Candidate Demonstration Project

Note: the questions with asterisk should be filled.

1.* Title of the project:
A Platform for Pioneering Proper Treatment of the Forgotten HIV-Infected Paediatric Patient

2.* Submitted by:

Left blank to facilitate impartial evaluation.

3.* Target disease or health condition:
(Focus on type II and III diseases and special R&D needs of developing countries in type I diseases where there is an identified health technology gap.)
This project will focus on Paediatric HIV/AIDS, which according to the WHO classification, is a Type III disease, as ‘there is very limited work on formulations to treat HIV in children and infants where the majority of the disease burden is in low income countries and there is no market incentives for commercial research’.

4.* The suggested health technology that project seeks to develop:
(e.g. medicine; diagnostic test; medical device; vaccine etc.)
In order to improve the treatment of the Paediatric HIV Patient, an innovative Drug Delivery System for the enhanced administration of antiretrovirals is proposed for development. The proposed system will be referred to henceforth as the WaferMat technology.

5.* Project summary:
The current project aims to provide a versatile pharmaceutical formulation solution for the challenges involved with the administration of antiretroviral drugs to treat paediatric HIV using a versatile and durable WaferMat formulation constituting an ultra-fast dissolving polymer matrix that can be placed on the inside of a child’s cheek for effectively and effortlessly treating HIV. This would provide a much needed alternative to the use of current adult-based formulations (tablets and capsules) whereby mothers have immense difficulty in ensuring effective antiretroviral therapy of their small children. Current liquid formulations result in significant drug stability issues for many front-line antiretrovirals and therefore liquid formulations are not available as a dosage form. Mothers are therefore forced to utilize tablet/capsule formulations that are designed for adult use by titrating the required doses accordingly. However, this is hardly possible due to the intricacies of drug stability in various solutions (e.g. if dissolved in the child’s milk, water, fruit juice or other liquids) and the inability of many mothers to actually understand the requirements of exact dosing science. Eventually this leads to inferior antiretroviral therapy, drug resistance and intensifying the scourge of HIV. The proposed WaferMat formulation will be manufactured with dimensions that will conform to the buccal route of administration for paediatrics. Prototype formulations will contain model antiretroviral (ARV) drugs such as abacavir and zidovudine (AZT) as well as newer NNRTIs such as etravirine and rilpivirine. When applied to the buccal cavity, the
formulation will be difficult to spit out, will pose no risk of choking and taste-masking technology will be included for bitter tasting antiretroviral drugs. Permeation enhancers will also be added to allow maximal drug absorption across the buccal mucosa.

The proposed WaferMat formulation will introduce the most ideal and convenient dosing system for better patient compliance and an optimal therapeutic outcome for treating paediatric HIV. It will be designed as an innovative oral dosage form with customized 'ultra-fast' release profiles of potent orally administered antiretroviral drugs with varied solubilities, maximizing their efficiency and masking the taste. The WaferMat formulation will be suitable for paediatrics and geriatrics. The formulation will be able to deliver antiretroviral medication without the need for water, chewing or swallowing. The wafers can be placed against the inside of the cheek to release the antiretroviral drug directly into the systemic circulation. The Ultra-Fast release feature will ensure that the wafer fully dissolves in the oral cavity within 3 seconds. The formulation may also be suitable for patients who are unconscious, mentally retarded, uncooperative, nauseous or on reduced liquid-intake/diets, have difficulties swallowing oral dosage forms, and patients under emergency conditions. The WaferMat formulation will be prepared based on gel-like barrier formation and dissolution regulation that will yield a unique smooth surfaced macroporous architecture. The formulation will also possess permeation enhancing capabilities to allow for effective and efficient absorption of the antiretroviral drug. The formulation components will be selected to provide a synergistic rigidity profile forming a robust matrix with rapid dissolution properties. This project will involve development of the WaferMat up to in vivo animal studies using antiretroviral drug molecules of varied solubility and permeation profiles. A development goal would be to ensure that the WaferMat formulation is able to provide enhanced drug absorption and onset, reduced frequency of drug intakes, complete matrix dissolution with no remnants, a non-gritty mouth feel, and improved drug bioavailability. This would translate into lower drug doses required and a reduction in potential side-effects. A PCT patent application has been filed to protect the preliminary invention.

(Approximately 500 words)

6.* Public health need that the proposed project aims to address:
(Explain the public health need in terms of burden of disease; prevalence; incidence; fatality rate; geographical spread; current interventions and their limitations; and what proposed new technology would change in terms of disease prevention, control, diagnosis, treatment etc. If detailed information is not possible at present then please provide some basic level information)

According to the WHO, an estimated 3.4 million children were living with HIV at the end of 2011. A staggering 91% of these cases were in sub-Saharan Africa. Acquisition of HIV in children is generally from their HIV-infected mothers during pregnancy, birth or breastfeeding [1]. The HIV virus progresses rapidly in children - treatment is vital to the survival of infected children; without treatment, one third of children living with HIV will die in their first year of life, rising to almost half of the infected children by two years old. Many HIV-related deaths among children could be avoided through timely provision of effective care and treatment. International guidance recommends that, if HIV infection is detected in infancy, immediate antiretroviral therapy is crucial; currently most children entering treatment programmes are older, however. In 2010, an estimated 250,000 children died of largely preventable AIDS-related causes. The vast majority of these deaths were preventable, either through treating opportunistic infections with antibiotics or through antiretroviral treatment [2].
To achieve optimal drug therapy, patients must receive the right dosage at the most convenient dosing interval [3]. One of the major factors causing a suboptimal therapeutic outcome is the lack of patient compliance which is often due to inconvenient dosing systems [4, 5]. Among the various routes of drug delivery, the oral route continues to be the most preferred route due to ease, convenience, safety and lower costs associated with drug administration. Per-oral application of drugs via the gastrointestinal tract (GIT) may also have limitations such as a slow onset of drug action, and in many cases, incomplete and erratic absorption. This may be the result of hepatic first-pass metabolism, degradation by GIT enzymes, an acidic pH environment or the presence of microbial flora in the GIT. Such events often lead to a significant reduction in the oral drug bioavailability. Furthermore, patient compliance may particularly be a problem with paediatrics that cannot ingest tablets or capsules. Therefore the buccal route of administration may be a much more suitable option for sensitive antiretroviral drugs. The buccal mucosa is robust and shows short recovery times after stress or damage [7–9]. Drug absorption is facilitated by the continual washing action of saliva (0.5-2L/day) over the buccal mucosal surface. This route also allows for accessibility and easy removal of the system in case of an adverse drug reaction [10]. Furthermore, the drug is not subjected to the destructive acidic environment of the stomach and therapeutic serum concentrations can be achieved more rapidly. In addition, the drug enters the general circulation without first pass metabolism in the liver. A combination of these factors leads to higher bioavailability [6] and supports the buccal cavity as a highly feasible and rational site for systemic drug delivery [11].

For safety and acceptability reasons, the preferred route of drug administration in paediatrics is the oral route. However, the availability of formulations that are suitable for paediatrics is a major concern. In paediatric practice, many parents and healthcare workers struggle daily with oral drug administration to achieve the correct dose. The lack of suitable formulations has a negative impact on drug compliance and causes side-effects and therapy failures in children. The main issues in paediatric formulations are ease of administration (with taste-masking) and dose flexibility. In particular, the suitability of oral formulations for paediatrics suffering from HIV is even more challenging. In large children’s hospitals such as the Chris Hani Baragwanath Hospital in Soweto (South Africa) and the Rahima Moosa Mother and Child Hospital in Johannesburg (South Africa), more than 90% of the paediatric HIV patients admitted are under 6 years of age. Due to the need for flexible dosing and the danger of choking associated with swallowing tablets, oral liquids are broadly used. However, limited liquids are available commercially for paediatric use. In some instances paediatrics are administered powdered versions of adult tablets that are titrated with the child’s feed and lead to gross inaccuracies in dosing. Liquids also have disadvantages such as bad taste, limited stability and drug solubility problems. As an alternative, tailor-made capsules can be prepared, but this process is labor-intensive, inefficient and of varying quality. Capsules need to be opened and the contents dissolved before administration. This carries the risk of dosing errors, clogging of feeding tubes and bad taste.

This project therefore proposes the oral WaferMat formulation to significantly improve paediatric dosing by healthcare workers and caregivers to the HIV-infected paediatric patient, for enhanced patient compliance and an optimal therapeutic outcome.

References
7.* Explain which new and innovative approaches and mechanisms to supporting financing and coordination of R&D this project would demonstrate?

(This is a very important part to be filled. The idea of these demonstrations projects is "to address identified gaps that disproportionately affect developing countries, particularly the poor, and for which immediate action can be taken" (WHA66.22). 66th WHA considered these demonstration projects as part of the efforts to “take forward action in relation to monitoring, coordination and financing for health research and development”. The assembly decided to identify such projects that: “(a) address identified research and development gaps related to discovery, development and/or delivery, including promising product pipelines, for diseases that disproportionately affect developing countries, particularly the poor, and for which immediate action can be taken; (b) utilize collaborative approaches, including open-knowledge approaches, for research and development coordination; (c) promote the de-linkage of the cost of research and development from product price; and (d) propose and foster financing mechanisms including innovative, sustainable and pooled funding; (2) The demonstration projects should provide evidence for long-term sustainable solutions.")

Address research and development gaps:
This project aims to design and develop an ultra-fast disintegrating WaferMat formulation that utilizes and alternative platform with several differentiating features for optimal buccal administration of antiretrovirals in paediatric HIV. The proposed WaferMat formulation is designed for oral antiretroviral drug delivery directly into the systemic circulation via the buccal mucosa (inside of the cheek) and avoids the GIT issues as highlighted earlier. The WaferMat is envisaged to be a small (8x3mm²) disc-shaped formulation that can be placed on the inside of the cheek where it dissolves in less than 3 seconds. There is no risk of accidentally swallowing the WaferMat because it rapidly adheres to the buccal mucosa while dissolving. The antiretroviral drug is released and absorption occurs through the inside of the cheek and reaches the systemic circulation without drug been swallowed. This strategy is crucial since antiretroviral drugs have poor solubility and permeability when delivered orally to the GIT. There are a few orodispersible adult dosage forms
commercially available such as Clarityne RediTabs® and Zofran Zydis® for treating allergic rhinitis and nausea, respectively. However, with these dosage forms, the drug is swallowed and absorption occurs in the GIT. Furthermore, they are extremely expensive and are not affordable or suited for the average paediatric HIV patient’s caregiver living in South Africa. The WaferMat can be used as a drug carrier for paediatrics and can be produced inexpensively in small manufacturing pharmacies for paediatric HIV patients even in rural areas if required. The materials used to produce the WaferMat are all FDA-approved and inexpensively available.

**Collaboration:**
In order to bring this project to fruition, the project combines academic expertise in the field of oral drug delivery technology based at the University of the Witwatersrand (WADDP at Wits) in Johannesburg (South Africa), with industrial expertise in oral formulation production technology from the 2nd largest pharmaceutical company in South Africa, Adcock Ingram (Pty) Ltd. in Aeroton, South Africa, as well as clinical expertise in paediatric drug research, treatment for infectious diseases at the Chris Hani Baragwanath Academic Hospital in Soweto, South Africa, the Empilweni Services and Research Unit and the Department of Paediatrics and Child Health at the Rahima Moosa Mother and Child Hospital in Johannesburg, South Africa. The available knowledge reaches from small-scale drug delivery formulations to the industrial level and from *in vitro* studies to evaluation of prototypes in animals and eventually in humans (paediatrics).

**De-linkage of cost of R&D from product price**
We at the WADDP support de-linkage of the cost of R&D from product price. Our diversely acquired pooled financing would ultimately facilitate this approach. However, to further promote this concept, the creation of a fund approach or ‘research innovation prize’ which rewards R&D efforts and progress in creating novel delivery systems for improving the delivery of existing drugs would facilitate de-linking R&D costs from the product price.

**Financing mechanisms**
This is discussed under Section 17, pp. 18 and 19.

*(Approximately 300 words)*

8.* **Evidence of market failure/research landscape:**
*(Explain why there has been no investment in this technology or why investment has not resulted in access to the health care product.)*

The drug delivery system (DDS) landscape is highly competitive and rapidly evolving. The global market encompasses numerous start-ups and major players in the medical device, pharmaceutical and biotechnology industries. This is a market with intensive intellectual property protection. Products that have been brought to market or that are in clinical trials often involve combinations of technologies from multiple players, with complex licensing and strategic partnering relationships. Translation of this global landscape to the local drug delivery arena highlights that the South African DDS research landscape is still in its infancy and local Pharmaceutical industry investment in promising drug delivery technologies is decidedly scarce. Thus in our instance, investment prospects for this technology has been sought abroad, with some companies showing a keen interest (but no funding to date); however, more holistic funding, as provided by the WHO through this call, would be most preferable to see the described wafer technology progress from the stage of R&D to reaching the market and being exploited as an innovative local health care product.
The WaferMat addresses a number of market needs and could have an advantage over competitor drug delivery systems, which have the following disadvantages:

- Complicated manufacturing processes of these technologies lead to high manufacturing costs.
- An increase in clinical efficacy using current products has not yet been proven.
- Highly trained personnel are needed to manufacture these systems.
- These systems do not increase drug or dosage form stability.
- Additionally, the development of new drug molecules (NCEs) as potential antiretrovirals is a long, risky and expensive process.

The benefits provided by our technology addresses many of the issues mentioned above. However, there could be future intent to partner with competitors. Additionally the following advantages make this technology very attractive:

- Existing products could be re-launched by coupling them with a delivery system and/or new dosage form, rather than developing new antiretroviral molecules - this would not only create safer and more effective drugs, but would also significantly reduce development time, risk and costs.
- The basic platform on which the technology is based has been patented. The patents covers the technologies to include various configurations, manufacturing processes and a range of applications that is not only limited to the ‘proof of concept’ application in the pharmaceutical industry.
- The WaferMat technology is designed to be reliable, cost-effective, applicable and to “turn a buck” in the marketplace.

Figure 1 below shows the positioning of our technologies relative to other drug delivery technologies and current conventional dosage forms on the market.

Figure 1: Positioning of our WADDP technologies in the drug delivery market.
The importance of DDS from a commercial perspective is apparent from the resources that pharmaceutical and biotechnology companies dedicate to the function. Here are some examples of why pharmaceutical companies would want our product i.e. the WaferMat:

1. According to Pfizer’s Michael Flakus, manager of strategic alliances, the company has about a dozen business development personnel dedicated to the worldwide search for delivery technology to meet the need for external DDS and a large network of specialists within R&D with expertise to participate in the evaluation and selection of the optimal technology for successful formulation of a new compound. Pfizer often conducts multiple feasibility studies of candidate technologies to increase the probability of success and provide options for deal structure and negotiation with DDT companies.

2. Johnson & Johnson acquired Alza for close to $13 billion in the summer of 2001. According to Atul Ayer, Ph.D., of Alza, and an inventor on 86 oral controlled release patents, the acquisition was motivated not only by the desire to apply Alza’s established technologies to Johnson & Johnson’s portfolio of compounds, but for the general DDS expertise of its personnel. Alza’s DDS capabilities and expertise is now applied to Johnson & Johnson compounds starting from the early stages of drug discovery leading to the development of compounds and macromolecules as therapeutic agents. All Alza personnel are now dedicated to meeting the needs of Johnson & Johnson’s growing presence in pharmaceuticals, using their established technologies and complementary external technologies. Dr. Kiron, who is responsible for establishing Alza’s drug delivery research and external strategy says, "Alza looks to partner with external DDS firms to complement its own internal research activities to enable the efficacious delivery of Johnson & Johnson compounds.

Thus, although there has been no investment in the WaferMat technology as yet, this evidence and global market landscape inexplicably highlights the need that pharmaceutical companies have for innovative DDS, which the WADDP has the expertise to provide.

(Approximately 200 words)

9. The scientific and technical feasibility:

(Describe the scientific and technical basis for the proposed technology in terms of the state of the art e.g. candidate molecules; biomarkers; pipeline; previous efforts, if any, to develop same or similar technology etc. Include some risk analysis)

Scientific and Technical Feasibility

Despite many advantages, oromucosal drug delivery is faced with the disadvantage of poor permeation due to low drug flux. Low flux may lead to incomplete transmucosal diffusion thereby, leading to low levels of drug in systemic circulation. Use of permeation enhancers is a means of overcoming these problems [1]. Permeation enhancers are compounds that may promote or enhance the absorption of drugs through the mucosa, usually by reversibly altering the permeability of the barrier system [2,3]. Compounds that have been investigated include, but not limited to, ethers, cholates, aprotinin, azone, benzalkonium chloride, cetylperidium salts, cyclodextrins, dextran, chitosan, lauric acid and its salts, propylene glycol, phospholipids, menthol, salicylates, ethylenediaminetetraacetic acid (EDTA), sulfones and various alkyl glycosides [4]. Retention of dosage form at the site of
absorption is an important criterion which necessitates the use of bioadhesive polymers (e.g. polyacrylic acid, polyethylene glycol, polyethylene oxide, hydroxypropylcellulose, hydroxypropylmethylcellulose and hyaluronic acid) as well as hydrophilic polymers capable of gelling and swelling to enhance bioadhesiveness [5].

Successful treatment of medical conditions and/or disease is not only dependent on novel active pharmaceutical ingredients (API), but it is also dependent on providing novel and effective pharmaceutical dosage forms to ensure delivery of the API to the intended target site within the human or animal being treated. In order to achieve effective API delivery at the intended site due consideration must be given to where the intended target is within the body, and to the physiological obstacles that may prevent effective delivery via various routes of administration. Often the time taken for the API to reach its target site is also important. This is of particular importance in API’s that provide pain relief or allergy relief. Extensive research has been conducted in the field of biocompatible polymers which have been developed to provide effective pharmaceutical dosage forms. These polymers are then formulated into various solid dosage forms such as wafers, tablets and capsules depending on their physico-chemical and/or physico-mechanical properties. Wafer technology is already used within the pharmaceutical industry as a species of pharmaceutical dosage form. Wafers are typically used when needing to deliver API through the mucosal membrane of the mouth cavity. Essentially, the wafer incorporates at least one active pharmaceutical ingredient (API) to be released in use. When formulating wafers, one needs to consider several variables, including, but not limited to the fact that: the API should be rapidly absorbed through the mucosal membranes in the mouth via transmucosal absorption; wafer technologies typically attempt to deliver API’s that cannot be effectively delivered via conventional oral solid dosage (OSD) forms (for reasons including that the API has a low gastric bioavailability, and that normal OSD’s may result in nausea of the patient making them unsuitable); a low dose of the API is typically required since the dosage form is not subjected to passage through the entire gastro-intestinal tract; and rapid action is often required, especially where pain and/or allergy relief is required. Known wafer technology typically relies on the formulation of the active pharmaceutical ingredient (API) within a water soluble polymeric/excipient blend to dissolve rapidly in the mouth, thereby releasing the API for absorption and transport to its desired target. To be effective, the formulation requires that the following performance aspects are met: the polymers and/or excipients used to manufacture the wafer must be soluble at physiological temperature (about 37°C) without the aid of heating or stirring; the API taste must be masked by the excipients; the wafer should not be excessively hygroscopic and must have an acceptable shelf life; the total wafer size should not exceed a diameter of about 2 cm and the mass should be less than about 800 mg for ease of use for the patient; and the wafers should dissolve completely and leave no residue after disintegration.

The manufacture of rapidly dissolving dosage forms, particularly wafer type dosage forms, for the rapid release of active pharmaceutical ingredient remains a difficult task. The lyophilized polymeric matrices of the dosage forms are not robust and present difficulty in handling with a risk of breaking when taking them out from the packaging (typically blister packs). Therefore, a specialized peel-off packaging is required for the same which further increases that final cost of the product. The complete solubility of the matrix components is very important as a gritty feel would compromise patient compliance. The disintegration, dispersion, and dissolution of the matrix should be very fast in order to provide enhanced permeability and taste-masking.
Existing products on the market include the Zydis® technology, which has been used for a number of commercial products including Claritin® Reditab®, Dimetapp® Quick Dissolve, Feldene® Melt, Maxalt-MLT®, Pepcid® RPD, Zofran® ODT®, and Zyprexa®. The existing products are known to use active pharmaceutical ingredients (APIs) including for examples: oxazepam, lorazepam, loperamide, and enalapril.

There is a need for novel and improved pharmaceutical dosage forms in order to improve effective delivery of APIs.

The aim of this study therefore, is to design and develop a rapidly disintegrating wafer system that could permeate rapidly across the buccal mucosa for the treatment of HIV/AIDS in children, the greatest essence being to overcome the unfavorable disposition kinetics, side effects and the pharmacokinetic and pharmacodynamic impacts of the model antiretroviral employed, e.g. zidovudine (AZT). When in contact with saliva, the wafer undergoes rapid hydration and dissolution thus disintegrating within 3 seconds and releasing the AZT rapidly through the buccal oral mucosa. Dosage form components for the various wafer dosage forms, and their specific function(s) include soluble chitosan derivative polymer - carbamoylglycinated-chitosan (rapidly soluble polymer, unique soluble polymeric ester providing the fibrous matrix for rapid water channeling and directional flow); soluble matrix forming agent - hydroxypropyl cellulose (soluble polymer and robust matrix forming polymer); ester containing derivative of an acrylic polymer - ester containing derivative of sodium polyacrylate (soluble polymer; ester components for initiation of rapid solubility); filler substance – maltodextrin (soluble bulk filler component, cryoprotectant), anti-collapsing agent - Diglycine (microhardness providing agent and/or prevents collapse of dosage form); taste masking agent - hydroxypropyl-β-cyclodextrin (solubilizing agent, permeation enhancer, and taste masking agent).

References:

Risk Analysis
From techno-economic evaluations done, the wafer process technology is relatively straightforward consisting of one mixing step, a filtration, followed by freeze drying and packaging. As a consequence, it is estimated that the capital costs are low, dependant on the number of doses and dominated by the vacuum freeze dryer, the dosing unit and the packaging unit.

The conclusions from this analysis are as follows:
• WaferMat technology can be used competitively for all low volume (< 2 MT/annum) applications where the API cost exceeds $500/kg
• products made with the WaferMat™ technology may be competitive at higher volumes and dosages if they are presently patent-protected (and hence higher cost) or prepared in a form other than oral solid dosage
• the technology is not competitive against existing OSD formulations at larger volumes (>5 MT/annum) and lower API cost due to the high cost of lyophilisation (which scales linearly with capacity) and the added cost of the formulation ingredients

(Approximately 500 words)

10. Reasons for proposing:
(Provide details if any priority setting and/or selection criteria that has underpinned the consideration to take up this area of technology for development.)

Our technologies at the WADDP, such as the proposed WaferMat system, are based on 'Market-Pull' rather than 'Market-Push'. New classes of pharmaceuticals and biologics are fuelling the rapid evolution of drug delivery technology. The benefits from targeted, localized delivery of certain therapeutic agents, such as direct access to the bloodstream, as achieved by the WaferMat technology, is one driving force in this market. Additional drivers include the desire to eliminate or minimize the danger of needle stick injuries (and blood-borne pathogens) to healthcare workers, increase patient compliance by simplified or reduced stigma delivery methods, reduced healthcare worker involvement and reduced health care costs. Increasingly, delivery devices and drugs will be more tightly coupled. In some cases, device development is beginning as early as the discovery phase of the pharmaceutical development process. To compete in this arena companies must be able to demonstrate the value that their combination of drugs and delivery devices and/or systems brings to the market. To improve the odds of a successful product introduction, companies must be implementing advanced development and technology portfolio plans that define the technologies and delivery devices that will be funded. Because drug development can be a 10-year undertaking, advanced development and technology portfolio plans need to be concerned with market requirements and value propositions more than a decade into the future. Short-sightedness in focusing only on near-term shareholder needs in the face of numerous drug patent expirations while neglecting the emerging delivery trends will fail to maximize the value potential of these opportunities. The WADDP is essentially market-driven as we aim to identify and then address shortcomings or gaps in current and emerging drug delivery technology trends employing highly innovative, intelligent solutions, ultimately creating a niche for our technologies in the growing drug delivery research milieu. This project's overall objective is to optimize the delivery of antiretrovirals employed in the treatment of paediatric HIV/AIDS that is inadequately treated as a result of poor patient compliance and low bioavailability due to ineffective modes of drug delivery. The alarming statistics for the incidence of paediatric HIV in sub-Saharan Africa alone was an ardent stimulator for the design of an innovative and effective paediatric DDS.

(Approximately 200 words)

11. Who could potentially develop the technology/carry out the research?
(Provide known details: individual researcher? Group of researchers? Research/coordination organization including PDPs? Group of research organizations
The research will be undertaken by a group of researchers, based at the WADDP, or with strong collaborative ties with the WADDP, and will be coordinated as described in the table below. Following development of the WaferMat up to Stage 2, scale-up will be undertaken at Adcock Ingram (Pty) Ltd., marketing landscaping will be via Wits Commercial Enterprise (Pty) Ltd., and pilot human biostudies will be performed at AddClin (Pty) Ltd.; with the research team highlighted below involved in each stage.
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<th>Name and Surname</th>
<th>Institution</th>
<th>Role in Project</th>
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<tr>
<td>Professor Viness Pillay</td>
<td>Wits University, Department of Pharmacy and Pharmacology, South Africa</td>
<td>Principal Investigator - Prof. Viness Pillay has extensive experience in drug delivery technologies. In 1999 he served as a Senior Researcher in Formulation Development at Scolar Pharmaceuticals Inc. in Washington State, USA. Since then he has risen within the academic ranks of international institutions including an Associate Professorship at Florida A&amp;M University's College of Pharmacy and Pharmaceutical Sciences (USA) and currently as a Personal Professor of Pharmaceutics at Wits University. During his PhD candidacy and at Scola...</td>
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<tr>
<td>Assoc. Prof. Yahya E. Choonara</td>
<td>Wits University, Department of Pharmacy and Pharmacology, South Africa</td>
<td>Co-Investigator - Prof. Yahya E. Choonara is an Associate Professor in Pharmaceutics and a senior formulation scientist at Wits University in Johannesburg, South Africa. He is involved in translational research within the team and is one of the Editorial Board Members of the</td>
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Mr. Pradeep Kumar  
Wits University, Department of Pharmacy and Pharmacology, South Africa  
Co-Investigator - Mr. Pradeep Kumar is a PhD candidate and a Lecturer in Pharmaceutics as well as a Molecular Mechanist and Image Analyst. He has experience with formulation design in paediatrics and co-authored over 25 peer-reviewed papers. He is responsible for molecular blue-printing the WaferMat formulation. He will be involved in Stage 1 for mechanistic elucidation and energetic profiling of the permeation enhancers within the WaferMat formulation and assessment of the WaferMat molecular stability via structure and electrostatic potential mapping as well as Stage 2 in terms of molecular transitions of the WaferMat for ora-compatibility and durability. Input at Stage 3 and 4 is also required.

Prof. Ashraf Coovadia  
Wits University, Department of Clinical Medicine, South Africa  
Co-Investigator – Prof. Ashraf Coovadia is Head of the Empilweni Services and Research Unit in the Department of Paediatrics and Child Health at Rahima Moosa Mother and Child Hospital in Johannesburg, South Africa. The hospital is the one of the largest hospitals that deals with challenges of providing efficacious treatment to the largest global population of paediatric patients suffering with infectious diseases including HIV. He has longstanding expertise in clinical practice in paediatrics with HIV and has presented many keynotes on paediatric HIV
12. Who could potentially manufacture the final product?  
*Multinational company? Local production? Joint venture? How the decision will be made about the producer?*

All of our technologies are developed to the stage of preclinical testing in-house. Clinical testing, regulatory approval, scaling-up of manufacturing, and product distribution and marketing of the final product will be outsourced under an Academic-Industry Partnerships model for biopharmaceutical research and development, if applicable, or to the pharmaceutical company acquiring the full-product license. Suitable partners conforming to the Joint Clinical Trials Model; committed to Public Health Priority Studies; and interested in Health Research & Education Projects will be contacted and have been identified in this regard.

13. What could be the role of WHO, if any, in this demonstration project to bring this venture to fruition?

As the current research landscape has indicated, assistance is needed to bridge the gap between the R&D stages of our technology and the technology reaching the target market, due to the local DDS market still being in its infancy. Projects such as the WHO Demonstration Projects go a long way to realizing and addressing gaps in the availability of innovative health care technologies due to market failures. Support of this project by WHO would pertinently encourage Pharmaceutical Industry interest in assisting with bringing the WaferMat system to, initially, the South African paediatric HIV market, and ultimately globally. The industry has significant growth potential should it be able to address key health challenges such as HIV/AIDS. However, it can be expected that the financial sector will continue to regard the sector as high risk for some time to come. WHO-led planning and active support of the sector by the State (encouraged by WHO) may entice more development finance than is presently forthcoming, however the costs and policy consequences of this need to be considered. Industrial planning by the State should centre on fostering that legislative and business climate which can generate the finance that the sector needs. This would transfer the cost of financing from the initial funder to the private enterprise, which is better equipped to generate the finance and manage it.

14. Please outline a timeframe and projected milestones for the project covering the first 5 years. This should also highlight the immediate actions that need to be taken?
The aim of this project is to design and develop a polymeric formulation, in the form of a lyophilized wafer matrix, capable of providing ultra-fast buccal release of an antiretroviral drug for treating paediatric HIV. The formulation components will be selected to provide a synergistic rigidity profile forming a robust matrix with rapid dissolution properties. In addition, readily available and comparatively cheap raw materials will be employed for product manufacture. The manufacturing process will be scaled-up, while keeping all costs implicated in the process at a minimum. In order to achieve this aim the following objectives will be fulfilled over a period of 5 years in commensurate with the funding available. The following activities are implicit in designing a market-ready WaferMat formulation, with major objectives subsequently elaborated on:

- Pre-formulation
- Formulation and optimization
- Stability/quality control
- Product evaluation
- In vitro / in situ studies
- In vivo animal studies
- Pharmacokinetic analysis
- Product toxicity
- Process/scale-up
- Pilot human biostudies

**STAGE 1 (1.5 years)**

**Major objective 1:** Preparation and pharmaceutical evaluation of the antiretroviral drug-loaded WaferMat formulation employing a Design of Experiments (DOE) approach.

**Sub-activities for achievement of this objective:**
1. Computer-aided prototyping for preparation of a glycinated copolymer as the formulation matrix
2. Co-polymer synthesis and characterization via structural blueprinting
3. Conjugation of permeation enhancers and taste-maskers via Turbiscan® colloid stability analysis
4. Preparation of the WaferMat employing the engineered copolymer with antiretroviral drug-loading
5. Drug incorporation efficiency, matrix erosion, swelling and pre-optimized drug release studies
6. Box-Behnken formulation design template construction for WaferMat formulation optimization
7. Morphological characterization of the WaferMat employing Bench-Top MRI image mapping
8. Assessment of remnant detection of ultra-fast wafer disintegration via ZetaSizer NanoZS analysis
9. Textural profiling to determine the physicomchanical performance of the WaferMat formulation
10. In vitro release of drug from the optimized WaferMat employing tandem USP2 and UV analysis
11. Final pharmaceutical stability studies in order to proceed with in vivo drug release analysis

**STAGE 2 (1.5 years)**

**Major objective 2:** Ex vivo assessment and preclinical in vivo pharmacokinetic optimization studies on the antiretroviral drug-loaded WaferMat formulation in the Large White Pig animal model. Toxicity analysis is concurrently undertaken.

**Sub-activities for achievement of this objective:**
1. Ex vivo permeability studies for buccal permeation of antiretroviral drugs
2. Cytotoxicity studies employing a suitable cell line such as Caco-2
3. In vivo studies on healthy Large White Pigs for WaferMat formulation performance assessment
4. Harvesting and treatment of blood samples for antiretroviral drug concentration analysis
5. Vevo 2100® animal imaging of the bio-distribution and bio-erosion of the WaferMat formulation
6. UPLC assay development for determining in vivo concentrations of antiretroviral drugs
7. Histomorphological characterization of tissues post WaferMat formulation buccal administration
8. WinNonLin®-based pharmacokinetic modeling analysis

STAGE 3 (1 year)
Major objective 3: Market landscaping and process scale-up of the WaferMat formulation.

GMP manufacturing will be undertaken at Adcock Ingram (Pty) Ltd. (WHO accredited, 2nd largest pharmaceutical company in SA)

Sub-activities for achievement of this objective:
1. Intensive landscaping of the South African and global oral paediatric ARV DDS market – undertaken by Wits Commercial Enterprise (Pty) Ltd.
2. Compilation of a specific laboratory process description
3. Consideration of costs of all raw materials implicated
4. Definition of costs of overheads for manufacturing of the technology
5. Site availability for manufacturing the formulation
6. Equipment availability for manufacturing the formulation
7. Overall cost analysis of the entire large-scale manufacture of the WaferMat formulation

STAGE 4 (1 year)
Major objective 4: To perform pilot human biostudies as an in vivo comparison by means of volunteers serving as an in vivo dissolution model in order to ensure therapeutic efficacy in humans.

AddClin Research (Pty) Ltd. (c/o Adcock Ingram) will conduct Pilot Human Bio-Studies
AddClin will provide a complete turnkey project with no outsourcing
Addcock will provide us with their global Pharma networks for on-licensing of technologies

Sub-activities for achievement of this objective:
1. Preparation of required documents i.e. Protocol (signed at least by the principal investigator), Patient Information Sheet/Consent Form, Investigator’s Brochure, Subject recruitment procedures (e.g. advertisements)
2. Selection of subjects and sampling considerations (e.g. sampling times)
3. Administration of the WaferMat formulation to healthy subjects, blood sampling, and preparation for blood plasma analysis – to be outsourced to AddClin Research (Pty) Ltd.

(Approximately 200 words)

15. What is the intellectual property (IP) landscape relative to this project? Is there any IP, e.g. patents that need to be licensed in to be able to develop and market the product in developing countries? How would IP and related intellectual assets, including knowhow, proposed to be managed in this project?

The following IP landscape currently exists for the Wafer technology on which the WaferMat formulation is based:

Management of this Intellectual Property is crucial, and these activities will be focused on identifying and assessing pertinent IP emanating from the WADDP for statutory protection and commercialisation potential, possible infringements, management of funds and projects secured for drug delivery research and development activities; effective transfer of technology from WADDP to clients, and management of license, and other related deals. All new and novel developments will be protected, initially through the filing of South African Provisional patent applications. Trademark registration will be applied for in those instances where a suitable mark is designed for a product/process. Patent searches have been carried out for PCT application (International Search Report) from which it is concluded that the specific examples are novel and will not infringe other patents. A full freedom to operate review needs to be done when the products are closer to commercialisation.

(Approximately 400 words)

16.* What would be the strategy to ensure access to the product once it is developed?

(Access is an important dimension of these demonstration projects, it is important for the projects to begin with the end in mind, explain how this project would deliver the technologies to the needy patients i.e. price and affordability; modes of supply; storage; prescription; dispensing; and compliance; WHO will develop guiding principles for ensuring access to any products coming out of the demonstration projects)

Embodied within the aim of this project is the optimization of the performance of the incorporated ARV for paediatric delivery through proprietary wafer technology. There is a need to balance access to more innovative therapies (which would be at a slightly higher cost) with the need to maintain affordable health coverage. The ultimate goal is to bring currently available ARVs to market as a branded DDS with improvements to deliverability and effectiveness, as well as enhanced commercial potential. In order to make this project a success, access to the product will be achieved as follows:

**Price and affordability**

Low cost GRAS polymers, permeation enhancers and excipients will be employed. Techno-economic analysis and has been undertaken to provide an initial manufacturing process to minimise costs. The modeling has shown that the WaferMat technology is competitive for volumes between 100 kg/annum and 2 MT/annum.
**Modes of supply**
There are currently over 200 ongoing health partnerships with the pharmaceutical industry aimed at promoting health in developing countries such as South Africa through a wide range of access, capacity building and R&D programs. These were established with the overall goal of achieving the health-related Millennium Development Goals and focus on a wide range of priority health issues, which include HIV/AIDS. Such partnerships should be exploited to ensure and equitable supply of the manufactured WaferMat to hospitals, pharmacies and ARV clinics nationwide.

**Storage**
The WaferMat is a highly stable lyophilized system, which eliminates the stability concerns associated with the currently available suspensions, which also require refrigeration upon reconstitution. The WaferMat can be stored at room temperature following packaging in blister packs.

**Prescription and dispensing**
An improvement in prescribing and dispensing practices of paediatric ARV’s is anticipated. Patient counseling is facilitated through the availability of a paediatric dosage form that does not require reconstitution or storage in a fridge, and that promotes ease of administration to infants and children. Doctors will be encouraged to prescribe a dosage form with proven efficacy in attaining effective ARV drug levels (as per the results of preclinical studies and pilot human biostudies).

**Compliance**
A significant advantage of the proposed WaferMat technology is its potential to significantly improve patient compliance due to the ease of administration to the paediatric patient. The health care professional or caregiver need only place the WaferMat on the inside of the cheek of the paediatric patient (where in-built advanced mechanisms will allow immediate adhesion of the wafer to the buccal mucosa with ensuing dissolution of the wafer and permeation-promoted drug absorption). Accuracy of dosing is also pertinently improved compared to paediatric syrups or suspensions which are difficult to measure and may be spat out, or cause emesis on swallowing.

(Approximately 400 words)

17. **How could the project be financed paying particular attention to the need to demonstrate new and innovative forms of financing? Also provide an estimated cost of the project.**
The WADDP is a financially dependent entity of the university with incomes generated mainly by the former BioPAD (now Technology Innovation Agency - TIA) as well as NRF funding, grants, contract research and quality control and to a lesser extent by product development. Through our diverse financing channels, we are able to pool funding for 60%
(R3,000,000.00 / $302,679.00) of the overall project budget of R5,000,000.00 ($504,465.00), which would be allocated over the 5 years (4 Stages) of the project. Additional funding is required towards resource, expertise and research efforts necessary for progressing of the project outputs. The formulation, dosage form design and efficacy studies for the technologies simultaneously could involve a number of permutations that cannot be accurately expressed at this point in time. The table provided reflects the labour,
running and other costs for the technologies. CAPEX is also illustrated. The project budget requirements that we are requesting for funding is thus 40% (R2,000,000.00/ $201,786.00) of the overall project cost, and are given in the table below (costs are provided in South African Rands and US Dollars).

<table>
<thead>
<tr>
<th>Item</th>
<th>Budget*</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Human Resource Costs</td>
<td>20%</td>
<td>These costs comprise the &quot;Cost-to-Company&quot; for the time and expertise spent on the project by the project Principal Investigators as well as costs for employing Postdoctoral Fellows, Masters and PhD students to work on the project</td>
</tr>
<tr>
<td>Sub-total</td>
<td>R 400,000.00 ($403,572.20)</td>
<td></td>
</tr>
<tr>
<td>2. Running Costs</td>
<td>15%</td>
<td>These costs would cover the polymers, drugs, solvents, chemicals and other laboratory consumables required for completion of project and ensure delivery on all milestones</td>
</tr>
<tr>
<td>Based on average project expenditure to date @ R20,000/month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-total</td>
<td>R 300,000.00 ($30,267.90)</td>
<td></td>
</tr>
<tr>
<td>3. Costs for Equipment and Maintenance</td>
<td>10%</td>
<td>These costs have been budgeted for purchase for equipment maintenance, repairs and consumables that require regular replacement, calibration and replenishment</td>
</tr>
<tr>
<td>Estimated average maintenance costs of R8,000/month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-total</td>
<td>R 200,000.00 ($20,178.60)</td>
<td></td>
</tr>
<tr>
<td>4. IP Protection</td>
<td>5%</td>
<td>These costs provide for protecting the IP generated from the Platforms pipeline of technologies</td>
</tr>
<tr>
<td>Sub-total</td>
<td>R 100,000.00 ($10,089.30)</td>
<td></td>
</tr>
<tr>
<td>5. Overseas/local travel</td>
<td>10%</td>
<td>Marketing trips, additional ad hoc marketing information support and presenting to market/sell/licence the technologies to potential stakeholders.</td>
</tr>
<tr>
<td>Sub-total</td>
<td>R 200,000.00 ($20,178.60)</td>
<td></td>
</tr>
<tr>
<td>6. Overheads and Project Administration</td>
<td>5%</td>
<td>These costs comprise project administration (5% of project costs) and university overheads levies (25% of staff labour)</td>
</tr>
<tr>
<td>Sub-total</td>
<td>R 100,000.00 ($10,089.30)</td>
<td></td>
</tr>
<tr>
<td>7. Consultation</td>
<td>15%</td>
<td>These costs have been budgeted for consultation with experts on market landscaping and formulation scale-up</td>
</tr>
<tr>
<td>Sub-total</td>
<td>R 300,000.00 ($30,267.90)</td>
<td></td>
</tr>
<tr>
<td>8. Pilot Human Biostudies</td>
<td>20%</td>
<td>These costs comprise those implicated in AddClin (Pty) Ltd. conducting the pilot human biostudies</td>
</tr>
<tr>
<td>Sub-total</td>
<td>R 400,000.00</td>
<td></td>
</tr>
</tbody>
</table>
18. How could the project be governed and coordinated paying particular attention to the need to demonstrate better way of coordination?

Project co-ordination and administration

The project organization and management structure is the responsibility of Wits University and Wits Enterprise. Prof. Pillay, as Project Leader, will take full responsibility for the project. Prof. Pillay, together with a Steering Committee, will monitor the progress throughout the project duration, as well as during review meetings, to ensure good management. Prof. Pillay will inform WHO at the earliest stage of any potential problems that may cause serious delays or changes to the agreed schedule of activities. Overall administration, issues relating to legal and intellectual property matters, financial administration, co-ordination and submission of financial reports, and the payments to third parties will be the responsibility of Cristina Pinto, Business Development Manager at Wits Commercial Enterprise (Pty) Ltd. In 2002 Wits University identified a need to centralize consulting and research activities throughout the University in order to provide clients with easy access to the best possible combination of skills available. In addition it was recognized that academics were spending a large portion of their time on administrative and project management issues, which in turn impacted on their time spent on their core areas of expertise. Wits Enterprise was established to respond to these issues. Wits Enterprise is an autonomous, self-funding commercial company reporting into the University Research Office, and has specialist full-time staff to provide the requisite business, financial and administrative support base built on sound project management principles to ensure effective contract management and meeting deliverables on time and within budget. Project finances will be controlled using the Oracle, MS Project, and DevMan systems of the University/Wits Enterprise. Both Wits University and Wits Enterprise have auditors who monitor financial expenditure, with financial statements being prepared in accordance with generally accepted accounting practice. Administrative issues will also be discussed during review meetings and any differences in opinion or problems will be discussed and solved with proper consultation with the relevant parties. Interim reports on project activities and progress will be produced every three months, with full reports being produced at the end of the first year, and two months after completion of the project at 24 months. Minutes will be issued after Steering Committee meetings. All reports, communiqués, financial statements etc. arising from the project will be housed in project files, maintained by Wits Enterprise. Suitable precautions will be established for the protection of confidential information. Arrangements have also been made as part of the project plan to protect any potential intellectual property arising from the project activities. Decisions impacting on knowledge management and protection of intellectual property in the project will be undertaken by the project Steering Committee. Regular meetings, overseen by the project leader, will be held with the research team. This management oversight of the project will also ensure that information, knowledge and methodologies developed during the project are actively disseminated to all team members.
Technical management and oversight

Prof. Pillay will be responsible, overall, for the technical direction of the project and will coordinate the functions of the principal investigators and researchers, as well as ensuring that communication between all parties involved is facilitated. He, in collaboration with the other principal investigators and expert advisors, will ensure that the minimum research methodology standards are established and adhered to. Technical co-ordination will be facilitated by the existing standard operating procedures (SOP) been implemented in the WADDP research programmes. Students and staff members on all levels will be required to sign confidentiality/secrecy agreements regarding the technologies they will be involved in, as well as a comprehensive working contract for the duration of their contribution to the project will be agreed upon prior to any work been undertaken. All project data will recorded by students or staff members working on a particular technology, and a comprehensive report will be submitted to the Project leader on a quarterly basis or more frequently if required. Such data will be scrutinized by the principal investigators for any potential flaws that may arise and finally a final appraisal will be carried out by the Project leader. If the need arises the Project leader, in conjunction with the principal investigators, may call upon the research advisory panel if advice pertaining to key aspects needs to be solicited. Work will be published only once patents have been filed and all key stakeholders have agreed.

Project intellectual property and commercialization activities

There are existing and provisional patents for the WaferMat technology. Additional provisional patents on technology/application extensions may also be filed during the execution of the project. It is anticipated that arrangements with regards to background IP access and foreground IP sharing will be negotiated with WHO should this proposal be funded. Similarly, arrangements pertaining to a commercialisation vehicle for the technologies and/or products will also need to be negotiated. Preliminary discussions have taken place as to a suitable model for a commercialisation vehicle for project outputs. It is proposed a spin-off company may be ensued from the successes of this project. The background intellectual property could then be exclusively licensed to the new venture, with foreground intellectual property vesting in the company. Although no budget allocation has been made as part of this proposal for establishment of this company, or for retention of a suitably qualified individual to take responsibility for commercialisation of the developed drug delivery technologies and associated products, it is proposed that if WHO decides to fund the proposed work, in-depth discussions will take place between WHO relevant stakeholders, so as to expedite the establishment and funding of this commercialization vehicle as currently being done with the mature technologies of the WADDP.

(Approximately 200 words)

19. Have any donor agencies/governments already indicated interest in supporting the project?

No.

(Approximately 200 words)