ATMP GMP Guidelines outline the necessity for personnel in ATMP manufacturing to possess relevant qualifications and practical experience. They emphasise comprehensive training, encompassing GMP principles and specific requirements for manufacturing. They also require the onboarding of a qualified person, attributing additional responsibilities to this person (see *infra*). Stringent hygiene standards are stipulated, mandating appropriate clothing for various clean area grades and forbidding personal items in clean areas. Key personnel roles like production and quality control should be clearly defined and communicated within the organisation. The ATMP GMP Guidelines emphasise distinct responsibilities for these roles and insist on avoiding overlap or gaps in their duties, particularly stressing the separation of roles for production and quality control. Translated to a setting in Academia, the most challenging task most probably will be the transformation of personnel with a (bio)medical background into pharmaceutical production and quality control specialists.[175] Efforts should be made by Academia personnel in GMP training through certification courses. With sufficient training and study, existing staff should be able to adopt knowledge of the rules of pharmaceutical standards necessary for working in a GMP manufacturing facility.[176] [177]

Additionally, Sections 4 and 5 of the ATMP GMP Guidelines highlight the importance of purpose-built facilities that reduce contamination risks by focusing on cleanliness, ideal environmental conditions, and robust monitoring. This involves separating different manufacturing activities,

174 Vigano M., Giordano R., & Lazzari L., Challenges of running a GMP facility for regenerative medicine in a public hospital, Regen.Med (2017), 12(7), 803-813.

175 Vigano M., Giordano R., & Lazzari L., Challenges of running a GMP facility for regenerative medicine in a public hospital, Regen.Med (2017), 12(7), 807.

176 Vigano M., Giordano R., & Lazzari L., Challenges of running a GMP facility for regenerative medicine in a public hospital, Regen.Med (2017), 12(7), 807.

177 Vigano M., Giordano R., & Lazzari L., Challenges of running a GMP facility for regenerative medicine in a public hospital, Regen.Med (2017), 12(7), 807.

rigorous environmental checks, and maintaining specific air pressures in different areas. Paying attention to details like drainage, storage, quality control zones, and other spaces is crucial too. Equally vital is ensuring that equipment poses no risk to the product and meets specific standards. This includes making sure parts touching the product won't affect its quality and keeping components interacting with cells or tissues sterile. Proper installation, maintenance, and qualification protocols also help minimise errors and contamination risks. The ATMP GMP Guidelines also stress the need for validated cleaning procedures. Furthermore, they emphasise controlling equipment movement, especially from high-risk areas, to prevent cross-contamination. The ATMP GMP Guidelines thus impose significant demands on Academia environments striving for GMP certification. As a consequence, Academia might struggle to fulfil all these premises and equipment related GMP requirements.

5.4. Documentation

Section 6 of the ATMP GMP Guidelines stresses the need for meticulous documentation to ensure quality control. Documentation is critical for transparency and traceability, especially for investigational products. The ATMP GMP Guidelines also highlight the importance of clear policies and procedures relating to equipment, validation, and quality control measures. Ultimately, these documentation practices form the backbone of ensuring strict adherence to quality standards throughout ATMP manufacturing. Academia can invest in establishing robust controls overseeing, monitoring and documenting all activities that could impact the quality of ATMPs. The primary challenge here might be integrating these new systems with the institution's existing IT system, which does not always meet GMP standards.[178] .(Silva, Chrobok et al. 2022, Johanna, Daudeij et al. 2023)

5.5. Materials

The quality of starting materials and other raw materials is key for the manufacturing of ATMPs. The specifications for each starting material and/or raw material should identify the defined level of bioburden or need to be sterile, which should be abided by before introduction of these raw materials and/or starting materials into the manufacturing process.

As is the case for other pharmaceutical products, the manufacturer should thus at all times verify the compliance of the materials with the agreed upon specifications.

Particularly for starting materials, *i.e.,* human tissues and cells, the donation, procurement and testing of these human tissues and cells should be performed in accordance with Directive 2004/23/EC.

The manufacturer (or marketing authorisation holder) should ensure there are quality requirements established for, and agreed with the suppliers of, these starting materials. In addition, thereto, any agreement between the manufacturer and the supplier of these starting materials should include clear provisions on the transfer of information regarding these materials, *e.g.*, test results, traceability, and any other information which may have an impact on the quality or safety of the ATMPs that would be manufacturing with such starting materials.

For clarity, even the initial processing steps, such as isolation of cells and/or tissue, is considered a manufacturing activity and thus should be performed in accordance with GMP and in a GMP environment. The ATMP GMP Guidelines are strict in stating that the use of cells that have not been isolated in a GMP environment should remain exceptional and should only be possible after having performed a risk analysis before use in the manufacturing process.

178 Vigano M., Giordano R., & Lazzari L., Challenges of running a GMP facility for regenerative medicine in a public hospital, Regen.Med (2017), 12(7), 805.

5.6. Production Process and Quality Control

The ATMP GMP Guidelines focus on ensuring product quality and compliance. Section 9 of the ATMP GMP Guidelines highlights adapting manufacturing processes based on evolving knowledge and emphasises stringent handling of incoming materials. It also outlines requirements for utilities like water and gases, addresses preventing cross-contamination, and details aseptic manufacturing protocols. Complexities in packaging and labelling investigational ATMPs is also addressed. Protocols for handling finished, rejected, and returned products to ensure quality and compliance are emphasised. For its part, Section 12 of the ATMP GMP Guidelines discusses quality control principles and procedures (as part of the broader *quality system* (see *supra*)). It emphasises that quality control isn't limited to laboratories and should influence all decisions impacting product quality. It highlights responsibilities of the quality control lead, including approving specifications and overseeing testing, and stresses the importance of retaining samples, appropriate sample storage, and the need for documented sampling plans. Additionally, it addresses testing methods, validation, and a stability program post-authorisation. In dealing with these and various other matters in an Academia environment, decisions should consistently be driven by risk assessment. Meticulously elaborating on the reasoning behind decisions made in the clinical trial authorisation dossier and during communication with regulatory agencies is imperative for GMP certification in light of production process and quality control requirements.[179]

5.7. Qualified Person and ATMP committees

According to Article 48(1) EU Directive 2001/83/EC, each manufacturer must have at least one qualified person. In accordance with Section 11.2 of the ATMP GMP Guidelines, a qualified person must meet specific qualifications beyond standard requirements and possess expertise in areas such as cell biology, biotechnology, and ATMP manufacturing processes. Their primary responsibility involves certifying each batch's compliance with marketing authorisations, GMP regulations, and product specifications. A potential challenge arises due to the inadequate number of qualified persons, particularly within Academia contexts. This presents a substantial issue because, akin to industrial settings, every batch of ATMPs produced within Academia (often tailored for specific patients) necessitates approval from a qualified person before administration to the patient. Considering that certain ATMPs require immediate administration post-production, this time constraint further complicates the situation significantly.

Moreover, the training provided to qualified persons might predominantly focus on industrial contexts, overlooking the nuances of an academic or hospital manufacturing environment. The established role of qualified persons appears tailored to suit conventional manufacturing settings characterised by large batch productions of medicinal products and extended drug stability periods, conditions vastly distinct from those typically encountered in an academic ATMP manufacturing environment.[180]

As a consequence, alternative approaches must be explored to facilitate the approval process by a qualified person. One potential strategy involves introducing a so-called “QP officer”. Such QP officer is only tasked with the product release, requiring a less extensive training regimen compared to that of a qualified person. In this scenario, the qualified person oversees the preliminary certification of the manufacturing procedure. Upon completion of the ATMP manufacturing process, the QP officer's role involves verifying the fulfilment of basic criteria. Essentially, the qualified person provides conditional pre-certification for the ATMP contingent upon meeting specific requirements, which are managed by the QP officer. Another plausible solution involves granting authorisation for qualified person release conducted off-site. This process entails transmitting manufacturing data from the production site (*i.e.,* the institution) to a centralised qualified person situated at a different location. Subsequently, based on the provided data,

179 Vigano M., Giordano R., & Lazzari L., Challenges of running a GMP facility for regenerative medicine in a public hospital, Regen.Med (2017), 12(7), 805-806.

180 Bicudo E. & Brass I, Institutional and infrastructure challenges for hospitals producing advanced therapies in the UK: the concept of point-of-care manufacturing readiness, Regen.Med (2022), 17(10), 726.

the off-site centralised qualified person could authorise the release of the product.[181]

As the challenge of qualified person availability persists, Academia have made strides in augmenting other staff-related aspects to bolster in-house manufacturing readiness. Some Academia have established ATMP committees, designed to coordinate various departments and facilities, such as testing labs, pharmacies, and clinical wards, involved in processing ATMPs within the institutional setting. These committees serve as a bridge, facilitating communication and collaboration among these areas. Following their assessment, the committee orchestrates the allocation of hospital resources, including physical space, documentation updates, and other essential tasks required for ATMP processing. As the frequency of in-house ATMP manufacturing rises, these committees will likely assume a pivotal role, potentially expanding their duties or serving as a blueprint for the formation of more specialised committees within Academia.[182]

5.8. Outsourced Activities

According to Section 13 of the ATMP GMP Guidelines outsourced activities in pharmaceutical manufacturing should rely on clear contracts, ensuring responsibilities are defined and compliance is maintained. Before outsourcing, the assigning entity evaluates the contractor's capability, ensuring alignment with GMP. The assigning entity shares comprehensive product and process details and reviews records to uphold quality standards. Contractors must maintain appropriate infrastructure, personnel, and traceability measures. Any process changes need prior approval. Moreover, contractors must allow audits by both the assigning entity and regulators. This collaborative approach hinges on precise communication, strict adherence to standards, and agreement on any process modifications to maintain quality in outsourced activities.

It might not be desirable (or feasible) for all Academia to try to set up an entire GMP facility on its own.[183] Moreover, as already briefly touched upon above, certain specific GMP requirements might impose significant demands on Academia striving for GMP certification simply too high to meet. A realistic alternative might thus be to set up collaboration between such an *(uncapable* or *unwilling*) Academia and a contract manufacturing organisation. In such a case, even though the institution wouldn't be manufacturing (everything) by itself, the ATMP GMP Guidelines continue to impose stringent requirements, as discussed above.

181 Bicudo E. & Brass I, Institutional and infrastructure challenges for hospitals producing advanced therapies in the UK: the concept of point-of-care manufacturing readiness, Regen.Med (2022), 17(10), 726.

182 Bicudo E. & Brass I, Institutional and infrastructure challenges for hospitals producing advanced therapies in the UK: the concept of point-of-care manufacturing readiness, Regen.Med (2022), 17(10), 726.

183 https://www.komoptegenkanker.be/sites/default/files/media/2022-02/White%20Paper%20-%20cell%20therapy%20def.pdf

5.9. Risk-based Approach

As already set out above, the European Commission acknowledges the intricacy of ATMPs, emphasizing their inherent unpredictability. This unpredictability stems from the diverse biological traits of starting materials and the intricacies within the manufacturing process itself, resulting in variable risks across both investigational and commercial ATMPs. Furthermore, the dynamic nature of scientific advancements in the ATMP sphere significantly impacts manufacturing methodologies. Consequently, the European Commission recognises that the above considerations justify a certain amount of adaptability, both of the procedures and the related controls. This flexibility allows manufacturers to implement the measures that are most appropriate, having regard to specific characteristics of the manufacturing process and of the product. This is particularly important in the case of investigational ATMPs, due to the incomplete knowledge of the products and manufacturing methodologies involved.

More specifically, the European Commission recognises in the ATMP GMP Guidelines that ATMPs are often developed in an institutional setting "*under quality systems different to those typically required for the manufacture of conventional medicinal products*." Therefore, a certain amount of flexibility in adopting and adapting GMP procedures and controls can be expected. Nevertheless, such flexibility should not be interpreted as an intention of the regulator to lower the guardrails when it comes to ATMPs. The ATMP GMP Guidelines make it clear that, irrespective of their development setting – be it through Academia or industrial – ensuring the quality, safety, and efficacy standards of ATMPs, even within the risk-based approach framework, remains imperative.

For commercial manufacturing, when dealing with authorised ATMPs, it's important to align the use of the risk-based approach with the terms outlined in the marketing authorisation. While detailing the manufacturing process and its controls in the marketing authorisation application (or, where applicable, during a variation submission), adjustments or deviations from standard expectations can be justified based on the unique characteristics of the product or manufacturing process. When elements are not explicitly addressed in the marketing authorisation, the manufacturer is responsible for documenting why a particular approach was taken when employing the risk-based method. They must also justify that all measures taken are sufficient to guarantee the product's quality.

5.10. Compliance with applicable tissue regulations

Medicinal products consisting of cells or tissues are regulated by EU Directive 2004/23/EC. Article 2 of this directive, however, provides that where manufactured products are covered by other EU legislation, the directive shall apply only to donation, procurement and testing of human tissues and cells intended for human applications and of manufactured products derived from such human tissues and cells. Specific rules governing ATMPs are set out in the ATMP Regulation No 1394/2007. Therefore, this limitation of the scope of application of EU Directive 2004/23/EC is applicable to ATMPs. Consequently, EU Directive 2004/23/EC only applies to donation, procurement and testing processes for ATMPs. The donation, procurement and testing of the cells and tissues used as starting materials should thus be in accordance with EU Directive 2004/23/EC (and as of 2027, the SoHO Regulation, see section 4.2 of the scientific report).

6. EXISTENCE OF STATE AID

QUINZ

6.1. Condition 1: qualification of the state aid recipient as an "undertaking"

6.1.1. Defining an undertaking in EU state aid law: conditions and sector-specific considerations

First, for funding received by an Academia for creating ATMPs to be considered state aid, the entity must qualify as "an undertaking".

In this regard, an undertaking is an entity engaged in an economic activity, i.e., the offering of goods and services on a certain market.[184] The test to establish the existence of a market is particular, as the absence of an actual market or its imperfect state do not have any bearing on the assessment. The central question is whether the goods can in principle be offered on the market, i.e., in a situation where there is a demand, and a certain entity is willing to supply the product or service. Activities which are not economic are, on the contrary, those for which a market can, in principle, not exist.[185] The existence of a clear demand from patients who can be treated with the relevant ATMPs and the potential interest from actors such as Academia, confirms the existence of a market for ATMPs.

Furthermore, the qualification of an entity as an undertaking is also independent of its legal status (whether the entity is organised under public or private law) and its economic nature (the fact if it generates profits).[186] Hence, the fact that most Academia are organised as non-profit organisations does not affect their qualification as an undertaking.

The classification of hospitals, and other health care providers, as an "undertaking" has, however, long been debated in European doctrine. Regarding the qualification of regular health care services by hospitals as "(non-)economic", detailed guidance was provided by the European Courts and the European Commission.[187] For the realisation of academic drug development hospitals will, however, not simply offer their regular medical services. Instead, depending on the specific set-ups, hospitals are responsible for the process of – or part of it – developing, manufacturing, and even marketing/administering of drug products. The question thus arises whether or not a hospital, by performing these activities, qualifies as an undertaking as such.

However, the afore-mentioned R&D&I Framework can be used to assess the qualification of Academia as undertakings. The Framework provides clarifications and addresses the question of when "research organisations and infrastructures" perform non-economic activities and thus qualify as non-undertaking. To invoke the Framework, however, a step-by-step reasoning must be followed, which is outlined below.

6.1.2. Guidance in R&D&I Framework on the notion of "undertaking"

Step 1: the aided part of a project must fall within the scope of the R&D&I Framework

To start, the Commission identified a series of well-defined R&D&I measures that can benefit from the guidance given by the R&D&I Framework. Indeed, only aid provided for these defined projects can enjoy the Framework's guidance. (para. 13, R&D&I Framework)

The Framework covers, for example, the following categories.

"Aid for constructing and upgrading research infrastructures". The Framework covers this category as high-quality research infrastructures are crucial for facilitating groundbreaking research and attracting global talent to perform research. The Framework acknowledges that the high upfront costs

184 Para. 11 – 13, Commission Notice 2016/C 262/01 on the Notion of State Aid

185 Buts, C. , Nicolaides, P.& Pirlet, H. Puzzles of the State Aid Rules on RDI European State Aid Law Quarterly Volume 18, Issue 4 (2019), p. 494

186 Para. 7 – 9, Commission Notice 2016/C 262/01 on the notion of State Aid

187 Para. 24, Commission Notice 2016/C 262/01 on the Notion of State Aid

for state-of-the-art facilities and equipment often make it difficult to secure necessary financing from the market.

"Aid for constructing and upgrading testing and experimentation infrastructures". Such infrastructures refer to facilities, equipment, capabilities and resources like test beds, pilot lines, demonstrators, testing facilities or living labs, and related support services. The Framework explains that infrastructures are primarily used by businesses, which seek support for testing and experimentation, in order to develop new or improved products, processes and services, and to test and upscale technologies, to advance through industrial research and experimental development. Again, the Framework recognises that the high upfront investment costs, and an uncertain client base make financing challenging. Public funding for these infrastructures is subject to conditions: the infrastructures must be accessible on a transparent, non-discriminatory basis and market terms. User fees can be reduced according to relevant regulations to facilitate access.

Past case law demonstrates that when university hospitals are involved in the development of certain medicinal products and received public support, the European Commission often labels this support as aid for an "R&D project".[188] To qualify under this category, the activities performed in the context of the aided part of the project must qualify within one of the sub-categories of "R&D-aid", including "fundamental research", "industrial research" and "experimental development". (para. 13, (a) R&D&I Framework) The following activities qualify under these categories.

"Fundamental research" means experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundations of phenomena and observable facts, without any direct commercial application or use in view. (para. 16, (n) R&D&I Framework)

"Industrial research" means the planned research or critical investigation aimed at the acquisition of new knowledge and skills for developing new products (…) or aimed at bringing about a significant improvement in existing products, (…). It comprises the creation of components parts of complex systems and may include the construction of prototypes in a laboratory environment or in an environment with simulated interfaces to existing systems as well as of pilot lines (…) .[189] Pre-clinical tests, which include both in vitro and animal testing, also qualify under definition of industrial research.[190]

"Experimental development" means acquiring, combining, shaping and using existing knowledge and skills with the aim of developing new or improved products (…), in any area, technology, industry or sector. (…) It may comprise prototyping, demonstrating, piloting, testing and validation of new or improved products (…) in environments representative of real-life operating conditions where the primary objective is to make further technical improvements on products, (…). This may include the development of a commercially usable prototype or pilot. It does not include routine or periodic changes made to existing products, production lines, manufacturing processes, services and other operations in progress, even if those changes may represent improvements.[191] Following existing case law, phase I, II and III clinical trials appear to qualify under this category.[192]

188 Commission Decision, N 405/2007, Bioterials; Commission Decision N 709/2007, ADNA; Commission Decision N 65/2007, Ludwig Boltzmann Institut für Krebsforschung; Commission Decision N 610/2006, INTACT; Commission Decision N 769/2007, Genomics Centres

189 Para. 16, (r) R&D&I Framework

190 Para. 51, Commission Decision N 405/2007, Bioterials

191 Para. 16, (k) R&D&I Framework

192 Para. 52, Commission Decision N 405/2007, Bioterials

Step 2: research organisation and infrastructures as "(non-) undertakings"

Having established that the aid measure is destined for one of the categories of the well-defined R&D projects, the Framework's principles can be applied to the measure. Specifically relevant, is that the Framework clarifies under which circumstances an entity engaging in publicly-funded R&D&I activities qualifies as an "undertaking" for the proposes of EU State Aid law. (para. 18 – 22, R&D&I Framework)

The text explicitly discusses the **economic and non-economic nature** of the activities carried out by "research and knowledge dissemination organisations" ("research organisations") and "research infrastructures". (para. 20, R&D&I Framework)

In this regard, a "research organisation" is an entity, whose primary goal is to independently conduct fundamental research, industrial research or experimental development or to widely disseminate the results of such activities by way of teaching, publication or knowledge transfer. These entities include, for example, universities, research institutes, and technology transfer agencies. (para. 16, (ff) R&D&I Framework) Moreover, "research infrastructure" means facilities, resources and related services that are used by the scientific community to conduct research in their respective fields and covers scientific equipment or set of instruments, knowledge-based resources such as collections, archives or structured scientific information, enabling information and communication technology-based infrastructures such as grid, computing, software and communication, or any other entity of a unique nature essential to conduct research. Such infrastructures may be 'single-sited' or 'distributed' (an organised network of resources). (para. 16, (gg) R&D&I Framework)

On the one hand, research organisations and infrastructures **are not considered to be undertakings** under EU State Aid law if they are primarily engaging in the following non-economic activities. (para. 19-20, R&D&I Framework)

- Education for more and better skilled human resources.
- Independent R&D for more knowledge and better understanding.
- Research is independent, if not conducted in a contract research set-up and therefore not funded by third parties through fees and according to the wishes of the third parties.
- Wide dissemination of research results of such activities on a non-exclusive and non-discriminatory basis, including teaching, open-access databases, open publications or open software.
- The wide dissemination of results entails that the results of the research are easily available and that benefits are spread to all. As a general guideline the results should be findable, accessible, interoperable and reusable. Preferential access is thus not compatible with the principle of wide dissemination.[193]
- Knowledge transfer activities, including the licensing of IPRs, the creation of a spin-off, or other forms of management of knowledge created by the research organisation or infrastructure. Knowledge transfer activities are non-economic where they are conducted either by the research organisation or research infrastructure (including their departments or subsidiaries) or jointly with, or on behalf of other such entities, and where all profits from those activities are reinvested in the primary activities of the research organisation or research infrastructure. (para. 20 (b) R&D&I Framework).
- Importantly, the licensing of IP rights must be done on a non-exclusive and non-discriminatory basis.[194]

193 Buts, C, Nicolaides, P.& Pirlet, H. Puzzles of the State Aid Rules on RDI European State Aid Law Quarterly Volume 18, Issue 4 (2019), p. 498

194 Buts, C, Nicolaides, P.& Pirlet, H. Puzzles of the State Aid Rules on RDI European State Aid Law Quarterly Volume 18, Issue 4 (2019), p. 497

On the other hand, research organisations and infrastructures **are considered to be an undertaking** under EU State Aid law in the following cases. These cases involve consequently economic research.

When the hospital or research centre seeks to sell or commercialise the results of its R&D activities. (Article ETSAL, Puzzles of state aid, p. 496). Selling the results of the research differs from "knowledge transfer activities", since the sale of the research results involves a profit motive. In such case, the research organisation will not necessarily pump all revenue back into its independently conducted research.

If the R&D activities by the hospital or research centre are not performed "independently" but conducted in the context of contract research and thus shaped to the wishes of another third party. Contract research occurs when the participating parties are not equal in the relationship; where one-party acts as agent of the other.[195]

If the hospital or research centre enters into an "effective collaboration*" with another entity, its activities may qualify as either economic or non-economic. The collaborating research organisation loses its status as non-enterprise when it engages in collaborative research that will later be commercially exploited by the other entity.[196] A project is considered effectively collaborative when at least two independent parties work together towards a common goal. They jointly define the scope, participate in the design, contribute to implementation, and share risks and results. One party may cover all costs, relieving others of financial risks. Terms, including cost contributions, risk sharing, result dissemination, and IPR rules, must be agreed upon before starting the project.

In case public funding for research organisations or infrastructure is used for both economic and non-economic activities, a specific principle applies. If the organisation or infrastructure is used almost exclusively for non-economic activities, its funding may be exempt from state aid rules, provided the economic activities are ancillary. This means they must be directly related to, necessary for, or intrinsically linked to the main non-economic use and limited in scope. The Commission considers this to be the case if the economic activities use the same inputs as non-economic activities and do not exceed 20% of the entity's overall annual capacity. (§ 21 of the R&D&I Framework)

In the past, the Commission has qualified university hospitals participating in "R&D projects" as "research organisations" within the meaning of the Framework. (for example, para. 22-23, Commission Decision N 769/2007, Genomics Centres) To qualify as a research organisation, it seems essential that the hospital in question is affiliated to a university. Moreover, the Commission has often considered the R&D activities of university hospitals funded by public authorities to be non-economic in nature. For example, in the above-mentioned 2007 Bioterials-case, the European Commission reviewed a Dutch support measure which involved an R&D agreement between the University of Maastricht, the Maastricht Academic Hospital, and an enterprise active in manufacturing. The aid was provided for a R&D-project on new biologic materials – "Bioterials". The Commission confirmed the hospital's qualification as a research organisation and the non-economic character of its R&D activities. Consequently, the hospital did not qualify as an undertaking for the activities in question. The support by public authorities to the university hospital for the R&D project, therefore, did not qualify as state aid and was not subjected to a state aid analysis. (para. 10-11 and 39, Commission Decision, N 405/2007, Bioterials)

6.1.3. Services of general economic interest

As previously explained, according to EU State Aid principles, EU Member States can only provide financial support to undertakings under strict conditions to prevent unnecessary distortions of competition. Companies that provide Services of General Economic Interest ("**SGEI**"), however, are subject to a distinct set of state aid rules.

195 Buts, C, Nicolaides, P.& Pirlet, H. Puzzles of the State Aid Rules on RDI European State Aid Law Quarterly Volume 18, Issue 4 (2019), p. 502

196 Buts, C, Nicolaides, P.& Pirlet, H. Puzzles of the State Aid Rules on RDI European State Aid Law Quarterly Volume 18, Issue 4 (2019), p. 502.

SGEI encompass a broad spectrum of activities with unique characteristics. For a service to be classified as an SGEI, it must be demonstrated that (i) the market cannot adequately provide the service, or (ii) that the service would not be provided under the same conditions as respects price or quality. The existence of a market failure is a prerequisite for qualifying an activity as SGEI. (General Court of the European Union, judgment of 16 September 2013, Colt Telecommunications France v. European Commission, Case T-79/10, ECLI:EU: T:2013:463). Moreover, the SGEI should serve a public or societal interest. Member States have significant leeway in defining what constitutes an SGEI. This decision varies based on the organisation and traditions of each Member State and is therefore a politically induced choice. The discretion can be challenged by the Commission only in the case of manifest error. Examples of SGEIs are postal delivery, passenger rail transport and medical care.

For ATMP development, **the SGEI qualification seems defensible given the existence of a prominent market failure as previously identified in this report.** It could be argued that it is in the interest of the society to aim to promote ATMP research by entrusting certain hospitals with the management of a SIEG, in exchange for public funding.

The fact that some pharmaceutical firms currently produce certain drugs (albeit at exorbitant prices) does not undermine this possibility. In its Guide to the application of the European Union rules on state aid, public procurement and the internal market to services of general economic interest, and in particular to social services of general interest – the European Commission confirmed the potential existence of an imperfect private offer (in this case, due to inaccessibility) does not invalidate the SGEI qualification (question 11 of the Report). Specifically, if the market provides the service but not to the desired quality or price level (e.g., transport fares too high for low-income families), the service can still qualify as an SGEI.

The designation of ATMP development as a SGEI is further substantiated by certain clarifications on SGEIs by the European Commission. In this regard, the Commission has previously stated that the rules applicable to aid for SGEIs may be used to limit the risk of critical medicines shortages. (European Commission's Questions and answers: Addressing Medicine Shortages in the EU of October 24, 2023).

For the assessment of SGEIs under state aid rules, the European Commission has adopted several instruments. These instruments introduce a dual advantage.

On the one hand, it is provided that aid for SGEIs is **not considered state aid** if certain specific and limitative conditions are met. Specifically, the Altmark criteria, established by the European Court of Justice in the Altmark Trans GmbH case, determine when public service compensation does not constitute State aid under Article 107(1) TFEU. The four criteria are: (1) the recipient must be explicitly entrusted with clearly defined public service obligations; (2) the parameters for calculating compensation must be established in advance in an objective and transparent manner; (3) the compensation must not exceed what is necessary to cover the costs incurred in discharging the public service obligations, including a reasonable profit; and (4) if the undertaking is not chosen through a public procurement procedure, the compensation must be based on the costs of a typical, well-run undertaking. Meeting these criteria ensures that the compensation is proportionate, transparent, and does not confer an undue economic advantage, thereby not qualifying as State aid. (Case C-280/00 Altmark Trans [2003] ECR I-7747, EU:C:2003:415.)The SGEI Communication (OJ 2012 C8/4) further clarifies the conditions under which public service compensation does not constitute State aid in light of the Altmark criteria. Furthermore, the SGEI de minimis Regulation of 2023 (C(2023) 9701) establishes a threshold for compensation provided to SGEIs below which such compensation is considered free of state aid and exempt from EU State aid rules. Specially, the exempted compensation is limited to €750,000 over a three-year period to account for inflation. Starting from January 1, 2026, Member States will be required to register de minimis aid in a central register, either at the national or EU level

On the other hand, where SGEI aid qualifies as state aid, it may be regarded as **compatible with the internal market in specific circumstances**. Relevant for ATMP development is that SGEI Decision (No. 2012/21/UE) of

20 December 2011 by the European Commission, concerning the application of Article 106(2) TFEU to State aid in the form of public service compensation granted to certain firms entrusted with operating services of general economic interest. This instrument is further discussed in the scientific report under section 8.1.3.4. Moreover, the SGEI Framework (2012/C 8/03) outlines the European Commission's approach to assessing and authorising State aid granted to undertakings entrusted with the operation of services of general economic interest (SGEIs) following a notification of the European Commission.

6.1.4. Examples of undertakings & economic activities

Example: Academic ATMP manufacturing facility

A public authority provides financial support to Academia to establish a GMP-compliant ATMP manufacturing facility. After manufacturing, the ATMPs may subsequently be administered to patients via the hospital exemption or in the context of clinical trials. It is the intention that the ATMP manufacturing facility also manufactures ATMPs as CMO for third parties.

In the situation the ATMPs are manufactured for subsequent administration to specific patients in the context of hospital exemption and/or clinical trials said Academia, one could argue that the manufacturing takes place in the context of a non-economic R&D activity such as covered by the R&D&I-Framework.

Alternatively, where the ATMPs are manufactured for commercial purposes under a CMO set-up, it is not possible to invoke the R&D&I Framework. After all, the facility's activities do not qualify under the R&D umbrella but have a commercial character. Hence, the manufacturing unit will qualify as a company engaged in economic activities. In such cases clearly distinguishing the different type of activities will be needed to comply with State Aid rules.

Example: hospital is responsible for R&D, manufacturing and commercialisation (obtaining market authorisation)

A hospital receives funding by a public authority for R&D into ATMPs, for which it ultimately obtains a marketing authorisation. In this case, the hospital qualifies as an undertaking as it commercialises the results of the R&D activities.

Example: hospital develops and administers ATMPs via hospital exemption

A university hospital receives public funding for R&D, and subsequently administers the ATMPs to the patient under the umbrella of the "hospital exemption". In this case, the hospital might not be engaging in economic activities, as it does not commercialise the ATMPs but rather administers them to a specific patient, without obtaining a market authorisation. Thus, it could be argued that the hospital functions as a "research organisation" under the R&D&I Framework, by engaging in R&D activities such as developing "commercially usable prototypes" which it subsequently administers to a specific patient. The FAGG's interpretation of the hospital exemption as a clinical practice does not affect this conclusion. Especially since this nomination is made by the FAGG from a different (non-state aid) perspective. The operations performed under the hospital exemption may still be captured under the application of the R&D&I Framework regardless of this qualification by the FAGG.

However, when a hospital starts routinely producing and administering ATMPs on a larger scale, following a more frequent use of the hospital exemption for different indications (for each indication within the boundaries of the hospital exemption framework), it becomes difficult to argue that these activities qualify as mere R&D. Public funding for such routine manufacturing activities is more likely to qualify as an economic activity.

6.2. Condition 2: the support measure must confer a selective advantage

1. General description

Second, for a support measure to qualify as state aid, the recipient should receive an economic benefit which it would not have received under "normal market conditions", in the absence of a state intervention. Importantly, the effect of the measure must be considered, meaning it should improve the recipient's financial position. (para. 66, Commission Notice) Moreover, to constitute state aid, the advantage must be selective, favouring certain undertakings which entails that a general measure of economic policy does not constitute state aid. (para. 117-118, Commission Notice)

2. Examples of selective advantages relevant for ATMP development

Example: measures supporting ATMP development

A variety of measures supporting the capabilities of hospitals or research centres for ATMP development might qualify as a selective advantage.

In this regard, direct grants to entities participating in academic ATMP development will qualify as a "positive" advantage. On the other hand, a relief from an economic burden takes place when the Belgian State, covers (wholly or partially) the employment expenses of researchers conducting ATMP development projects or providing training for researchers participating in ATMP development projects, the provision of CRO support for the performance of clinical trials, assistance by a funded non-profit CMO for the manufacture of ATMPs or the waiver of certain government fees. Where the Belgian State takes on the responsibility for a liability insurance necessary for the development and commercialisation of ATMPs, this as well can constitute a selective advantage.

3. Dual nature of the notion "advantages"

For a public support measure to qualify as an advantage, the precise form of the measure is irrelevant. The notion of an advantage thus covers both positive economic advantages and the relief from economic burdens (i.e., reliefs of the inherent costs of the undertaking's economic activities). Because of this broad interpretation, the concept of an advantage covers a wide range of support measures. Moreover, the reimbursement or compensation of costs resulting from regulatory obligations imposed by the state, can, in principle, be considered as granting an advantage upon the undertaking. (para. 67 – 69, Commission Notice).[197]

4. Indirect advantages under the R&D&I framework

It is, however, possible that the same support measure confers both a direct advantage to the receiving entity and an indirect advantage to another undertaking, particularly, an undertaking operating at a subsequent level of activity. (para. 115-116, Commission Notice). The afore-mentioned R&D&I Framework clarifies in which occasions an advantage is conferred from a research organisation to another undertaking in a contract research or collaboration relationship.

If a research organisation receives an "adequate compensation" for its services in the context of a **contract research**, the Commission considers that no indirect state aid is transferred to a participating company. (para. 26-18, R&D&I Framework) There is an "adequate compensation" if one of the following conditions is met. (R&D&I Framework Communication, para. 26 – 27)

The university hospital provides its research service or contract research at market price; or

where there is no market price, the hospital provides its research service or contract research at a price which reflects the full costs of the service and generally includes a margin established by reference to those commonly applied by undertakings active in the sector of the service concerned, or is the result of arm's length negotiations where the hospital, in its capacity as service provider, negotiates to obtain the maximum economic benefit at the

197 Bellamy & Child, European Union Law of Competition, Oxford University Press, 2018, 1446

moment when the contract is concluded and covers at least its marginal costs.

Where the ownership of, or access to intellectual property rights remain with the research organisation, their market value may be deducted from the price payable for the services concerned.

In **collaboration projects** between undertakings and research organisations or infrastructures, the Commission considers that no indirect state aid is granted to participating undertakings if they did not receive support via "favourable collaboration conditions". (para. 28-31, R&D&I Framework) Favourable terms of cooperation exist if any of the following conditions are met. (R&D&I Framework Communication, para. 28 – 31)

The participating undertakings bear the full cost of the project; or

the results of the collaboration which do not give rise to IPR may be widely disseminated and any IPR resulting from the activities of research organisations are fully allocated to those entities; or any IPR resulting from the project, as well as related access rights are allocated to the different collaboration partners in a manner which adequately reflects their work packages, contributions and respective interests; or

the research organisations receive compensation equivalent to the market price for the IPR which result from their activities and are assigned to the participating undertakings, or to which participating undertakings are allocated access rights. The absolute amount of the value of any contribution, both financial and non-financial, of the participating undertakings to the costs of the research organisations or research infrastructures' activities that resulted in the IPR concerned, may be deducted from that compensation. The Commission further specified conditions to analyse if the compensation received is equivalent to the market price. (R&D&I Framework Communication, para. 30)

5. Public-private partnerships

It is also possible that for the purposes of ATMP development, that a vehicle is created in which public authorities take a stake alongside significant private participation. The participation of the public authorities in the form of a stake will not amount to the conferral of an advantage if the public authority has acted as a private investor. His intervention may not confer an economic advantage if is carried out under market conditions (para. 86-88 Commission Notice on State Aid)[198].

When a transaction is conducted under identical terms and conditions, with both public bodies and private operators sharing the same level of risk and rewards in comparable situations (a "pari passu" transaction), it can generally be inferred that the transaction aligns with market conditions. No state aid is conferred in this situation.

To analyse if an advantage is conferred the following aspects should be considered.

- Whether the interventions by public bodies and private operators are decided and executed simultaneously, or if there has been a time lapse and a change in economic circumstances between their interventions.
- Whether the terms and conditions of the transaction are identical for both public bodies and all private operators involved, considering the possibility of increasing or decreasing the level of risk over time.
- Whether the involvement of private operators has real economic significance and is not merely symbolic or marginal.
- Whether the starting positions of the public bodies and private operators involved are comparable concerning the transaction. This includes factors such as their prior economic exposure to the undertakings concerned, potential synergies that can be achieved, the extent to which different investors bear similar transaction costs, or any other specific circumstances that could distort the comparison.

198 https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52016XC0719(05)

6.3. Condition 3: the support measure must (threaten) to distort competition and affect trade

a. General description

A public support measure only constitutes state aid if it (threatens to) distort(s) or competition and only as far as it affects trade between Member States. Both elements are often combined into one analysis. (para. 185, Commission Notice) For a measure to constitute a – potential – distortion of competition, it must be capable of improving the competitive position of the recipient compared to other undertakings with which it competes. This applies irrespective of the question of whether the support helps the receiving undertaking to expand or gain market share. (para. 189, Commission Notice) Moreover, there must be an effect on trade. In this regard, no actual impact must be established, it is thus not necessary to define the market or to investigate in detail the influence of the measure on the competitive position of the beneficiary and its competitor. (para. 190 – 195, Commission Notice)

A support measure is deemed not to influence trade if the measures' value is below certain financial thresholds. (De Minimis Regulation 2023) Subject to exceptions for certain sectors – aid awarded to a single undertaking by a Member State may not exceed €300,000 over three years to benefit from the exemption. (article 3, (2) De Minimis Regulation 2023) Starting from January 1, 2026, Member States will be required to record de minimis aid in a centralised register, either at the national or EU level.

b. Effect on trade and risk of distortion following support measures to ATMPs

- Small population of patients

Support measures for the development of ATMPs (whose value is above the thresholds) in fact have the potential to distort competition and affect trade, provided that the resulting ATMP is set out to be made available under the marketing authorisation pathway. Even if only a small population of patients would be treated with the relevant ATMPs and thus no major market exists for the therapies, this conclusion remains unchanged. In fact, previous caselaw of the Court of Justice of the European Union ("**the Court**") clarified that a distortion of competition should not be considerably appreciable. (C-494/06 P, Commission v Italy and Wam, para. 50-53 and C-222/04 Cassa di Risparmio di Firenze and Others, para. 140) Instead, the measure should only be "liable" to distort competition, which can be argued, is potentially the case here. In this regard, other entities, such as pharmaceutical companies, which do not receive state support for the creation of ATMPs, could potentially miss profits. Moreover, the aid measure may also prevent other operators, not receiving public support, from entering the relevant market for ATMPs.

- Socially responsible licensing clause

Moreover, the attachment by the government of specific positive-impact conditions to a support measure does not influence the measure's qualification as state aid either. Positive impact conditions include, for example, the incorporation of a "socially responsible licensing clause" by which the government requires that the ATMPs will be offered at a reasonable price to patients (see also section 8.2.2.of the scientific report).

While it may be indeed desirable for a state to attach positive-impact conditions to aid measures, such conditions do not necessarily impact the classification of a measure as state aid. Hence, the limited prices which, for example, hospitals, can charge for the ATMPs bear no influence on the existence of the state aid. In this regard, it is understood that even if an entity which receives a state aid measure gains minimal or no net financial advantage following the measure, the aid can still distort competition. Aid for the development and distribution of ATMPs allows the receiving companies to introduce additional production or capacity in the market, potentially affecting other undertakings.[199]

[199] J. DERENNE and V. VEROUDEN, Chapter 5: Distortion of Competition and Effect on Trade, p. 172

6.4. Condition 4: the support measure must have a state origin

a. General description state origin condition and relevance to academic ATMP developments

Lastly, a support measure must have state origin, which entails it should be imputable to the state and provided by (in)directly using state resources. (para. 38, Commission Notice) A measure is both imputable, when a public authority grants aid to a beneficiary and, when a public authority designates an autonomous institution (private or public entity) to administer a measure. For example, consider the situation where the government sets up an intermediary to distribute a budget for the funding of ATMP development among various participating entities. The support distributed by the intermediary may still be considered state aid. (para. 39, Commission Notice)

Resources coming from the European Union or from international financial institutions are only considered as state resources if national authorities have discretion as to the use of these resources. (para. 60, Commission Notice) For example, projects 100% funded under Horizon Europe sponsoring academic ATMP developments, without active role for the Belgian State in choosing which hospitals receive the support. would not qualify as state aid. A practical example is the "Centre for Drug Design and Discovery (CD3)" which receives support from the European Investment Fund. Moreover, all resources by states are covered under the definition of state aid including those by intra-state entities operating at de centralised, federated, regional or other levels. (para. 48 and 51, Commission Notice) For academic ATMP developments, support from the government can originate not only from the Federal level but also potentially from regional levels like the Flemish government or other and also be considered state aid.