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Policy Review: Addressing the Complex Challenges of Regulating Biotherapeutics

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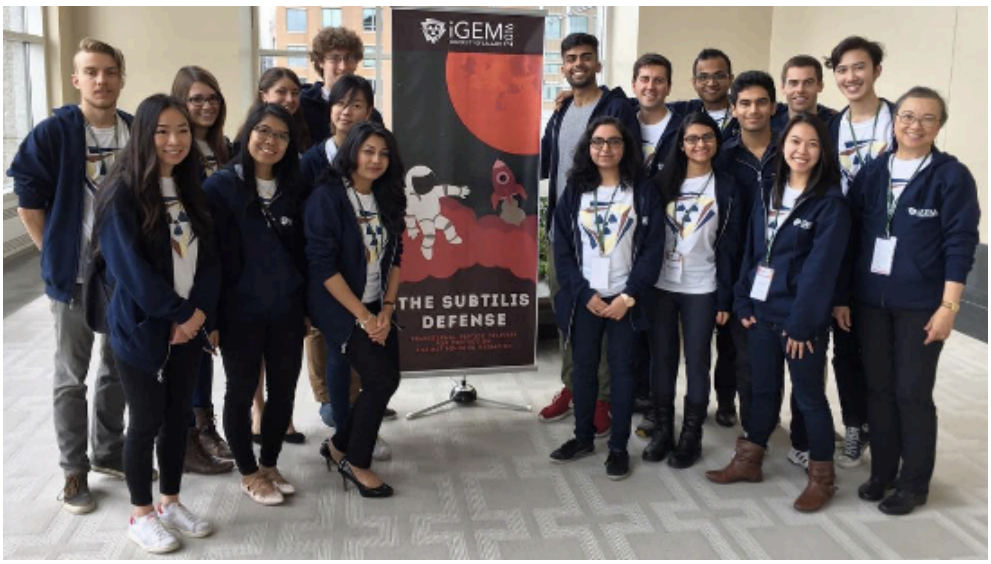

University of Calgary IGEM Team

University of Calgary iGEM team is composed of 15 undergraduate students from the faculties of science, medicine, and engineering. Each year they tackle solutions to real-world problems using synthetic biology. They present their work annually on the global stage amongst 250 teams at the International Genetically Engineered Machines (iGEM) competition.

Abstract

The advancing industry of biotherapeutics is providing the public with new promising and innovative drugs which may pose risks if their production, distribution, and marketing are not directly governed by legislation. Apart from international agreements, such as the Cartagena Protocol that governs the migration of biotherapeutics between countries, there are no specific and direct laws or regulations governing manipulated cell-based therapeutics in Canada. The introduction of these laws and regulations in Canada will allow for the safe research and use of biotherapeutics in a proactive manner.

Keywords: Biotherapeutics; cell-based therapeutics; regulations; Health Canada

Introduction

The emerging biotechnology sector in the global economy combined with the vast amount of research efforts into engineered cell-based therapeutics alludes to the imminent creation and marketization of engineered cell-therapy drugs (hereby referred to as biotherapeutics) [1]. Effective planning of regulations and economics will be necessary to better prepare for the introduction of these biotherapeutics into the market. Specific regulations can both serve to encourage expansion in this novel field, deter misuse of this technology, and prevent potential incidents that elicit risks from the use of this group of drugs.

In the research community, biotherapeutics have been appraised as the emerging "third pillar" of pharmaceuticals after synthetic chemicals and biologics [1]. Biologics are large molecules products that are manufactured from living systems (live cells), whereas biotherapeutics involve the use of these live cells directly [1]. The use of live cells on site of the human body offers detection, production, and administration of therapeutics in a responsive manner [1]. This offers completely novel solutions to drug administration with a lot of therapeutic potential. For instance, the treatment of type 1 diabetes can be revolutionized by planting engineered cells in the body which can secrete insulin specifically after detection of high blood glucose levels [1]. This would eliminate the need for attaching extraneous electronic devices to the bodies of diabetics. Other applications of this novel technology include the use of engineered bacterial cells to treat disorders of the human microbiome (such as *Clostridum difficile* infections), B lymphocytes to combat Epstein-Barr viral cancers, or providing regulated production of lactase for individuals who are lactose intolerant [1].

Previous literature reviews have extensively covered the therapeutic potential of biotherapeutics.[2][3] In the scientific field, there is a surge of promising therapeutics that emerged from cells modified using genetic engineering technologies.[4,5] Many of these technologies are expected to enter clinical trial stages in the upcoming years. North America has experienced tremendous growth in the biotechnology sector in the last 5 years, with the number of biotechnology companies increasing by 400% since 2011 [6]. The biotechnology sector currently totals $108.8 billion annual revenue [7]. Furthermore, 68.4% of biotechnology companies focus mainly on human health technologies, which is evidence for the increasing availability and prevalence of biotherapeutics [7]. Thus, an appropriate policy framework would need to be installed to ensure these technologies are properly regulated and contained. Policy frameworks will also serve to streamline the process of bringing biotherapeutics to the market.

The current Health Canada regulatory frameworks (and international standards) are shaped to address potential incidences with chemically synthesized drugs, some biologic products, and some stem cell therapy applications [8,9]. These Health Canada regulations give some mention to synthetic biology/genetically engineered products, but these are descriptive at best [8,9]. Prior experiences pertaining to the introduction of biologics has elucidated the importance of parallel development of technological discoveries and policy to avoid accidents [10]. Early planning for preventative purposes is particularly important for biotherapeutics due to the rapid and far-reaching consequences that could occur if they are misused [11].

The fragmentation of applicable regulatory policies in separate guidance documents, the dispersion of responsibilities across ministries and agencies, and a limited infrastructure appropriate for manufacture of this novel technology could pose potential challenges in its implementation. Biotherapeutics are governed by many separate guidance documents under the current framework, particularly through a combination of cell-based therapeutics and gene therapy documents [9]. This separation leaves many

regulatory gaps where the interactions between separate genes, as well as between genes and cell types are not considered. This absence of specific guidelines also deters individuals from entering the field of biotherapeutics as a whole, which impedes its growth.

This policy brief presents strategies that can build an effective policy framework for biotherapeutics and develop a comprehensive knowledge base to guide, accelerate and improve action.

Strategies for Action

The introduction of specific regulations pertaining to the development, manufacturing, and ongoing surveillance of biotherapeutics is pertinent to facilitate the safe and effective use of this drug technology. For such regulations to be practical, they must:

- build off of existing framework;
- involve the coordinated efforts of relevant ministries, academic institutions, companies, and other relevant partners;
- require the financial and technical support of governmental institutions, and;
- acquire political confirmation and support of international institutions.

The strategies outlined below should be seen as complementary to one another, but should be implemented concurrently for maximum impact.

Existing Policy

Currently, Health Canada has separate categories of regulation for gene-engineering products, including genetically modified foods and drug products[12], and cell-based therapeutic products, which includes guidance on cell, tissue, and organ transplantation.[13] Under the select agent compliance program of Canada, risk classification of each cell type/gene type is conducted based on origin and intended use.[14] With risk considerations in mind, the therapeutic is then given an overall risk-benefit score to determine approval. The assessment of a genetically engineered cell-product would warrant first a risk assessment of the cell type, as well as an assessment of the gene origin separate from one another under the current policies.[11] Although this approach is effective in filtering out certain agents of the high-risk variant, it leaves gaps where the cell-genetic interaction is not considered. For example, transformation of select genes from ebola virus into low risk organisms may not warrant high-risk classification even though the gene of ebola origin would be considered high risk. Or perhaps interaction between a low risk gene and a low risk organism, for example the introduction of antibiotic resistance genes in certain gut bacteria for probiotic applications, could warrant higher risk classifications as a therapeutic.

Adaptive Drug Assessment Process

The United States Environmental Protection Agency has classified intergeneric microorganisms as being distinct from other microorganisms and has created regulations specific to them [15]. Canada should adopt a similar policy regarding modified microorganisms that account for their unique properties, namely the likelihood of emergent properties. Emergent properties refer to the possibility of unpredictable phenotypes arising due to the interactions of exogenous genes with endogenous genes, other cellular components, or other cells. Because of the unpredictability of these emergent properties, it will be necessary to improve current risk assessment procedures as well as introduce long term plans for effective monitoring of manipulated cells once they are released to the market [16].

The translation of research for biotherapeutics (particularly from research in model organisms to clinical research in humans) is not as linear as drugs currently on the market, due to these emergent properties [11]. Thus strategies to mitigate adverse effects during translational research is compulsory. Consequently, the research ethics board will need to take extra precaution when assessing present research for clinical studies involving biotherapeutics, as well as set up frequent

monitoring of adverse effects while clinical trials are conducted. This may require the government to impose additional measures in authorization of such translational research.

Standard Indicators

Although there is no single standard that can reveal the entire complexity of whether a biotherapeutic will have undesired side effects, a number of design specifications of a biotherapeutic technology should be considered when assessing the safety of the technology. These design specifications include, but are not limited to:

- the presence of kill-switch technology (genes incorporated such that certain environmental exposure causes the cell to commit to apoptosis);
- the presence of auxotrophy (knocking out genes for essential nutrients of the cell so that it cannot survive without an abundance of said nutrient in its immediate surroundings);
- reporting on reproductive capabilities of cell product;
- whether the cell type is likely to retain integrated genes for an extended period of time (linked to the insertion site of gene, *e.g.* plasmid *vs.* chromosome)
- promoter strength (how likely gene is to be transcribed and translated into product, as it relates to dosage);
- reporting on therapeutic cells' localization and migration abilities;
- cell type and origin; (with reference to existing cell-therapy regulations)
- gene type and origin, and; (with reference to existing select agent compliance regulations)
- the differentiation of *in vivo vs. ex vivo* transformations.

Users should be aware that any one of these points would not be sufficient to assess the safety of a biotherapeutic product; instead, reference to multiple standardized indicators may be required. Benefit-risk analysis should be conducted with reference to standardized indicators on a case-by-case basis. Standardized indicators could offer a fast way to review incoming biotherapeutic proposals, although it will need to work in conjunction with current assessments to inform decision regarding drug approvals.

Improving Pharmacovigilance Practices

To best implement biotherapeutic technologies for use in the future, it is important for pharmacovigilance practices to be up to the same standards as the drug approval process [17, 18]. This is especially important for biotherapeutics due to the proliferative and adaptive properties of cells, which makes even the smallest contamination issue potentially far-reaching and detrimental [19]. Although Canada currently has mandates for pharmacovigilance under section C.05.010(f) of the Food and Drug Regulations, numerous systematic reviews have cited the pitfalls of Canada's current pharmacovigilance system, particularly the issues of under-reporting of adverse drug events and long processing times [9]. A qualitative study of Canadian pharmacovigilance identified that only 3% of all adverse reactions get reported, and the overall reviewing times take months after the actual occurrence of said adverse drug events [9, 10]. Under these circumstances, even modest modifications could yield significant results. The proposed modifications to consider include:

- an increase in reporting frequency by encouraging participation of both community and institutional pharmacists, physicians, and affiliated institutions as well as giving individual patients the option of reporting of adverse drug events;
- imposing accountability measures for companies and professionals that do not report adverse events in compliance with good pharmacovigilance practices, including the mishandling or intentional release of products;

- an intuitive online reporting system with categorical data that is easily compiled for reviewing purposes, and;
- a coordinated effort between epidemiologic personnel in the Public Health Agency of Canada and the pharmacovigilance review board to react quickly to adverse events or leaks.

Optimal use should be made of the above strategies, but there are certain limitations to each and alternative or fastidious strategies might be necessary. These modifications are meant to be restricted to any future biotherapeutic products, as implementation for all drugs could be costly and cumbersome.

Building Local Expertise and Know-How

Historically, the release of any novel technology has faced opposition from the public and lobby groups due to a lack of understanding. Often, individuals who might benefit from the technology miss opportunities due to misconceptions and stigmas. For these reasons, training and public education are particularly vital to avoid misuse and to obtain maximum benefit. Training with these new technologies should be extended to relevant ministries, authorized health professionals, and community advocates. In terms of content, the training should involve both theoretical science and physical handling skills of each biotherapeutic. Individuals should know its basic operation as well as troubleshooting and emergency reaction protocols upon training completion. Public education concerning the science involved in genetically engineered devices is equally vital to prevent stigmatization. This involves an integrated effort between education boards and health ministries. The advantages of professional training and public education include the access of biotherapeutics by individuals who need them to maximize societal benefit, as well as minimizing incidence of misuse.

International Harmonization

Biotherapeutics also offer many advantages in foreign settings, including but not limited to ease of use, minimal maintenance, and self-reproducibility [1]. With increasing international travel and migration, there is a resulting increasing demand for the pharmaceutical industry to be regulated on the global scale, as the development in the biotechnological industry is occurring around the globe. Local, national, and international efforts are needed to gain more insight on the potential ways to increase safety and efficacy of biotherapeutics; this may include specific international guidelines established through the International Conference of Harmonization (ICH) [20].

Building Innovative Research Networks

Ensuring the safety and efficacy of biotherapeutics should involve coordinated efforts across many sectors – the health, education, labor, civil service and private sectors – and the Canadian regulatory system, academic institutions and other stakeholders. It is therefore important to distinguish and strengthen mechanisms that bring together producers, regulators, and end users of biotherapeutic products. This could be achieved by increasing awareness and funding of biotherapeutics in government. Potential benefits include increasing drug research innovativeness, consolidation between the lab bench and the public, and higher ability to better address health demands while still being strict on issues such as bioterrorism.

The Cartagena Protocol is a step that the international community has taken to get closer to increasing cooperation between sectors by governing the movement of biotherapeutics from one country to another, and it has valid points regarding the development of biotherapeutics [16]. In practice, such a network does not yet exist on the international scale. Canada, as an international leader of progressive health policies, should develop strategies toward this end.

Conclusion

The advancing industry of biotherapeutics is supplying society with novel, promising drugs which may pose risks if their production, distribution, and marketing are not governed by legislation. As there are no specific regulations in Canada governing manipulated cell-based therapeutics, the introduction of these laws and regulations in Canada will be beneficial in authorising the safe research and use of biotherapeutics.

Strategies attempting to address this gap in therapeutic regulation should include an adaptive drug licensing process which makes use of existing standard indicators commonly used by researchers, a cooperative pharmacovigilance strategy for post-market monitoring, as well as a local and international research network which increases access to biotherapeutics for those who need it while preventing misuse and bioterrorism acts.

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