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Concise Review

Expert Consideration on Regulatory Aspects for Perinatal Derivatives in Clinical Settings

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Abstract

Perinatal derivatives (PnD) are drawing growing interest among the scientific community as an unrestricted source of multipotent stem cells, secretome, and biological matrices. They are useful for the treatment of diseases that currently have limited or no effective therapeutic options, but they require the development of regenerative approaches. With this development, the question of regulation of donation, processing, and distribution has therefore become more important. Within the European Cooperation in Science and Technology (COST) community, we compiled a group of international experts on PnD technologies, who revised and compared existing EU national regulations. Notably, despite clear European directives, each EU Country has developed their own implementation and standard levels for cell- and tissue-based therapies. To enable extended applications of PnD treatments within the EU community and worldwide, harmonization is highly recommended. This paper aims to provide an overview of the various options available to introduce PnD into clinical practice. For this purpose, the different aspects resulting from (1) the type of PnD, (2) the amount of available data, (3) the degree of manipulation, and (4) the intended application and the process toward a possible commercialization will be presented. In the future, it will be important to find a balance between regulatory requirements and the best medical quality of the PnD product.

Key words: perinatal tissues; placenta; European regulation; cell therapy; ATMP.

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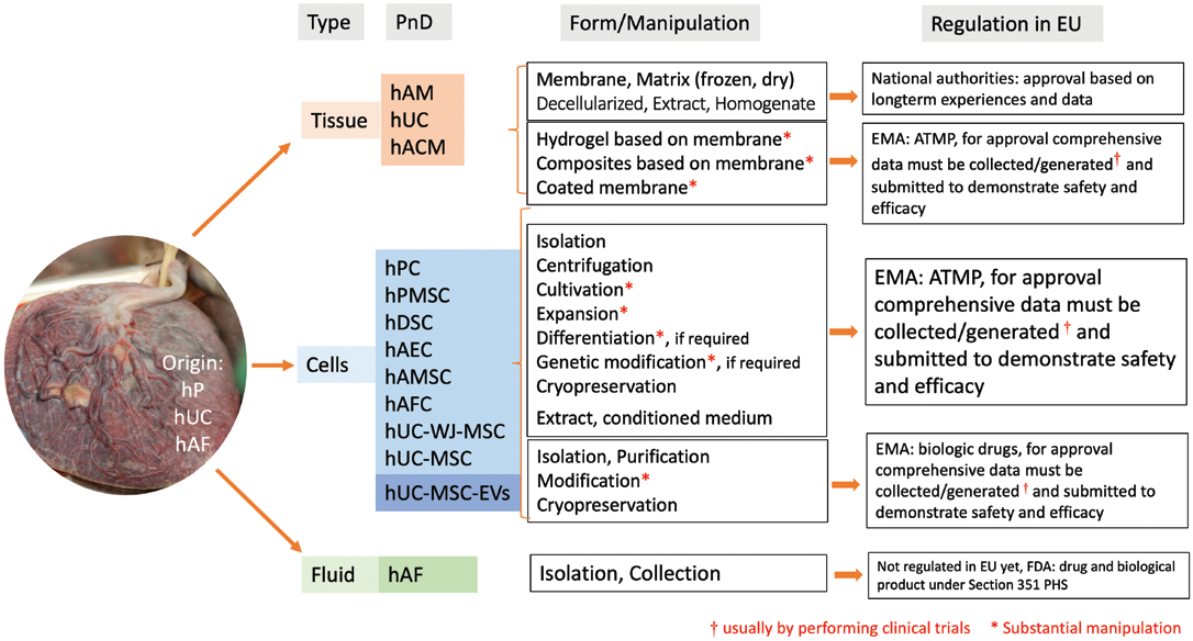
Graphical Abstract

This summary shows the origin of different types of PnD related to the degree of manipulation. The various PnD are typically processed to different degrees, so the resulting products are subject to distinct regulatory pathways. The higher the degree of manipulation, the more extensive are usually the requirements for approval.



Significance Statement

Perinatal derivatives (PnD) are drawing growing interest among the scientific community for the treatment of diseases. To enable extended applications of PnD treatments institutions in charge of translational research have to be aware of the regulatory constraints and their evolution in order to obtain the necessary authorizations for clinical use. The paper aims to give an overview over these important steps.

Introduction

The consensus is that perinatal derivatives (PnD) have enormous potential for both innovative and traditional forms of therapy. PnD products include both fetal and maternal tissues and cells, with human amniotic membrane (hAM) being the first and most frequently used medical product. Additionally, multipotent stem and progenitor cells which can be found floating in amniotic fluid or embedded in different parts of the placenta or the umbilical cord (hUC) have recently gained recognition as effective treatments for several congenital or chronic disorders. Moreover, both tissue and cellular extracts or secreted mediators (ie, extracellular vesicles, EVs) have attracted attention as promising candidates in regenerative medicine. Human amniotic membrane has been successfully implemented in wound healing treatment for more than 100 years, and since 1940 it has claimed a leading position in the treatment of ophthalmological defects[1].

Since the first half of the 20th century, a growing amount of alternative therapeutic options based on different PnD products have been proposed and investigated[2], seldom resulting in approved therapies. Such limited integration into established clinical portfolios is mainly due to the sparse initiatives proposed and tested by different groups worldwide, without a systematic approach. Furthermore, the process leading to market approval commonly requires strategies to overcome critical challenges, frequently resulting in a delay in translational success, particularly for innovative treatment procedures. The strategies which must be taken into consideration for the successful development of a new drug candidate or therapy extend now beyond research and clinical topics and should include a business perspective (funding of clinical trials including a pivotal trial), good manufacturing practice (GMP) (scalable and cost-effective drug production process without change of the product identity), market analysis (availability and cost of the current therapies), cost of the new drug and reimbursement scenarios, intellectual property and freedom to operate, regulatory framework in different countries (also outside Europe), and among other issues. It is worth mentioning that all these issues should be carefully investigated during non-clinical tests or even at the stage of basic research, that is, patents, otherwise all the efforts and resources invested in the development of the new product might not result in this product being available for patients. Finally, incomplete guidelines or unclear regulatory requirements frequently cause delays and jeopardize the implementation of promising applications and innovative technology into clinical practice.

This paper aims to provide an overview of the various options available for the introduction of PnD into clinical practice. For this purpose, the different aspects resulting from (1) the type of PnD, (2) the amount of available data, (3) the degree of manipulation, and (4) the intended application and the process toward a possible commercialization will be presented.

Procedures Required for the Approval of a Therapy Using PnD

1. Type of PnD

The procedure required to grant regulatory approval for a PnD therapy vastly depends on innate characteristics, such as the type of PnD product and manufacturing procedure. Different PnD products are scrutinized by different regulatory requirements for a marketing authorization.

The graphical abstract offers an overview of the variety of components that can be used for clinical application. From different parts of the human placenta, the umbilical cord and amniotic fluid, different therapeutic products can be generated. These products are classified as tissues, cells, fluids, or biologic drugs (EVs).

Among the tissues, the hAM and amnion-chorion membrane (hACM), as well as the hUC are particularly noteworthy for their widespread use in medical practice. Furthermore, a wide range of cells with stem and progenitor characteristics have been described and isolated from perinatal tissues, recently revised and characterized in Gindraux et al, 2022. In addition, there is growing interest in extracellular vesicles (EVs) derived from umbilical cord mesenchymal stromal cells (hUC-MSCs), secreted in vivo and in vitro. EVs are classified as biological drugs and may be used as an alternative to allogenic MSCs. Biological fluids, such as amniotic fluid (hAF), contain different components including cells, cell secretome, that is, growth factors, EVs, antibodies, and also metabolites, that is, fetal urine. In most cases, hAF is purified and its components are extracted for further production, that is, MSCs.

2. Amount of available data

The next step in the decision process toward approval of a therapy is based on the amount of already available data on the PnD used. When a sufficient amount of evidence and knowledge exists on the proposed PnD product and its therapeutic application, such as the human amniotic membrane, which has been clinically used for centuries, the approval and authorization processes for distribution significantly accelerate or result in advanced clinical trials (phases 3-4).[3]

3. Degree of manipulation

The regulatory requirements are also determined by the degree of manipulation. For cell and tissue transplants, for example, membranes that are used in their native form as a matrix, less action is required for approval of their clinical use but requirements may depend on the intended indication. The use of hAM, hACM, and hUC tissues processed as substrate has been an established method for decades. Currently, in the European Community, hUC and hAM/hACM products fall under the regulation of Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells.[4] In addition, further requirements are necessary as detailed in Directive 2001/83/EC,[5] Regulation (EC) No. 726/2004,[6] Commission Directive 2006/17/EC,[7] Commission Directive 2003/63/EC,[8] Commission Directive 2006/86/EC,[9] Commission Directive (EU) 2015/565,[10] and eventually in the Commission Directive (EU) 2015/566.[11]

However, since these directives have been transposed into national laws or guidelines in the different European Countries, the regulatory requirements are not always uniform. A questionnaire about the *status quo* of regulation within the EU Member States has been compiled by members of the COST SPRINT Action (CA17116; https://www.sprint-cost.org/) (Annex 1), highlighting heterogeneity in the implementation of the directive.

Furthermore, a growing amount of data is already available on perinatal tissue preparations, leading national authorities to approve their use in advance and to limit additional experimental and preclinical validations, provided that the requirements for the quality of the transplants are also met. In Germany, for example, 17 hAM preparations are currently approved for clinical use by the higher federal authority Paul-Ehrlich-Institute (PEI)[12] and more will follow. In Europe, 183 Tissue Establishments (TE) are currently registered as approved for procurement, processing, preservation, storage, and distribution of hAM, hACM, and/or hUC, including products commercialized by biotech companies.[13]

The situation described above is different for other PnD tissues, characterized by more than minimal manipulation. When hAM, hACM, or other cells and tissue PnD are modified, altered, or combined with other components,[14] or when living cells are involved, additional guidelines must be followed for both their application and their approval in medical practice.

In Europe, such tissue- or cell-based therapies are regulated as advanced therapy medicinal products (ATMPs) and are evaluated by the Committee for Advanced Therapies (CAT) at the European Medicines Agency (EMA). Specifically, regulation 1394/2007[15] defines somatic cell therapy, gene therapy, and tissue-engineered products as ATMPs. Cell therapy and tissue-engineered products consist of viable cells or tissues which have been either substantially manipulated or engineered as defined within this legislation [see Art. 2.1(c) of the regulation, and graphical abstract(non-substantial manipulation: cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solution, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, cryopreservation, vitrification)],[15,16] or applied in a non-homologous manner (ie, not used for the same essential function in the recipient as in the donor). The regulatory framework governing the safe and effective use of these types of products must accommodate their heterogeneity in the characteristics, GMP manufacturing, and clinical tests while ensuring that the therapeutic potential and safety concerns, typical of these type of products, are adequately addressed.[17,18]

Currently, there are 16 approved ATMPs in the EU, 13 of which are gene therapy medicines, 1 is a somatic cell therapy medicinal product (Alofisel), and 2 are tissue-engineered products (Holoclar, Spherox); none of them is/comes from a PnD. Notably, 13 of the current approved ATMPs are medical strategies for orphan diseases.[19]

4. Intended application: from hospital exemption to PnD commercialization

In addition to the type of PnD and modification level, another critical parameter is the extent to which the PnD product will be available to patients.[3] In other words, a decision must be

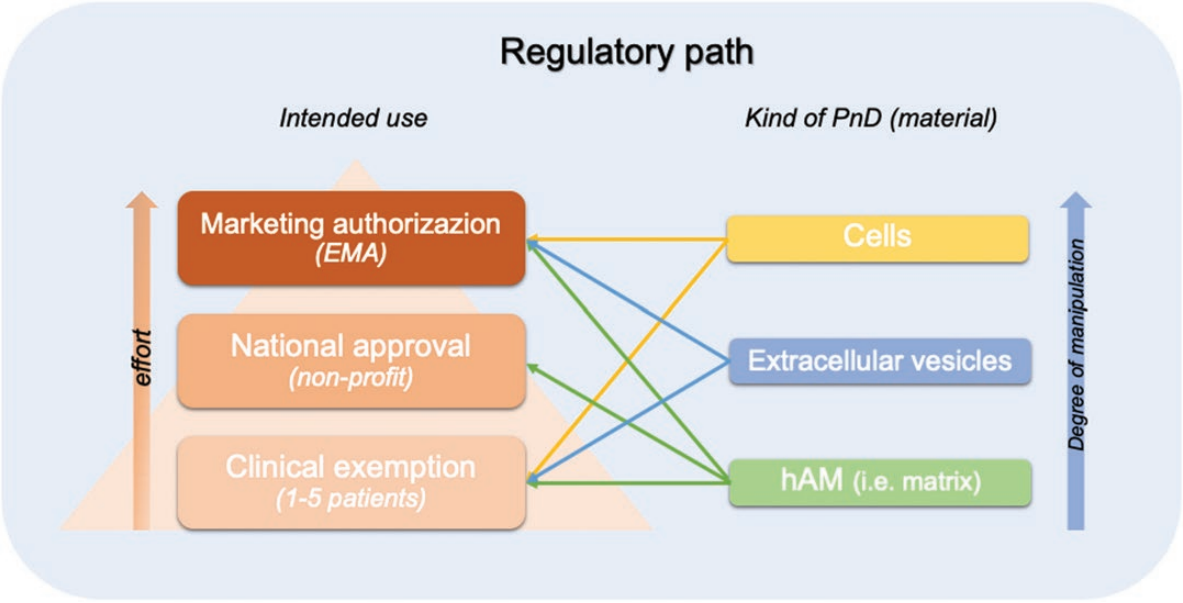


Figure 1. Possible regulatory path depending on intended use.

made on whether the product is intended for commercialization and will be available as paid therapy for everyone or if it will be used locally on a not-for-profit basis. If the initial aim is to cure patients selectively with personalized PnD products, national approval may be sufficient for tissue/cell manipulation and (local) distribution (Fig. 1). As previously mentioned, a national authorization is also sufficient for tissue preparation or cell-based therapies with documented not-for-profit experience, only for limited local use (ie, approval of tissue preparations according to §21a AMG, §13 AMG, and authorization of ATMP: non-routinely produced ATMPs in accordance with Section 4b AMG [German Medicines Act,[20]]).

Conversely, when EU distribution is intended for a cell-based therapy or tissue-engineered products, the canonical market authorization approval (MAA) via the EMA is required, under the conditions described below.

All ATMPs must receive market authorization from the European Commission after an evaluation from EMA and CAT to be considered for commercialization. A similar process is required for drug authorization in other counties, that is, approval of New Drug Application (NDA) by FDA in the USA. Market authorization is required for any commercial use of the drug product. The commercialization strategy depends on the drug product development process, for example, the approach to register hAM is different from that for new ATMPs and EVs drug products.

As recently pointed out,[2] the most used PnD products in clinical trials by far are technologies based on living cells, mainly hUC-MSCs. Support is provided by authorities regarding the decision as to whether and when it will be classified as an ATMP (Fig. 2, PEI[21])[22] [cf classification EMA/CAT/600280/2010 rev 1].

If the approvals for clinical use are to be obtained for these cell-based therapies in Europe, the EMA's guidelines on ATMPs must be followed. The EMA provides detailed instructions for obtaining a marketing authorization (Table 1).

To help developers of gene therapy medicinal products (GTMPs) and cell-based medicinal products (CBMPs) to navigate the most important quality-related regulatory requirements, the EMA has recently published guides, flowcharts, and checklists on quality, non-clinical development and clinical development.

Cell-Based Biologic Products: Extracellular vesicles (EVs)

Recently cell-based biologic products such as EVs, have been investigated and proposed for clinical use. Within EU regulation, EVs and extracellular particles are classified as biologic drugs, despite their similarity to ATMPs. Biological drugs (biologicals) are produced by living cells, in most cases as cell secretomes or cell extract. The main difference between MSC-derived EVs (biologic drug) and MSCs (ATMP) is that the latter are living cells and EVs are non-viable nanoparticles with an average size of less than 500 nm. EVs contain proteins, growth factors, mRNA, and other molecules encapsulated in a lipid sphere. All these factors are responsible for the therapeutic effect of EVs. EVs usually have similar effects to their cells of origin, such as MSCs, in terms of therapeutic activity, but EVs do not have the key disadvantages of living cells, that is, low stability, viability issues, tumor, and rejection risk. EVs can be easily and safely delivered into different tissues and organs in vivo. Last but not least, EVs can be produced at significantly lower costs than MSCs (ATMPs), which is important in product commercialization and availability of the therapy for patients.

However, clinical approval for EVs biologic drugs is more complex than for ATMPs for many reasons. EVs are brand new products with a complex production process and no comparators existing on the market. EVs are classified as biologic drugs but their complexity and multi-modal mechanism of action are more similar to ATMPs when compared to classical biological drugs available on the market. This requires additional efforts from both EVs drug manufacturers and the regulatory authorities to develop new standards for this type of drug products.

Commercialization of EVs biologic drugs must follow the same principles as ATMP and other drugs described above. EVs safety and efficacy must be supported by pre-clinical

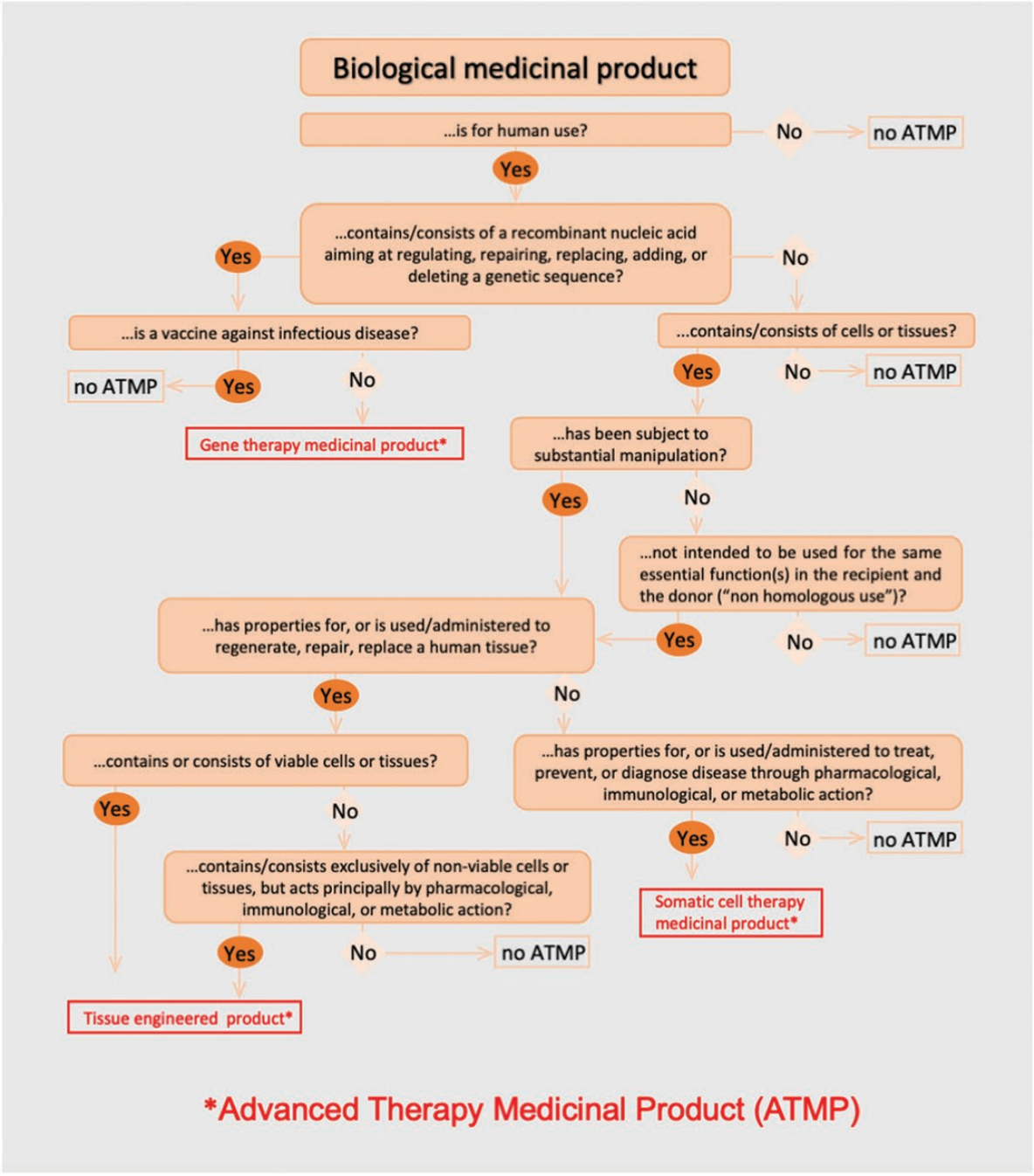


Figure 2. Decision tree for the classification as ATMP (modified from Ref.[21]).

data and tested in clinical trials to prove that they are applicable to patient treatments. EVs drug product qualification assessment requires full declaration of cell source, culture conditions, and cell's identity recorded on the parental cells before EVs collection and purification process. The EV production must be controlled in terms of microenvironment around the cells: physical (support of culture), mechanical, and chemical (culture media and other factors if primed) and modulated around the cell type originating such soluble mediators [23] (Lener et al 2015)]. Quality and purity of the EVs drugs are correlated with the parent cells quality, for example, hUC-MSCs must be continuously tested for viability during EVs production to avoid contamination of the drug product with apoptotic bodies which are of similar size to EVs. Extensive information about EVs is provided by the International Society for Extracellular Vesicles in the recent MISEV2018 guidelines.([24]

Conditions for Manufacture and Distribution of PnD Products

The distribution of PnD products requires transparent, rigorous, standardized manufacturing steps at an authorized manufacturing site, which is crucial for delivering a safe and effective treatment to the end user, regardless of the intended number of patients or commercial status of the product.

Table 1. Instructions for obtaining a marketing authorization.

Research and development	Marketing authorization	Post-authorization
Formal support for advanced-therapy developers through: • Scientific advice and protocol assistance • Orphan designation • The micro, small, and medium-sized enterprise (SME) office • Classification of ATMPs • Certification of quality and non-clinical data for SMEs	Advanced therapy classification: Criteria for ATMPs are set out in Article 17 of Regulation (EC) No 1394/2007	Pharmacovigilance for advanced therapies: Guideline on safety and efficacy follow-up—risk management of ATMPs
Scientific guidelines and information about • GMP requirements • GCP requirements • GLP requirements	Marketing-authorization procedures for advanced-therapy medicinal products: • Procedural advice on the evaluation of ATMPs • Dossier requirements and submission dates • Guidelines on the risk-based approach according to Annex I, part IV of Directive/2001/83/EC applied to ATMP • Procedural advice on the re-examination of Committee for Medicinal Products for Human Use opinion • Procedural advice on the consultation of notified bodies in the case of a combined ATMPs	

Donor cells or tissues are isolated, manipulated, and preserved before implanting them in the recipient(s). These steps need specific requirements for quality and risk management, validation processes, and peculiarity in recruitment of donors and consent for PnD.

Quality and Risk Management

Several non-clinical studies in combination with clinical experience in pathophysiology manifestations support the proof of concept and the choice of clinically relevant endpoints to determine both the safety and efficacy of new interventional approaches. However, the standard approach for development of the new therapy is to perform a prospective clinical trial to demonstrate the safety and efficacy of a new drug. Likewise, clinical development may require progressive evaluations through phases I, II, and III clinical trials followed by marketing authorization of the new drug product. Registered clinical trials are mandatory for all new drug products intended for marketing authorization. A flexible approach named "risk-based approach" was introduced with the revision of Annex 1, part IV of Directive 2001/83/EC,[5] as amended by Directive 2009/120/EC.[16] Such an approach is optional and aims at performing a case-by-case pharmaceutical development, following the scientific and regulatory guidelines relating to the quality, safety, and efficacy of medicinal products.

A drug product intended for human use must be manufactured according to the Good Manufacturing Practice (GMP), which requires the implementation of a defined quality system. GMP and quality requirements are applicable for the production of any drug product for human use, including case studies or small phase I clinical trials. The quality and risk management (QRM),[25] as well as validation of the final product, require formal documentation detailing all preparation activities. The donation and testing of the tissue are performed according to tissue and cell legislation. Thus, GMP manufacturing process starts with initial quality control of the tissue for the production of ATMP and continues with description and analysis of every step until final batch distribution. To warrant transparency and maximal quality of the final product, it is necessary to: (1) define the regulatory context (including donation, procurement, testing, processing, storage, distribution, and import/export activities); (2) use a robust QRM in compliance with the legal requirements; and (3) obtain the regulatory authorization for every specific activity.

Validation Process

The quality assurance (QA) and validation activities (VA) warrant the safety of the final users and patients. QA and VA require a complete and clear understanding of the risks associated with the whole process and every critical step, which must be detailed in the risk matrix documentation. The term "qualification" is applied to equipment, facilities, and personnel involved in the process (specifically, cleanrooms, GMP facilities, equipment, materials, and operators). The term "validation" is usually used for processes and assays. Successful qualification of the premises and equipment is a prerequisite for validation. The validation and qualification must be conducted before the first use, and repeated at predetermined intervals, or once significant modifications have been introduced in the standard operating procedures (SOP). The methods implemented in the QA and VA must be described and the acceptance criteria must be documented and approved by a responsible person for quality. The validation must be performed by trained and qualified persons and the results are compared with the acceptance criteria. The resulting document is commonly known as the validation plan. The risk-mitigation strategies should be developed to protect both donor and recipient(s).

Full validation of the GMP production process and quality control must be completed during the clinical trials. At the early stages of the clinical trials, full validation is not mandatory except for safety tests. However, all the procedures must be sufficiently tested and qualified until phase III of the clinical trial to obtain a GMP certification for drug manufacturing from the national regulatory authorities.

Peculiarity in Donor Recruitment and Consent for PnD

The PnD products are generated from starting material, such as organ/tissue donated from donors, upon signed informed consent. The modality of informed consent depends on the type of donor, the specific circumstances, and different legal systems for consent.[26] In many countries the certified tissue banks (or tissue establishments) are responsible for procurement of biological materials intended for drug manufacturing, including donor selection, consent, collection, testing, and release of the material for human use or further manufacturing. Tissue banks cooperate with the Ethics Committees and are responsible for sample anonymization or pseudo-anonymization, compliance with GDPR directive, and traceability of the biological material.

The acceptance criteria for donors in PnD require both to minimize the risk of transmitting microbial or genetic diseases to a recipient (implemented by the use of prenatal and neonatal screening) and to exclude any tissues or cells whose quality may be adversely affected (such as maternal immune-reactive cells).[27] During donor evaluation, confirmation of the consent and donor identity are essential steps. In the European Union, the selection criteria are detailed in Annex I/III of Directive 2006/17/EC[7] implementing the previous Directive 2004/23/EC[4] as regards donation, procurement, and testing of human cells and tissues. Individual member states of the European Union can establish their acceptance criteria based on this Directive. The consent for the use of fetal tissues is granted by a legal representative, typically the mother or both parents. Such consent is valid for the first 18 years of life, or until the newborn reaches the legal right to grant continuation of consent. When consent for fetal tissues cannot be extended or the donor cannot be identified and renewed consent cannot be signed, all the products and materials originating from the fetal tissues must be disposed of and destroyed.

Quo vadis? Future Evolution of Regulation

The current binding directives concerning the procurement, processing, and distribution of tissues and cells are currently under revision. A draft regulation is available but it is now being reviewed and discussed. This regulation would replace Directives 2004/23/EC[4] and 2002/98/EC[28] in the future when adopted. A transposition into national law would no longer be necessary and a higher degree of harmonization among the individual member states will be aimed for. Technical specifications will no longer be included in the regulation. These will be specified in the associated guidelines of the European Directorate for the Quality of Medicines & HealthCare (EDQM) and the European Centre for Disease Prevention and Control (ECDC), namely in the guide to the preparation, use, and quality assurance of blood components,[29] and the guide to the quality and safety of tissues and cells for human application,[30] which will then become legally binding. It is therefore not possible yet to estimate if and how this will impact the possibilities of translating new PnD therapies into clinical practice.

Conclusion

The therapeutic potential of PnDs has been extensively explored over the past 20 years, but it must be recognized that current clinical applications do not reflect this investment. It is important that the institutions in charge of translational research are aware of the regulatory constraints and their evolution to obtain the necessary authorizations for clinical use. Finally, another critical aspect impacting the success of a PnD technology in clinical use relies on the reimbursement possibility and quantification. Without adequate payment by health insurances or Institutional Healthcare, the inclusion of established treatments based on PnD innovative strategies into the clinical practice will be quite unlikely and time-consuming. Not to mention that the selective eligibility criteria and restricted access to such innovative therapies would be designed for a small part of the population and limited by socio-economic inclusion criteria rather than medical needs. There might be no successful innovative PnD therapy available for everyone without a successful commercialization. This may sometimes require an additional step with a cost/effectiveness study, so there might still be a long way ahead.

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Conflict of Interest

The authors declared no potential conflicts of interests.

Author Contributions

N.H.: conception and design, collection and/or assembly of information, data analysis and interpretation, manuscript writing. X.L.: conception and design, data analysis and interpretation, manuscript writing. M.A.: data analysis and interpretation, manuscript writing, review and editing. N.F.: manuscript review, and editing. L.G.: manuscript writing, review and editing. R.G.: conception and design, data analysis and interpretation, manuscript writing, review and editing. M.J.: data analysis and interpretation, manuscript writing, review and editing. H.K.: manuscript writing, review and editing. R.N.: manuscript writing, review and editing. J.S.: data analysis and interpretation, manuscript writing, review and editing. V.S.: manuscript writing, review and editing. F.J.N: conception and design, manuscript writing, review and editing. F.G.: conception and design, data analysis and interpretation, manuscript writing, review and editing.

Data Availability

No new data were generated or analyzed in support of this research.

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