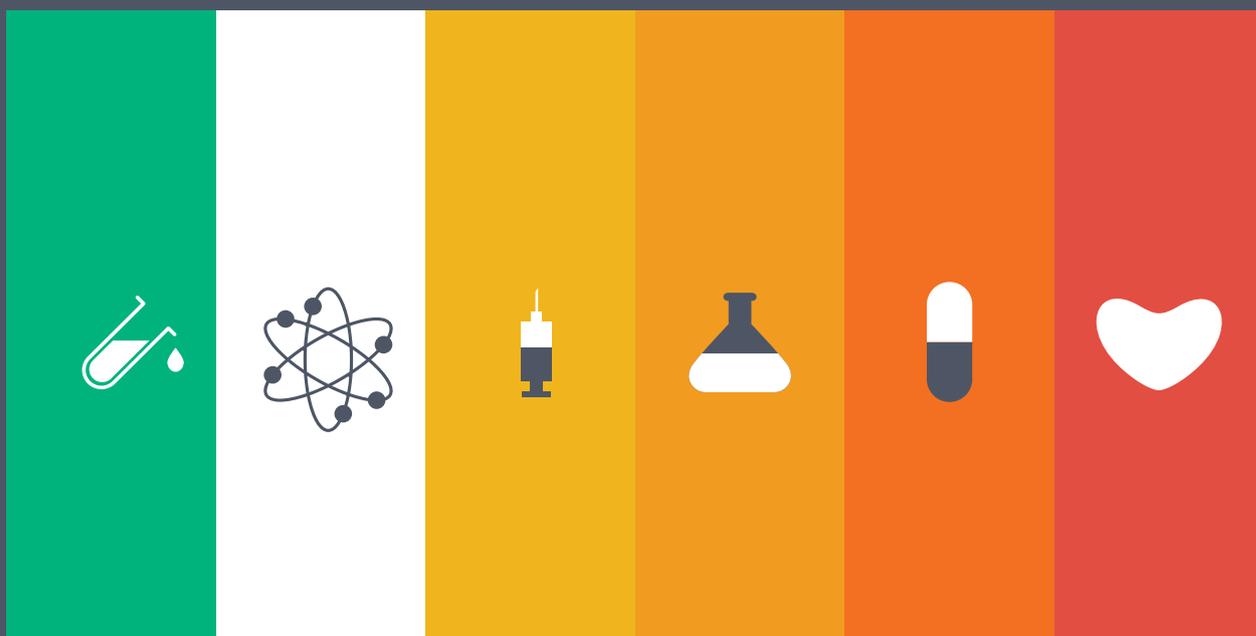




R-2-M

ROUTE-TO-MARKET GUIDE FOR INVENTORS



A UCT EDITION

Pharmaceutical Products

AN INNOVATION
GUIDE FROM LAB TO
COMMERCIALISATION

2018



About the Route-to-Market Series

The Route to Market (R2M) series is being developed by the Department of Research Contracts & Innovation (RC&I) at the University of Cape Town using funding from the Department of Science and Technology's National Intellectual Property Office (NIPMO). Each booklet focuses on a specific sector/product type and highlights the key steps and considerations in bringing such a product to market in that sector – with an emphasis on the local South African context. The hope is that this and other booklets will be useful to both Researchers and Innovators, as well as Technology Transfer professionals working at institutional Technology Transfer Offices (TTOs). The books have been released under a Creative Commons license to enable

other institutions to customise them for their own use.

Technology Transfer professionals generally have to deal with a multitude of inventions that span a broad range of categories. This can be challenging for new entrants to the field as well as to those whose invention falls into a 'new' sector that the TTO has not previously worked in. Researchers are often unsure of the steps that lie ahead in the areas of development and innovation that follow once their research has been completed. As the support for creating impact from research outputs grows, Researchers are increasingly finding good sources of innovation funding.

Hardcopies of this and other publications may be obtained at cost by contacting innovation@uct.ac.za. A number of sector experts have provided RC&I with material and we are grateful to them for their valuable contribution.

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TABLE OF CONTENTS

1	INTRODUCTION	3
2	STAGES OF DRUG DISCOVERY AND DEVELOPMENT	4
3	TECHNOLOGY READINESS LEVELS	10
4	UCT'S INVOLVEMENT IN THE DRUG DISCOVERY PROCESS	11
5	COMBINING EFFECTIVE IP PROTECTION AND PUBLICATION: THE UCT STRATEGY	14
6	ROLE OF THE TECHNOLOGY TRANSFER OFFICE	18
7	SEED & INNOVATION FUNDING	21
8	COMMERCIALISATION FROM A UCT PERSPECTIVE	22
9	PATENTING AND DATA EXCLUSIVITY AS PROTECTION STRATEGIES	24
10	KEY CONSIDERATIONS IN SETTING UP CLINICAL TRIALS	25
11	ETHICS	29
12	REGULATORY ISSUES	30



1 INTRODUCTION

This guide provides information on the steps involved in taking a new pharmaceutical drug to market. During a National Intellectual Property Management Office (NIPMO)-funded project in which Dr Richard Gordon reviewed the pharmaceutical portfolio at the University of Cape Town (UCT), it was evident that UCT was patenting too early when compared to industry.

This, coupled with a slower progression to market entry, shortens the patent life that remains when the new drug eventually reaches the market, which significantly reduces the value of the intellectual property (IP). A strategy has been developed to overcome this, which is described in this guide.

It was also found that in many instances different research groups were building expertise related to screening the potential drugs for their efficacy / properties, which itself took time and slowed progress. To avoid this, it is preferable to outsource these key tests and make use of platforms such as the H3-D Drug Discovery and Development platform hosted at UCT.

“Biopharmaceutical Research & Development: The Process Behind New Medicines” is an excellent external guide that has been produced by the Pharmaceutical Research and Manufacturers of America (PhRMA) and is a valuable reference that has been drawn on in preparing this guide.¹

Over just more than the last decade, there has been a significant trend in the pharmaceuticals sector, where companies have consolidated

and curtailed research and development (R&D).

Drugs are costing ever increasing amounts to take through the regulatory hurdles and into the market. To improve their profitability, companies have looked to more of the high-risk early stages of new drug discovery, opening up opportunities for universities.

This high-risk space is ideal from an academic research perspective and it is generally grant-funded by government and philanthropic individuals/organisations. Pharmaceutical companies can then cherry-pick promising drugs to augment their pipelines, cofunding further research and establishing collaborations with leading research groups.

Another trend has seen pharma companies buying small biotech companies who have sufficiently derisked new drugs. The biotech companies raise funding to develop promising compounds outside a university environment and look to focus on test work and research that will sufficiently derisk them, making them attractive to next-stage investors or pharma companies.

“Derisking” primarily involves proving the drug's efficacy and safety.

Biotechs can create significant value by merely moving a drug closer to the market but without ever getting physical products onto a truck.

Strategic patenting and the granting of patents when associated with leading compounds also significantly increases value.

¹ http://www.phrma.org/sites/default/files/pdf/frd_brochure_022307.pdf

2 STAGES OF DRUG DISCOVERY AND DEVELOPMENT

2.1 Overview

The Pharmaceutical R&D process is a well-validated process (Figure 1) during which new drug candidates are discovered as active compounds in biochemical assays and are developed into life-saving medicines. Most compounds are synthesised, and companies often have extensive libraries of compounds that are screened for efficacy. Often a robot-assisted, high-

throughput screen is used to find the “needle in the haystack”.

Bringing a new drug to market is a lengthy process which requires the skills of a number of scientific teams working together to deliver a desired outcome. The mechanism of the drug's action needs to be understood. Globally, this is a highly regulated industry that is carefully controlled in the interest of public safety.

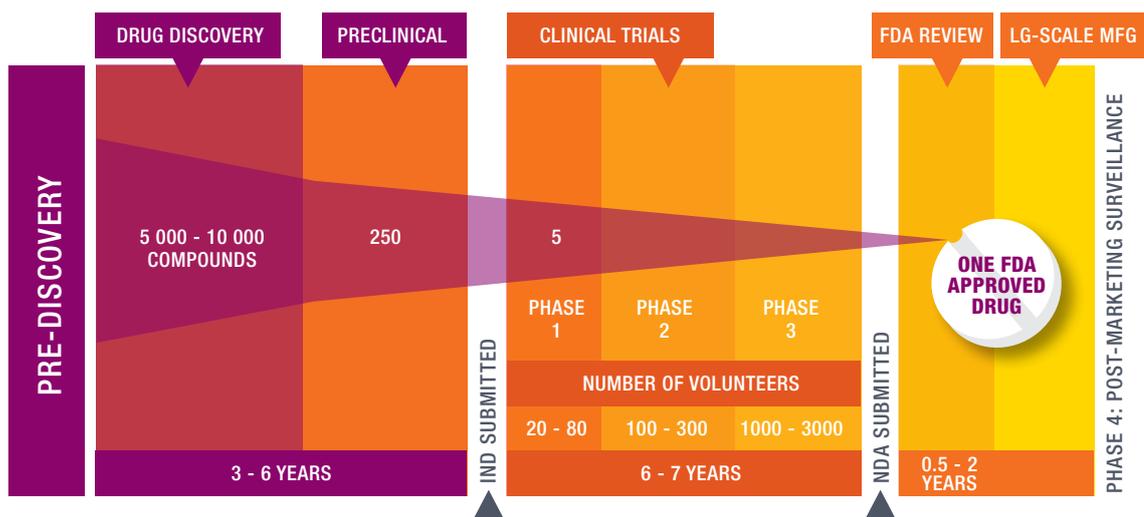


Figure 1: Drug Discovery and Development: A long, risky road (based on PhRMA drawing)

A key part of this is the use of biochemical assays to identify active compounds. At the end of the process the final product is highly purified, standardised and tested.

A consequence of the high-level legislative regulations and the fact that the mode of action is often poorly

understood, the process of getting a drug from the ideation phase to commercialisation is a difficult one. A number of studies have shown that on average around 14 years is required to complete the process. This is assuming that certain efficiencies are involved. Unfortunately, university systems operate at a sub-optimal efficiency with the net

¹ http://www.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf

result being that the process typically takes longer there.

The high cost of development is another reason very few drugs reach commercialisation. The cost of getting a single drug to the market is around US\$150 million. If one includes the cost of failures along the way, this amount can be as large as US\$800 million.

The ability to patent a drug is, therefore, paramount for successful commercialisation. Any disclosure prior to patenting destroys the patentability. The knock-on effect is that a pharmaceutical firm cannot recoup its investment in the drug and hence would not invest in its development. Often philanthropic researchers have thought that by strategically publishing to prevent patenting would ensure accessibility to the drug. But without the patent protection to give a pharmaceutical firm even a modest opportunity to recover costs, the drugs just do not make it to market.

Manufacturers of generic drugs hover in the wings, waiting to launch their alternative products the moment a patent expires. But these manufacturers are often reliant on the data that the original manufacturer submitted to the regulator, e.g. the FDA.

The FDA have, depending on the length of the regulatory process, restricted access beyond the patent life which also gives the primary manufacturer more time to enjoy market exclusivity. In contrast, the clinical trial is more about efficient operations and 'translation.' Clinical trials distinguish themselves from other industries with regard to late development stages as they are

characterised by extensive product evaluation and testing, external market approval in a highly regulated environment, a complex stakeholder setup in an iterative network model, a high relevance of the speed to market, and extremely high R&D expenditure.

There are three key value inflection points along this process. The first is at the end of preclinical trials where initial proof of concept needs to have been established. The second follows first phase data, which establishes or proves the concept. Finally, receiving regulatory approval is the last inflection point. Typically, at this point the drug enters large scale manufacture before entering the market.

2.2 Drug Discovery

This is a generic term summarising the activities of Hit-to-Lead (H2L) and Lead Optimisation (LO). H2L is the process where compounds display some activity against a chosen organism (or molecular target) and a series of compounds are synthesised to explore whether this is a general phenomenon associated with each chemotype. This process typically requires a team of 3-4 experienced chemists, working on several chemical series, in parallel. At the end of H2L, preferred series are chosen to progress into Lead Optimisation (LO).

It is very unlikely that projects entering the LO would be a perfect drugs, as fewer than 1 in 20 programs progress to any degree. LO is a process whereby each chemical series of interest would be optimised by medicinal chemists who would attempt to improve certain features of the lead compound. These optimisations would typically include:

- Increased potency of the chemical series (and preferably a back-up series as well).
- Enhanced physicochemical properties of the molecule including (for example):
 - o Solubility
 - o Metabolic stability
 - o Toxicity: cellular, genetic, cardiac and cytotoxicity
 - o Permeability
 - o Plasma Protein binding

This LO process would require a large number of iterative compounds to make test cycles involving integrated teams of medicinal chemists, biologists, pharmacologists and computational chemists. LO projects typically take 12-18 months to complete with a team of 8-10 scientists. Typically, 1 in 5 LOs are successful where a lead compound series is established with sufficient target potency, selectivity and a favourable pharmacological profile.

One or two compounds would then be proposed for drug development. The best of these is generally called the “lead” compound while a “backup” compound, commonly from a different chemical class, would be developed in parallel. Patents are usually filed at the END of LO.

2.3 Pre-clinical activities

For the compound to enter the market, it needs to undergo pre-clinical development and human clinical trials – a process which typically takes between 6 and 8 years. The product, if successful in Phase I development, will then undergo Phase II and III studies. Pre-clinical activities are routinely carried out to address:

- Toxicology
- Drug Metabolism and Pharmacokinetics (DMPK)
- Formulation studies

- Active Pharmaceutical Ingredient (API) production
- Product Registration (Medicines Control Council (MCC) for clinical trials).

Phase I /First in Man (FIM) studies:

These studies are carried out to ensure compounds are safe in humans and that blood levels are achieved for them to have a therapeutic effect. Patients will be monitored to evaluate if any side effects are present and that doses are tolerated.

The Budgets for these activities are typically:
Pre-Clinical studies: R15m-R20m per compound

First in Man Studies: R5-R10m per study

Phase 2 study: R50-100m*

Phase 3 study: R300-500m*

* conservative estimates.

ADME and toxicity

During pre-clinical testing ADME testing is a key requirement. In vitro ADME (Absorption, Distribution, Metabolism and Excretion) studies have long played a critical role in optimizing both pharmacokinetic (PK) and pharmacodynamic (PD) properties of drugs, thereby decreasing attrition rates in drug development.

Because transporters regulate the cellular entry and exit of most small molecules, they are critical determinants of every aspect of drug ADME properties. In particular, many new molecular entities (NCEs) synthesised today are hydrophilic compounds with low cell membrane permeability, which are more dependent on transporters to achieve acceptable bioavailability, desirable tissue distribution, and optimized PK profiles.

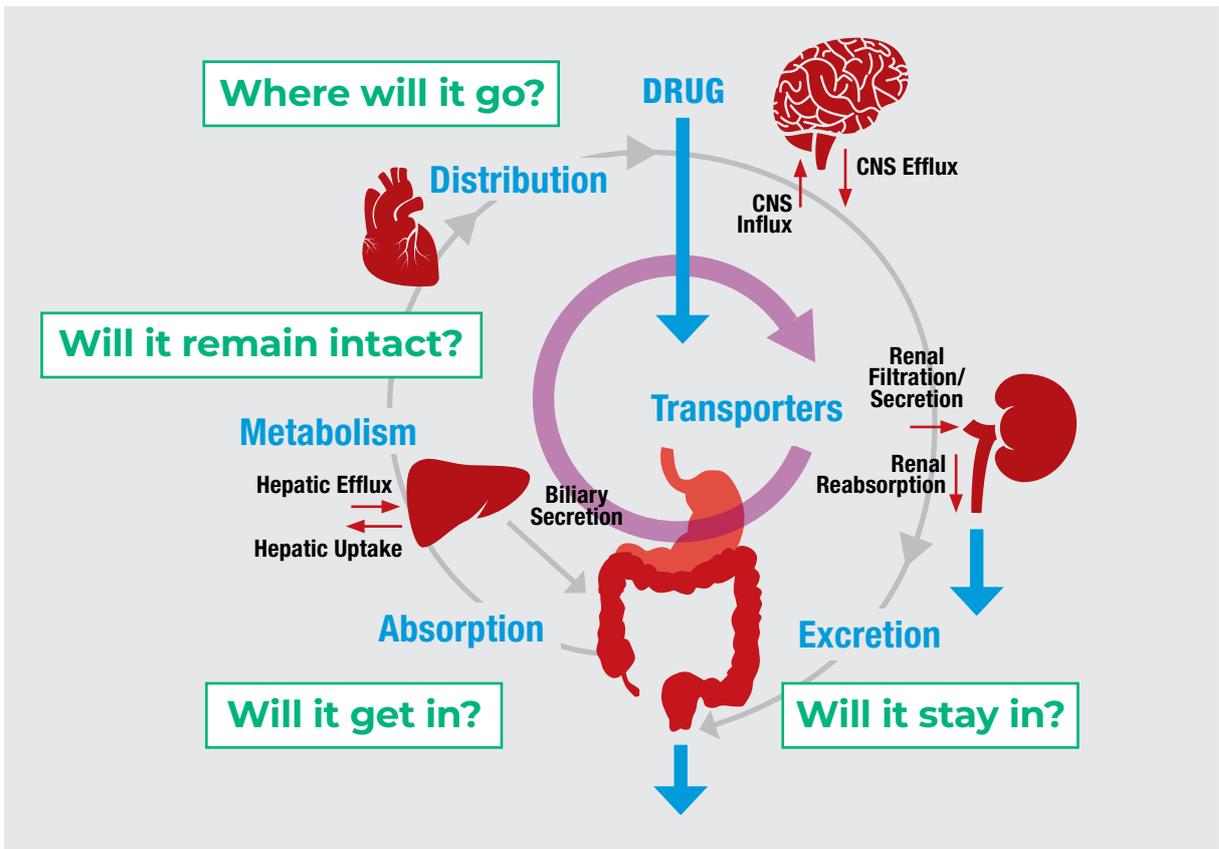


Figure 2: Transporters are key determinants of drug ADME properties.

Animal trials

By law, all new medicines must first be tested on animals¹ to ensure patient safety and are referred to as “pre-clinical” trials. When these tests have been shown to be successful, clinical trials will be conducted on humans.

It is important to note that animals are only used in medical research when absolutely necessary and unavoidable - after ethical review and in situations where appropriate alternatives are not available.

UCT has an Animal Research Ethics committee that operates separately from the Human Research Ethics Committee.

Often specific animal models are developed to study the drug’s action in terms of controlling a particular disease.

2.4 Clinical trials

Clinical trials are typically a highly dynamic and competitive environment that requires a complex network of stakeholders and alliances. There are four main ‘actors’ to be considered:

- Trial sponsors – most often pharmaceutical companies
- Sites – mostly hospitals or clinics
- Subcontractors – often research organisations
- Patients

¹ <http://www.abpi.org.uk/our-work/mandi/Pages/animals-research.aspx>

These trials can take between 6 and 7 years. Throughout this period, all these actors depend on each other to conduct ethical and efficient work.

It is during this time that formal go/no-go decisions are made with respect to drug testing. Most clinical trials happen in three phases. We take a more detailed look below:

PHASE	PHASE I	PHASE II	PHASE III
Duration	6 months to 1 year	1-2 years	2-5 years
Patients	<100 Healthy subjects or patients with the target disease	100-500 Patients with the target disease	500-5000 Patients with the target disease in multiple centres
Scope	Determine the safety and tolerability over a wide range of doses Define a pharmacokinetic profile of the drug Obtain preliminary pharmacodynamics evidence	Assess the effectiveness of the drug (pharmacodynamics) Assess the dose(s) for phase III and the frequency of administration Determine the common short-term side effects and risks	Demonstrate the therapeutic efficacy, tolerability, and safety

Table 1: Summary of Clinical Trial Phases (Buonansegna *et al.* (2014)¹

Phase 1: Perform initial testing in a small group of healthy human volunteers

During this phase, the candidate drug is tested in people for the first time. This normally involves a cohort of about 20 to 100 healthy volunteers.

The main goal here is to establish whether the drug is safe for humans. In order to do this, researchers have to look at the pharmacokinetics:

- How is it absorbed?
- How is metabolised and eliminated from the body?

They also have to study the drug’s pharmacodynamics:

- Does it cause side effects?
- Does it produce the desired effects?

Phase 1 trials are closely monitored and aim to

help researchers determine whether a drug should move on to further development and what a safe dosing range would be.

Phase 2: Test in a small group of patients

During Phase 2, the candidate drug’s effectiveness is evaluated in a cohort of about 100 to 500 patients with the disease or condition under study.

Researchers also have the opportunity to examine any possible short-term side effects and risks that could be associated with the drug.

The aim is also to answer the following questions:

- Is the drug working by the expected mechanism?
- Does it improve the condition in question?

¹ <https://onlinelibrary.wiley.com/doi/epdf/10.1111/radm.12053>

The optimal dose strength is established and so are schedules for using the drug. If the drug continues to show promise, preparations are put in place for the much larger Phase 3 trials.

Phase 3: Test in a large group of patients

This phase is all about generating statistically significant data about safety and efficacy. Research is conducted in a large cohort of patients, numbering between 1,000 and 5,000.

Phase 3 is key in establishing whether the drug is truly safe and effective and also provides the basis for labelling instructions.

Unsurprisingly, these trials are the longest and costliest, as they typically include hundreds of different sites across the country and even internationally. Coordination of sites and data is key and makes for a rather monumental task. Simultaneously, researchers will also be conducting many other studies required for FDA approval. These may include plans for full-scale production and preparation of the complex application.

Chemical Process Scale-Up

Another important aspect that will not be covered in this booklet, but may be in another R2M booklet in the series, is the scale-up of the manufacture of the actual pharmaceutical product. Pharmaceuticals are generally made through extraction from, or purification of a natural resource (e.g. a medicinal plant) or chemically synthesised, or biologically synthesised, e.g. as a natural product of a microorganism, or expressed by genetically modified microorganisms that will produce products (often

proteins) from a range of expression platforms, such as mammalian cell culture, yeast or *E. coli* fermentation or through transient expression in plants, such as tobacco.

Whilst one is working through the pre-clinical stage the chemical or biological process needs to be scaled-up to ensure that sufficient quantities of the active pharmaceutical ingredient (API) can be produced to support commercialisation. This is where techno-economics will play a role in selecting synthesis routes from a number of different options, in terms of the number of steps involved (the fewer the better) and the yields at each stage and the complexity of operation. Disasters have happened where one of the enantiomers or isomers of a molecule can be beneficial to health and the other deleterious.

As part of the process development, the impact of variations in raw materials will be understood, different sources evaluated and specifications for them drawn up. It is likely that the API will need to be formulated with other ingredients to produce the final product – often dependent on the mode of delivery (inhaled, tablet, capsule, injectable, drip, etc.) and to improve shelf life. Both cold-chain requirements and shelf life studies would also be required and form part of the dossier that is ultimately submitted to the regulator.

APIs need to be produced under Good Manufacturing Practice and often for clinical trials, the manufacture of batches of test product will be outsourced to a suitably certified facility to manufacture on a “toll” basis.

3 TECHNOLOGY READINESS LEVELS

Technology readiness levels (TRL) are a method of classifying technology maturity as one moves from TRL 1, where the research had been initiated to TRL 9, where the technology has been commercialised and has been in the market for some time.

RC&I developed the table below, which provides definitions of technology maturity at each TRL in a number of different sectors. Funders are increasingly using TRLs to describe the target of the funding that they provide and

also to understand the level of maturity that will be reached once a funded project has been completed.

TRLs are useful, as one can classify a project within UCT and understand the steps that need to be taken to bring a product or service to market.

TRLs were conceived by NASA¹ and their current nine-level scale has gained wide acceptance.

Level	TRL 1	TRL 2	TRL 3	TRL 4	TRL 5	TRL 6	TRL 7	TRL 8	TRL 9
Science & Engineering	Basic Idea	Concept Developed	Experimental Proof of Concept	Lab Demonstration	Lab scale validation (early prototype)	Prototype demonstration	Capability validated on economic runs	Capability validated over range of parts	Capability validated on full range of parts over long periods
				Component and/or system validation in laboratory environment	Laboratory scale, similar system validation in relevant environment	Engineering/pilot-scale, similar (prototypical) system validation in relevant environment	Pilot system demonstrated	System incorporated in commercial design	Proven system ready for full deployment
Software			Software to test and evaluate basic concepts on simple model problems representative of final need.	Escalate model to more realistic representation of industrial system. Confirm basic formulation.	Model contains all major elements of need. Solve industrial strength problems by code developers OR achieve functionality by expert users. Document performance. GUI.	No specialist intervention required from programmers/developers. This includes basic GUI interface. If required, programming to be according to ISO standards.	Install, run and evaluate software in actual goal environment (e.g. prospective client's computers). Demonstrate use by clients	Evaluation done by target representative clients on representative hardware platforms. Complete GUIs, users manuals, training, software support etc. Typical user driven "bug hunting"	Product proven ready through successful operations in operating environment.
Medical Science	Basic Research		Preclinical Research		Late Preclinical Research	Phase I Trials	Phase II Trials	Phase III Trials	Phase IV Trials
Phase	Research			Translation/Development				Commercialisation	

Figure 3: Technology Readiness Levels

¹ You can read more on the NASA website: https://www.nasa.gov/directorates/heo/scan/engineering/technology/txt_accordion1.html

4 UCT'S INVOLVEMENT IN THE DRUG DISCOVERY PROCESS

Whilst UCT does not take a drug right through to market, different groupings within UCT actively participate in all the stages of drug discovery and development, which is shown in Figure 4. A significant amount of funding coming into the university is related to clinical trials that are undertaken.

These clinical trials attract top international academics who work with global pharmaceutical companies and importantly provide access to drugs and treatments that may not have been otherwise available to patients in the Western Cape.

These are a few of the groupings participating in drug discovery and development at UCT:

IDM

The Institute of Infectious Disease and Molecular Medicine (IDM) is a trans-faculty, multidisciplinary postgraduate research enterprise that operates in the fields of infectious disease and molecular medicine research. It is distinguished by the ability to drive world class research at the laboratory-clinic-community



interface by engaging a wide range of scientific and clinical disciplines.

Together, the Members of the IDM represent more than 20 research groupings of varying size, scope and type.

These include:

Three multi-investigator groups that operate in the TB/HIV space

- The Clinical Infectious Diseases Research Initiative (CIDRI)

- The Desmond Tutu HIV Centre (DTHC)
- The South African Tuberculosis Vaccine Initiative (SATVI)

Four extramural units of the South African Medical

- Research Council (MRC)
- Immunology of Infectious Diseases Unit
- Drug Discovery and Development Unit
- Molecular Mycobacteriology Research Unit

Within UCT itself:

- Human Genetics Unit
- The Centre for Computational Biology (CBIO)
- The Biopharming Research Unit
- The Structural Biology Research Unit
- The UCT node of the DST/NRF Centre of Excellence for Biomedical TB Research

H3D Drug Development & Discovery Centre

H3D is an accredited University of Cape Town research centre within the Faculty of Science. It has strong affiliations with the Faculty of Health Sciences and, more specifically, the Division of Pharmacology and the Institute for Infectious Diseases and Molecular Medicine (IDM). H3D operates within UCT's world-class translational medicine research environment. H3D is Africa's first integrated drug discovery and development centre. The Centre was founded at UCT in April 2011 and pioneers world-class drug discovery in Africa. It focuses on the identification of new drug candidates to combat diseases such as malaria and tuberculosis, but also the development of African scientists.



Founder, Prof Kelly Chibale says that historically, several factors have hampered African-led innovation in drug discovery. Among these was the absence of a critical mass of appropriately skilled scientists, along with poor access to infrastructure to enable technology platforms and expertise.

Scientific Computing

The Scientific Computing Research Unit (SCRU) directed by Prof Kevin Naidoo is built from the following laboratories:

- Computation & Modelling Laboratory¹
- Cancer Translational Science Laboratory²
- Informatics & Visualisation Laboratory³

The SCRU's research groups are mostly interested in the development and application of methods useful to Life Scientists and Material Scientists.

They develop computational and informatics software, using methods in applied mathematics and physics to construct algorithmic solutions useful to chemists and biologists.

The Cancer Translational Science Laboratory applies the computation and informatics technologies to provide models for experimental scientists aiming to achieve Translational Research goals in medical and chemical science.

Visit the Scientific Computing website for more details⁴.



Pharmacology

UCT's Pharmacology division provides a clinical and laboratory service to Groote Schuur hospital, as well as secondary and primary centres.

Some of the services it offers include:

- Therapeutic drug monitoring with input from clinical pharmacologists for a wide variety of drugs, including antiretroviral and anti-tuberculosis drugs
- Clinical consultation to regional hospitals
- Policy advice in the rational and cost-effective use of drugs for local hospitals, the Western Cape Provincial Coding Committee, the National Essential Medicines List Committee, and international guidelines on HIV, TB, and malaria.
- Pre-clinical and clinical research focused on drugs for malaria, tuberculosis, and HIV.

The division also contributes to national medicines regulatory and pharmacovigilance activities of the Medicines Control Council and internationally through the Uppsala drug safety monitoring centre.

The Medicines Information Centre provides a telephonic consultation service for healthcare professionals and runs the National HIV & TB Healthcare Worker Helpline. The division produces the South African Medicines Formulary, currently in its 12th edition.

The research in these fields is broad and encompasses drug discovery, pharmacokinetics and pharmacodynamics, pharmacometrics, pharmacogenomics, clinical trials, pharmacovigilance, and pharmaco-economic evaluation.

¹ <http://www.scientificcomputing.uct.ac.za/scru/research/computation-modelling/>

² <http://www.scientificcomputing.uct.ac.za/scru/research/cancer-translation-laboratory/>

³ <http://www.scientificcomputing.uct.ac.za/scru/research/informatics-visualisation/>

⁴ <http://www.scientificcomputing.uct.ac.za/>



Figure 4: Key Phases in Taking a Pharmaceutical to Market.

5 COMBINING EFFECTIVE INTELLECTUAL PROPERTY PROTECTION AND PUBLICATION: THE UCT STRATEGY

5.1 When to patent? Managing the patenting/ publishing tightrope walk

In his 2014 review of the UCT pharmaceutical IP portfolio, Dr Richard Gordon concluded that UCT files patents several years too early, when compared to a pharmaceutical company's practice (Figure 5).

The difference stems from the need to publish in a university environment.

To meet the novelty requirement in patenting one needs to file a provisional patent application ahead of publication or public presentation of the work on which the invention is based.

Drug Discovery Value Chain

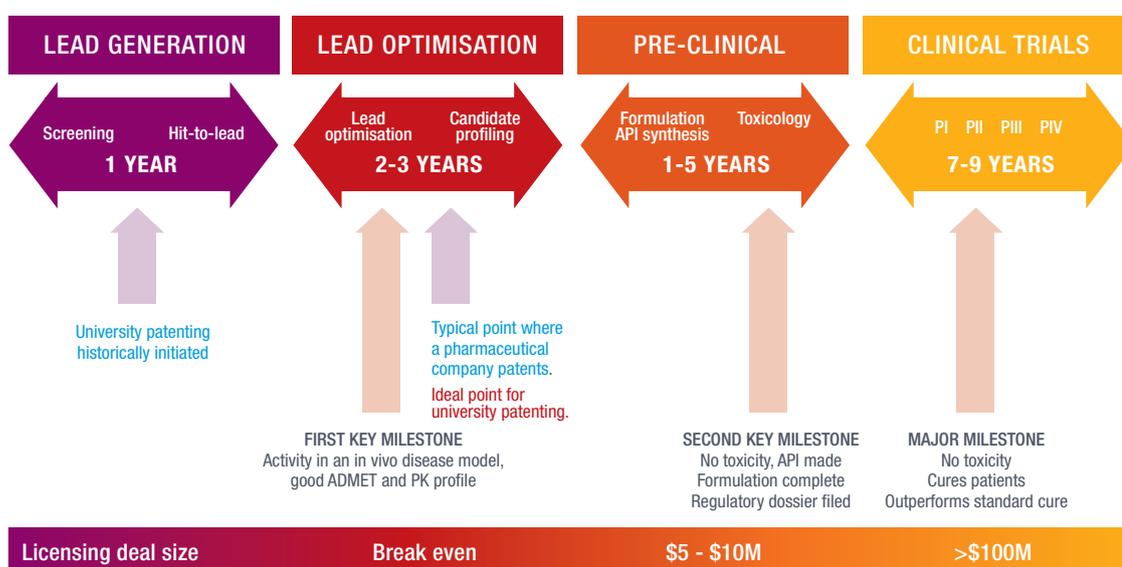


Figure 5: Industry vs University Patenting Point and Value Propositions

Early patenting negatively impacts the value of the IP by shortening the commercial life of the patent. A patent has a life of 20 years and it takes 12 to 15 years to get a pharmaceutical product to market. So, ideally one needs to patent as late as possible, else the commercial partner would only have as little as five to eight years in which to recoup their investments costs and generate a return.

One strategy to address this has been the introduction of a confidential thesis procedure at UCT, which enables a PhD thesis or and MSc dissertation to be maintained confidential for a period, whilst drug development is actively pursued, without impacting on the student's graduation.

The second strategy attempts to rapidly

determine whether there is any merit in protecting the IP by conducting the necessary screening tests (generally achieved in 3 to 6 months). If the outcome of the tests looks promising, then hopefully the researchers will see the benefit of delaying publication by a couple of years whilst development is fast-tracked; RC&I will assist with fund raising for the development work

and outsourcing to suitable service platforms. Once the provisional patent is applied for at the end of the fast-tracked development period, publication can proceed (Figure 6).

Should the initial tests prove negative, there will be no merit in protecting the IP and the publication can proceed immediately.

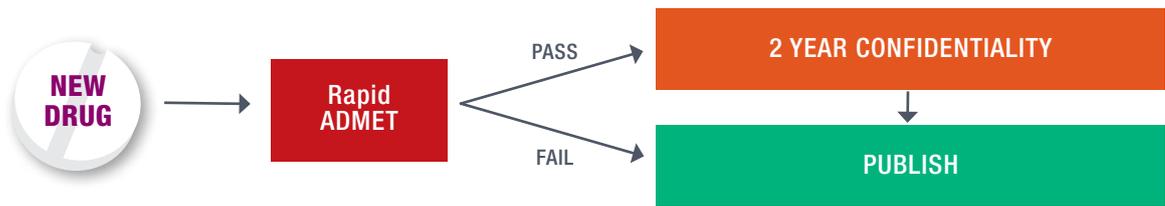


Figure 6: Assessment and Publish / Patent Decision

UCT’s Preferred Drug Development Strategy



5.2 Why file a patent?

In the pharmaceutical space there has been tension between patent protection of pharmaceutical drugs and affordable access especially in developing countries and for specific diseases (e.g. TB and HIV, etc.).

An issue is, however, that market protection is required to encourage a commercial partner to invest the significant amounts required to bring the drug to market, taking it through the regulatory approvals, building up a production facility and distributing the product.

A patent provides temporary protection

for the commercial firm, during which time they can recoup their investment. When patents expire, generic drugs are generally waiting in the wings and enter the market rapidly, significantly lowering prices.

UCT elects to file patents for HIV and TB-related drugs, in particular, as a means of ensuring the drug has the potential to reach the market and it permits the university to control the terms of the licensing deal. This is also in line with the Intellectual Property from Publicly Financed Research and Development Act, which requires UCT to protect and importantly commercialise IP emanating from UCT’s research wherever possible

– particularly where there is a societal benefit as opposed to a purely financial one.

Currently in South Africa, one would need to partner with a foreign commercial partner who has access to the funding required to bring a product to market. In licensing, UCT would seek to negotiate with the licensee to ensure that the drug was made available in South Africa and developing countries at an affordable price – especially to the public sector.

5.3 Patenting a drug

Details of the patenting process, the requirements for novelty, inventiveness and utility are available in both the UCT Inventors Guide and on the RC&I website: www.rci.uct.ac.za. They will not be dealt with here. Some specific issues will, however, be discussed.

Compound claims can be made quite broad by using a generic structure onto which different chemical groups can be substituted; these are known as “Markush” patent claims.

An example in Figure 7 taken from a UCT patent on dibemethins and their use as anti-malarials.

In subsequent, often dependent claims, one will seek to cover specific molecules that are regarded as leads in the drug discovery programme. One can then relate the use of the drug for application in the treatment or prevention of a particular disease, e.g. for use as an anti-malarial. One may also claim a pharmaceutical composition, in which the active is combined with pharmaceutical carriers, binders, etc. The formulations may also

be specific to the mode of intended administration.

Finally, if the method of synthesis is novel, that too may be considered for protection.

Need for Examples

For each of the “classes of variant” in a Markush structure one should have a representative example included in the patent specification to support the claims being made. Often inventors rely on the 12-month provisional period to complete the set of examples as they may not all be available at the time of filing the provisional patent application.

Exclusions

UCT filed a patent, which protected analogues of the natural molecule ajoene, which is found in garlic, for their anticancer properties. The natural

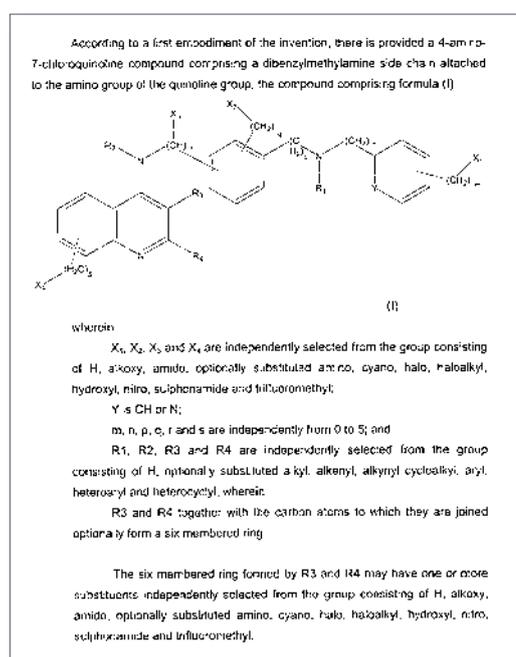


Figure 7: UCT Patent example

molecule was characterised and known, so was not included in the patent and a molecule that had been published as part of a thesis was also specifically excluded.

Should one protect drug targets?

Historically, patents tended to be filed for a drug target and, in UCT's case, crystal structures were protected for the Angiotensin Converting Enzyme (ACE) C and N domains.

This IP is profiled in our *Innovation at UCT 2010 book*¹, available as a download from the RC&I website. The real value lies, however, in the actual drugs that are developed based on the target.

In the case of ACE, it was developing novel C-domain-selective inhibitors – these inhibitors can be patented in their own right and two lead molecules have been patented.

An infringer of a patent can only be pursued once a patent has been granted, which can take more than four years. Typically, the university researcher would want to publish the new drug target as soon as a provisional patent application had been filed.

Drug discovery companies could use the target in their screening from the time that it is published and would likely have identified their lead molecules by the time the patent for the target actually came into force. It is only when the target has been kept confidential that it has real commercial value.

More recently, in line with international trends, UCT focuses patent resources on protecting the actual drugs that are developed, rather than the targets.

*A blog post by Joel Kirschbaum (UCSF Technology Transfer Director) provides insight into whether or not drug discovery targets identified through university research should be patented*².

Novelty Searches

An excellent resource on search for so-called "prior art", i.e. published literature and patents that could disclose your particular molecule(s), is Chemistry and Pharmaceuticals Searching Best Practices by Intellogist³:

They highlight the challenges that are encountered by a searcher, especially where Markush patent claims (as described above) are involved. With different naming conventions it is possible for a compound to also have more than one formal name, although this is often overcome by using the Chemical Abstracts Service (CAS) 10-digit unique compound identifier.

Chemspider⁴ is a free database, provided by the Royal Society of Chemistry, which collates chemical structure information from a variety of sources and also enables structure searches to be conducted by drawing your structure using several different types of on-line editor.

The European Bioinformatics Institute (EBI)⁵ also launched a free database that allows searches to be conducted on 15 million chemical structures.

Derwent, a proprietary patent database, which has had a long association with the pharmaceutical industry, uses specific electronic indexing of chemical formulae to facilitate searching.

¹ http://www.rci.uct.ac.za/sites/default/files/image_tool/images/100/innovation2010.pdf

² <http://mysdscience.com/group/scienceentrepreneurs/forum/topics/2110706:Topic:2035>

³ http://www.intellogist.com/wiki/Chemistry_and_Pharmaceuticals_Searching_Best_Practices

⁴ <http://www.chemspider.com/>

⁵ <https://www.ebi.ac.uk/chembl/search/>

6 ROLE OF THE TECHNOLOGY TRANSFER OFFICE

The Research Contracts and Innovation Department (RC&I) acts as the liaison between UCT's research community and the private sector with regards to intellectual property, commercialisation and business development activities. RC&I has helped to transfer numerous technologies from the university laboratories to industry both locally and internationally.

RC&I provides three key areas of support:

1. **IP Protection.** Assistance with the screening of research outputs and the protection of intellectual property (IP) generally through patenting;
2. **Technology Development (Innovation).** Fundraising to support the maturation of the technology, and outsourcing where necessary and moving the project through the various Technology Readiness Levels (TRLs); and
3. **Technology Transfer / Commercialisation.** Understanding the specific market that a drug will be entering (e.g. competitor drugs, etc.), marketing or advertising the IP both generally and to identified targets, e.g. to pharmaceutical companies whose product portfolios your drug will complement.

Funding: a fund is needed to develop projects to a point where they are commercially attractive. The fund needs to be sizeable, and flexible to drive projects forward quickly.

Outsourcing: The quickest way to progress a project and fill key information gaps is to outsource key components. Cambridge

Enterprise outsources most/all of these activities as this is seen as the most effective way to complete a pre-clinical dossier. Having experts do the work, in a quicker time should be seen as an investment in future returns and not a liability.

6.1 Intellectual Property (IP) Protection

RC&I assist researchers with the identification, review and protection of IP arising from their research and liaise with patent attorneys who are appointed by RC&I to prepare and file patent applications and manage the patent examination process. UCT has funding to support IP protection (which is supplemented by the National IP Management Office [NIPMO]) that is administered by RC&I.

Following disclosure of an invention to RC&I the patent process involves the filing of a provisional patent (which runs for 12 months), filing of a Patent Co-operation Treaty (PCT) international patent application (which lasts for 18 months) and finally regional and national phase applications which, following successful examination where applicable, result ultimately in granted national patents.

A patent's lifespan is 20 years, and this runs from the time of filing the full application (most commonly this is the PCT filing).

The patenting process is covered in more detail in the UCT Inventors Guide¹.

¹ http://www.rci.uct.ac.za/usr/rcips/ip/inventors_handbook.pdf

6.2 Technology Development

Outsourcing key components to access skills (for small studies) is a wise strategy and is simple to implement. For drug discovery, there are three key activities that need to be considered:

- *In vitro* ADMET: This is a minimum requirement and is cost effective. It gives a guide to the physicochemical properties of the molecule and highlights any issues that may be encountered. These properties include: solubility and cardiotoxicity (hERG), etc
Budget: R10-20,000.
- *In vivo* pharmacology (PK): This is a basic requirement, as it is simply not possible to make claims on the potency of a substance. Companies offering these services and include¹:
 - **Covance:** www.covance.com
 - **PPD:** www.ppd.com
 - **Parexel:** www.parexel.com
 - **Quintiles:** www.quintiles.com

The companies mentioned above are enormous global CRO's who focus mainly on clinical trials. They do however, do *in vivo* pharmacology.

- **BioFocus:** www.biofocus.com
- **Wuxi App Tech:** www.wuxiapptec.com
- **ChemPartners:** www.shangpharma.com/chempartner
- **Pharmacopeia:** www.pharmacopeia.com
- **Albany Molecular:** www.amri.com
- **Fideltia:** www.fidelta.eu/
- **Syngene:** www.syngeneintl.com

- *In vivo* disease models: Does it cure the disease in an animal model? Very few models are available in South Africa and would need to be outsourced globally. This study phase presents the key hurdle in determining whether a compound is worth patenting, as activity in the disease model is the value point of inflection. It is vital that the DOSE is known. Models can be carried out at Contract Research Organisations who tend to specialise in these areas. Prices vary considerably depending on the model, species of animal and number of animals used. For example: CNS and Alzheimer's experiments cost more than \$10,000 per compound, while Respiratory models cost \$7,000-8,000 per compound.

Examples of organisations include:

- **Argenta:** <https://www.argentaglobal.com/>
- **Asthma: Newcastle University, Australia**
<https://www.newcastle.edu.au/>
<https://www.newcastle.edu.au/highlights/our-researchers/health-medicine/biomedical-sciences-pharmacy/lessons-from-experimental-models-of-disease>
- **Oncology: Oncodesign**
<http://www.oncodesign.com>
- **CNS: Porsolt, Evotec**
<http://www.porsolt.com;>
www.evotec.com
- **Various: Envigo - formed in 2015 by the amalgamation of several companies, including Huntingdon Life Sciences to become the largest non-clinical CRO in Europe.** <https://www.envigo.com/>

¹ UCT does not endorse any of the companies listed and the list merely indicates some current service providers. Other service providers will have been omitted through no intention of the university.

A commercial partner or a major translational research organisation could also provide an alternative approach to access such models and assays could be accessed through a collaboration. For example, Cancer Research UK would be an ideal partner to access cancer Xenograph models. Although ideal, these relationships tend to take longer and become clouded by IP constraints – hence outsourcing is normally considered a more attractive model.

If a program is showing promise, a clinical candidate package can be completed and a dossier compiled for commercial partners. These studies typically cost about R1.5M and include key toxicology studies such as 7-14 rat toxicology, Maximum Tolerated Dose (MTD) calculations, etc. If these studies are successful, the program will have significant commercial potential, which a commercial partner may find of interest.

6.3 Gate Review

For effective innovation, three parallel processes need to be managed holistically to keep them synchronised. These are technology development, intellectual property protection and commercialisation (which includes market research).

They need to be matured simultaneously as they impact on one another, e.g. knowledge of potential international markets will inform the patenting strategy and identifying the countries in which patents should be applied for to maximise IP value. Knowledge of a market will also influence technology development, e.g. scale of manufacture, quality or regulatory entry barriers (e.g. clinical trials, certification), etc.

RC&I has established and is refining a stage-gate process, largely driven by the stages of the patenting process (Figure 8), to review these areas and guide prudent spending of UCT's patent budget.

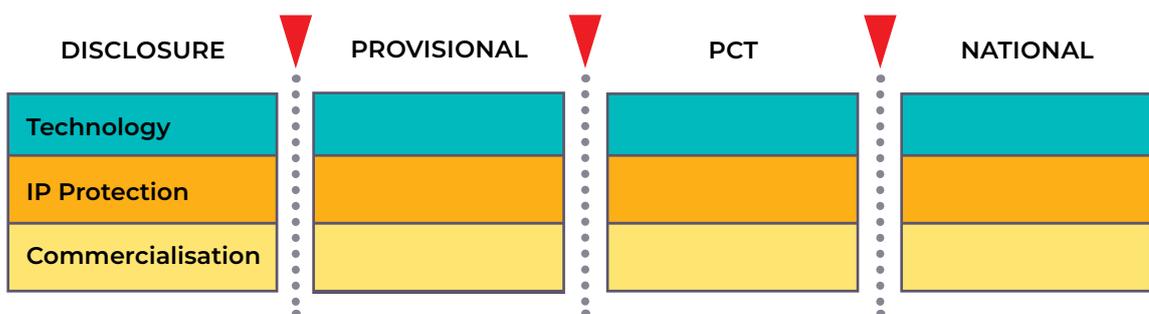


Figure 8: Stages of the Patenting Process

7 SEED AND INNOVATION FUNDING

7.1 Seed Funding

Various forms of seed funding are available within UCT and are administered by RC&I, such as the PreSeed Fund and the Technology Innovation Agency (TIA) Seed Fund.

These smaller amounts of funding can be used to support outsourcing of ADMET testing, or for certain focussed experiments that aim to address significant concerns or provide key proof of concept. This speeds up the drug discovery process and can inform patenting decisions, but importantly the outcomes reduce risk for a next-stage investor.

Information regarding current seed funding can be found on the RC&I website¹. You can also visit the TIA website² to find out more.

Regular calls also go out on the Research Funding mailgroup.

7.2 Innovation Funding

Multimillion-Rand funding can be sourced from a number of different organisations, both in South Africa and overseas, with funders typically having a particular focus.

Sources that UCT researchers have accessed include:

- TIA
- The South African Medical Research Council (SAMRC) through its Strategic Health Innovation Partnerships (SHIP) unit³. This is a partnership between

the SAMRC and the Department of Science and Technology. They also create pools of funding that rely on co-investment by overseas organisations to leverage South African funding. SHIP funds innovation projects focused on the development of new drugs, treatments, vaccines, medical devices and prevention strategies.

- Bill & Melinda Gates Foundation: www.gatesfoundation.org
- Medicines for Malaria Venture (MMV): www.mmv.org
- Wellcome Trust: www.wellcome.ac.uk
- Partnerships with large pharmaceutical companies, typically following their licensing of UCT IP.



¹ <http://www.rci.uct.ac.za/RC&I/fundinnov/overview>

² www.tia.org.za

³ <http://www.samrc.ac.za/innovation/strategic-health-innovation-partnerships>

8 COMMERCIALISATION FROM A UCT PERSPECTIVE

UCT approaches technology licensing and commercialisation on a case-by-case basis and can adopt a variety of strategies to achieve this, such as entering into both exclusive and non-exclusive license agreements, or considering the outright sale of its intellectual property, as well as taking equity (i.e. holding shares) in start-up and spin-out companies depending on the circumstances.

We also look for potential partners who are able to assist the innovation process through technology development, especially through scale-up, clinical trials and regulatory approval. We often form consortia and partnerships to access funding to support these initiatives. One of our core objectives is to stimulate the growth of the South African economy by fostering small business development



and/or the creation of jobs through the commercialisation of UCT's intellectual property. In the pharma sector, however, UCT needs to partner with a biotechnology- or large pharmaceutical company to take the new drug to market, due to the level of investment that is required. There can be scope for the creation of a biotech start-up to focus on drug development outside of the academic environment. Large pharma companies often look to acquire these small biotech firms to fill their pipelines.

RC&I would negotiate an agreement with the commercial partner, which could be in the form of:

- **An exclusive license** to the intellectual property for commercial exploitation – this can be further limited to a particular field (e.g. type of disease) or a region (a particular territory where there is patent protection). This would mean that the licensee would have the sole right to use the IP for commercial purposes. Note that UCT retains a right to continue to use the IP for research and teaching purposes.
- **A non-exclusive license**, which means that one or more parties may have rights to the IP.
- **As assignment of the IP:** Although less frequent, it can sometimes be possible to transfer the ownership of the IP to the other party.

By virtue of the terms of some research contracts, IP may also be automatically assigned to the funder, which is another mode of innovation. In other cases, a funder - such as the Bill and Melinda Gates Foundation (BMGF) - may have specific requirements in terms of commercialisation of the IP emanating from

their funded research (in the case of BMGF it is according to their "Global Access Policy").

Assignment Agreements usually include a single payment for the IP at the time of signing the contract, although instalments can be negotiated so that staggered payments are made on completion of certain milestones (e.g. completion of different stages of clinical trials). Licenses tend to be based on royalties pegged as a certain percentage of invoiced sales, but again may include a combination of upfront (on signing) and milestone payments. These would effectively lead to a degree of risk-sharing, i.e. the licensor does not receive everything upfront but is rewarded as the drug is derisked and moved through the hurdles.

Inventors may also be interested in forming spin-off companies based on the IP that they have developed, and RC&I will assist them with developing Business Plans and conducting market research. RC&I Pre-Seed funding is available to support these activities, which often require the advice of consultants.

Licensing, as opposed to spin-off company formation is, however, the most likely mode of commercialisation that UCT uses in the pharmaceutical space. This is due to the amount of funding that is involved, the need for the scale-up of the actual chemical manufacture of drugs under Good Manufacturing Conditions (GMP) for both clinical trials and commercial sales, the clinical trials and regulatory approvals process and the marketing.

9 PATENTING AND DATA EXCLUSIVITY AS PROTECTION STRATEGIES

Intellectual Property (IP) protection plays a crucial role in providing companies with incentives to invest in the long, costly journey of drug discovery. Strong IP protection makes it possible for companies to recoup their investments, make a return for their shareholders and fund future research. Clinical trial data is submitted to a regulator as part of the approval process. Generic manufacturers (competitors) may rely on the original company's data to save the cost of having to do trials themselves and also to fast-track their applications.

Certain countries (e.g. USA's FDA) will grant a period of "data exclusivity" and only permit

generic manufacturers to rely on the data once the period has ended. This tends to delay the competitor's entry into the market, although it does not preclude them from paying for and gathering their own data. This can provide the initial applicant with a short additional period of "protection" beyond the life of the patent.

Generic manufacturers typically target launching their own products immediately on the expiry of the patent. In certain instances, a generics company may negotiate a deal with the data owner to gain early access to it.

The FDA also offers two other key targeted incentives:

- Companies can receive an additional six months of exclusivity when completing and submitting paediatric studies that meet the terms of a written request from FDA.
- The first company obtaining FDA approval of a designated drug developed to treat a rare disease or condition can receive seven years of market exclusivity (i.e. another product for the same disease or condition cannot be approved during the seven years). These "orphan" or "neglected" diseases are often overlooked due to their comparatively small market sizes. But as "large markets" become congested with little room to create a new drug that has significantly greater benefit, these neglected disease markets are becoming increasingly attractive. You can read more about this in section 12.2.



The PhRMA website is a great resource for finding out more about protection strategies .

10 KEY CONSIDERATIONS WHEN SETTING UP CLINICAL TRIALS

'A properly planned clinical trial is a powerful experimental technique for assessing the effectiveness of an intervention'¹.

Regulatory and ethical requirements for the management and reporting of clinical trials were originally developed for trials involving medicinal products. However, these are now considered best practice for all trials involving human participants, including trials for complex interventions.

What follows is a summary of **key requirements** for setting up clinical trials from two sources: the South African Good Clinical Practice (GCP) Guidelines² and the South African Medicines Controls Council (MCC) regulatory requirements³.

10.1 Definition and aim of clinical investigation

Clinical evaluation is the assessment and analysis of clinical data pertaining to an intervention in order to verify the clinical safety, efficacy and/or effectiveness of the intervention.

10.2 Sponsorship of a clinical investigation

The sponsor is an individual, company, institution or organisation taking responsibility for the initiation, management, and/or financing of a clinical trial.

The sponsor ensures that quality assurance and quality control principles apply to the investigation. An individual is highly unlikely to take on the full role of sponsor; typically, if a study is funded by industry then industry takes this role.

However, a key component of being a sponsor is the provision of indemnity (including no-fault insurance) for the

investigator (person taking responsibility at the investigational site), and others, against claims arising from the trial. If the funding body is unable to provide indemnity OR fulfil the roles of sponsor according to GCP-SA then UCT will need to take this responsibility. In order for this to be agreed by the Faculty of Health Sciences, there is a process to be followed.

You can read more about it on the Clinical Research Centre website⁴.

10.3 Clinical investigation protocol (CIP)

The protocol is drawn up, agreed and justified by the sponsor, the Principal Investigator (PI), and/or sub-investigators.

The Clinical Research Centre (CRC) at UCT has produced a template to assist PIs to complete a CIP ensuring all aspects of the trial are considered in advance of applying for ethical approval.

You can find it on the CRC website⁵.

Templates are provided for trials of medicinal products and trials of complex interventions. Key considerations at this stage include:

- 1. The Investigator's Brochure (IB)** - for unregistered products, indications, doses or uses, etc. This must be available to provide the PI with the preclinical, clinical and/or performance data of the intervention thus far.
- 2. Case Report Forms (CRFs)** - these forms must be carefully designed to ensure that all relevant participant data is captured for the analysis. The CRFs are the subject of the monitor- and audit reviews. They may be in paper or electronic format and must be

¹ http://www.phrma.org/sites/default/files/pdf/frd_brochure_022307.pdf

² <http://www.crc.uct.ac.za/gcp>

³ <http://www.crc.uct.ac.za/mcc>

⁴ <http://www.crc.uct.ac.za/crc/sponsorship>

⁵ <http://www.crc.uct.ac.za/crc/services-facilities/study-design-and-protocol-development>.

subjected to quality control or assurance checks throughout the study by the trial staff, monitors and/or auditors.

3. **Monitoring Plan** – The sponsor will designate a monitor and formulate a risk-based monitoring plan for each study. Monitoring of a study is a constructive and collaborative evaluation of adherence to the CIP and GCP-SA by the study team. Non-adherence is reported to the sponsor who addresses the issue with the relevant team or client.
4. **Site selection and training** – every member of a study team at every site must be GCP-SA trained and trained in the study specific documents.
5. **Data Safety and Monitoring Committee (DSMB)** – the sponsor may decide to establish a DSMB depending on the category of risk for the intervention and for the participants.
6. **Agreements and Contracts** – These should be drawn up between the sponsor, the PI, any outsourced components, e.g. laboratories, and should be taken through the FHS approval process before reaching the contracts office at UCT.

10.4 Clinical investigation conduct

The clinical investigation must be conducted according to the CIP. Planning the conduct of the investigation is arguably the most important stage of the investigation. Time spent here can save money and achieve study closure on schedule.

As part of the plan, a full delegation log for roles and responsibilities must be drawn up and signed by each team member. It is the responsibility of the sponsor and the PI to ensure each team member is adequately trained for their designated role. The ability of a team to adhere to the CIP is evaluated by the monitor as described above.

A summary of considerations can be found at on the CRC website¹.

10.5 Clinical investigation documents and documentation

The general rule of thumb in clinical trials is that if it is not written down, it did not happen. This is intended to reduce risks to the patient and ensure adherence to the CIP. The safety of participants is continuously logged and monitored.

A key component of documentation is the amendment of documents such as the CIP, informed consent, IB and the CRF as required throughout the investigation. Documents must be version controlled and logged.

Further elaboration on the documents required for clinical investigation can be found on the CRC website².

10.6 Investigational product accountability

Access to the investigational product is controlled and it may only be used in the investigation according to the CIP.

The sponsor either takes responsibility for, or delegates, the role of ensuring and documenting the physical location of all products from shipment to investigation site until return or disposal.

10.7 Safety evaluation and reporting

All adverse events (AE) must be adequately evaluated for relevance to the intervention or the study in general. A report must be completed and submitted to the HREC, MCC and the sponsor according to their requirements.

Forms for reporting AEs are available on the Faculty of Health Sciences website³.

¹ <http://www.crc.uct.ac.za/crc/toolkit>

² <http://www.crc.uct.ac.za/crc/toolkit>

³ www.health.uct.ac.za/fhs/research/humanethics/about

10.8 Research governance

Oversight of the planning, conduct, safety and quality control of an investigation is achieved by the establishment of a Trial Steering Committee (TSC) and a Data Safety and Management Board (DSMB). Members of these two committees are determined by the sponsor and the PI.

A key member of the DSMB is a statistician. If the trial is small, the role of the two committees may be subsumed by the TSC.

10.9 Investigation close-out and report

Routine close-out activities include ensuring that:

- all documents are complete, and quality checked
- all data queries are addressed,
- remaining investigational products are returned or disposed of
- all outstanding issues are resolved, and all necessary parties informed (HREC, MCC etc.)

A written Clinical Investigation Report (or equivalent) is then completed and submitted to all parties.

10.10 Why clinical trials fail

A large percentage of new drug candidates fail to reach the market during clinical trials. Of course, this holds massive

financial implications for pharmaceutical companies. Buonansegha et al.¹ (2014) found that there are a number of factors that contribute to the failure of clinical trials. These include:

- chaotic and slow patient recruitment,
- lack of experience in choosing and monitoring partners,
- lack of feasibility of the study protocol,
- low quality of the registered data,
- too high incidence of serious adverse events and severe incidents,
- unmanageable level of portfolio complexity,
- incorrect assessment of the market potential or returns.

According to a recent study by The Tufts Center for the Study of Drug Development (Tufts CSDD), which analysed the reasons for clinical failures of 410 drugs, there are different reasons for failure in each of the different phases.

The leading cause of Phase I failures proves to be commercial viability, as opposed to safety.

Safety issues account for one-third of all drugs that failed in Phase I and Phase III studies; and for 17% of all Phase II failures.

Efficacy issues account for more than half of the failures in Phase II and Phase III (54% and 52% respectively).

Reasons for Clinical Failures by Phase

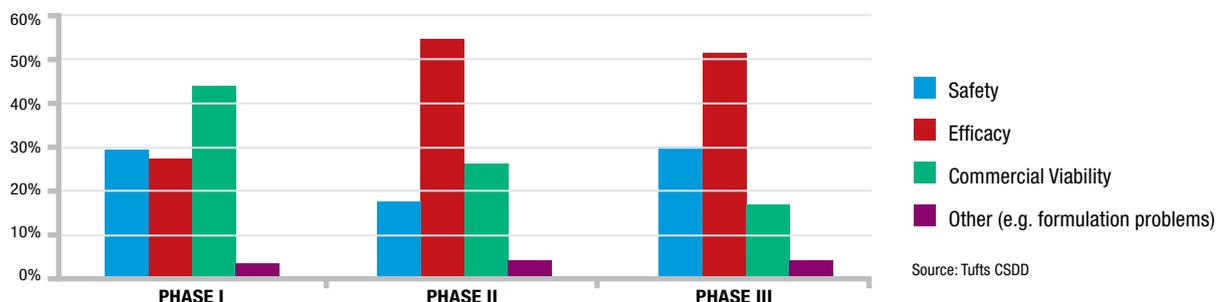


Figure 9: Commercial viability - as opposed to safety - is the leading cause of Phase I failures

¹ <http://www.appliedclinicaltrials.com/reasons-clinical-failures-phase>

11 ETHICS

All clinical investigations should be conducted in accordance with the ethical principles embedded in the Declaration of Helsinki¹. The principles described here are the rights, safety and well-being of human subjects which are most important and should prevail over the interests of science and society.

UCT has a strict code of ethics for research involving human participants. The following has been adapted from the full document that is available on the UCT website.

UCT adheres to standards and principles under which its investigators must aim to conduct research with scholarly integrity and excellence. It requires close attention to social responsibility, and respect for the dignity, self-esteem, and human rights of the individuals who may be involved in or affected by research.

The University aspires to articulate standards of conduct and procedures that ensure proper accountability. In the pursuit of its ideals, the University subscribes to the interdependent principles of scholarly responsibility, integrity and honesty of human dignity and of academic freedom and openness.

Of specific relevance to investigators in health sciences and those who may pursue novel medical agents, drugs, therapies, and devices with implications for intellectual property, UCT affirms the requirement that all research involving human participants be subject to prior ethics review. This must be in accordance with faculty guidelines and the standard operating procedures of the ethics committees charged with the review and oversight of research.

For purposes of ethics and responsible conduct, investigators assume broad and full responsibility for the following:

- The quality and originality of their research questions (avoiding both waste

and redundancy, and anticipating needs for reliability, replicability, and verification);

- The design, methodology and execution of their research;
- The development of a research plan that yields a high degree of validity;
- The identification, where appropriate, of alternative hypotheses, methodologies, and interpretations of data;
- The dissemination of findings, and their limitations, to ensure accessibility and opportunities for peer-review.

When planning their research, researchers should consider and articulate the appropriateness and foreseeable consequences of their research in the research proposal. In health science research, this often requires consideration of the full range of adverse events and problems that may occur and distinguishing which are likely, serious, and relevant to the choice of participation. This merits explanation in study materials. Researchers should also keep in mind the requirement of prior research ethics review and clearance when planning the timeframes for their research. Ethics approvals may not be obtained retrospectively.

Ethics considerations for research participants are paramount. Research participants should not be harmed in the course - or as a consequence of research, except in those cases where the research participants have no moral claim not to be harmed in the ways that the research may harm them.

Researchers wishing to undertake research that may harm participants must demonstrate that, according to faculty guidelines, the participants have no moral claim not to be harmed in the relevant ways. Risks of harm must be minimised (though not necessarily eliminated as this may not be possible) and balanced against benefits. Specifically,

¹ World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013 Nov 27;310(20):2191-4.

investigators must minimise or avoid exposure of participants to foreseeable legal, physical, psychological, or social harm or suffering that might be experienced in the course of research.

The risk of harm and the likelihood of direct benefit to participants must be discussed as part of the consent process. Researchers should be especially sensitive to the interests and rights of vulnerable populations such as minors, elderly persons, very poor and/or illiterate persons.

As a guiding principle in human subjects research, participants should give informed, voluntary consent, when appropriate, to participation in research. This includes respect of the right of individuals to refuse to participate or, having agreed to participate, to withdraw their consent at any stage without prejudice.

Investigators should provide information that explains the aims and implications of the research project, the nature of participation and any other considerations that might reasonably be expected to influence their willingness to participate. This information must be provided in language that is understandable to the potential participants. While the importance of informed consent does not preclude research that uses observation or deception as part of its methodology, such research must be justified in its protocol and comply with best practices and ethics codes of its scientific or scholarly discipline.

Finally, the privacy and confidentiality interests of participants must be taken into account in the research process. Information that may identify individual persons should not be used in research findings, unless the person has expressly agreed to its release, having had the opportunity to consider the implications of such release.

Future uses of data and/or biospecimen samples that may be obtained in the course of health science research are especially and

increasingly important considerations that bear on innovation. They relate to the responsible conduct of research defined as responsibility and care for the relationships on which the discovery and dissemination of knowledge depends, and the resonance between the conduct of research and the context(s) in which the research takes place and/or has effect.

No research may be conducted on human subjects without the signed permission of a Human Research Ethics Committee (HREC).

The HREC will consider many aspects of the study including the following principles:

1. Improper influence or inducement
2. Participant informed consent, confidentiality and privacy
3. Compensation and additional health care
4. Responsibilities of the personnel and their designated roles during the investigation.
5. Study design and participant inclusion. It is considered unethical to carry out an inappropriate study design in order to answer the question.
6. If National and Regional HREC requirements are less strict than the International requirements for the project, then the stricter requirements will be upheld

In addition to ethical approval, if the study is to be carried out on patients at a provincial hospital, it needs to be approved. You can read more about this on the CRC website¹.

This may seem like a daunting process but there are many people with the expertise to assist you if you are new to clinical trials, and there are flow charts and tools designed to make your journey easier. You can find the full policy document on the UCT website².

To take a study from conception to start-up at UCT, please contact the CRC for further information or assistance or visit the toolkit on their website: <http://www.crc.uct.ac.za/crc/toolkit>

¹ <http://www.crc.uct.ac.za/crc/services-facilities/regulatory>

² http://uct.ac.za/downloads/uct.ac.za/about/policies/humanresearch_ethics_policy.pdf

12 REGULATORY ISSUES

12.1 Regulatory Bodies

There are various regulatory bodies whose job it is to ensure that only drugs that are safe and effective make it to market.

The following two are most relevant to drug development at UCT:

FDA Center for Drug Evaluation and Research (CDER)

The US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research regulates both over-the-counter and prescription drugs. Apart from medicines, it is also responsible for regulating personal care products such as fluoride toothpaste, antiperspirant, certain shampoos and sunscreen.

SAHPRA (formerly MCC)

Formerly known as the Medicines Control Council (MCC), the South African Health Products Regulatory Authority regulates the manufacture, distribution, sale, and marketing of medicines. They work according to a set of standards laid down by the Medicines and Related Substances Act (Act 101 of 1965).

12.2 NDA versus ANDA review process¹

A New Drug Application (NDA) is required for any drug entering the market for the first time and can only be completed once preclinical and clinical data proving its safety and efficacy has been gathered.

An Abbreviated New Drug Application (ANDA), on the other hand, is required

when a generic drug product that is the therapeutic equivalent to an existing drug approved by the FDA is ready to enter the market. The existing drug is known as the reference listed drug (RLD). In order for an ANDA to be approved, there must be sufficient information to show that the proposed generic product is pharmaceutically equivalent and bioequivalent (therefore therapeutically equivalent) to the RLD. To be pharmaceutically equivalent, the generic drug needs to contain the same active ingredient(s) as the RLD. It must also be identical in strength, dosage form, route of administration, and meet compendial or other applicable standards of strength, quality, purity, and identity.

The sponsor must also be able to demonstrate that the proposed generic drug is appropriately labelled and that all patent protection issues have been resolved.

Fig. 10 provides a comparison between the requirements of an NDA and an ANDA. The primary difference between the application requirements is that the preclinical and clinical data in the NDA that establishes the safety and efficacy of the drug product do not need to be repeated for the ANDA.

Apart from the differing requirements in the submission of clinical data, the remaining requirements including those for chemistry, manufacturing, controls, testing, and labelling are similar, regardless of whether the application is an ANDA or NDA.

¹ http://www.researchgate.net/profile/Mi_Furness/publication/8617391_Regulatory_considerations_of_pharmaceutical_solid_polymorphism_in_Abbreviated_New_Drug_Applications_%28ANDAs%29/links/54f4d3ad0cf2ba61506421e0.pdf

NDA versus ANDA Review Process

BRAND NAME DRUG NDA Requirements	GENERIC DRUG ANDA Requirements
1 Chemistry	1 Chemistry
2 Manufacturing	2 Manufacturing
3 Controls	3 Controls
4 Labeling	4 Labeling
5 Testing	5 Testing
6 Animal Studies	6 Bioequivalence
7 Clinical Studies	
8 Bioavailability	

Figure 10: Comparison between NDA and ANDA requirements¹

12.3 Approval FDA drug development and approval^{2,3}

In the US, CDER is the largest of the FDA's six centres. It has responsibility for both prescription and over-the-counter (OTC) drugs. The other five FDA centres have responsibility for medical and radiological devices, food and cosmetics, biologics, veterinary drugs, and tobacco products.

A drug company wishing to sell a drug in the United States must first have it tested to prove its efficacy and safety. Once this is done, the evidence of these tests is sent to the CDER.

A team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists reviews the company's data and proposed labelling. If they come to the conclusion that a drug's health benefits outweigh its known risks, the drug is approved for sale.

The center does not actually test drugs itself, although it does conduct limited research in the areas of drug quality, safety, and effectiveness standards.

FDA's priority review voucher (PRV) program⁴

The FDA reviews most drugs under "standard" review times, meaning it has ten months per product to make a decision.

However, the review clock stops each time the FDA requests additional information from a sponsor, adding several months to the review process. The FDA has the ability to accelerate its review in the hopes of getting products to market more quickly. Drugs intended for "serious conditions," or which "demonstrate the potential to be a significant improvement in safety or effectiveness," are reviewed under the FDA's Priority Review Designation (PRD) pathway, which takes six months instead of the standard ten.

¹ S Raw, Andre & Furness, Mi & S Gill, Devinder & C Adams, Richard & O Holcombe, Frank & X Yu, Lawrence. (2004). Regulatory considerations of pharmaceutical solid polymorphism in Abbreviated New Drug Applications (ANDAs). *Advanced drug delivery reviews*. 56. 397-414. 10.1016/j.addr.2003.10.011.

² <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm>

³ <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/>

⁴ <http://www.raps.org/Regulatory-Focus/News/2015/07/02/21722/Regulatory-Explainer-Everything-You-Need-to-Know-About-FDA%E2%80%99s-Priority-Review-Vouchers/>

The FDA offers priority review vouchers (PRVs) as incentives to spur the development of new treatments for diseases that would otherwise not be deemed worthy of a company's time and effort to develop.

The table below provides a list of tropical diseases that are eligible to PRV:

When considering whether a drug is suitable for use of its intended purpose, SAHPRA assesses its relative risk against its benefits.

Like the MCC, SAHPRA operates through external experts who are members of Council Committee structures. The Council has 9 active technical

Eligible diseases under the Tropical Disease Priority Review Voucher System		
Malaria	Blinding trachoma	Schistosomiasis
Buruli Ulcer	Cholera	Yaws
Dengue/Dengue haemorrhagic fever	Leishmaniasis	Tuberculosis
Dracunculiasis (Guinea-worm disease)	Lymphatic filariasis	Fascioliasis
Human African trypanosomiasis	Leprosy	
Soil transmitted helminthiasis	Onchocerciasis	
Added by Congress		
Cuevavirus	Ebolavirus	Marburgvirus
Added by FDA Order		
Chagas	Neurocysticercosis	

12.4 Approval FDA drug development and approval

SAHPRA drug development and approval
The South African Health Products Regulatory Authority (SAHPRA), formerly known as the Medicines Control Council (MCC), fulfils a similar role as the FDA. The Medicines and Related Substances Amendment Acts of 2008 has given SAHPRA final authority over the approval of new products and medical devices. Previously, this required the approval of the Minister of Health, often causing significant time delays.

committees, with more than 14 members from various institutions in the country.

These include the Clinical Committee, Pharmaceutical and Analytical Committee, Clinical Trials Committee, Names & Scheduling Committee, Veterinary Clinical Committee, Pharmacovigilance Committee, Biological Medicines Committee, Complementary Medicines Committee, and Legal Committee.



H3D Drug Discovery and Development Centre was founded in 2010 as a University of Cape Town accredited research centre. H3D currently consists of >60 dedicated personnel working across the integrated medicinal chemistry, biology and Drug Metabolism and Pharmacokinetic (DMPK) platforms.

In addition to supporting our existing portfolio of projects and collaborations, H3D offers standard screening assays as a service. H3D is a TIA (Technology Innovation Agency) platform and can offer these services at cost for local academic collaborators.

Biology:

- *In vitro* whole cell screening against *Mycobacterium tuberculosis* (Tuberculosis, TB), *Plasmodium falciparum* (Malaria) and Gram negative bacteria
- Biology triage and target identification studies for TB
- *In vivo* efficacy studies for malaria

DMPK:

- Suite of *in vitro* assays, including solubility, microsomal metabolic stability, and permeability
- *In vitro* and *in vivo* metabolite identification studies
- *In vivo* PK/PD (pharmacokinetic and pharmacodynamic) studies in rodents

We are also open to collaborating on drug discovery projects, particularly in our focus area of infectious diseases.

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To be the leading organisation for integrated drug discovery and development on the African continent



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