REPORT DOCUMENTATION PAGE

Form Approved OMB NO. 0704-0188

1. REPORT DATE (DD-MM-YYYY)	2. REPORT TYPE	3. DATES COVERED (From - To)
23-04-2020	Final Report	28-Sep-2017 - 30-Jun-2019

4. TITLE AND SUBTITLE
Final Report: Market potential for perfluorcarbon based formulations for use in pressurized metered dosed inhalers for pulmonary drug delivery

5a. CONTRACT NUMBER
W911NF-17-1-0585

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER
106011

6. AUTHORS

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS (ES)
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P.O. Box 12211
Research Triangle Park, NC 27709-2211

10. SPONSOR/MONITOR'S ACRONYM(S)
ARO

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
72315-SD-ICR.1

12. DISTRIBUTION AVAILIBILITY STATEMENT
Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES
The views, opinions and/or findings contained in this report are those of the author(s) and should not contrued as an official Department of the Army position, policy or decision, unless so designated by other documentation.

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	15. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			David Irwin
UU	UU	UU	UU		19b. TELEPHONE NUMBER 303-652-0572

RPPR Final Report
as of 24-Apr-2020

Agency Code:

Proposal Number: 72315SDICR **Agreement Number: W911NF-17-1-0585**
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DUNS Number: 041096314 EIN: 846000555
Report Date: 30-Sep-2019 Date Received: 23-Apr-2020
Final Report for Period Beginning 28-Sep-2017 and Ending 30-Jun-2019
Title: Market potential for perfluorcarbon based formulations for use in pressurized metered dosed inhalers for pulmonary drug delivery
Begin Performance Period: 28-Sep-2017 **End Performance Period:** 30-Jun-2019
Report Term: 0-Other
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Distribution Statement: 1-Approved for public release; distribution is unlimited.

STEM Degrees: **STEM Participants:**

Major Goals: The overarching goal of the SEMPer Fi (saving lives with emergency medical perfluorcarbons) program is to develop and commercialize aerosolized therapeutic formulations, based on perfluorocarbon (PFC) chemistry. Advanced development of these formulations are meant to bridge a technology gap that will allow pharmaceutical hydrophilic compounds to be delivered directly to the lungs via a pressurized metered dose inhaler (pMDI). For the military this technology will provide a faster and more efficacious means to target the Hypoxic Pulmonary Vasoconstrictive (HPV) response, which hinders physical and mental performance of military personnel working in hypoxic environments.

To develop this technology the UC Denver scientific team has been assigned a scope of work to achieve a Technology Readiness Level 7, (TRL7) rating. The TRL7 rating designates that the formulation has demonstrated safety in human clinical trial(s). Achieving a TRL 7 milestone provides a significant valuation for this technology that is required for continuation into the advanced development stages to meet the program goals of commercialization. To date, the UC Denver team is currently working toward a TRL 5 rating for development of perfluorocarbon (PFC) emulsion technology. We achieved a TRL 4 milestone 2017 with the completion of proof-of-principle animal studies demonstrating efficacy of inhibiting the HPV response by intrapulmonary delivery of ambrisentan in a PFC emulsion. In achieving this milestone, we also identified key critical assumptions in our understanding of the path to commercialization, which if addressed would enhance the valuation of our technology and de-risk the uncertainty pertaining to the market need and size of the problem in both the military and civilian

populations.
To address this uncertainty the UC Denver team enrolled in the winter cohort of National Science Foundation Innovation Corps (I-CORPS) program (Funded by DoD proof of concept commercialization BAA). The purpose of I-CORPS program is to address the uncertainty of developing technological innovations to meet the needs of end-users. Thus, the work described herein, is the results obtained through the I-CORPS program for viable commercialization of PFC formulations for delivery of hydrophilic drugs via a metered dose inhaler to treat pulmonary illnesses.

II. I-CORPS PROGRAM OVERVIEW

The I-Corps methodology to facilitate the commercialization of an emerging technology is creating a business thesis and the business model canvas through an interview-based approach. The conceptual framework to interview is to (in)validate assumptions regarding the use of the technology. This is primarily taught through a hands-on, out-of-classroom customer discovery process. Weekly webinars are meant to keep teams on pace and to teach business fundamentals that lead to testable business hypotheses.
In the I-Corps program the UC Denver team comprised of the Technical lead (TL): David Irwin, Ph.D; Entrepreneurial Lead (EL): David Pak, BS; and Industry Mentor (IM): Arlen Meyers, MD MBA; UC Denver created “LoTorr Pharmaceuticals” as the team name. Based on the business canvas metrics at the conclusion of the course teams provide an evidence-based go/no-go decision on continuing the commercializing their unique technology. “No-go” decisions do not always necessitate the abandonment of the technology but suggest that based upon the current evidence there is more work to be done before the technology is ready to move forward with commercialization. This could mean that more customer discovery is warranted to find the correct customer or there are other barriers that need to be resolved in order to move forward with the technology.

Accomplishments: Business Thesis
A business thesis is designed to be a concise statement that captures what the emerging technology does, who it is for, and why the customer would want it. The business thesis evolved over 7-week course period to reflect information gained in interviews:

LoTorr Pharmaceuticals provides an intrapulmonary therapeutic for patients with pulmonary arterial hypertension to improve exercise tolerance and reduce the 1-year morality rate by 50%.

Interviews
UC Denver team completed over 130 interviews consisting of more than 130 interviews of stakeholders in the biopharmaceutical industry were completed including: 28 physicians/health care workers, 25 C-Suite personnel, 12 managing partners, 10 military personnel, 7 VP or senior strategists, 6 pharmacists, 5 business development managers, 3 investment analysts, 3 technology transfer specialists, 2 lawyers, and 28 “other” stake holders. The interviews provided clarity in understanding the workflow and ecosystems to providing a new therapeutic to the end user. The military and “civilian” ecosystems (see below) provided insight to the specific problems the ecosystem may face, and how the technology could potentially address the problems they have.

Business Model Canvas
The business model canvas captures the data obtained during the interview process validating / invalidating technology benefits and economic assumptions and is broken into 9 segments. Below is the compilation of data collected in 120 interviews validating who the customer segments are, what gain our technology provides, and how our technology will reach our customer.

Customer Segments/Value Propositions

Military ecosystem:
Interviews with military stakeholders including war fighters, corpsmen, and program managers validated that high-altitude illness is major problem faced by warfighters deployed to high altitude. Personnel from many varying backgrounds in the military were excited to learn about a therapeutic for high altitude illness. Current treatment is symptomatically based and does not always relieve the underlying problems. The fast-acting relief, portability, and ease-of-use were aspects of the technology were the most important and interesting aspects to the military ecosystem. However, the route to commercialize a fast-acting therapeutic to treat high altitude illness to affected warfighters must go through the civilian market and process.

Biopharmaceutical ecosystem:

Interviews of over 120 stakeholders in the biopharmaceutical field validated the need for improvement in therapies to treat pulmonary hypertension and pulmonary fibrosis. In this ecosystem, the major customer segments were broken down into the “producer”, “payer”, “influencer”, and “user” who each have a different interest in the potential of the technology.
“Producer” refers to business development managers, or merger and acquisition managers, at biopharmaceutical companies such as Gilead, GSK, Pfizer, etc. The producers took interest in the potential patent extensions and expanding the field of use for existing medication using the technology from LoTorr Pharmaceuticals. Generally speaking, pharmaceutical companies may seek partnerships, licenses, or acquire promising candidates once clinical Phase 2b safety studies are completed.
“Payer” is related to the insurance specialists, or third-party payers in the healthcare system. It is important for a code to be generated from CMS and is generally used as the standard for coverage across insurance companies. Value is added for these stakeholders in the cost saved per patient per year. For pulmonary hypertension patients, this would mean to reduce the frequency of emergency room visits and potentially lower cost for the therapeutic. The new therapy could be 20% cheaper with 50% increase in exercise tolerance and reduction in1-year mortality rate.
“Influencer” refers to the physicians treating patients with pulmonary hypertension and pulmonary fibrosis. They are considered prime influencers and early adopters of new medications. Sildenafil is the current standard of care for pulmonary hypertension, yet 50% of these patients will move on to more advanced therapy. These physicians are seeking a cure and improved therapy for their patients and are happy to see their improvement and tolerance of the disease.
“Users” are the patients diagnosed with pulmonary hypertension who are dissatisfied with the current treatment options. A new, effective therapy would reduce the frequency of physician visits. The patient would like to continue with activities that were affected by his or her disease, and the new form a therapy provides the potential to do so.

Customer relationships
The customer relationship aspect of the business model canvas is focused around how to get, keep, and grow the customer base. For LoTorr Pharmaceuticals, customers are primarily gained from patients unsatisfied with current treatment options (have failed options). Physicians and known opinion leaders are vital for growing the customer base by increasing awareness of the therapeutic and its efficacy in treating patients. By expanding the field of use for the inhaled therapeutic, new relationships and uses can also come from this technology. Additionally, we discovered that our emulsion technology would be very beneficial, if adopted, to deliver anecdotes to neutralize chemical agents in chemical warfare.

Channels
We have identified channels in which the therapeutic will get into the hands of the user. As the primary manufacturer, LoTorr will have to work with pharmaceutical wholesaler companies. Metered dose inhalers are not manufactured or prepared on-site at any specialty pharmacies, thus distribution of completed product needs to be from a central manufacturer. These will also be distributed at hospitals where there is a prominence of pulmonary hypertension and pulmonary fibrosis (ie University of Colorado Hospital & Children’s Hospital Anschutz Medical Campus). Pharmacies like this, or specialty pharmacies, will be more willing to carry special forms of the therapeutic.

Key activities
In moving forward and through the customer discovery process, we have identified key activities, resources, and partners that are essential to the successful commercialization of the technology that include:
- Patent protection
- Preclinical safety assessment
- IND application approval
- Clinical testing (Phase 1 –4)

Key resources:
- Patent protection
- Contract research organizations (CRO)
- Contract manufacturing organization (CMO)
- Manufacturing facilities
- Patent Lawyers/Tech Transfer Office personnel

Key Partners
- Department of Defense/Office of Naval Research

- Pharmaceutical companies
- Pharmaceutical wholesaler distributors

Market potential
The global market for PAH drugs has reached USD 5 billion in 2015 and is expected to exceed USD 9 billion in 2025. Pulmonary hypertension is currently treated primarily with the use of phosphodiesterase-5 (PDE-5) inhibitor and endothelin receptor antagonist oral medications. Intravenous and subcutaneous infusion as well as dry powder therapeutics exist but are less common among patients. There are currently no pMDI therapies for pulmonary hypertension.
Despite all of the therapy regiments that exist, there is little to no evidence of a decrease in mortality rate for patients with pulmonary hypertension while using any single therapeutic. Seventy-five percent of patients may start on the PDE-5 inhibitor therapy, but more than 50% of them will move to more advanced or combinatory therapy as the disease progresses. There is a USD $2.5 billion market size for patients prescribed oral medication for endothelin receptor antagonists, and we propose market penetration for $250 million based upon the number of patients and physicians failing previously prescribed therapy.

Training Opportunities: Nothing to Report

Results Dissemination: Please see the accomplishment section

Honors and Awards: Nothing to Report

Protocol Activity Status:

Technology Transfer: UC Denver has obtained a patent with the University of Colorado Denver for its specialty drug formulation, and our currently seeking a second patent with the API of protein based therapies specific to the treatment of sickle cell disease. Following successful pre-clinical proof-of-principle, our industry partners are performing feasibility testing of our prototype inhaled formulation and we are aiming to complete safety and toxicity testing in Sep 2019.

PARTICIPANTS:

Participant Type: PD/PI
Participant: David Irwin PhD
Person Months Worked: 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

Participant Type: Other Professional
Participant: David B.S Pak
Person Months Worked: 7.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

Participant Type: Other Professional
Participant: Arlen Meyers MD. MBA
Person Months Worked: 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:

RPPR Final Report
as of 24-Apr-2020

National Academy Member: N
Other Collaborators:

FINAL REPORT FEBRUARLY 5 2020
FPROOF OF CONCEPT COMMERCIALIZATION PILOT PROGRAM OFFERED BY DOD

INNOVATION CORPS (I-CORPS)
NATIONAL PROGRAM,
SEATTLE COHORT
September 28, 2017-June 30, 2019

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EXECUTIVE SUMMARY

Background: The Innovation Corps (I-Corps) program is designed to facilitate the commercialization process of basic research innovations. Entrepreneurial teams seeking to commercialize their innovative technology are comprised of a Technical lead (TL), Entrepreneurial Lead (EL), and an industry mentor (IM). At the end of the course, teams provide a "go/no-go" decision on continuing the commercializing of their unique technology based upon evidence collected in the program. The University of Colorado Denver Team completed the I-CORPS training in the Seattle Winter Cohort (01/16/18 – 03/02/18).

Validation process: The business model canvas is a tool used to help guide the development of the business model, and "go/no-go" decisions are based on validation of a scalable and economically feasible business model that solves an unmet need for a specific customer segment. The business model hypothesis that UC Denver team sought to validate was whether or not the development of the perfluorocarbon emulsions to deliver hydrophilic drugs via pressurized metered dose inhalers to treat both mountain sickness and pulmonary vascular diseases solved a significant unmet need in both the military and civilian sectors.

Discovery: The business model and commercialization process was learned primarily through customer discovery interviews. Stakeholders agreed that there was a market for creating an inhalable formulation to administer hydrophilic drugs with a pressurized metered dose inhaler (pMDI) system. In the civilian market, beyond pulmonary hypertension (PH) and pulmonary fibrosis (PF) there was some uncertainty about which patients would benefit most from utilizing an inhaled therapeutic to treat their illness. There was overwhelming agreement that an economic and effective inhaled therapy for PH and PF using a pMDI had market value. Stakeholders agreed with a strategy to begin with an approved drug (ambrisentan or other) as the API to demonstrate overall safety and efficacy. Similarly, military personnel agreed that high altitude illness was an issue faced by the warfighter. It is agreed that the pathway to bring most new therapeutics into military is first by the commercialization and approval for use in the civilian population.

Conclusion: Based on the collective interview responses of experts in the biopharmaceutical industry, our stage of development, a clarity in better understanding the biopharmaceutical ecosystem, and validating our path forward into clinical trials, afforded us a strong evidence-based GO Designation.

Future steps: The next steps will be to continue on our established path toward commercialization that includes filing a non-provisional patent, completion of a pMDI prototype, initiation of animal toxicity testing followed by human clinical trials.

I. INTRODUCTION

The overarching goal of the SEMPer Fi (saving lives with emergency medical perfluorcarbons) program is to develop and commercialize aerosolized therapeutic formulations, based on perfluorocarbon (PFC) chemistry. Advanced development of these formulations are meant to bridge a technology gap that will allow pharmaceutical hydrophilic compounds to be delivered directly to the lungs via a pressurized metered dose inhaler (pMDI). For the military this technology will provide a faster and more efficacious means to target the Hypoxic Pulmonary Vasoconstrictive (HPV) response, which hinders physical and mental performance of military personnel working in hypoxic environments.

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III. RESULTS

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IV. Future Plans

UC Denver has obtained a patent with the University of Colorado Denver for its specialty drug formulation, and our currently seeking a second patent with the API of protein based therapies specific to the treatment of sickle cell disease. Following successful pre-clinical proof-of-principle, our industry partners are performing feasibility testing of our prototype inhaled formulation and we are aiming to complete safety and toxicity testing in Sep 2019.

UC Denver / University of Mainz is currently funded by the Office of Naval research and additionally seeks to raise $3 million Series A funding to complete prototype development,($220K currently obligated), preclinical safety and toxicity assessments (Estimated $2.5 million based on Charles River and iiTri quotes), by July 2019. Following

preclinical safety development, the process of FDA IND submission will be in place, and we expect an additional $5 million will be sought to follow to complete phase 2 clinical trials.