Artificial Lung Product Development Plan for Health Canada

RGA6224: Regulation of Biomedical Product Commercialization by Health Canada

[1]Jinit Patel, [2]Dr. Yuen Shek

[1]Student, [2]Professor
Regulatory Affairs,
Northeastern University, Toronto

Abstract: Medical devices play a pivotal role in today's healthcare system, significantly impacting the quality of care provided. Essential for patient safety across various medical settings, medical devices incur substantial financial costs in both developed and developing healthcare systems. Health Canada defines medical devices as instruments or components used for treating, diagnosing, or preventing diseases or abnormal conditions in humans. Unlike medicinal items, the primary mechanism of action of medical equipment is not metabolic, immunological, or pharmacological, encompassing a range of equipment, implants, or machines designed for specific medical objectives. This paper discusses the regulatory strategies and factors related to addressing the unmet therapeutic need of end-stage lung failure (ESLF) through lung tissue engineering.

Index Terms **-** Medical Devices, Healthcare System, Patient Safety, Health Canada, Regulatory Strategies, End-Stage Lung Failure, Lung Transplantation, Lung Tissue Engineering, Therapeutic Need.

I. INTRODUCTION

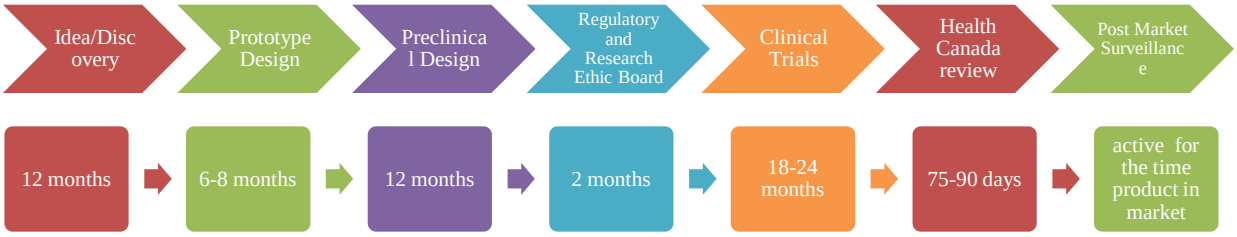
The fourth greatest cause of death globally is an end-stage lung disease, also known as a chronic obstructive pulmonary disease (COPD). Due to a shortage of donor organs, only a small percentage of end-stage lung failures are cured by transplantation. Although long-term artificial organ support technologies such as ventricular assistive devices provide therapeutic choices for end-stage heart failure patients as a bridge to transplantation or destination therapy.

Biomaterial and regenerative medicine advancements have paved the foundation for artificial lung development. The development of effective transplantation operations employing tissue-engineered tracheas has been a significant development in the field. These are made from an artificial scaffold that serves as the trachea's extracellular matrix (ECM).

The engineering of the bioartificial lungs inside surfaces, where the essential purpose of gas exchange between blood and air takes place, is critical to its success. The alveolar and vessel walls of the human lung make up this surface, where it is perfused with air and blood through the bronchi tree and pulmonary vasculature's complex branching networks. A healthy adult lung has 300–500 million alveoli and a total surface area of roughly 100 m^2. (Francesco Petrella, 2018) Furthermore, the pulmonary alveoli wall is 0.5 m thick, and pulmonary arteries can be as narrow as 5 µm across. Reproducing the intricate multi-scaled structure of the extra-cellular matrix of a human lung for of with cells appears to be an impossible challenge. It is also important to check for the ability to seed a lung scaffold with the proper quantities of epithelial cells (EPCs) and endothelial cells (ECs) found in the normal lung.

Extracorporeal lung support for a limited time is possible today. The existing technological solutions do not allow for the long-term usage of lung transplant systems in the form of implantable artificial lungs. There are several of these: Clot development occurs in the system because of biocompatibility issues, particularly in the areas under unphysiological flow conditions. Moreover, proteins, fibrin, and cells are coated on membranes, reducing gas exchange efficacy, and preventing long-term use. (Francesco Petrella, 2018) As a result, lung support technologies are currently not a long-term support option for patients with terminal lung illnesses. Based on the status of the technology and therapeutic needs at the time, the healthcare industry is seeking long-term active implantable artificial lungs.

These deficiencies and unmet therapeutic requirements lead to the development of long-term implantable artificial ArtiLung. To help the long-term usage and implant of ArtiLung, coordinating basic and translational research is needed to tackle these difficulties. The strategies are needed for increasing the biocompatibility of external surfaces, new anticoagulation regimes, gas and blood flow optimization, and reduction of these systems. (Jutta, Oliver, & Axel, 2020).



II. PRE-CLINICAL REQUIREMENTS

Preclinical examination of medical devices designed to be implanted in the human body must undergo various in vitro and in vivo examinations before being approved by regulatory bodies. The main objectives are to evaluate the biocompatibility of the biomaterials that compose up the medical device, which is described as a material's capacity to operate in a certain setting with an adequate host reaction as well as to assess the potential for any unacceptable adverse biological effects caused by the device's biomaterials interacting with body tissues.

Preclinical Research

The active implantable ArtiLung must go through a process of preclinical testing -> Design improvement -> preclinical testing until the design is refined and tested to the point where it can be manufactured and tested in humans. Initial in vivo evaluations of device implants and removals in live animals and basic evaluations of device efficacy and safety are possible with feasibility studies. In most cases, extensive post-surgical histolo-gy is not needed. GLP investigations, on the other hand, are much more extensive and have more precisely defined outcomes for safety or effectiveness. Testing required to meet the preclinical requirements is mentioned below. (Health Canada, 2018)

1. Bench Testing: Laboratory testing to decide the device's functionality and safety and to ensure it performs as intended.
2. Technical Testing: For the identification of the ArtiLung device accuracy and reliability, the device undergoes engineering and quality testing of the biomaterials used for the designing of artificial lungs.
3. Computer Stimulation Testing: The implementation of computational fluid dynamics (CFD)–based flow and gas exchange computer simulation, visualization of flow by particle image velocimetry (PIV), experimental flow measurement, and MRI must better understand the flow conditions of blood and gas exchange. This allows for added system improvement, which is needed for the artificial lungs to be used as a permanently implanted system.
4. Animal Studies: After succeeding in the above three steps, ArtiLung is tested on the animals for biocompatibility, toxicology data, and other potential safety concerns.
5. Biocompatibility Testing: ArtiLung must go under biocompatibility testing as per the ISO 10993-1 standard. The tests performed, the standards used, the test method, the pass/fail criteria proved with reason, and a description of the outcomes and conclusions taken all must be included in the summaries. (Ministry of Health, 2012)

Regulatory and Ethics Review

ArtiLung is an artificial lung is a high-risk medical device that is classified in class IV. According to Health Canada regulations, contacting the Office of Research Ethics ahead of submitting the application to Health Canada's Investigational Testing Authorization (ITA) program is required before conducting a Phase I clinical trial for artificial lungs. The investigational medical devices are classified by Health Canada. The submission for investigational testing for ArtiLung with humans must include a copy of the medical device classification designation letter from Health Canada. (Health Canada, 2018) The application form for filing the ITA is here.

Documents required for filing ITA application:

1. ArtiLung description and material information
2. Manufacturer Information
3. Device Labelling
4. Marketing history
5. Risk assessment (ISO 14971)
6. Informed Consent for participants
7. REB approval
8. Results of Animal and Clinical studies
9. Standards and Declaration of Conformity (DoC) (Can be found here)

For the beginning of clinical trials, the study documents must be approved by Institutional Review Board (IRB). The Device Evaluation Division of Health Canada's Medical Devices Bureau evaluates proposed artificial lung device research that involves humans. A Research Ethics Board must notify Health Canada that the study has received ethics clearance. Following Health Canada's examination of the application of Investigational Testing, after we receive "No Objection Letter" (NOL) signifying Health Canada's approval of the research. Completing the regulatory and ethics review leads to the next step in the development process of ArtiLung is clinical testing on humans.

III. Clinical Trial Testing

Before initiating clinical trials for ArtiLung, it is required to file Clinical Trial Application (CTA), Research Ethics Board attestation with the clinical trial site information to Health Canada. Moreover, a protocol is required to submit which describes intended clinical trial objectives, risks, methods, benefits, and conditions. The clinical trial can be initiated after Health Canada evaluates and approves CTA and is given ethics approval by Research Ethics Board (REB).

To validate the clinical safety and efficacy characteristic of the ArtiLung System, a retrospective review of clinical data is necessary. Clinical data for ArtiLung is analyzed retrospectively for product safety and effectiveness for cardiopulmonary (ECLS) and respiratory (ECMO) support. The suitable clinical trial study design for the ArtiLung is a Controlled Comparative study with an existing therapeutic device available in the market like HemoLung by ALung Technologies and NovaLung by Xenios AG. (USFDA, 2020)

The clinical trial begins with a preliminary study with 10 to 30 people taking part. The primary safety and performance data is decided at this stage. The device advances to a pivotal study if ArtiLung confirms it is effective and safe at this stage. This phase enlists 150 to 300 participants with End-Stage Lung Failure who assess the safety and efficacy of the treatment on a larger population of patients. If the ArtiLung is considered to be safe and effective during this phase, it is filed to Health Canada for approval. (Genesis Research Services, 2018)

IV. Process Validation Studies

Validating the performance, adequacy, durability, and effectiveness are the key methods to be used in the medical device manufacturing process necessitates process validation studies. Validation of sterilization, packing, and shelf-life is required for ArtiLung process validation; other validation studies are also required.

1. Sterilization Testing: The method of sterilization and requirements of cycle parameters with the detailed sterilization procedure and requirements of the standard approach applied for process validation; the test results, and Sterility Assurance Level (SAL) all must be provided as part of the sterilization process validation information.
2. Packaging Validation: As part of medical device license application, a packaging validation evaluation is required to provide to Health Canada. All packaging elements, including the material used to cover the ArtiLung device, must be documented. Moreover, packaging must be evaluated for sustaining device characteristics and sterilization for the specified shelf-life, in accordance with approved acceptance standards.
3. Shelf Life Validation: The product's shelf life must be clearly outlined. Data supporting the product's expiration date must be provided . Stability evaluations must evaluate the device's important specifications to confirm that it meets all the device's initial specified requirements for the duration of its shelf life, under predetermined device storage conditions.

V. Regulatory Submission Documentation Requirements

Food and Drug Regulation	Document Required	Detailed Description of Documentation
Introductory Documentation		
Subsection 81(a)	Manufacturer or Importer Identification	Providing contact detail, email address, phone number, and fax number on the device labelling as the manufacturer of ArtiLung.
Subsection 81(b)	Device Identification	Providing labelling with the ArtiLung name that identifies the device with the medical device risk-based classification.
Subsection 81(c)	Device Description	This part includes a description of ArtiLung, hardware, biomaterial used for manufacturing, and packaging. It also includes the description of photographs, engineering diagrams of ArtiLung.
Subsection 81(d)	Design Philosophy	Providing description about ArtiLung's purpose and its principle of operation. Moreover, the device equivalence with NovaLung and HemoLung devices.
	Indications for Use, Intended Use, Contraindications	Providing details about the conditions in which ArtiLung should be used as well as any possible adverse effects.
Subsection 81(e)	Marketing History	This section does not apply as the device is being applied in Health Canada only.
Subsection 81(j)	Device Labelling	Providing bilingual label of ArtiLung to ensure that the device is not used other than defined study protocol. Also includes marketing brochures, copies of the product datasheet, indications for use, and training manual.
Risk Assessment and Reduction Measures		
Subsection 81(f)	Risk Assessment	Risk assessment is used for ArtiLung's risk identification for patients and measures taken to reduce these risks to an acceptable level. For identifying risks ISO standard 14971 part 1 is used.
Subsection 81(f)(i)	Previous Studies	Providing documentation that shows previous research, bench testing, pre-clinical, and clinical trials conducted to identify ArtiLung's safety and efficacy. These test results include biological safety, sterilization validation, animal and clinical testing.
Subsection 81(f)(ii)	Alternate Treatments	Predicate devices like NovaLung and HemoLung are available in the market for treating COPD.
Subsection 81(f)(iii)	Precautions	Providing labelling with caution, warnings, and adverse effects of using ArtiLung.

Subsection 81(g ,h)	Institutional Information	Investigator's details like name, mailing address, contact details are required to mention where the testing is conducted as per subsection 83(2).
Subsection 81(k)	Investigator Agreement(s)	Providing investigator agreement that outlines that testing conducted during the clinical trial complies with the regulations. The template for the investigator's agreement is provided here.
Subsection 81(h)	Research Ethics Board (REB) Approval	REB approval must be obtained from each proposed institution before an ITA authorization is issued for ArtiLung.
Subsection 81(i)	Protocol	It is required to provide a study protocol that complies with ISO 14155 in detail, including the version number and date of the last revision. Study protocol also includes a variety of other details like prevalence, diagnostic criteria, disease or medical condition to be treated, and available treatments, study design, study hypothesis, inclusion and exclusion criteria, study objectives, study participants requirement, investigation's duration, and patient follow-up period. Investigator's Brochure (IB): Investigator's brochure with appropriate up-to-date safety, clinical data, and non-clinical data for ArtiLung in accordance with ISO 14155. Informed Consent Form (ICF): A copy of ICF used in clinical trial mentioning the possible risk and benefits of participation is required to submit.
	Additional requirements for the study protocol	The study design has the minimum bias, it must comply with the TCPS-2 and ISO 14155. Moreover, it is required to be in maximum compliance with ICH Document E11.[1]The study protocol also requires defining statistical methods for evaluating the safety and efficacy of ArtiLung.[2]

VI. HEALTH CANADA REGULATORY APPROVAL PROCESS

Step#	Review Process	Detailed Explanation of process
1	Defining Class of Medical Device	ArtiLung is defined as a class 4 medical device according to Canadian Medical Devices Regulations (CMDR) SOR/98-282, Part 1 as published by Health Canada.
2	Implementing ISO 13485	The quality management system must be compliant with ISO 13485 under the Medical Device Single Audit Program (MDSAP), which includes the CMDR's specific requirements.
3	ISO 13485 Certificate	After an Auditing Organization approves the QMS system, the ISO 13485 is issued.
4	ISO 10993-1 Certificate	Biocompatibility evaluation of ArtiLung within the framework of the risk management process.
4	Applying for Canadian Medical Device License (CMDL)	As a class 4 medical device, it is required to file Medical Device License (MDL)
5	Medical Device License (MDL) application	For ArtiLung, MDL is required to file along with the Declaration of Conformity, Labelling, MDSAP Certificate, clinical trial data.
6	Health Canada (HC) Review of Application	HC will review the MDL application and Premarket review document for identifying the safety and efficacy of ArtiLung. The time for HC review is 75 to 90 days.
7	Health Canada Decision	If the device is got approved, the issued license will be uploaded on the Health Canada website with the summary of approval.
*The process of Health Canada approval is mentioned above is in ideal condition. In the case of additional documents or audits required by Health Canada, the review of the application process can take more time than required.		

[1] Clinical Investigation of Medicinal Products in the Pediatric Population and the Health Canada Guidance Document: https://database.ich.org/sites/default/files/E11_R1_Addendum.pdf

[2] Health Canada's adoption of ICH guidance: E9: Statistical Principles of Clinical Trials. https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/e9-eng.pdf

VII. POST MARKETING STRATEGY

Even after the ArtiLung is approved for marketing in Canada, regulations are required to follow to safety and effectiveness of medical devices. Steps required for post-marketing are mentioned below.

1. Surveillance and Inspection[3]: As a manufacturer, we are responsible for maintaining product safety under the Food and Drug Act. In the case of any new information available for adverse effects identified including failure of ArtiLung to provide the desired output.
2. Adverse reaction reporting[4]: The identification of potential benefits and risks of ArtiLung done during the clinical trials is limited as only a few hundred people participated in the clinical trial. As a result, for properly understanding the therapeutic benefits and risks of ArtiLung, we must continue to monitor their safety and effectiveness after they are marketed. For adverse event reporting, it is required to take follow-ups from the healthcare professionals and patients implanted with ArtiLung. It is also required to submit the preliminary and final report to Health Canada.
3. Risk Management: Using reporting data to identify, minimize, and prevent known or potential risks to patients, as well as updating ArtiLung device labeling.
4. CAPA Plan: After identifying all the possible risks, updating the corrective and preventive actions, and implementing them for public safety.
5. Annual Summary Reports[5]: Drafting an annual report that outlines whether ArtiLung device's benefits have decreased; (ii) the risks are more prevalent; (iii) the implications for patient or users are more serious if a risk arises; or (iv) any significant threats have been found.
6. Maintaining Distribution Records[6]: Keeping track of the procedures and the people involved. It's also necessary to define the records that can be used to locate ArtiLung products during a recall.

VIII. MARKETING STRATEGIES

To market ArtiLung in Canada, the company's marketing strategy is vital to its success. The basic purpose of marketing strategy is to focus all resources on the best chances with the goal of boosting sales and generating a long-term competitive advantage. The medical device market is highly regulated, and purchasing decisions are based on a variety of variables that necessitate a mix of medical, scientific, and business expertise.

Market dynamics

The dynamics of demand and role are important aspects of medical innovation. The formation of marketing strategies for new technologies depends on several circumstances at the patients' end of the spectrum. ALung Technologies, Breathe, McGowan Institute for Regenerative Medicine, Haemair, Lung Biotechnology PBC, Michigan Critical Care Consultants, MedArray, Miromatrix Medical, and Xenios are the leading companies in the worldwide artificial lungs market. (insightSLICE, 2021) However, these companies currently have extracorporeal and paracorporeal artificial lungs available in the market. These artificial lungs can support patients for a few days or a week. In such a situation, ArtiLung which gives years of ventilation support in the situation of COPD, gives a great breakthrough in the market. As well as the shortage of availability of organ donation also in favor of marketing ArtiLung medical devices.

Intellectual Property Rights

Stronger intellectual property protection is likely to encourage the development of novel medical devices that increase the quality of care and, in many circumstances, lower the overall long-term costs of treating specified medical conditions.

In many of the device industries, patents are of lesser value. It is possible to patent the fundamental principle of an implantable device, however, it is not feasible to patent the ArtiLung device. In general, there are a variety of techniques to develop a medical device for a particular use. The basic idea applied in the function is frequently the source of innovation. Patents, on the other hand, serve a different role in the invention process. The development of ArtiLung is protected by one or many patents is aaion for potential investors. As a result, patents are frequently used to encourage investment in the medical device market. (Tiffany E Chao, 2015)

In the marketing of medical devices, trademarks are quite important. The company's brand can be built on a line of artificial lung implants that are considered for their ease of implantation, durability, and low in vitro degradation. Affiliating a trademark with the brand will identify the source of the ArtiLung medical device to hospitals, healthcare professionals, and patients, and will help boost the product's recognizability among consumers over time, as well as assist customers to differentiate the product in their minds. (Rapacke Law Group, 2018)

[3] Clinical Investigation of Medicinal Products in the Pediatric Population and the Health Canada Guidance Document: https://database.ich.org/sites/default/files/E11_R1_Addendum.pdf

[4] Health Canada's adoption of ICH guidance: E9: Statistical Principles of Clinical Trials. https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/e9-eng.pdf

[5] Food and Drugs Act , Complaint Handling, [SOR/2011-82, s. 3], 57

[6] Food and Drugs Act , Incident Reporting, [SOR/2020-262, s. 13], 59(1)

IX. CONCLUSION

Currently, only an artificial organ transplant can is the available treatment for the loss of organ function permanently. Lung transplantation, on the other hand, is limited to a small population of participants due to the scarcity of transplantable organs. Although artificial organ transplant for the kidney and heart has been a viable treatment option for several years, artificial lung function can only be replaced for a short length of time. An artificial lung, on the other hand, could help patients with terminal chronic lung diseases live longer, have a higher quality of life outside of the hospital, and reintegrate into society.

Despite technological advances, biocompatibility issues and inadequate flow properties in the oxygen generator cause blood clotting in the oxygen generator, cannulas, or pump, and protein is deposited on the gaseous exchange membranes, increasing the diffusion rate and reducing the oxygenator's gas exchange capacity. As a result, extracorporeal and paracorporeal lung support is now used primarily for short-term bridging of gas exchange, in acute lung failure.

In the future, ArtiLung has the long-term alternative of a lung transplant, temporary respiratory and circulatory systems. The paracorporeal device is easier to create and maintain from a maintenance and engineering standpoint, but an ArtiLung would provide patients with the benefits of an absolute organ transplant: free movement, no restrictions in clothing or physical attributes, less danger of accidental physical damage, and a sense of incorporation. The ArtiLung artificial lung could potentially be useful in the rehabilitation of patients who have suffered a lung injury. Eventually, the artificial lung could replace the need for high functioning donor lungs, medical devices for respiratory and circulatory systems, making it a viable option for lung transplantation.

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