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The Magistral Preparation of Advanced Therapy Medicinal Products (ATMPs)

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Abstract

Advanced Therapy Medicinal Products (ATMPs) embody innovative therapies that have created great hope for patients suffering from previously untreatable diseases. Unfortunately, the pharaonic cost to produce and authorise ATMPs is a challenge for both patients and public health care systems, ultimately reducing patients' access to treatment. Over the last 11 years, only 15 ATMP marketing authorisation applications received a positive draft opinion from the European Medicines Agency's (EMA's) Committee for Advanced Therapies (CAT). Moreover, due to poor return on investment, several ATMPs have already been removed from the market. In addition to the centralised procedure to obtain a marketing authorisation, the legislator foresees an alternative route for authorising ATMPs, the so-called "ATMP Hospital Exemption". However, such ATMPs must be produced on a limited scale, on a non-routine basis. As a result, valuable ATMP therapies that have been used for years in hospitals may disappear. To avoid this, we propose, in this paper, an additional possibility to regularise ATMPs: the "Magistral Preparation of ATMPs". It is a feasible pathway, which was already proposed for bacteriophage therapy, and which is particularly suitable for personalised therapies and considerably decreases the cost of the final products. We also discuss the practical impact of the ATMP regulation for (for-profit) industries and for (non-profit) hospitals. Two practical examples, the cultured human chondrocytes and the cultured human keratinocytes, are discussed.

keywords: *advanced therapy medicinal product; ATMP; bacteriophage therapy; phage therapy; cell therapy; magistral preparation; personalised medicine; regenerative medicine; tissue engineering; quality assurance; quality control; regulatory*

Introduction

The European regulatory framework [Regulation (EC) No 1394/2007] [1] for approval of Advanced Therapy Medicinal Products (ATMPs) came into force in 2009, allowing pharmaceutical companies to apply for, and obtain, marketing authorisation for innovative ATMP-based therapies. After obtaining marketing authorisation and appropriate reimbursement, pharmaceutical companies are expected to commercialise evidence-based, qualitative, safe and effective medicinal products. These companies provide patients with access to the best available innovative treatments as long as they can obtain a return on investment, meaning the market size is sufficient and third-party reimbursement mechanisms (social security system) sustain the commercialisation efforts. Due to their extremely high costs [2] the affordability of ATMPs is a concern and a challenge for both patients and public health care systems [3]. If the return on investment cannot be achieved, due to high manufacturing and regulatory costs (validation, re-assessment and inspection), products are either no longer developed or are removed from the market (e.g. market discontinuation of ChondroCelect), restricting patient access to therapies and leaving patients with unmet medical needs. The scientific advance in the field of ATMPs is remarkable [4], partly thanks to the contribution of academic developers, who were also actively involved in applications for ATMP marketing authorisation. However, these academic actors are limited by insufficient financial support, lack of experience with regulatory aspects, and clinical trial complexities and costs [5,6].

According to the European Medicines Agency's (EMA's) Committee for Advanced Therapies (CAT monthly report, November 2019), over the last 11 years, only 15 ATMPs received a positive CAT draft opinion [7]. However, in the absence of commercially available therapeutic products, the legislator permits the use of ATMPs without the need for marketing authorisation. The "hospital exemption" legislation stipulates that these (exempted) products can only be used under the responsibility of a medical practitioner and can only be prepared on prescription, on a non-routine basis, for an individual patient. Moreover, each hospital exemption must be authorised by the competent authority and the ATMPs under exemption must comply with the same national requirements concerning quality (Good Manufacturing Practice standards), traceability and pharmacovigilance that apply to authorised medicinal products.

Keratinocyte cultures for the treatment of patients in the Burn Wound Centre of the Queen Astrid Military Hospital in Belgium are examples of ATMPs. Although not commercially produced and used, such keratinocyte cultures were perceived by the Belgian

regulatory authorities as 'routine' activities. Consequently, the "hospital exemption" status was not considered applicable for these products in Belgium. Of note, obtaining a marketing authorisation, or even a hospital exemption, would in any case mean a dramatic raise of the product price, posing a threat to the availability of the therapy to the hospitals.

Besides the ATMP hospital exemption, the Medicinal Product Directive 2001/83/EC also foresees an exemption for medicines prepared as a magistral formula [8]. On this basis, similar to the magistral preparation of human bacteriophage therapy products [9] we would like to propose the "Magistral Preparation of ATMPs" as an alternative regulatory pathway for ATMPs that will not be commercialised. We believe this can considerably reduce the cost of the final products, in favour of patients and health care systems.

The European Union Cell and Tissue Directives (EUCTDs) / ATMP Regulation

In 2003, the ATMP concept was originally introduced in the Community pharmaceutical regulation through the publication of the so-called "new Annex I" (Directive 2003/63/EC) [10], which amended the Medicinal Product Directive (2001/83/EC) [8] and laid down the dossier requirements for gene therapy and somatic cell therapy medicinal products. In 2004, the European Commission (EC) issued the EU Cells and Tissue Directives (EUCTDs) (2004/23/EC, 2006/17/EC and 2006/86/EC) [11-13]. These directives were designed to assure harmonized and high standards of Quality and Safety (QS) for the donation, procurement, testing, processing, preservation, storage and distribution of human cells and tissues, to facilitate their cross border movements and to ensure availability in the EU. In 2007, the Medicinal Product Directive and the EUCTDs were supplemented with a Regulation on Advanced Therapy Medicinal Products (ATMPs) (EC 1394/2007) [1], which was developed to cater for human tissue engineered products and combined ATMPs, and introduced additional requirements. This ATMP Regulation was intended to allow for free movement of ATMPs within the EU market, to realize better patient access to these products, to assure the highest level of health protection to the patients, to assure EU competitiveness in a key biotechnology area and to assure growth of an emerging industry. With these Directives and the ATMP Regulation, the EC did however enforce adherence to pharmaceutical industry standards and, hence, a series of expensive requirements. For instance, for Human Cell- and/or Tissue Products (HCT/Ps), classified as ATMPs, full-blown "GMP for ATMPs" is required. This implies major investments in upgrading manufacturing facilities. Suddenly, the HCT/P field was confronted with regulatory provisions, practices and systems exceeding the requirements for the production of tissues and cells of human origin, which were previously only required in pharmaceutical licensing and manufacturing [14].

Practical Impact of the ATMP Regulation

For (For-Profit) Industry

With the introduction of ATMP Regulation, the legal framework for ATMPs was standardised in Europe. Centralised marketing authorisation procedures for ATMPs were introduced and the CAT, a multidisciplinary committee, became responsible for assessing the quality, safety, and efficacy of ATMPs. This standardised framework was supposed to attract investments and facilitate patient access to safe, effective and high quality ATMP products. Huge expectation was placed on the availability of a great number of new ATMPs to address unmet medical needs and previously untreatable diseases [15]. However, because the niche indications

Table 1. *ATMPs with valid marketing authorisation (Source: [18] with the following disclaimer: this table contains no information as to whether the preparations are available on the market). According to the European Medicine Agency official website, Glybera, Zalmoxis and Maci are withdrawn from use in the European Union.*

ATMP name	Marketing Authorisation Holder	License Number	License date
Gene Therapy Medicinal Products			
Glybera	uniQure biopharma B.V.	EU/1/12/791/001	25.10.2012
Imlygic	Amgen Europe B.V.	EU/1/15/1064	16.12.2015
Kymriah	Novartis Europharm Ltd.	EU/1/18/1297	23.08.2018
Luxturna	Spark Therapeutics Ireland Ltd.	EU/1/18/1331	22.11.2018
Strimvelis	GlaxoSmithKline Trading Services Limited	EU/1/16/1097	26.05.2016
Yescarta	Kite Pharma EU B.V.	EU/1/18/1299	23.08.2018
Zynteglo	Bluebird bio (Netherlands) B.V.	EU/1/19/1367	29.05.2019
Somatic Cell Therapy Medicinal Products			
Alofisel	TiGenix S.A.U.	EU/1/17/1261	23.03.2018
Zalmoxis	MolMed S.P.A.	EU/1/16/1121	18.08.2016
Tissue Engineered Products			
Holoclar	Chiesi Farmaceutici S.P.A.	EU/1/14/987	17.02.2015
Maci	Genzyme Europe B.V.	EU/1/13/847	27.06.2013
Spherox	Co.don.AG	EU/1/17/1181	10.07.2017

that are most often addressed by ATMPs are probably not appealing enough for large pharmaceutical companies, ATMPs were and still are mainly developed by academia, hospitals and small or medium sized companies [16]. In addition to high financial burdens, these organisations are facing quality issues in the development of ATMPs and hurdles related to the translation of ATMPs from research to GMP environments and clinical applications [6]. As mentioned in [15], recent reports show a high development of activity in the ATMP field, which does not seem to match the limited number of ATMPs currently authorised, let alone available on the European market. Even though over 500 clinical trials were performed with ATMPs between 2009 and 2018 [17], this led to only 22 marketing authorisation applications submitted to the European Medicines Agency (EMA) (CAT monthly report of November 2019) [7]. Fifteen applications received positive draft opinions, four applications received negative draft opinions and six applications were withdrawn. At the end of 2019, only twelve ATMPs (Table 1) had obtained a valid centralised marketing authorisation (MA) [18].

Over time, several withdrawals of licenses and product marketing discontinuations by companies had been made for commercial reasons [2]. As mentioned in [2], one major factor for the financial unfeasibility of ATMP production and commercialisation is that they are made to treat only a small number of patients, often qualifying for orphan drug designation. In addition, these innovative therapies are often accompanied by a "media-over-hype", resulting in unrealistic expectations. Another issue is the difficulty in obtaining third-party reimbursement for these products. When the marketing of a product is stopped due to a negative financial balance, there is not only a loss for the patient, but also for the society who has invested in the development of this particular treatment.

Key Messages

- For industry, the ATMP Regulation is the mandatory "standard track" for market placement of (therapeutic) products. When financially feasible, they can follow this track up to market placement.
- There is a "media-over-hype" and "unrealistic expectations" are created.
- Key for industry (and patients) is to obtain third-party (social security) reimbursement.
- Hospitals are seen as service centres and clinical trial sites.
- Over time, many "spin-offs" were created and a lot of "stock market money" was realised, mostly based upon promises. Today, this money is spent, but the patients have no broad access to new innovative ATMPs. More than 10 years into the ATMP Regulation, only a very small number of ATMPs are actually on the market.

For (Non-Profit) Hospitals

Hospital Exemption

The ATMP Regulation foresees the possible implementation of national procedures to regulate the manufacturing and use of certain non-routinely produced ATMPs for individual patients, outside the scope of the Medicinal Product Directive 2001/83/EC [8]. European Biopharmaceutical Companies recognize that a number of innovative treatments find their roots in hospital and academic environments, but they also state that medicinal product development should not be the primary interest of these institutions [19]. "Hospital Exemption", they state, should not turn into a parallel circuit for small-scale locally produced ATMPs competing with centrally authorised products [20]. At the end of 2018, in Europe, only eight countries have issued a "Hospital Exemption" status to some products [19]. In Belgium, both an "ATMP- Hospital Exemption Dossier", approved by the Belgian Competent Authority (BCA), as well as a GMP certificate (related to the production of the "Exempted" product) are required. This incurs extremely high costs that cannot be afforded by holders of a hospital exemption, which are small players such as hospitals and academia, spin offs and small companies. Moreover, for some products that have been produced for many years and are therefore no longer considered to be produced on a non-routine basis, hospital exemption cannot be accorded. In both cases, this might lead to the unavailability of the product.

Key Messages

- Hospitals are blocked because they do not have the necessary funding to support the full-blown regulatory burden stemming from the "hospital exemption" procedure.
- "Hospital exemption" appears not to be workable (in Belgium) since the investments required are not in relation to the number of patients treated.
- Accordingly, there are patients in need of treatment, but the products are not available.
- In spite of scientific progress and patients' needs for HCT/Ps, there is currently no possibility to secure a sustainable way for producing and offering this type of products to patients. Centralised marketing authorisation leads to unavailability because of an unbalance between cost and income. The "hospital exemption", as defined in Belgium, leads to unavailability because the exemption can almost never be applied (e.g. activity seen as routine activity) or because of unaffordable costs related to GMP requirements.

Practical (European) Examples

Human Cultured Chondrocytes

In 2011, the Belgian Minister of Social Affairs notified a Belgian stock market listed Biopharmaceutical Company of the approval of a convention agreement for the reimbursement of ChondroCelect. ChondroCelect mainly consisted of autologous chondrocytes for the treatment of symptomatic knee cartilage lesions in well-indicated patients in specialised centres [21,22]. ChondroCelect was not only the first cell-based product to obtain centralised European marketing authorisation from the EMA, it was also the first ATMP to be granted national reimbursement. The reimbursement price (19,837 EUR for one application, excluding surgical and hospital costs) of ChondroCelect was almost ten times higher than the Belgian price (2,117 EUR for one application) of conventional autologous chondrocyte cultures, a non-ATMP and not approved by EMA [21,22]. Due to high costs, reimbursement of the procedure was limited to patients under 50 years of age. The conditional reimbursement of this first ATMP approved in Europe to only a selection of potential patients indicated that it might be difficult, if not impossible, for social security systems to reimburse future ATMPs. In Belgium, healthcare insurance is part of a social security system. Medical expenses are reimbursed by a health insurance fund and the government sets the reimbursement rates. Reimbursement rates for "conventional" products based on human cells and tissues have been published in a ministerial decree. The price set must cover the actual costs of procurement and processing, without making a profit. With conditional reimbursement, as is the case for ChondroCelect, only a part of Belgian patients in need can benefit from ATMP, which is in contradiction with the fundamental principle of equal access to healthcare, one of the leitmotivs of the Belgian public health system. This example illustrates that

the increase in pharmaceutical production costs and marketing authorisation requirements indirectly hinders patient access to advanced therapies. On July 5, 2016, the relevant Belgian Biopharmaceutical Company announced via a press release that they stopped the production of ChondroCelect for financial reasons [2]. Lack of reimbursement of ChondroCelect in important European target countries was one of the reasons invoked to justify this cessation [21].

Human Cultured Keratinocytes

Since 1987, in Belgium, more than 1.000 patients were grafted with (autologous/allogeneic) cultured human keratinocytes produced by the public keratinocyte bank of the Queen Astrid Military Hospital (QAMH), Brussels, Belgium (Supplementary Material 1: Keratinocyte QAMH). These cell cultures were (and still are) primarily used to accelerate the healing of burn wounds, to initiate the healing of chronic skin ulcers and to stimulate the healing of skin donor sites. Keratinocytes are delivered to the wound bed in the form of sheets or sprays. The keratinocyte bank of the QAMH has always been compliant with all relevant Belgian and European legislation [23] and has always been licensed upon inspection by the Belgian Competent Authority (BCA). Since 2008, the Quality Management System (QMS) of the QAMH keratinocyte bank is also ISO 9001 certified. This QMS governs all aspects of procurement, testing, processing, distribution and traceability of the grafted keratinocytes, in accordance with the EUCTDs' provisions. In 2012, the BCA notified the QAMH that their keratinocyte productions all fall under the ATMP definition and that the administration of these products to patients as it was performed would no longer be allowed beyond 30 December 2012. The Belgian "ATMP Hospital Exemption" framework was not applicable, because these cultured cells are produced and used routinely. In April 2019, the BCA organised a "GMP for ATMP" inspection in the QAMH. The conclusion of this inspection was that "the company is, in general, not compliant with the GMP for ATMP guidelines" because the products are manufactured without "approved dossier". Making these activities fully compliant with the European ATMP Regulation will imply a dramatic and unbearable increase in production costs for the hospital. As a consequence, keratinocyte therapy, an established therapy, which has shown its usefulness in the past [24-26], would no longer be available to severely burned patients.

In an attempt to comply with the medicinal product legislation, Belgian Defence had previously signed (in 2003) a four-year contract (2003-2006) with a Belgian biotech company, which aspired the worldwide commercialisation of keratinocyte products. The keratinocyte productions of the QAMH were (temporarily) outsourced to this company. Already in November 2004, however, the biotech company started phasing out their keratinocyte productions. Comparing to their business plan, not enough sales were generated and in June 2005, the company stopped the cooperation with the QAMH. So, the QAMH had to re-launch its own activities head over heels and is today still producing keratinocyte sheets and keratinocyte sprays. The actual (2020) hospital-based cost for culturing and delivering keratinocyte cultures to the patient (fully reimbursed by the Belgian social security system, without being fully compliant to the ATMP regulatory framework) is 6.74 EUR/cm2. The mean adult male human body-surface is 18,000 cm2. Most keratinocyte grafts go to high-care patients with keratinocyte grafting costs ranging from 24,000 EUR [20% total body surface area (TBSA) burned] to 110,000 EUR (90% TBSA burned). Implementing ATMP legislation on the actual keratinocyte productions would increase the production-costs at least 10-fold [22]. There are no commercial keratinocyte grafts available in Europe. The QAMH is not interested in the production and market placement of medicinal products, as this is not one of Belgian Defence's core businesses. Moreover, the "Marketing authorisation" of keratinocyte cultures would impose a too heavy financial burden with little or no added value. Submission of a clinical trial dossier to evaluate the clinical safety and efficacy of keratinocytes that are in (documented) use in the QAMH for more than 30 years and are today considered as "Advanced Therapy Medicinal Products" would not be very useful or motivating either. For these reasons, alternative regulatory pathways had to be investigated.

Alternative Pathways

Declaration of Helsinki

Art 37 of the Declaration of Helsinki (World Medical Association of Helsinki 2018) [27] states the following: "In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available" [27]. Compliance with Art 37 of the Declaration of Helsinki means that not licensed ATMPs could be used by the physician to treat a patient, if alternatives are unavailable or ineffective, and new information with regard to the unlicensed ATMPs safety and efficacy is recorded. However, the Declaration of Helsinki, although at the international medical community level well-established as a basic (ethical) document, is not legally binding. This means that it has no national juridical value and as such could put the practitioner in a position of juridical vulnerability [9]. Moreover, Art 37 deals with unproven interventions, which is conflicting with the clinical reality of keratinocyte grafts, which have been used for 30 years in clinical practice.

Magistral ATMP Preparation

In European and Belgian legislation, the notion of a magistral preparation (compounded prescription drug product in the US) is defined as "any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient" (Article 3 of European Directive 2001/83/EC and Article 6 quater, § 3 of the Belgian Law of 25 March 1964) [8,28]. Magistral preparations are formulated based on particular constituent ingredients by a pharmacist (or at least under his/her supervision), for a given patient according to a prescription by a physician and following the technical and scientific standards of the pharmaceutical art. The magistral formula is a practical way for a medical doctor to personalise patient treatments to specific needs and to make medications available that do not exist commercially. Some medicines, such as natural hormone combination products and allergens, are not produced by commercial manufacturers and are actually delivered as magistral preparations. Owing to the emergence of innovative medicines for rare diseases or for personalized therapies, the demand of magistral preparations is increasing [9]. We propose to apply the concept of the magistral preparation to not centrally authorised ATMPs. ATMPs, which are claimed in the Regulation to be "cells or tissues that have been subject to substantial manipulation", making them subject to the pharmaceutical legislation (EC No1394/2007) [1], would be seen

as the Active Pharmaceutical Ingredients (APIs) of these magistral preparations [10]. An advantage of this magistral preparation pathway for ATMPs is that the practitioner would be in a less vulnerable position, since the current medicinal products legislative framework covers magistral preparations (Therapeutic Magistral Form / FAMHP, available on line [29]). As opposed to on-label use of authorised medicinal products, magistral preparations are delivered under the sole responsibility of the prescriber and the pharmacist. With this in mind, the QAMH submitted, on September 19, 2019, a request for a "Scientific-Technical Advice Type 1" (FAMHP Scientific-technical advice, available online [30]) to the BCA enquiring if the "magistral preparation" production pathway could be considered [9]. The human cultured keratinocytes would then be seen as the Active Pharmaceutical Ingredient (API) to be used in the magistral preparation of keratinocyte products.

Production and Delivery of Magistral Preparations

Inspiration: The Regulatory Pathway for Magistral Bacteriophage Preparations (Belgian Precedent)

In Belgium, to comply with the legislation on medicinal products, several regulatory routes are possible.
Current options for ATMPs are:

- Submission of an application for a centralised marketing authorisation (MA) to the EMA together with the submission of an application for obtaining a manufacturing authorisation (GMP certification) for an 'authorised' advanced medicinal product.

OR

- Submission and approval of a clinical trial application, supported by an investigational medicinal product dossier (IMPD), supplemented with the application of an authorisation for the manufacturing of an advanced investigational medicinal product.

OR

- Submitting an application for hospital exemption (HE) to obtain an approved ATMP-HE dossier, with the submission of an application for GMP inspection for obtaining the required GMP certificate.

For the cultured human keratinocytes, an additional regulatory route is considered here, inspired by the magistral approach recently proposed (and advised positively by the BCA) in the field of bacteriophage therapy [9]. Through the Belgian Scientific-Technical Advice (STA) procedure (FAMHP Scientific-advice, available on line [30]), the competent authority concurred that natural bacteriophages could be processed by a pharmacist as an API in magistral preparations. The magistral preparations should be delivered to a specific patient under the responsibility of a prescriber (medical doctor) and a pharmacist. The relevant characteristics and quality aspects of the API should be described in an internal monograph. This magistral formula regulatory approach is applicable only if a certificate of analysis is issued by an officially approved analytical laboratory demonstrating compliance with the internal monograph. In cooperation with the BCA and several experts, an internal monograph was elaborated to describe bacteriophage production and testing as an API for use in magistral preparations and this monograph was deemed appropriate (Supplementary Material 2: Phage General Monograph) [31]. The internal monograph has now been submitted for consideration and possible follow-up by the European Pharmacopoeia Commission (EDQM Technical guides, available online [32]).

Applied to ATMPs: The Regulatory Pathway for Magistral ATMP Preparations

Currently, we are discussing the possibility of bringing cultured keratinocytes (Supplementary Material 3: Keratinocyte Information Leaflet) as magistral preparations to the patients. The final products would be produced tailored to the patient's need, on request, subscribed by a medical doctor, and delivered by the hospital's pharmacist. The same procedure to obtain scientific technical advice will be initiated, as the one we went through for the bacteriophages. As it was decided that keratinocytes are medicinal products (ATMPs), they are covered by the pharmaceutical legislation. This legislation foresees pathways other than the traditional marketing authorisation pathway, such as magistral preparations [9]. In line with the Belgian legal provisions for magistral preparation, we have proposed to the BCA that we would produce, test and deliver cultured keratinocytes that comply with the requirements of an internal monograph. The API testing, as described in the internal monograph, would be outsourced to an external Belgian approved laboratory. It should be noted that, as it is the case for several HCT/Ps, the formulation of the keratinocytes' final preparation will only require a limited amount of steps and handling, meaning that the final product will be not so different from the API. Accordingly, API testing will reliably reflect the quality of the final magistral preparation. Moreover, its quality/safety will be further secured by a strict compliance to the provisions of EUCTDs (and their National transpositions).

Examples of Cultured Human Keratinocytes Magistral Preparations

For the application to a patient of autologous cultured human keratinocytes, derived from a skin biopsy obtained from a named patient, a medical doctor would prescribe the topical application of cultures of the patient's keratinocytes under the form of sheets, sprays or in combination with another product (e.g. cultured keratinocytes in combination with a dermal matrix). The cultured patient's keratinocytes should have been previously tested by an officially recognized analytical laboratory and found compliant with the supplier's API internal monograph. A (trained) pharmacist would then, under his responsibility, use the cultured autologous keratinocytes to formulate the requested magistral preparation (sheets, sprays or combined). Under the responsibility of a prescriber, these magistral preparations could then be administered to the patient.

In order to stimulate wound healing, allogeneic cultures of human keratinocytes could also be applied to patients, e.g. on skin donor sites or recalcitrant wounds. Similarly, to the autologous application, a medical doctor could prescribe allogeneic keratinocyte cultures for a specific patient (to be applied in the form of sprays, sheets or as a combined product). Based on a certificate of analysis, issued by a recognized analytical laboratory, which demonstrates compliance with the supplier's API monograph, a pharmacist could formulate the final magistral preparation and the prescriber could then apply, under his responsibility, the magistral preparation on a specific patient.

Conclusions & Perspectives

- In view of meeting patients' medical needs, we would welcome a return to a simpler and more pragmatic regulatory framework for non-commercial (non-industrially produced) somatic cell- and tissue products for human use,

without compromising quality and safety. According to the scheme proposed here, the final product would be released under the responsibility of the person in charge of the tissue establishment (when referring to the EUCTDs) and/or under the responsibility of a pharmacist (when referring to the magistral preparations of an ATMP), with a dedicated recording of subsequent information (as prescribed in the Helsinki Declaration).

- For commercial ATMPs, we subscribe to the European ATMP regulatory framework (EC No 1394/2007) [1], including marketing authorisation approval, particularly for gene therapy medicinal products.
- Although innovative therapies created great hope for patients, the ATMP regulatory framework seems to be inadequate for now. In reality, there are only very few and very expensive ATMPs available on the market today, more than 10 years after the ATMP regulatory framework came into force.
- It is important to fund a large array of basic research, but when it comes to applied research, we would like to stress that it might be important to investigate, in advance and at early stages, through Health Technology Assessment (HTA) and by consulting payer representatives, what the chances are that researched therapy could actually become available, at a payable rate and with sufficient return on investment.

Supplementary Materials

Supplementary Material 1: Keratinocyte QAMH
Supplementary Material 2: Phage General Monograph
Supplementary Material 3: Keratinocyte Information Leaflet

Authors Contributions

Gilbert Verbeken (Writing)
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Other Authors (Reviewing)

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