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GMP-grade allogeneic musculoskeletal primary progenitor cell types: Standardized candidates for general or pharmacopeial monograph elaboration

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Abbreviations: API: Active Pharmaceutical Ingredient; ATMP: Advanced Therapy Medicinal Product; CDEA: Cultured Dermal-Epidermal Autograft; CEA: Cultured Epithelial Autograft; EC: European Commission; GMP: Good Manufacturing Practices; TEP: Tissue Engineering Product; TPA: Therapeutic Products Act.

Regarding translational developments of cell therapies and tissue engineering products (TEP) in Europe over the last decade, considerable concern is raised around hampering effects of current regulatory frameworks on innovative product or protocol implementations, particularly in hospital settings regarding treatments provided to their own patients. The adoption of Directive 2001/83/EC, Regulation 726/2004 and subsequent amending Regulation 1394/2007 of the European Parliament, as well as National renewed Transplantation and/or Therapeutic products (Swiss) Legislation have indeed drastically modified both the landscape and specific requirements for the development, manufacture and use of Advanced Therapy Medicinal Products (ATMP), aligning them closely to those for medicinal products [1-5]. Notions of substantial manipulation and standardized transplant products therefore require inherent conjugation with industrial standards of Good Manufacturing Practices (GMP) when considering both autologous and allogeneic cell therapy protocols comprising *in vitro* cellular expansion steps. The formidable ensuing direct and indirect costs of manufacture and regulatory submissions may therefore only be borne by restricted numbers of public and private sponsors highly interested in overseeing novel regenerative medicine products reach patient bedsides, considering that concerned patients may only represent a reduced market in terms of return on investment. Decisively, a disruptive aspect in the implementation of aforementioned legally binding frameworks resides in the absence of differentiation between large pharmaceutical multinationals and hospital pharmacy departments manufacturing cell-based products for internal institutional use, respectively vital treatments for their own patients. This multifaceted problematic is currently at the heart of active multidisciplinary debates around the operation of Burn Centers in particular, as numerous institutions use protocols comprising autologous or allogeneic keratinocyte culture methods for salutary cultured epithelial graft manufacture [6,7]. Jeopardizing interpretations of European legislation by many national Regulators have led to denunciations of many well-established hospital practices around cell therapy protocol implementations, directly endangering the lives of severely traumatized patients such as burn victims. Fundamental ethical conflicts therefore arise for clinicians, as interventions which are documented as lifesaving become disputed in terms of legality. Pragmatic and rapid solutions are therefore sought, in order to limit legal exposure of clinicians and hospital departments, while ensuring conformity with both existing multi-tiered legislations and the vital needs of treated patients [8,9].

Several differential regulatory pathways were proposed to encompass and respond to the clinical need-driven and continued production of historically used and proven therapies in Burn Centers, putatively considered as orphan drugs or used under hospital exemptions and in compassionate use for patient betterment [7-10]. Elegant solutions to the potential upcoming regulatory deadlocks regarding hospital internal production and use of novel ATMPs are the classifications of such products as hospital pharmacy officinal or magistral preparations, as defined by the Swiss Federal Therapeutic Products Act (TPA), allowing a marketing authorization exemption under certain conditions (Article 9 para. 2 TPA) [4,5,11]. The first category describes products manufactured, on demand or serially, by an authorized pharmacy following a recognized formula or monograph and to be used for treatment of the institution's own patients. The second category describes products manufactured, on demand or serially, by an authorized pharmacy following a medical prescription and intended for the treatment of a determined patient or subset of patients [4,11]. Therefore, an optimal workflow may be devised in hospitals when considering a hybrid interpretation of both definitions for continued use of innovative products which have not yet been submitted to formal clinical evaluation and regulatory authorization.

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Cell therapies or TEPs for specific clinical indications would then be manufactured on demand or serially by the hospital pharmacy, under the responsibility of a pharmacist, under GMP requirements, following a medical prescription referencing an approved general monograph or formula, for a specific patient or group of patients treated within the institution. To this end and in view of continued optimization and standardization of novel therapeutic products, specific monographs can be drafted for appropriate approval before entry in institutional, national or international repositories and compendia, ideally a Pharmacopoeia, based on existing local GMP documentation systems and clinical experience around such product types [11]. This approach may be considered in the close future for cultured epithelial autografts (CEA) or cultured dermal-epidermal autografts (CDEA) for use in treating severe burn victims, as many Burn Centers have adopted such protocols since the 1980's, generating substantial hindsight [6,7,9].

The specific example to be elaborated herein is based on internal clinical experience around the use of banked allogeneic fetal progenitor dermal fibroblasts for managing donor-site wounds, second degree burns and chronic ulcers [12-15]. Such products have been used in our University Hospital since the 1990's and were already classified as magistral preparations at the time [7,9]. Indeed, preliminary safety and efficacy data have been gathered over the past two decades for this technology, while regulatory approvals for related clinical trials have been obtained in Taiwan, Japan and the USA by private sponsors working on standard ATMP development (ClinicalTrials.gov identifiers: NCT02737748 & NCT03624023). By extension, numerous intrinsic technical and biological characteristics of various musculoskeletal progenitor cell types of interest favor them as optimal substrates for transposition to semi-industrial and industrial-scale GMP manufacture, as they are optimally standardized. Therapeutic biological components are indeed extremely robust, with high consistency and stability in all considered aspects [13]. Extensive tiered cryopreserved cell banks may be derived after a single organ donation regulated under a Transplantation Program and be maintained for decades, while various cell types differentially isolated from musculoskeletal tissues may serve for the potential manufacture of several billion therapeutic product units [14,15]. These specificities enable the optimized elaboration of general monographs intended for local or official compendia or Pharmacopeial inclusion, which must by nature describe maximally standardized biologic materials. Banked primary progenitor cells are epitomes of therapeutic cell choice optimization, as they are particularly well suited for GMP workflows, which may in turn be adapted to general monograph structures regarding definition of the biological starting material or active pharmaceutical ingredient (API), precise manufacturing process description (including environment, equipment and materials), risk management, in-process controls, quality and release testing, qualifications and specific prescriptions. Such monographs have already been elaborated for novel APIs such as bacteriophages in the context of magistral preparation developments or for cells of fetal origin to be used as vaccine production substrates (following Pharmacopeial dispositions) [11,16]. The adequate levels of approval for such monographs are to be defined, as well as the target compendia. They nonetheless may provide effective ways to implement highly specialized therapeutic tools in public institutions as exposed herein and constitute tremendous steps towards optimization and standardization of cell therapy protocols and TEPs for vital clinical applications failing to elicit tangible interest from the pharmaceutical industry [6,9,10].

Conclusion

In conclusion, due to highly restrictive current regulatory burdens in Europe with regard to ATMP development, which have drastically diminished the number of market approval requests and products on the market, the development of hospital officinal/magistral preparation workflows seems well adapted to ensure availability of innovative life-saving treatments to patients in dire need [6,9]. Based on extensive scientific and clinical experience, banked primary progenitor cells appear to be optimally adapted for standardized monograph description of novel APIs. The inclusion of such monographs in recognized compendia such as Pharmacopoeias is justified for various specialized products clinically used for several decades. This in turn shall surely widely benefit translational developments in musculoskeletal regenerative medicine and potentiate chances of groundbreaking innovations to reach the bedside of patients relying on the latter with their lives.

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Conflicts of interest

The authors declare no conflicts of interest.

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