



## **HIV VACCINE DEVELOPMENT PROGRAM EXECUTIVE SUMMARY January 31, 2014**

Immunity Project, a Y Combinator-backed non-profit, is working to take its HIV vaccine candidate developed using a novel data-driven approach quickly through Phase I clinical trials. The HIV vaccine developed by Immunity Project will be manufactured in Immunity Project facilities or licensed royalty free to a manufacturer clearing the way for eventual large scale production of the vaccine available world wide at no cost to the end consumer.

Much of the HIV vaccine research community is working on developing a neutralizing antibody vaccine that would function in much the same way as most vaccines used commonly today for other diseases. Because the neutralizing antibody vaccine development effort, which relies on an immune system B-Cell response, has not yet born fruit, we have chosen to focus on T-Cell immunity to suppress the virus. Our idea is to use a vaccine to train the T-cell immune system of an individual to attack the HIV virus at specific points identified by a data-driven analysis of actual individuals' immune systems, which is why Immunity Project is using its vaccine delivery technology to present antigen (targets) to T-cells. Should research in neutralizing antibody vaccines head in a direction that would benefit from our technology, we would be delighted to work with workers in that part of the field.

Until There's A Cure, a registered 501(c)3 organization is the fiscal sponsor for Immunity Project. Immunity Project was created as a non profit activity of Flow Pharma, Inc. The fiscal sponsorship agreement between Until There's A Cure and Flow Pharma stipulates that Flow Pharma will provide all of its intellectual property on a worldwide, perpetual, royalty free basis to Immunity Project for development, and distribution of the HIV vaccine. No funds raised on behalf of Immunity Project will be used for any for profit activities by Flow Pharma, Inc. Flow Pharma, Inc. will not profit from the HIV vaccine, now or in the future.

HIV has taken nearly 30 million lives since it was first identified as the cause of AIDS in 1983. An estimated 34 million people are living with HIV, and each day an additional 7,000 become infected with the virus. Current responses to the pandemic are insufficient to match the challenge posed by HIV: For every person who gains access to antiretroviral drugs today, two are newly infected by the virus. This is especially true in South Africa where the need for an HIV vaccine is of the utmost urgency.

An intensive data-driven effort was able to identify specific targets target (regions of HIV proteins) on the virus surface favored by individuals who naturally suppress the virus. [ 1 ] These beneficial targets may represent the best possible targets for the body's killer T cells, because an attack at these points forces the virus to mutate into a weakened state.

These targets, however, which are only about a dozen amino acids long, will not produce a robust immune response with memory if injected alone into a host. In fact, even when combined with adjuvants known to promote an immune response, these small peptides are essentially unrecognized when injected into mammals and, as such, will not cause an immune response to be developed.

The situation is made more complex by the fact that these candidate targets for use in an HIV vaccine are believed to be HLA restricted requiring that the individual receiving the vaccine have an HLA type matched to a particular vaccine target.[2] Determining an

individual's HLA type requires a blood draw and an expensive laboratory test. A "master" vaccine containing all possible targets capable of being recognized and processed by individuals with different HLA types would be an ideal approach allowing the administration of a single vaccine to all recipients, at least in a given region of the world.

Immunity Project addressed the question "Could multiple targets be incorporated into a single vaccine that would produce an immune response with memory after administration even though only one target would be recognized by the recipient?"

After two years of research and development including one clinical trial and large scale mouse experiments, Dr. Reid Rubsamen and his team at Immunity Project were able to answer this question in the affirmative: "Yes, multiple targets could induce an immune response with memory in mice if they were incorporated in biodegradable microspheres and combined with toll-like-receptor (TLR) agonists in a specific way." Further, the Immunity Project team was able to show that the immune response after intradermal injection was robust, reproducible and not associated with inflammation at the injection site. In addition, the microsphere size was consistent with that required for developing a nasal delivery formulation which would have obvious benefits for large-scale distribution and administration in a third world environment.

These microspheres make the very small targets look large and threatening to the immune system, provoking an immune response after a single dose. Immunity Project has conducted extensive experiments with a C57BL/6 mouse model showing that biodegradable microspheres properly formulated with the target antigens and toll-like receptor (TLR) adjuvants can produce a reliable immune response with memory after a single dose.

Immunity Project's delivery system differs from the live-pathogen vectors, typically adenoviruses, that have been used in HIV vaccine trials to date.[3] Unlike these virus-based dosage forms, Immunity's candidate vaccine contains no "live" components.

Formulating, generating and packaging fine particle pharmaceutical products suitable for testing and ultimate sale after regulatory approval requires a special set of skills. The Immunity Project team has a depth of pharmaceutical expertise with many years of experience in the pharmaceutical industry which includes expertise in world-wide clinical trial design and implementation in the fine particle space under the control of the US FDA and various other international regulatory bodies. While the team members worked at Aradigm Corporation, they led multiple projects including inhaled insulin, inhaled morphine, and inhaled fentanyl with manufacturing and clinical testing occurring in multiple sites including Australia, the UK and the United States.

The objective of Immunity Project is to take this vaccine design from concept to clinical trials in humans. The development of an inhalable vaccine is a long, expensive and complicated process that will require many studies to prove the concepts are safe and develop the technology and documentation to navigate the regulatory pathway. The technology has already yielded positive results in the early stage animal studies but there is a great deal of preparation and testing that remains. The vaccine will require testing in a controlled clinical trial setting(s) to prove it is safe and effective in humans.

Additionally, the Immunity team will develop manufacturing processes, technology and specifications so that the vaccine can be reproduced, consistent to our quality standards. We will be submitting regulatory filings in the US and South Africa and partnering with a) contract manufacturing organizations "CMO's", to safely and efficiently provide our product for testing in clinical trials, and b) contract research organizations "CRO's", to efficiently conduct the studies, testing and trials necessary to meet research objectives and regulatory requirements. The current plan anticipates a small clinical trial in the US starting late 2014 then bridging to clinical trials in South Africa in 2015. We feel this will provide the most expeditious route to starting our program in the clinic. Our budget estimate to complete development and execution of Phase I Clinical Trials in the US and South Africa is \$25 million USD. Funding confirmation is needed as soon as possible to maintain the current project goals and timeline.

Immunity Project is a non profit development program with all knowhow and relevant

patents made available to facilitate further clinical development and ultimate large scale manufacturing on a royalty-free basis. Furthermore, the mission of Immunity Project is to ensure that the final vaccine formulation is made available to end consumers at no cost.

Amino acid sequences of beneficial targets are synthetically manufactured as peptides, and incorporated on and within the PLGA micro-particles (microspheres). It is these peptides that the antigen presenting cells (APCs) will present to the immune cells to elicit both activation and memory.

Immunity Project's microsphere fabrication technology, Flow Focusing, allows these proteins to be incorporated into precisely sized Poly (D,L-lactide-co-glycolide (PLGA) microspheres without using organic solvent systems common to other manufacturing techniques that can damage proteins and peptides during the fabrication process.[4, 5] We believe that precisely sized PLGA microspheres loaded with specific antigens required for effective delivery of a particular vaccine could be designed so that only one sphere, on average, will interact with one antigen presenting cell. The micro-particle vaccine prepared by Immunity Project's Flow Focusing technique have characteristics that should enable these micro-particles to elicit a strong and lasting memory immune response to the disease in question with little or no toxicity to the individual.

### Regulatory Requirements – US and South Africa

Immunity Project intends to conduct all clinical testing of its products under development in a manner consistent with US FDA and European guidelines regardless of which regulatory bodies around the world actually control the conduct of a particular study.

US and South Africa have been selected for the Phase I clinical trials. We have a two pronged clinical approach utilizing a small initial Phase I study in the US to get an early start then focusing on South Africa for two reasons (a) the clinical need for an HIV vaccine is most acute there (b) the scientists and research infrastructure developed in KwaZulu-Natal over the past several years has produced an unparalleled platform for HIV

vaccine development in Durban. (c) The South Africa pharmaceutical development regulatory authorities generally act to clear clinical testing approximately six months after the US FDA clears a similar protocol.

### US FDA Investigational New Drug Application

An Investigational New Drug Application (IND) is the mechanism by which a sponsor requests authorization from the United States Food and Drug Administration (FDA) to evaluate the safety and efficacy of an experimental drug in specific indications. An IND must contain sufficient information in the following three general categories to allow the FDA to determine that research subjects will not be exposed to unacceptable risks:

1. Animal pharmacology and toxicology: this includes evidence that the experimental drug has the potential to be efficacious in the proposed indication as well as information on the safety evaluations conducted in relevant animal species. The types and duration of safety studies required is dependent on the stage of clinical trials, the composition of the experimental drug, and the disease indication. This category also includes information on previous experience with the experimental drug in humans (e.g. clinical trials conducted outside the US).
2. Chemistry, manufacturing, and controls (CMC): this section includes information regarding the composition, manufacturing process, manufacturer, stability, and controls (release testing, manufacturing process controls, etc.) of the experimental drug substance and drug product.
3. Clinical information: this section includes detailed information on the proposed clinical protocol, the clinical investigators, the institutional review board (IRB), and the experimental subject informed consent letter.

Within the FDA, jurisdiction for vaccines is with the Center for Biologics Evaluation and Research (CBER). Upon receipt, of an application CBER has 30 days to review an IND to determine that research subjects will not be exposed to unacceptable risk. If within

the 30 day period CBER does not prevent the initiation of clinical trials (referred to as clinical hold), then the sponsor is allowed to initiate clinical trials. The Immunity Project team feels that the timing to start in the US is faster than South Africa, therefore we can quickly initiate our study in the US then move to South Africa when all of their regulatory requirements are satisfied.

### South Africa Clinical Trial Application

Immunity Project will be preparing and filing a Chemistry Manufacturing and Control (CMC) package for a US IND filing with the FDA. Simultaneously, Immunity Project will file a Clinical Trial Application (CTA) in South Africa for a Phase I clinical trial there. The South African regulatory system is similar to the European authorities (EMA). The CTA is submitted for each study a sponsor plans to do and takes an average of 6 months to approve. CTA clearance can take as long as 2 years. The logic to file an IND in the US is because it would expedite the CTA in South Africa. Once the IND clears in the US we will inform the South African authorities which may expedite their processing but we should still anticipate approximately 6 months for CTA clearance.

Immunity Project believes that an African based HIV vaccine testing program, regulated and run by Africans with dotted lines back to the US development effort, is the most efficient way to move forward with clinical testing. To this end, Immunity Project's regulatory strategy is to work with a South African Clinical Research Organization (CRO)/Principal Investigator to design and implement the Phase I HIV vaccine clinical trial. This approach will provide a logical portal for continuing studies into Phase III Durban where the HIV conversion rate is the highest in the world, allowing for vaccine efficacy to be assessed rapidly with the smallest number of test subjects possible.

### Vaccine Manufacturing

The HIV Vaccine will be produced in an aseptic facility by a Contract Manufacturing

Organization (CMO), under the supervision and management of Immunity Project. The product is formulated for spray drying by dissolving the components in acetone. The final formulation will contain about 4% PLGA and a few percent peptide and adjuvants. The formulation can be dispersed by one of two methods, commercial spray drying or using Immunity Project's Flow Focusing nozzle and process which will generate a tighter droplet size distribution than a conventional spray drying nozzle.

In a typical commercial spray drying process, a nozzle creates a continuous spray of fine liquid droplets which are mixed with heated air and passed through a drying chamber to evaporate the solvent. The dry particles are collected downstream from the chamber in a cyclone or other particle trap. The solvent is removed from the process with the drying gas. The particle trap can be engineered to reject particles above or below specific target sizes.

The Flow Focusing process is similar to any commercial spray drying process except for the formation of droplets at the nozzle. The Flow Focusing nozzle generates a tighter droplet size distribution than a conventional spray drying nozzle, and thus a tighter particle size distribution. The product is designed for injection and will need to be sterile. This will be done using aseptic manufacturing processing.

The manufacturing of the vaccine will take place in a clean room environment at the CMO, following the cGMP guidelines and industry best practices for similar products. The manufacturing area will be designed and tested to incorporate the following capabilities:

1. Manufacturing processes will be managed and controlled through the use of Standard Operating Procedures "SOPs"
2. An aseptic isolator environment for manufacturing of the particles and filling of the individual dose containers.
3. A clean room for staging and preparation
4. A gowning room for entering and exiting the clean room.
5. A positive airflow and differential pressure gradient from the cleanest to the



less clean areas.

6. Commissioning and Validation documentation of the facility and support utilities
7. Calibration and maintenance of facilities support instruments and equipment.

The material handling requirements will include the following criteria:

1. All materials will be purchased from qualified vendors per specification
2. Sterility will be maintained by manufacturing in an isolator.
3. An Isolator will be located inside a controlled clean room environment.
4. The interior of the isolator and the spray dryer will be sterilized prior to each manufacturing operation.
5. The formulation will be sterile filtered prior to introduction into the spray dryer.
6. Bulk product collected in the cyclone is sealed while still within the sterile isolator.
7. After release testing for content, particle size distribution, sterility and endotoxin, the bulk product is repackaged into individual dose containers within a sterile isolator.

### Stability Testing

Samples of each lot of the Immunity drug substance and drug product manufactured for the trial will be included in a stability program in accordance with the ICH-Q1A(R2) Harmonized Tripartite Guideline “Stability Testing of New Drug Substances and Products”. Samples will be stored at the recommended long term storage and at an accelerated temperature condition, at a minimum, to detect any significant changes during storage. The stability studies will include evaluation of attributes of the drug substance and drug product that are susceptible to change during storage and are likely to influence quality, safety, and efficacy.

The studies will be performed under pre-approved protocols defining the stability testing plan and responsibilities, requirements and procedures regarding the stability sampling and packaging, storage conditions, sample quantities required at each storage condition, testing frequency, testing procedures, acceptance criteria and reporting requirements. The testing plan will define the physical, chemical, biological, and microbiological attributes to be tested utilizing appropriately qualified analytical procedures.

### Quality Assurance

Immunity Project quality systems are responsible for implementation and maintenance of a phase- appropriate pharmaceutical quality system that ensures the safety and quality of products intended for use in clinical trials and establishes a process for applying phase-appropriate Good Manufacturing Practices during the development of products from the R&D stage through Phase 3 clinical trials. This is accomplished with quality oversight and management of internal and external operations, appropriate selection and training of personnel, establishment of a robust document and records control system and maintenance of product and process control systems (change management, deviations, investigations, continuous improvement, risk management, corrective and preventive action, vendor qualification and management).

## Immunity Project Research Team

### Reid Rubsamen, M.D., CEO/Co-Founder

The Immunity Project Team is under the supervision of Reid M. Rubsamen, M.D., the CEO and Co- Founder of Immunity. Reid is a Board Certified anesthesiologist having received his medical training at Pacific Medical Center, San Francisco and Massachusetts General Hospital, where in 1989 he served as Chief Resident in Anesthesia. He was also a doctoral candidate in the computer science department at the Massachusetts Institute of Technology, leaving in 1990 to found Aradigm Corporation. He left Aradigm in 2000 to enter private practice and found Immunity Project. Dr. Rubsamen holds an A.B. in biochemistry and computer science from the University of California, Berkeley, and an M.S. in computer science and an M.D. from Stanford University. Dr. Rubsamen is a named inventor of more than 65 issued U.S. patents. Dr. Rubsamen is Director and CEO of Flow Pharma, Inc.

### CV Herst Ph.D., Science Officer

Charles Vincent Herst MPH, Ph.D., MBA received his BA in Bacteriology and his MPH in Biomedical Laboratory Sciences from UC Berkeley in 1978 and 1980, respectively. He subsequently received his Ph.D. in 1989 from Northwestern University, Chicago, IL in Tumor Cell Biology. After completing a post-doctoral fellowship at M.D. the Anderson Cancer Center Hematology Department in Houston, Texas, he established a twenty-four-hour, seven day-a- week high complexity clinical laboratory testing as laboratory director of Oncore in Houston.

He then built and brought on line a analytical chemistry laboratory at Aradigm Corporation leaving in 1997 to found R.E.D. Laboratories, in Brussels, Belgium where he served as CEO until 2006 establishing high complexity clinical laboratory and research facility and developing a wide variety of assays to measure changes in the levels of clinically

important proteins and nucleic acid species in the cells and sera of patients with chronic immune and infectious diseases. He then served as Laboratory Manager at Zogenix Corporation doing product development for a needle-free parenteral drug delivery system. He has served as a consult to Immunity Project since 2004 and has been Immunity Project's Science Officer since 2011.

Jack Lloyd, Advisor

Mr. Lloyd has served as a founder, officer, and Director of medical and high technology companies since 1970. He was co-founder of Nellcor (now Covidien), the developer of Pulse Oximetry, and served as its first President and Chief Executive Officer from 1981-1990, during which time he grew the company from a start-up to annual sales of \$150 million. Prior to his experience with Nellcor, from 1974 to 1981, Mr. Lloyd was founder and President of Humphrey. More recently, Mr. Lloyd served as Chairman and President of Aradigm corporation a developer of aerosol drug delivery systems, from 1993 to 1997. He was also the founder of Alere Medical Inc., a provider of disease management services utilizing electronic home monitoring, sold to Inverness Medical in 2007. Mr. Lloyd is a Director of Flow Pharma, Inc.

Steven Farr, Ph.D., Advisor

Stephen J. Farr, Ph.D. is a co-founder of Zogenix and has served as President and as a member of Zogenix's board of directors since May 2006. From May 2006 to October 2006, Dr. Farr also served as Zogenix Chief Executive Officer and since October 2006, Dr. Farr has served as Zogenix Chief Operating Officer. From 1995 to June 2006, Dr. Farr held positions of increasing responsibility within pharmaceutical sciences and research and development at Aradigm Corporation, and serving most recently as Senior Vice President and Chief Scientific Officer. In 2003, he played a key role in identifying and acquiring the DosePro™ technology and became technical director and executive sponsor for the development of sumatriptan DosePro at Aradigm Corporation. From 1986 to 1994, Dr. Farr

was a tenured professor at the Welsh School of Pharmacy, Cardiff University, U.K., concentrating in the areas of physical pharmacy and biopharmaceutics. He is a fellow of the American Association of Pharmaceutical Scientists and a visiting Associate Professor in the Department of Pharmaceutics, School of Pharmacy, Virginia Commonwealth University. Dr. Farr is a registered pharmacist in the U.K. and obtained his Ph.D. degree in Pharmaceutics from the University of Wales. Dr. Farr is a Director of Flow Pharma, Inc.

Igor Gonda, Ph.D.

Dr. Gonda has served as President and Chief Executive Officer of Aradigm since August 2006, and as a director since September 2001. From December 2001 to August 2006, Dr. Gonda was the Chief Executive Officer and Managing Director of Acrux Limited, a publicly traded specialty pharmaceutical company located in Melbourne, Australia. From July 2001 to December 2001, Dr. Gonda was Aradigm's Chief Scientific Officer and, from October 1995 to July 2001, was Aradigm's Vice President, Research and Development. From February 1992 to September 1995, Dr. Gonda was a Senior Scientist and Group Leader at Genentech, Inc. leading inhalation development of products for severe respiratory disease. Prior to that, Dr. Gonda held academic positions at the University of Aston in Birmingham, United Kingdom, and the University of Sydney, Australia. Dr. Gonda holds a B.Sc. in Chemistry and a Ph.D. in Physical Chemistry from Leeds University, United Kingdom. Dr. Gonda was the Chairman of Aradigm's Scientific Advisory Board until August 2006.

Tikoos Blankenberg, Laboratory Medicine Advisor

Tikoos Blankenberg is a founding partner of Redding Pathologists. He attended Medical School at the University of California, Los Angeles after receiving his bachelor's degree in Engineering and Materials Science from Northwestern University. Dr. Blankenberg subsequently completed his Pathology residency at the University of California at Davis and a Pathology Fellowship at Stanford. Dr. Blankenberg is Chief of Staff St Elizabeth's

Hospital, Red Bluff, California. He is on the Board of Directors of Benecor, Inc. and is on the Community Board of Dignity Health, Northern California Service Area.

Dr. Blankenberg is a director of Flow Pharma, Inc.

**IMMUNITY PROJECT  
Phase I Clinical Trial Budget Summary**

<u>Description</u>	<u>Budget</u>
Product Development (Animal & TOX Studies)	\$ 4,500,000
Manufacturing/Process Development	5,000,000
Quality Assurance	2,000,000
Management and Control of HIV Program	2,000,000
Preparation for US and South African Clinical Studies	1,500,000
Grant Support From Microsoft Research	\$ (1,000,000)
<b>SUBTOTAL</b>	<b>\$ 14,000,000</b>
Product Manufacturing for Phase I Clinical Trials	200,000
Clinical Study in the United States (Estimated 20 Patients)	200,000
Clinical Study in South Africa (Estimated - 60 Patients)	600,000
<b>TOTAL BASELINE HIV VACCINE PROJECT BUDGET</b>	<b><u>\$ 15,000,000</u></b>
NASAL FORMULATION DOSE DEVELOPMENT	8,000,000
NASAL FORMULATION PHASE I CLINICAL TESTING ARM	800,000
<b>SUBTOTAL NASAL FORMULATION OPTION</b>	<b>\$ 8,800,000</b>
<b>TOTAL BASELINE IMMUNITY PROJECT BUDGET WITH NASAL DOSE OPTION</b>	<b><u>\$ 23,800,000</u></b>

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### **1. Background and Significance of Immunity Products**



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a. Immunity Project's platform technology and products:

Immunity Project has developed the Microsphere fabrication technology for the HIV Vaccine and has established that its proprietary microencapsulation technology is applicable to other materials. A special set of skills is required to formulate, generate and package fine particle pharmaceutical products suitable for testing and ultimate sale after regulatory approval. The Immunity Project team has a depth of pharmaceutical expertise with many years of experience in the pharmaceutical industry which includes expertise in world-wide clinical trial design and implementation in the fine particle space under the control of the US FDA and various other international regulatory bodies.

Microsphere fabrication: Presentation of antigens to the immune system is a critical component of vaccine delivery. Immunity Project's microsphere (micro-particle) fabrication technology, Flow Focusing, allows proteins to be incorporated with high-efficiency into precisely sized PLGA microspheres without using organic solvent systems common to other manufacturing techniques that can damage proteins and peptides during the fabrication process. Immunity Project has conducted multiple pre-clinical studies and one clinical trial evaluating the use of PLGA microspheres as antigen delivery systems capable of inducing an immune response with memory to an HLA-matched target. Using light microscopy video imaging of microsphere phagocytosis in healthy human volunteers and a mouse model allowing immunization with various microsphere formulations, Immunity Project has identified the appropriate excipients and adjuvants for a candidate dosage form. Work to date has been with intra-dermal dosing but Immunity believes that a nasal dosage form can be developed using its microsphere-based vaccine.

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Scientific Rationale for Immunity Project Micro-particle Vaccine Design: The micro- particle vaccines prepared by Immunity Project’s Flow Focusing technique have unique and proprietary characteristics that should enable these micro-particles to elicit a strong and lasting memory immune response to the disease in question with little or no toxicity to the individual. The rationale for the selection of chemical components used in the formulation of these micro-particles is presented below.

For an antigen to effectively trigger an adaptive (i.e., memory-based) immune response, the antigen must be correctly “presented” to the cells of the immune system. This presentation event is the initial cellular event and it begins with the uptake of the antigen by specific antigen-presenting cells (APCs) of which macrophages and dendritic cells are central. These cells phagocytize the antigenic material and process it intracellularly. The processed antigen is then presented on the cell surface in a form that other immune cells, specifically T- and B-cells will recognize as foreign. This interaction between APCs and T- and B-cells is critical to the activation of the immune system, without which a long-lasting memory-based (i.e., protective) response will not occur.

APCs recognize as antigen as foreign, in part by Pattern Recognition Receptors (PRRs) that recognize chemical signatures unique to the surface of pathogens such as viruses, bacteria and fungi. PRRs include the Toll-like receptors (TLRs), a group of receptors that recognize widely varying molecules such as double-stranded RNA (resembling viral intermediates), non-methylated nucleic acids (resembling bacterial DNA), and flagellin (the major protein component of bacterial flagella) to name just a few. Another trigger for APCs is recognizing a group of molecules referred to as Pathogen-Associated Molecular Patterns, or PAMPs. This group of signals

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includes the branched chain carbohydrate structures common to the surface of many bacteria such as mannose. [6]

Finally, the size of the antigen is important in that if the antigen/organism is too large, it will be impossible for the APC to phagocytize it. Conversely, if too small, the antigen may not be recognized as foreign or may be taken up by the cell using a process called pinocytosis which does not process the antigen in the same way as phagocytosis.

Given these requirements and constraints of APCs, the vaccine candidate in question must be packaged in a way so as to be taken up and processed correctly by the APC, without which the immune response will not be robust and the vaccine will not protect the individual from infection.

The chemical components used to make Immunity Project's micro-particles are as follows:

- i. Poly (D,L-lactide-co-glycolide), or "PLGA": PLGA has been extensively studied as a polymer for the production of controlled release of drugs and other molecules. Various researchers have demonstrated that PLGA microspheres are taken up by phagocytic cells but that PLGA by itself is not immunogenic. Micron-sized PLGA microspheres dissolve in aqueous medium over days, as opposed to weeks or months with similar sized pharmaceutical polymers such as caprolactone. [7] Using the Flow Focusing device, the reproducible and predictable manufacture of PLGA micro-particles of the correct size can be critically controlled.
- ii. Peptide as antigen: Specific targets identified with a data-driven approach comparing individuals with varying ability to suppress the virus, are incorporated into the PLGA microspheres.

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- iii. MPLA as adjuvant: Adjuvants are often combined with noninfectious vaccine antigens (e.g., proteins, nucleic acids) to generate an immune response that is stronger and longer lasting than the response elicited with antigen alone. Monophosphoryl Lipid A (MPLA) is a derivative of lipopolysaccharide (LPS, an integral part of the cell walls of Gram-negative bacteria) that has ~0.1% of the inflammatory toxicity of LPS while still generating clinically useful immune responses, including antibody and TH1- dependent cytotoxic T-cell activity, important for combating intracellular pathogens such as HIV. MPLA works by binding to Toll-like receptor 4 (TLR-4). [8] MPLA is an adjuvant in the FDA approved cervical cancer vaccine Cervarix.
- iv. Mannose as PAMP: Many invading microbes (e.g., bacteria, viruses) have on their surface complex carbohydrates. The immune cells of the body recognize these carbohydrate structures as Pathogen-Associated Molecular Patterns, or PAMPs. Mannose, a six-carbon sugar, and its multi-chain branched derivative, mannan, is a common PAMP [8], identified on organisms as varied as HIV, tuberculosis, and yeast. Including mannose in the formulation of PLGA microspheres is intended to make the microspheres mimic the structure of an invading microbe, allowing for a more rapid and intense conditioning of APCs, enhancing the phagocytosis of micro-particles.
- v. CpG-B: A Toll-like Receptor (TLR-9) agonist which enhances an immune response. CpG-B has the ability to enhance peptide-specific CD8<sup>+</sup> T-cell responses in human peripheral blood mononuclear cells (PBMCs)[8, 9].

In conclusion, the Immunity Project vaccine design model is to use 11 micron-sized particles to deliver target targets using two TLR adjuvants, and to construct these micro-particles using PLGA that degrades over days so that memory CD8<sup>+</sup> T cells can develop efficiently, and incorporates mannose to further enhance the immune response.

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b. Importance of this vaccine program and its impact on HIV/AIDS worldwide:

The micro-particle vaccines prepared by Immunity Project have characteristics that should enable these micro-particles to elicit a strong and lasting memory immune response to the target targets.

On a fundamental level, Immunity Project believes that its microencapsulated target delivery formulation used in conjunction with a diluent-suspended adjuvant MPLA represents an approach that (a) avoids using a pathogen vector and (b) uses an adjuvant very similar to that employed by marketed HPV vaccine products. Immunity Project believes that this basic design represents a potentially non-toxic starting point for an target vaccine delivery system.

Immunity Project is focused on Africa for two reasons (a) the clinical need for an HIV vaccine is most acute there and (b) the scientists and research infrastructure developed in KwaZulu-Natal over the past several years has produced an unparalleled platform for HIV vaccine development in Durban.

### **2. Regulatory overview and requirements for Phase I Clinical Trial in South Africa**

a. Regulatory Strategy statement from Immunity:

There are a number of problems that currently impact the review of HIV vaccine clinical trial protocols and that could delay the progress of vaccine development. Most regulatory challenges arise from the fact that regulatory approvals are granted at the national level, but many developing countries lack the expertise, well-defined processes, clear delineation of authority, and/or other system components needed to make regulatory decisions expeditiously. As a result, clinical trial applications are often granted in these regions based on prior approval in the US or Europe and/or endorsement by the WHO.

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Immunity Project intends to conduct all clinical testing of its products under development in a manner consistent with US FDA and European guidelines regardless of which regulatory bodies around the world actually control the conduct of a particular study.

Immunity Project believes that an African based HIV vaccine testing program, regulated and run by Africans with dotted lines back to the US development effort, is the most efficient way to move forward with clinical testing. To this end, Immunity's regulatory strategy is to work with a South African Clinical Research Organization (CRO) to design and implement, working with Immunity and the local Principal Investigator, the Phase I HIV vaccine clinical trial. This approach will provide a logical portal for continuing studies into Phase III in Durban, South Africa where the HIV conversion rate is the highest in the world, allowing for vaccine efficacy to be assessed rapidly with the smallest number of test subjects possible.

Immunity Project has identified these action-item priorities: (1) harmonize the regulatory requirements in different countries, (2) facilitate regulatory decision making, possibly using regional approaches (3) build manufacturing and regulatory capacity, (4) perform risk/benefit evaluations based on the regional/country needs and resources, (5) identify and remove potential obstacles to obtain rapid regulatory decision, and (6) address ethical issues that interface with regulatory decisions.

b. Program to follow FDA Guidelines and will submit an Investigational New Drug (IND) application to the FDA:

Immunity will be preparing and filing a Chemistry Manufacturing and Control (CMC) package for a US IND filing with the FDA. See 4 a. "Filing of Investigational New Drug (IND) application with the FDA"

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c. Comparison of FDA and South Africa regulatory requirements:

Simultaneously with the IND Filing, Immunity Project will file a Clinical Trial Application (CTA) in South Africa to the Medicines Control Council (MCC) and local ethics committee for a phase I clinical trial. The South African regulatory system is similar to the European authorities (EMA). The CTA is submitted for each study a sponsor plans to do and takes an average of 6 months to approve. CTA clearance can take as long as 2 years. The logic behind filing an IND in the US is the advantage of expediting the CTA in South Africa. Once the IND clears in the US we will inform the South African authorities of this fact. Although it will expedite their processing we should still anticipate about 6 months for CTA clearance.

d. Selection of a Contract Research Organization (CRO) for Clinical Trials in the US and South Africa:

The review and approval process in South African for a clinical trial is currently averaging 6 months from the time an application is submitted to the MCC until a decision is rendered. After the submission, there is a one-week validation process when the MCC can request information omitted from the original submission. Four to five weeks after the original submission, the clinical trials committee (CTC) meets to discuss the application and may provide feedback to the applicant. Another five weeks after this, the MCC meets to discuss the application and responses. The results of the assessment are delivered to the applicant after the MCC meeting.

All clinical trials for nonregistered biopharmaceuticals must be reviewed by the MCC. A comprehensive application form must be accompanied by the investigator brochure, the completed trial protocol, and the informed consent form, together with a variety of other documentation such as proof of GCP training for the investigators and trial insurance details. There is a fee for each application. An approval letter from the MCC allows the study to commence

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and also permits the importation of the study drug.

In addition to MCC approval, all clinical trials must be approved by an accredited ethics committee (EC). In South Africa, an EC is typically associated with the particular hospital, clinic, or academic center where a study is to be conducted, but there is also an alternative, centralized EC process. The application requirements are similar to those required by the MCC, and a small application fee is typical. The average turnaround time for ethics committee reviews is about two weeks. The MCC and EC application processes can take place in parallel.

Given the complexities and timeframe of the clinical trial application process in South Africa, it is essential for Immunity Project to work with a local partner experienced in preparing applications for the MCC and local ECs. An organization that is familiar with the many complex requirements can help draft the regulatory submission to expedite the process and avoid undue delays.

Key attributes that Immunity Project is seeking in a South African partner include:

- The capability of supporting both a US and South African Clinical Trial.
- A potential partner should have a proven track record of successfully conducting studies in South Africa, with a demonstrated ability to recruit investigators and subjects, meet deadlines, and produce solid data—as well as the capability to obtain regulatory approval for new trials without undue delays.
- Access to extensive databases of potential subjects/healthy volunteers for Phase I study.
- Adequate resources in South Africa to perform the functions required, including management resources, trained monitors or other personnel.



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- Thorough knowledge of, and commitment to comply with, ICH and GCP guidelines during the trial.
- Well-established quality assurance systems, standard operating procedures (SOPs), and other internal controls, processes, and procedures to maintain quality and ensure compliance with all regulations and study requirements.
- Adequate infrastructure to support the trial, including communications and information technology systems.
- Ability to work closely with Immunity by maintaining strong lines of communication and supplying continuous oversight and feedback throughout the trial process.

Immunity believes that an African based HIV vaccine testing program, regulated and run by Africans with dotted lines back to the US development effort, is the most efficient way to move forward with clinical testing. To this end, Immunity's regulatory strategy is to work with a South African Clinical Research Organization (CRO) to design and implement, working with Immunity and a local Principal Investigator, the Phase I HIV vaccine clinical trial. This approach will provide a logical portal for continuing studies into Phase III in Durban where the HIV conversion rate is the highest in the world, allowing for vaccine efficacy to be assessed rapidly with the smallest number of test subjects possible.

### **3. Animal Studies**

- a. Pharmacology: The peptide that will be used clinically was designed to specifically interact with human HLA subtypes and subsequently are not recognized by other animal species. Therefore, to demonstrate the in vivo ability of a PLGA-encapsulated peptide to elicit an appropriate immune response where the peptide alone was ineffective, an analogous mouse-

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specific peptide was generated and encapsulated using the same process.

- b. Toxicology: The primary goal for the preclinical safety assessment of a novel therapeutic is to provide evidence to assure the safety of subjects in the proposed clinical investigation. This is accomplished by conducting appropriate toxicology studies in animals that will a) allow for the selection of a safe clinical starting dose and appropriate dose escalation, b) identify potential target organs, and c) identify potential unexpected toxicities. For vaccines toxicology evaluation in a single species is generally acceptable by the FDA. The final design of the IND-enabling toxicology study will be discussed with the FDA in a pre-IND meeting.

**4. Experimental Design and Methods (first in human)**

- a. Filing of Investigational New Drug (IND) application with the FDA:

An Investigational New Drug Application (IND) is the mechanism by which a sponsor requests authorization from the United States Food and Drug Administration (FDA) to evaluate the safety and efficacy of an experimental drug in specific indications. The experimental drug can be a new entity which has not received marketing authorization for any indication or a marketed drug for which approval for a new indication, change in dosage or route of administration, or change in approved patient population is being sought. An IND must contain sufficient information in the following three general categories to allow the FDA to determine that research subjects will not be exposed to unacceptable risks:

- Animal pharmacology and toxicology: this includes evidence that the experimental drug has the potential to be efficacious in the proposed indication as well as information on the safety evaluations conducted in relevant animal species. The types and duration of safety studies required is dependent on the stage of

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clinical trials, the composition of the experimental drug, and the disease indication. This category also includes information on previous experience with the experimental drug in humans (e.g. clinical trials conducted outside the US).

- Chemistry, manufacturing, and controls (CMC): this section includes information regarding the composition, manufacturing process, manufacturer, stability, and controls (release testing, manufacturing process controls, etc.) of the experimental drug substance and drug product.
- Clinical information: this section includes detailed information on the proposed clinical protocol, the clinical investigators, the institutional review board (IRB), and the experimental subject informed consent letter.

Within the FDA, jurisdiction for vaccines is with the Center for Biologics Evaluation and Research (CBER). Upon receipt, of an application CBER has 30 days to review an IND to determine that research subjects will not be exposed to unacceptable risk. If within the 30 day period CBER does not prevent the initiation of clinical trials (referred to as clinical hold), then the sponsor is allowed to initiate clinical trials.

- b. Outline of Clinical Trial including expected end point data to be collected:

See Immunity Proposal “HIV Vaccine Clinical Research Protocol Synopsis”

- i) Statistical overview of population including HIV infection and HLA in South Africa.

- c. Stability Testing/Stability Protocol:

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Samples of each lot of the Immunity Project drug substance and drug product manufactured for the trial will be included in a stability program in accordance with the ICH-Q1A(R2) Harmonized Tripartite Guideline “Stability Testing of New Drug Substances and Products”. Samples will be stored at the recommended long term storage and at an accelerated temperature condition, at a minimum, to detect any significant changes during storage. The stability studies will include evaluation of attributes of the drug substance and drug product that are susceptible to change during storage and are likely to influence quality, safety, and efficacy.

The studies will be performed under pre-approved protocols defining the stability testing plan and responsibilities, requirements and procedures regarding the stability sampling and packaging, storage conditions, sample quantities required at each storage condition, testing frequency, testing procedures, acceptance criteria and reporting requirements. The testing plan will define the physical, chemical, biological, and microbiological attributes to be tested utilizing appropriately qualified analytical procedures.

### **5. Specific Target endpoint**

Measurable immune response with memory from the delivery of one of the identified HLA restricted targets in humans in a safe fashion.

For an antigen to effectively trigger an adaptive (i.e., memory-based) immune response, the antigen must be correctly “presented” to the cells of the immune system. This presentation event is the initial cellular event and it begins with the uptake of the antigen by specific antigen-presenting cells (APCs) of which macrophages and dendritic cells are central. These cells phagocytize the antigenic material and process it intracellularly. The processed antigen is then presented on the cell surface in a form that other immune cells, specifically T- and B-cells will recognize as foreign. This interaction between APCs and T- and

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B-cells is critical to the activation of the immune system, without which a long-lasting memory-based (i.e., protective) response will not occur.

### 6. Description of Resources and the Manufacturing Environment

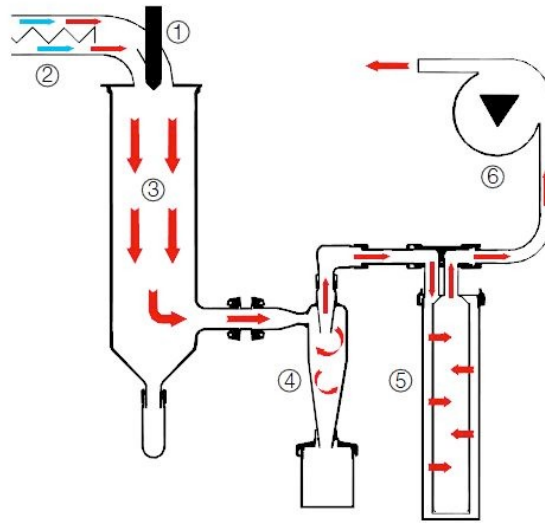
#### a. Product Formulation:

The HIV Vaccine will be produced by a Contract Manufacturing Organization (CMO) under aseptic conditions. The product is formulated for spray drying by dissolving the components in acetone. The final formulation will contain about 4% PLGA and a few percent peptide and adjuvants. The formulation can be dispersed using Immunity's proprietary Flow Focusing process. Commercial equipment is shown below to illustrate the general footprint of Immunity's process.



Small Scale Commercial Spray Dryer

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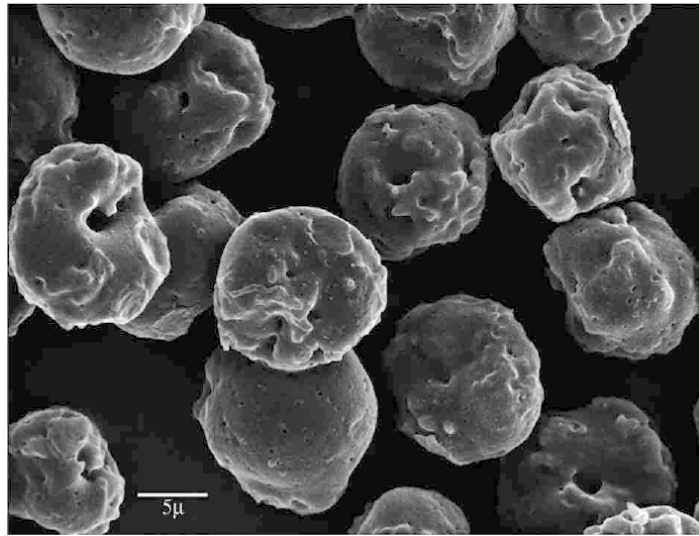


Spray Drying Process Flow

In a typical commercial spray drying process, a nozzle creates a continuous spray of fine liquid droplets which are mixed with heated air and passed through a drying chamber to evaporate the solvent. The dry particles are collected downstream from the chamber in a cyclone or other particle trap. The solvent is removed from the

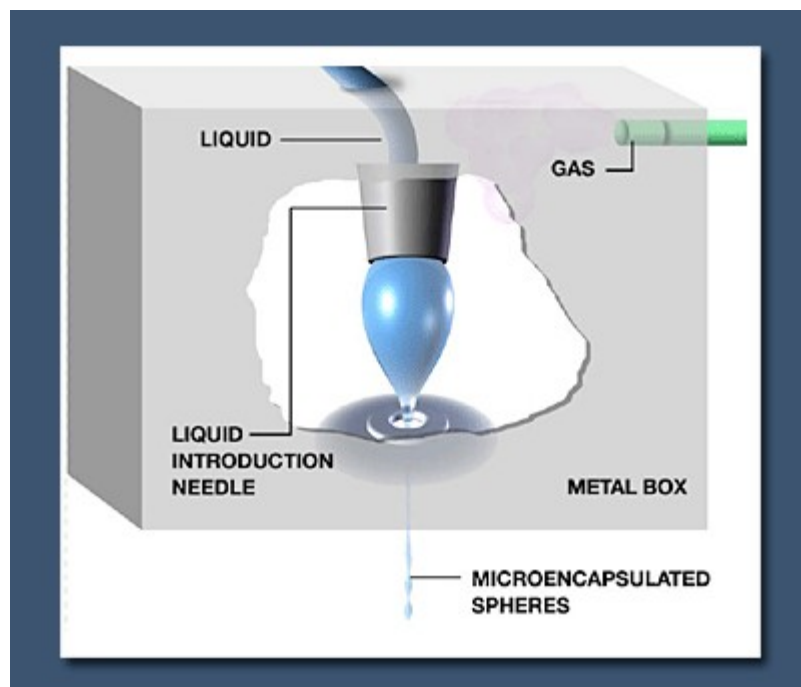
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process with the drying gas. The particle trap can be engineered to reject particles above or below target sizes.



11 µm PLGA microspheres loaded with peptide targets

The Immunity Project process is similar to any commercial spray drying process except for the formation of droplets at the nozzle. The nozzle uses a technique called flow focusing to generate a tighter droplet size distribution than a conventional spray drying nozzle, and thus a tighter particle size distribution.



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Powders for injection (PIs) constitute an important category of dosage forms for active molecules. Because of their instability in the aqueous environment, PIs cannot be marketed as ready-to-use injectables. Instead, they are marketed as dry powders to be reconstituted with a suitable vehicle just before administration. The final form after reconstitution may be either a solution or a suspension. This vaccine is a peptide encapsulated in a PLGA microsphere. The microsphere with peptide is a stable solid that is obtained by evaporative spray drying in aseptic conditions. The product can then be packaged by directly filling the sterile dry-powder drug into pre-sterilized vials. The dry-filling process is much more cost effective than aseptic liquid/lyophilization filling because it requires lesser infrastructure as well as a reduced amount of energy and a shorter amount of time to produce a batch. The dry-powder fill approach involves depositing a drug (plus excipient) into individual vials using suitable filling equipment. The vaccine formulation may consist of drug only or drug plus excipient. Complexities may result from the presence of an excipient (e.g., interactions with the active molecule and product performance). Particle and bulk properties primarily control derived powder properties such as flow. At the particle level, the forces are influenced by several fundamental physicochemical properties, including particle density, particle-size distribution, particle morphology (i.e., shape, habit, surface texture), and surface composition (e.g., absorbed moisture). These characteristics have an important effect on powder bulk properties. Flow is the most important bulk property that influences the filling of the vaccine into primary packaging containers. It is a function of the principal adhesive forces between particles (e.g., Van der Waals forces and electrostatic forces). The particle size of the drug can affect the formulation by influencing the syringeability of the suspension. The Immunity Project vaccine contains particles of 11 microns in diameter and will be of low concentration when reconstituted. Particle size also affects the level of pain at the site of injection with



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suspensions. The particle-size distribution of the vaccine will be controlled at the sterile bulk drug manufacturing facility. Attempts to modify particle-size distribution by milling and sieving could seriously affect sterility and levels of particulate matter. Immunity's equipment will produce particles with diameters in the desired 11 micron range. This innovative approach eliminates the need for milling and/or sieving.

Control of particulate matter in the vaccine: It is widely recognized that the level of particulate matter in an injectable product, apart from the systemic hazards, is a measure of quality that directly reflects the success with which a manufacturer applies good quality control. Particulate matter consists of mobile, randomly sourced, extraneous substances other than gas bubbles. Injectable solutions, including solutions constituted from sterile solids intended for parenteral use, essentially should be free from particles that can be observed on visual inspection. Furthermore, the *USP* limits for sub-visible particulate matter in the small-volume parenterals by light obscuration technique are not more than 6000 and 600 per container for particles  $\geq 10$  and 25 microns in diameter, respectively.

Particulate matter in dry-powder injectables remains a primary area of concern. The problem of particulate matter in PIs assumes greater significance because no active approach such as filtration can be applied during the manufacturing stage. However, judicious application of preventive approaches can help achieve desired standards of particulate matter. In the bulk API powder production process the acetone formulation liquid containing the PLGA and peptide is sterile filtered prior to introduction into Immunity's spray dryer. The spray dryer chamber has been rinsed with sterile filtered acetone to assure a low particulate space. The spray dryer itself is enclosed in an isolator to further reduce particulate contamination.

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The bulk powder vaccine API is packaged directly into a sterile particle free container.

Control of sterility in the vaccine: As indicated above, in the bulk API powder production process the acetone formulation liquid containing the PLGA and peptide is sterile filtered prior to introduction into Immunity’s spray dryer. The spray dryer and the interior of the isolator has been sterilized using vapor phase hydrogen peroxide. The bulk containers used to package the bulk sterile API are sourced sterile and particle free. The bulk sterile API, after successful release testing for content, particle size distribution, sterility and endotoxin is then packaged at a contract manufacturer specialized in the filling of small quantities of powder into the final packaging (glass vial with rubber stopper).

b. Manufacturing Environment for Aseptic Processing:

The product is designed for injection and will need to be sterile. We are testing the possibility of using a terminal sterilization process to reduce cost: however the current plan includes the more expensive route of aseptic processing.

The manufacturing of the vaccine will take place in a clean room environment at the CMO, following the cGMP guidelines and industry best practices for similar products. The manufacturing area will require the following high level criteria:

1. Manufacturing processes will be managed and controlled through the use of Standard Operating Procedures “SOPs”
2. An aseptic isolator environment for manufacturing of the particles and filling of the individual dose containers.
3. A clean room for staging and preparation
4. A gowning room for entering and exiting the clean rooms
5. A positive airflow and differential pressure gradient from the cleanest

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to the less clean areas.

6. Commissioning and Validation documentation of the facility and support utilities
  7. Calibration and maintenance of facilities support instruments and equipment
- c. The material handling requirements will include the following criteria:
1. All materials will be purchased from qualified vendors per specification
  2. Sterility will be maintained by manufacturing in an isolator. (a glove box)
  3. The isolator will be located inside a controlled clean room environment.
  4. The interior of the isolator and the spray dryer will be sterilized prior to each manufacturing operation.
  5. The formulation will be sterile filtered prior to introduction into the spray dryer.
  6. Bulk product collected in the cyclone is sealed while still within the sterile isolator.
  7. After release testing for content, particle size distribution, sterility and endotoxin, the bulk product is repackaged into individual dose containers within a sterile isolator.

### **7. Quality Assurance**

The Immunity quality systems are responsible for implementation and maintenance of a phase-appropriate pharmaceutical quality system that ensures the safety and quality of products intended for use in clinical trials and establishes a process for applying phase- appropriate Good Manufacturing Practices during the development of products from the R&D stage through Phase 3 clinical trials. This is accomplished with quality oversight and management of internal and external operations, appropriate selection and training of personnel, establishment of a robust document and records control system and maintenance of product and process control systems (change management, deviations, investigations, continuous improvement, risk management, corrective and preventive action, vendor qualification and management).

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