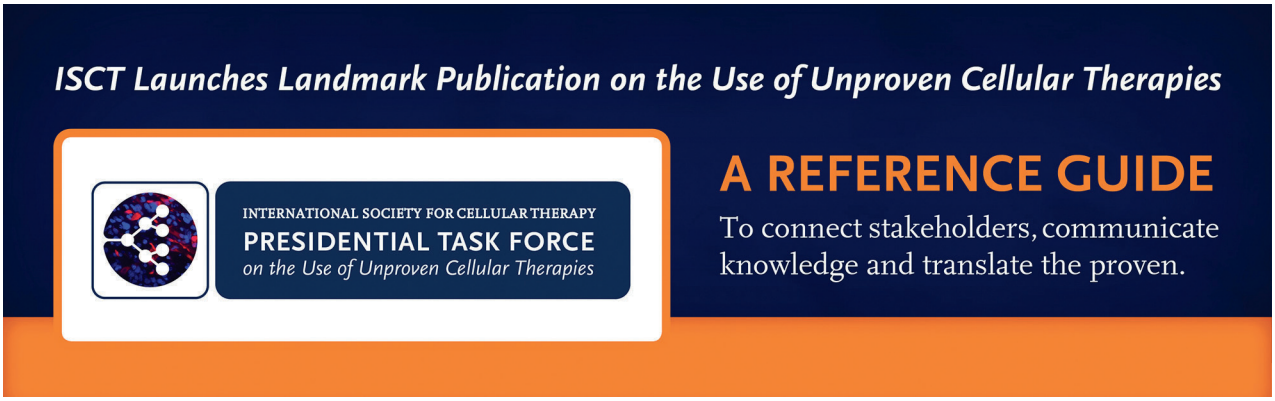

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Part 4: Interaction between unproven cellular therapies and global medicinal product approval regulatory frameworks

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Introduction

Medicinal product (drugs, devices and biologics) regulatory requirements are primarily based on preventing public harm and promoting public health. Harm or injury can occur when a patient is exposed to a medical treatment or device for which the consequences of using that product are not well understood. Therefore, regulations are mostly focused on minimizing potential risks of harm when using unknown, untested or new medical treatments. Cellular therapies are medical treatments. As explained in previous parts, the diseases and conditions treated are numerous and fall under the aegis of either direct effect (for example, cell or tissue replacement with the same systemic effect) or indirect effect (such as cell-to-cell interaction or immunomodulation) [1]. Use of cellular therapies is complicated by the fact that a positive result could be the outcome of one or more different mechanisms of action from the same treatment. There is no way to be completely certain that a cellular therapy is free from harm. Therefore, regulations provide the framework whereby treatments can be provided through the use of a reasonable risk/benefit paradigm. Regulations should not be more burdensome than is required to appropriately reduce risk while allowing access to treatments by needy patients.

Cellular- and tissue-based products are subject to complex regulations that vary widely according to country and product type. Consequently, it is often difficult to determine how different products will be categorized and regulated, especially in advance of using them in clinical practice [2]. Such confusion is compounded when existing regulatory frameworks for conventional pharmaceuticals are used to regulate cellular and gene therapies.

With so many countries grappling with how to balance patient safety with patient and economic demand for unproven cellular therapies, it is meaningful to analyze maturity levels of different national

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and regional regulatory structures and identify the gaps and limitations in their design and enforcement. Interagency and international collaborations and third-party accrediting organizations should also be considered with regard to improving, enforcing and supplementing regulations. This is done with appropriate regard for variations in socio-economic development, cultural norms, regulatory capacity and medical infrastructure.

Country list by population

There are 56 countries with populations greater than 20 million people [3,4]. They are located in all developmental regions [5], with no guarantee that a highly populated country is also indicative of a highly developed country. It would be convenient to argue that the rigor of regulatory framework for any healthcare product can be correlated roughly to economic developmental maturity—developed, in transition or developing economies [6]—however, this is not always the case. Economic development and regulatory maturity are on separate sliding scales but are not mutually exclusive. Economically developed regions are characterized by several features: the transition from an agriculture-based economy to an industry-based economy, an ability to adopt and utilize technologies, a high standard of living and access to healthcare and a highly educated and trained workforce. Rapid economic growth can outpace the creation and implementation of health product regulations, leaving uncertainty and a structural vacuum until the government is able to catch up [5]. Opinions vary as to whether certain regions have reached a mature state of economic development or are in the process of achieving such. There are several organizations that have attempted to define countries and regions in this way; however, it is not the purpose of this part to endorse or analyze these definitions.

Regulatory structures by development status and geography

Economically developed countries typically have a regulatory infrastructure that has come as a result of early failures [7] in public protection. Decades of legislation created an intricate set of regulations designed to protect public safety and assure that any products sold for detection, treatment or cure of disease are required to demonstrate safety, purity and efficacy. For the most part, this process works. However, the introduction of new therapies, such as cell or gene therapies, is often implemented through a long period of regulatory approval, which consequently delays patient access to these programs. For patients most in need of new therapies, this lag between introduction and access can literally be too long, because while waiting, their disease may have progressed beyond the point for any interventional therapy to be effective. The extended approval time reflects the regulatory uncertainty as authorities work to find a path forward using existing frameworks.

For patients and clinicians in particular, it is important to understand that a given country's degree of economic development is not necessarily indicative of its regulatory capacity for overseeing the quality and efficacy of any unproven cellular therapy. A growing economy in a developing country may have a "products and services vacuum" that can attract all manner of goods and activities that might exploit this gap [8]. Intent on building a thriving economy, national leadership may be so eager to attract industry and entrepreneurs that it does not adequately understand and weigh the potential risks of those therapies or evaluate the training and skills of their manufacturers and providers. Lack of education, lack of regulation, ease of access to potential patients and low barriers to entry may all contribute to the continuing risk to patients using unproven cellular therapies.

Table IV provides an overview of regulatory authority for medicinal products by country or region. Often, but certainly not always, more "regulatory-developed" countries offer more regulatory options or pathways, especially for products that target diseases with few effective treatments. These options have come about primarily because patient communities have advocated strongly for access to new medicines in time to make a difference for their constituents. Several examples of products that have been accelerated or "fast-tracked" through a nation's regulatory approval process include HIV drugs, treatments for certain orphan diseases and forms of cancer [66]. In permitting access to a product before it has completed a country's formal process for pre-market approval, regulators may rely on a partial dataset and defer, but not waive, the requirement for the complete safety and efficacy data package that is normally required. To convert to a full approval, the product manufacturer remains accountable for studies that are required to fulfill all pre-approval requirements.

Inter-agency collaborations

Many countries have engaged in cross-border efforts to exchange information about medicinal products and healthcare in general and to harmonize regulations. These efforts primarily have occurred between developed regions. Some examples include:

- The US FDA's "Global Initiative" is dedicated to increasing collaboration with other countries