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# Stem cell therapy clinical research: A regulatory conundrum for academia☆

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ABSTRACT

The encouraging pace of discovery and development in the field of regenerative medicine holds tremendous potential for bringing therapies to the clinic that may offer meaningful benefit to patients, particularly in diseases with no or suboptimal therapeutic options. Academic researchers will continue to play a critical role in developing concepts and therapies, thus determining whether regenerative medicine will be able to live up to this potential that clearly excites clinicians, researchers and patients alike. This review summarises recent developments in regulatory frameworks across different countries that aim to ensure adequate oversight of the development of regenerative medicine products, which are unique in structural and functional complexity when compared to traditional chemical drugs and fully characterised biological drugs. It discusses the implications of these developments for researchers aiming to make the challenging transition from laboratory to clinical development of these therapies and considers possible pragmatic solutions that could accelerate this process that is essential to maintain research credibility and ensure patient safety.



**Contents**



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## 1. Introduction

Regenerative medicine has come to be a widely accepted term for the varied research efforts made in the last few decades to understand the basic science underlying regeneration of human tissue, organs and cells and translate this growing knowledge into potential therapeutic modalities for diseases hitherto not amenable to management or possible cure [1]. Stem cell therapies hold the potential to provide effective disease modification and possible cure for these diseases that have posed a tremendous challenge to clinicians and a heavy burden in terms of impaired quality and quantity of life for patients [2]. These diseases are associated with a burgeoning cost of suboptimal care for the community and the healthcare system. Successful regenerative medicine has the potential to address all these issues [3].

Numerous stem cell therapies are currently in an exciting but critical clinical translational phase of development, as borne out by clinical trial registries across the world. As of June 2016, there are 4479 studies investigating use of different cellular therapies in various disease indications, of which 998 are industry-sponsored studies, as shown by listings on the National Institute of Health global clinical trial registry [i]. In stroke, for instance, of the 48 ongoing studies, 18 are sponsored by industry [ii]. It is interesting to observe that most ongoing research to date has initially been conducted in academic institutions. Industry has until recently, adopted a very cautious attitude in terms of involvement in development of these therapies [4]. Basic research is yet to provide broadly acceptable answers to key questions concerning structural and functional characterisation of different cell therapies. The challenges posed in terms of regulatory uncertainty and potential commercialisation models have meant that the key drivers in this field have been academic institutions and small to medium enterprises. Lack of experience in addressing regulatory requirements and limited financial and human resources often challenge such entities. As cell based therapeutics move into clinical translation phase, these issues assume critical significance as failure to address these efficiently can be a significant roadblock in procuring funding and approval for meaningful clinical studies critical to ensuring accelerated translation in this field [5].

The inherent complexity of stem cell products and the still evolving understanding of the basic science underlying their mechanistic pathways of action pose a difficult challenge, especially when applied to chronic diseases where there is still an incomplete understanding of disease pathophysiology. The characterisation of chemical drugs has been relatively well understood, leading advanced standardisation and regulation. However, the structural characterisation and mechanism of action for cellular products is poorly understood. Additional work around the validation and global standardisation of preclinical efficacy assays is needed, which makes these therapies not amenable to standard pharmacokinetic characterisation. This unfortunately makes the regulatory pathway difficult and unpredictable. These aspects create multiple challenges for scientists involved in the development of such therapies as they navigate their way through the complexity of development [6].

In recent years, feedback sought from researchers in academia and industry concerning challenges in the development of regenerative medicine products has highlighted the lack of awareness and understanding of regulatory pathways as a significant deterrent to progress in this field [7–9]. This seems to be more prominent amongst academic researchers, which may potentially lead to the loss of many innovative developments in this field [7–9]. In light of the frantic pace of scientific advancement in molecular biology and its application in the area of regenerative medicine, it becomes even more critical that speedy, accurate and practical access to expertise in regulatory science is made available to academic researchers and clinicians, who are still the predominant drivers of translational research in the field of regenerative medicine. Recognition of this need for mechanisms for interdisciplinary collaboration is likely the first step towards accelerating the future pace of development of regenerative medicine.

In this review, we provide a concise description of key developments in regulatory pathways in regenerative medicine across the globe, aimed particularly at researchers in academic settings. This will enable expanded understanding of the key challenges faced in the development of regenerative medicine products and provide a summary of approaches initiated to address them.

## 2. Regulatory pathways in different jurisdictions

### 2.1. United States of America

The Food and Drug Administration (FDA) in the United States has been issuing guidance periodically for development of human cells, tissues, and cellular and tissue-based products (HCT/Ps) for clinical use utilising a tiered, risk-based approach [10]. The extent of FDA oversight required in the development process is dependent on two key considerations: the level of cell manipulation (minimal/more than minimal) and the intended use of cell therapy (homologous/non-homologous) [11]. An HCT/P is regulated under section 361 of the *Public Health Service Act 1944*, which entails an abbreviated review, if it is minimally manipulated, is intended for homologous use only and does not involve the combination of the cells or tissues with other materials, which may raise new clinical safety concerns. The products that undergo more than minimal manipulation and/or are used in a non-homologous manner are deemed 'biological products' (Fig. 1). These undergo an extensive development process with the approval of clinical trials in humans requiring compilation of pre-clinical evidence, the submission of an Investigational New Drug Application (IND) and the submission of a Biologics License Application (BLA) under section 351(i) of the *Public Health Service Act 1944* and related regulations. (See Figs. 2–5.) Q5

The FDA issued 'Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products' in 2015 [12] providing recommendations for clinical translation of HCT/Ps that fulfil the criteria for being a biological drug product, thereby requiring regulatory oversight under section 351 (Table 1). These recommendations pragmatically acknowledge the fact that the distinctive characteristics and feasibility challenges with these products influence the design considerations of early-phase clinical trials of HCT/Ps. The recommendations also acknowledge the limitations in the extrapolation of pre-clinical data to inform early phase study design especially in context of highly humanised or species-specific cell based products. In addition, the FDA developed recommendations for preclinical assessment of cell therapy products, which reflect the authority's openness to move beyond the established pre-clinical guidance based on small molecule therapies, supported by reasonable and scientifically sound evidence [13].

These recommendations lay particular emphasis on the characteristics of cell therapy products such as their ability to express molecules and factors that affect and are in turn, affected by the local microenvironment, and their ability to migrate and differentiate in vivo into undesired cell types. In addition, the impact of potential viral vector contamination and any adventitious therapy/intervention (e.g. immunosuppression/invasive procedures/combination therapies) needs to be evaluated in detail to ensure the safety of potential research participants in clinical trials.

The FDA recognises that the challenges with manufacturing these products may determine feasible doses and emphasises potential issues with the variability within different lots of the products. The guidance underscores the importance of establishing and maintaining GMP standards early in development of the product.

Whilst the principal intent of early phase trials is the assessment of safety and feasibility, as most cell therapy products are likely to be investigated in disease populations to justify the risk inherent in these therapies, the recommendations encourage preliminary assessment of efficacy and obtaining 'proof of concept' data in humans in early phase trials to better inform further development. To that end, activity



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