A Work Project, presented as part of the requirements for the Award of a Master's degree in Impact Entrepreneurship and Innovation from the Nova School of Business and Economics.

DECA PHARMACEUTICALS: FIGHTING FUNGAL INFECTIONS WITH ORGANOMETALIC COMPOUNDS, INNOVATION'S OVERVIEW AND ECOSYSTEM MAPPING

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16/12/2022

Abstract

To better comprehend who can benefact from the value of an innovation, the entrepreneur should acquire knowledge about the topic, as well as identifying all potential partners in a value chain, to obtain valuable insights and progress faster.

Xaniglucan is the first product from Deca Pharmaceuticals, aimed to cure resistant *C. glabrata* infections. Leveraging on the product's characteristics and by relying on IP protection, the team can hope to validate assumptions with the stakeholders identified to develop the drug into later stages of clinical trials.

The entrepreneur now understands who plays a key role in different stages of development.

Keywords

Innovation, Patent, Stakeholder, Invasive Fungal Infection, *C. glabrata*, Pharmaceutical, R&D, Caffeine, Nickel, Mode of Action, Clinical Trials, Organometallic Chemistry, ESG.

This work used infrastructure and resources funded by Fundação para a Ciência e a Tecnologia (UID/ECO/00124/2013, UID/ECO/00124/2019 and Social Sciences DataLab, Project 22209), POR Lisboa (LISBOA-01-0145-FEDER-007722 and Social Sciences DataLab, Project 22209) and POR Norte (Social Sciences DataLab, Project 22209).

EXECUTIVE SUMMARY

Humankind has always tried to stay ahead of disease-causing agents by creating new solutions that interfere with their proliferation, thus avoiding illness or death to infected individuals. Fungal pathogens are a good example of this adaptative fight, continuous and sometimes negligent use of existent measures to eradicate fungal infections, such as the likes of anti-fungal medications, have created resistant isolates, responsible for more deaths *per annum* than Malaria or Tuberculosis. That is a death toll of 1.7 million lives lost to invasive fungal infections.

About 70% of nosocomial invasive fungal infections, responsible for the above-mentioned deaths, are caused by the *Candida* species, being *C. albicans* and *C. glabrata* the main contenders of that percentage.

Despite all efforts, these molds and yeasts are becoming ever more resistant to known means of treatment. Presently, despite the need, no new classes of antifungals have been in the market since 2006, due to the large investment needed and low returns.

Facing this concern, our recently formed company - Deca Pharmaceuticals was created, pursuing novel ways, aside from the traditional classes of antifungals, to deal with the growing number of resistant fungal infections.

To relieve patients of these infections, and governments of costly health burdens that can top up to billions, we present a breakthrough that has already been proved to have fungistatic capabilities. By leveraging on complex organometallic chemistry as an innovation to circumvent resistant fungal pathways, our researchers are synthetizing caffeine (a xanthine derivative) with

nickel, as raw materials to produce a batch of molecules, in which our first compound, Xaniglucan, will emerge.

Our product can effectively eradicate *C. glabrata* resistant isolates, while maintaining a high safety index for human cells. Current projections show that the compound will be fairly cheap to produce due to its raw materials (caffeine and nickel), benefitting as well from a low minimal inhibitory concentration (or dosage), and therapy combination synergies with other drugs.

The pool of molecules is still being tested and more data is being acquired to enable the compound, or compounds, to finish pre-clinical trials and reveal whether a greater scope of fungal pathogens are encompassed, amidst other potentialities.

While the pharmaceutical industry is known for its innovations' cash-burning efforts, development milestones for phases I, II, III, were planned. The team aims to raise up to $39 million mainly from Venture Capital (VC) funds and corporate investors to face our capital needs until the end of phase II in 2026, where we expect to be an interesting prospect to be acquire by a large pharmaceutical company. As a contingency plan, if no opportunities at the end of stage II appear, we forecast funding needs of at least $100 million, to complete phase III with little to no setbacks.

To be able to maximize Return on Investment (ROI), we present a few exit scenario alternatives to our investors, with the ideal goal of being acquired by a major pharmaceutical firm, such as Pfizer. In case we need to go to market by 2030, going public through an Initial Public Offering (IPO) is a suitable option to get funded and to ensure our investors profit from their shares. Concerning ROI, selling royalties on drug sales also suits as a part of the contingency plan.

Several players and key partners were identified for us to understand the ecosystem and who can help us grow throughout our development stages. Value is generated for every stakeholder, either being monetary, moral, or both, resulting on mutual interest.

Regardless of the heavy presence of centurial pharmaceutical companies, which focus lies greatly on profits, today more than ever small bio-tech companies such as ours can play an important and revitalizing role in supplying new ideas to the pipeline of these market giants.

THE SOLUTION

Call-to-action

Considering this situation, the priority of developing effective antifungals is quite overlooked, with a fairly disseminated interest in developing drugs for other fields, such as oncology drugs. This happens because the anti-infectants market is seen as a less profitable businesses than the others. Being difficult to produce, some antibiotics can cost more than a billion, while the yearly revenues averages at $46 million, making it less relevant for big investments (Plackett 2020). As could we also conclude form Filipe Assoreira, MBA, interview (See Interview notes section, in the Appendix – "Any insights on product distribution and marketing of these products?").

New drugs were still developed nonetheless; however, they fall on the existent categories of modes of action (MOA) or classes (i.e.: Isavuconazole), meaning these new compounds act on already documented inner-cell mechanisms, thus grouping them into categories with the main ones being Azoles, Polyenes, Allylamines, and Echinocandins.

Tackling the urgency of developing new antifungals under these tough conditions, Deca Pharmaceuticals was born. This is our call-to-action, we are working to anticipate a growing concern of the number of ailments and deaths caused by resistant fungus strains, by proposing a new class of antifungals that circumvent resistance mechanisms, while being easily affordable, in

contrast with other new anti-infectants that are usually expensive as per our interviewees: Dr. Cristina Toscano and Dr. Ana Rita Domingues (See Interview notes section, in the Appendix).

By not leveraging on already known mechanisms of action, we took a step back and created a new class of antifungals that interfere with the pathogen's oxygen intake. The solution is supported by the therapeutic qualities of metals as anti-infectant. Metal complexes have unique geometric features, electronic properties, and reactivity that, when combined with organic molecules, can display new MOAs that are not usually found in organic molecules alone (Karges, Stokes, and Cohen 2021, 523).

We explore complex organometallic chemistry to create molecules with antifungal properties. As some metals are quite expensive, by recognizing the need for a cheap solution, our first line of products uses nickel, which is cheap to obtain.

Yet, far from solving the issue on all invasive fungal infections, our company makes its first step into the potential of what an innovation can bring. Showing effectiveness on a few species of fungal pathogens acts as our proof-of-concept for future developments and increasing scope to deal with more pathogens.

ESG compliance

Our innovation is aligned with the UN Sustainable Development Goals (SGDs). By tackling fungal microorganisms that can create bloodstream infections in particular situations; where an estimate of 1 billion people per year suffers from any form of fungal infection, and among those around 1.5 million die as a result (Bongomin et al. 2017, 1), our solution plays an active role in diminishing the said statistics.

Our first product already shows selectivity for *C. glabrata*, known to be quickly adapting to known means of treatment and the second most prevalent pathogen responsible for Candidemia. This blood infection comprises of 1.05 million cases of the universe of 1.5 million. Depending on the country *C. glabrata* incidence can vary, going from 8% to almost 30% (Guinea 2014, 6). For the sake of this example, assuming that only 15% of lethal Candidemia cases are caused by *C. glabrata*, at least 157.5 thousand people could be saved every year.

Deca Pharmaceutical's innovation falls within the Sustainable Development Goals (SDG), goal number 3 – "Ensure healthy lives and promote well-being for all at all ages", more precisely the target 3.d, the reinforcement of the capacity for all countries, especially under development ones, to improve their health risk management. The indicator used by the UN to measure this goal is the 3.d.2, that gives respect to bloodstream infections causes by resistant microorganisms.

It also falls in the framework of the target 3.b that, in short, reinforces the support of Research and Development (R&D) of new medicines accessible for developing countries at an affordable price. The indicator used by the UN to measure this goal is the 3.b.3, that gives respect to healthcare facilities having a sustainable and recurrent stock of affordable medicines to treat their patients.

THE PRODUCT

Description

Fungal infections can have many forms, and they are caused by a variety Species, inside the Genus: *Candida*, *Aspergillus*, *Streptococcus*, among others.

Patients that suffer from nosocomial infections, opportunistic pathogens that invade the body, usually immunosuppressed, account for more deaths than Tuberculosis every year. In turn, nosocomial fungal infections reach mortality rates of 40%, as per our scientific team.

The proposed innovation results on the synthesis of nickel complexes based on xanthine. Out of this organometallic chemistry, one of the several molecules created (see figure 15) is capable of stopping the development of infections caused by *Candida* spp., precisely of *C. glabrata*, one of the main *Candida* spp. responsible for problems such as: UTI's, genital and mouth infections, and more seriously, bloodstream infections that cause systemic failure.

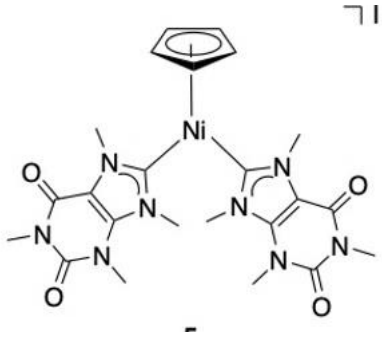

Figure 1 - Biscarbene complex 5[NiCp(NHC)2]+

It is [the molecule] synthesized out of purified caffeine and powdered nickel, both very cheap to obtain. Caffeine is a derivative of xanthine (a purine base/ or a heterocyclic aromatic organic compound, consisting of two rings, pyrimidine and imidazole), which part of its molecular structure comprises of an imidazole unit, azoles group, known for their highly therapeutical potential to treat fungal infections (Siwach and Verma 2021, 1-2). As for the nickel, being a metal, with the right synthesis and structure, it is known for antifungal properties as well (Chohan et al. 2006, 11).

The compound has high selectivity, which means it targets the pathogen without harming healthy human cells. This is very difficult to achieve since both cells [*fungi* and human], are eukaryotes and share many similarities.

The drugs' posology means of administration, and mode of action are still unknown since the innovation is on level 2 (out of 9) of technology readiness level. Nonetheless, knowing the mode of action, and therefore the class of antifungal this innovation would fit in, would not stop the drug from progressing to clinical trials. In fact, by being a new product that fulfills the need for decreasing the mortality rate in Intensive Care Units (ICUs), improving the offer of healthcare systems, positive pressure can induce the pipeline into developing this solution faster than usual (as witnessed in development of the SARS-CoV-2 outbreak in 2019). Thus, the bigger the need, the more investment will be channeled.

Testing of the innovation shows synergetic effects with commonly prescribed antifungals such as Fluconazole – a fungistatic drug, member of the azoles class, that acts on the reproducing mechanism of the fungal cell, since it cannot make multiply itself, it will eventually die out.

Combining drugs to deal with resistance fungal infections is known as antifungal combination therapy and holds one of the best treatments available to circumvent drug resistant molds and yeasts in immunosuppressed patients.

Although the focus will be in on the above molecule, with selectivity to *C. glabrata*, other molecules are being tested, some show selectivity against *C. albicans* as well, however, they present high toxicity to human cells likewise. This development is imperative as *C. glabrata* infections are rising and becoming a reason for concern due to highly resistant isolates and *C. albicans* which constitutes around 70% of fungal infections around the world (Talapko et al. 2021).

IP protection

In the pharmaceutical domain, it is important to have intellectual property protected at the soonest, under the threat of the innovations being eventually replicated or becoming prior art. It is important to find the right balance between protecting the most out of the innovation without extensively writing claims, under the issue of infringing third-party rights or paying more than expected.

Being the only organization working on an innovation, the IP holder can assure a sustainable competitive advantage over other players, as well as security in disclosing ideas and internal processes of the innovation publicly without fearing of being copied or infringing other inventors, and generate profits from the laborious task of developing the idea from project to the market, or even other forms of profit generation such as licensing (Sammon 2022).

In the first half of the present year, Deca Pharmaceuticals has submitted a manuscript through NOVA university (the holder of the IP) with 2 claims: (1) the production of the compounds, (2) and their application as antifungals, with priority date as of 29th of March, 2022, as a provisional patent application, in Portugal. Up until now, no claims whatsoever exist for this patent.

After gathering more data on checkerboard assays to test our drug for combination therapy, which should fall within the time scope of the provisional patent in Portugal, a third claim will be added to the manuscript, protecting the unique synergetic interaction of Xaniglucan with other already existent classes of antifungals and their drugs - its usage as a drug adjuvant.

Further plans include filling a draft and submit a provisional patent cooperation treaty (PCT) patent (which offers patent coverage internationally, if the countries are a part of Patent Cooperation Treaty), after 12 months has passed from the submission of the provisional patent in

Portugal, that being 29th of March 2023. The provisional PCT patent will last for 18 months and the priority date that will be visible on the document, will be the one submitted in the Portuguese patent (29th of March 2022). Any compound production process, or the aforementioned application of the raw materials hence, thereafter, will be considered prior art, since our innovation was registered first.

Applying for a patent is expensive, the cost varies with the complexity of what needs to be protected with a mean range between $6 and $12 thousand, plus up to $100 thousand for a PCT patent, and $200 to $400 per hour if a specialized attorney is needed to help on the process. As a strategy to manage the funds, Deca Pharmaceuticals submits provisional patents to protect our innovation early on, taking advantage of 2.5 years of exclusivity (after the Portuguese patent submission date) with minimal costs. Throughout this window, if needed, we can plan to add more claims as our innovation develops, while applying for funding to be able to pay for an international patent.

After the 29th of September 2024, before the PCT expires, we will pay the needed amount for the PCT patent to be active. From this point onwards, the patent will protect our innovation for the upcoming 20 years (World Intellectual Property Organization 2022), in the meanwhile, the process of producing Xaniglucan plus its application to treat fungal infections will be maintained, with proper fee submissions; 3.5, 7.5 and 11 years after the submission of the PCT patent (Thervo 2022).

After the 29th of September 2044, our patent will no longer be protected and a generic, cheaper version of our drug will appear on the market.

Potential development

To better explain how the innovation can reach its full potential, first we need to distinguish two different categories: (1) **Per definition**, (a) as a stand-alone drug, or (b) as a adjuvant. After climbing through the development roadmap steps, considering the possibility that the molecule does not pose interest to possible partners, after phase III the management Team will submit an non-disclosure agreement (NDA) to the Health Authority in order to be able reach the market in 2030. Long by then, the conclusive testing will show the best application for the molecule, either being a stand-alone drug, effectively treating one or more resistant isolate species, or a adjuvant, increasing the effectiveness of other antifungals by treating one or more resistant isolate species. We can discover in the short-term, for example, that the molecule boosts the effectiveness of other molecules, with a wider scope of *fungi* species. Which leads us to the other category: (2) **per action spectrum**, since we found ourselves in very early stage of development, as referred on the description section, other molecule configurations of the same raw ingredients will be tested, as well as the main contender, on other resistant isolates of the *Candida* spp.: *C. parapsilosis, C. krusei, C. lusitaniae* and other spp.: *Cryptococcus neoformans* and *Aspergillus fumigatus*.

In short, up until now, out of the tested molecules, only one shows selectivity against *C. glabrata* and at the same time, being non-toxic for human cells. Further studies are going to determine if this and the other molecules will act along strongly in one kind of fungal pathogen, or have a much greater scope, increasing our product's therapeutic availability.

Both dimensions will reach a conclusive state in the short-term. Optimal scenarios comprise of Xaniglucan being able to cover the gap where Fluconazole is rendered ineffective against azole resistant isolates, by using drug combination therapy. Since Fluconazole is still one of the most prescribed antifungals presently (as per Dr. Ana Rita Domingues, see Interview notes section, in the Appendix), a synergetic effect where increased value is created for both sides is an

expected possibility. Another optimal scenario is one where the scope of Xaniglucan is rendered with high levels of effectiveness, that could spark the interest of financing parties in investing in a new way of fighting fungal infections. More capital going to R&D enables the creation of better and improved products that can one day be used as one of the main choices of prescribing doctors to cure a myriad of fungal diseases.

STAKEHOLDER MAP

For Deca Pharmaceuticals to better understand how the ecosystem is defined, a stakeholder map needed to be developed, since there are entities that have an important role to play in leading our company's innovations from plan to reality. The value created along the chain also benefits our stakeholders, whose relationship is above all symbiotic. The creation of this map comes as well to serve as a tool to guide the management Team's planning, these are imperative for us to understand our landscape. With this tool we can target potential partners, visualize the schema of our long-term strategy, anticipate key moments and validate assumptions.

The stakeholders of our value chain are described as per follow:

- **Governments:**

Governments exist to serve their citizens. It has an interest for the wellness of the taxpayers for a myriad of reasons: happy citizens are more efficient, votes are more likely to bestow upon the present rulers, the country is more attractive for diverse forms of investment, and many more. However, one reason for the State's interest in companies such as ours is emphasized by the will to guarantee quality health care – they are health related costs. In the US alone, on the year 2018, fungal infections burdened the country with $6.7 billion (Beeson 2022). For comparison, that is

the equivalent of building 4 and a half Golden Gate bridges, in today's terms (Golden Gate Bridge, Highway and Transportation District 2022). For this reason, not only for being the wardship of Health Regulators, but our innovation also serves as an interest to the government as an efficient contributor in healthcare;

- **Health Regulators:**

Responsible for the protection of public health, these stakeholders are usually tied to the State, with duties that foresee the admission overview of new drugs into the market, responsible for surveilling, evaluate, authorize and supervising investigational activity and clinical trials in laboratories. Duties may as well include the inspection of production, distribution, and usage of food, personal hygiene, medical devices, and cosmetics, that affect human health.

Acting as a control entity, under strict rules that companies need their products to abide to, it is ensured that no characteristic of these products can jeopardize individual or overall health. Moreover, for the repertoire of already circulating products (drugs, foods, cosmetics, devices), these entities carefully monitor their effect, safeguarding possible adjustments, having the power to withdraw a given product from the entire market.

Lastly, these organisms act as hubs that allow the alignment of medical institutions, hospitals, pharmacies, retail, stores, policy makers, insurance companies, universities, citizens, among others (U.S. Food and Drug Administration 2022-b), (Infarmed 2016).

The roles of health regulators and their responsibilities can change between countries as there is no standard framework, regardless, examples comprehend the Food and Drug Administration (FDA) in the US, the National Authority of the Drug and Health Products

(Infarmed) in Portugal, the Federal Institute for Drugs and Medical Devices (BfArM) in Germany and Italian Medicines Agency (AIFA) in Italy.

It is clear the importance of Health Regulators, since they are responsible for surveying and auditing the procedure throughout clinical trials stages. Any setbacks mean the Health Regulator would not accept the commercialization of the drug in the market and we would end up spending increasingly more cash the longer it takes, resulting in less return for investors;

- **CDMO (Contract Development and Manufacturing Organization):**

Not every pharmaceutical company has the internal structure or big enough market share that enables for substantial profits, and subsequent investments in a fully-fledged manufacturing-line.

In these cases, a CDMO may be a reliable partner in the business model. Such services vary from formulation, blending and coating, from converting, analytical studies, and regulatory processes, and from packaging and shipping. By possessing expertise on drug development and matching equipment, a CDMO is a service provider well suited for small pharmaceutical companies within all stages, from concept to stage III and beyond, with the facilities that allow scalability to be reached (Tapemark 2022)

Moreover, there are also CMOs, that provide only the manufacturing services, and CROs, that provide only research and development services, but for the sake of simplicity, CDMO, CRO and CMO are a part of the same block in this stakeholder map.

Examples of these firms are, as aforementioned: PCi pharma services, Patheon, Syngene and Tergus Pharma.

As a way to outsource an otherwise very capital consuming asset to acquire, these organizations provide a wide range of services, depending on their customer's needs. In our particular case, comprising of a small research lab, a bridge between stage I and the market, needs to be laid between.

The inexistence of relationship with this stakeholder, on the research services, would severely hinder our progress since more funds need to be redirected to data and evidence acquiring in clinical trials, delaying our development goals considerably due to inexperience. On the manufacturing services alike, due to the lack of facilities and equipment, an increasing amount of cash would be needed. This also implies more funding and less ROI, since the outcome will be the same, only more expensive and increasingly delayed;

- **Hospitals (and Clinics):**

As the main focal point of our product, it is where doctors work where the first contact point with the patient is established, both the case for not life-threatening fungal infections, in Hospitals and Clinics, and nosocomial fungal infections, in Hospitals, that as already discussed further above, display mortality rates over 40%.

In the case of other innovations in the ecosystem, physicians and healthcare practitioners undergo continuous medical education to be kept up to date on new discoveries and breakthroughs in modern medicine.

It is of utmost interest that these facilities provide an unparalleled and state of the art service to their customers, contributing to the wellness of their patients and the safeguard of human life. Notwithstanding, Hospitals also act as a business, so there are some constraints in providing a quality service that might be too expensive. It is therefore important to always consider the value

a product creates, and costs involved. The Da Vinci - robotic assisted surgery for patients, provides the Hospital with quality sub-millimetric surgeries, however, for budget constrained facilities, the existence of cheaper alternatives that deliver slightly inferior results are preferred.

It is convenient that a solution is presented at a cheaper and affordable price, that said, facing the growing concern of fungal super-resistance to known means of treatment, it is foreseeable that Hospitals will show interest for our product, instead of a "coin toss" when an immunosuppressed individual falls ill to invasive fungal infections.

Having patients to remain in intensive care units or transferring to other hospitals due to lack of means constitutes an increase of running costs. The purposed solution contributes for not only saving human lives, but as well improved efficiency in what concerns dealing with fungal prone infections.

Hospitals act as a sell point, where they constitute the buyer, while the patient is the user. Whether being by word-of-mouth or by case-studies, the more the product proves its efficacy, the greater the buyers will be. Success cases and medical breakthroughs are discussed between healthcare practitioners, mainly in seminars, conferences, google searches for reliable sources and committees. This creates mutual value for many of the stakeholders in the value chain and it is of paramount importance for Deca Pharmaceuticals growth;

- **Pharmacies:**

Pharmacies are usually a healthy profit business, focused to sell drugs, holistic medicines, supplements, cosmetics, medical devices, equipment, and other health and neonatal products, to an always present need.

They act as the main player, aside the Hospitals. Patients with not life-threatening forms of infections and diseases, that can by themselves pick-up the prescribed drugs, will in the great majority of cases opt for the nearest or local pharmacy.

According with Bruno Tubarão, MSc (See Interview notes section, in the Appendix), pharmacies' stocks can vary, depending on several variables: region, data on most common and uprising diseases/ malaises, repeated doctors' prescriptions, the existence of generics, and market trends. To keep customers satisfied, pharmacies try to have their inventory up to date, thus avoiding ordering and telling customers the medicine will arrive in the next couple of days. This entails having fast-mover products, representing only a short percentage of the total products, but allowing for a great portion of profits.

Although an antifungal would not constitute a fast-moving product, after proving its efficacy throughout the first years of market presence, our products will be an increasingly known solution to some fungal strains that cause infection. The more doctors prescribe the medicine, the more likely it starts to become available in pharmacies, a sell point. Enough to underline that here, the patient is still not considered to be the direct buyer, since it can only buy the product with a prescription from the doctor. The doctor is an enabler of the buying action of the patient. Alike Hospitals, the acceptance of our product as an effective and cheap solution constitutes good reasons for Pharmacies to have our antifungal drug in stock, contributing for our company growth;

- **Pharmaceutical companies:**

Established pharmaceutical companies, are big enterprises with vast knowledge on the drug market, aside with long established partnerships with the market's stakeholders. The most successful players have more than one century of activity, market caps over $200 billion, hundreds

of products extending in a wide range of medical fields, with individual doses of each product reaching several billions in numbers each year. This market generates large amounts of capital, with revenues estimated to reach $1 trillion by 2026 (Pistilli 2022).

These corporations have a large capacity to finance their activity, such as feeding the pipeline with new breakthroughs, acquiring smaller bio tech firms, improving or repurposing existent products, manufacturing, supply chain management, R&D, distribution, quality control and government programs. Having this capacity, means pharma companies can streamline the process of creating new compounds, from research to market, in less time with higher success rates. Even selling mass production services to other laboratories.

Examples of the most successful drug producer companies are, not necessarily in order: Pfizer, Roche, Novo Nordisk, Johnson & Johnson, and Eli Lily.

Our main endeavor as a resolution for this project is an exit strategy that enables maximum returns for our efforts, for our company and its employees and investors, therefore, being acquired by a pharmaceutical company will hold paramount importance. Synergetic value is created since it is a multisided-win situation. As mentioned on the benchmark topic of the project, big pharmaceutical companies are more focused in drugs that ensure higher profits, leaving room for innovations. Hence, they can leverage and benefit from smaller biotech firms' work, as they largely come up and focus in novel solutions.

Not having a Merger and Acquisition (M&A) proposal from a pharmaceutical company would force Deca Pharmaceuticals to opt for going to the market, either selling or licensing. Although also suitable as a strategy, this would entail more investment and in turn less ROI;

- **Investing partner(s):**

Due to its capital-intensive efforts to fund R&D, small bio tech firms do not usually have their own means of funding. Grants and awards alone help but are of insufficient quantity to sustain the cash-burning phase of new pharmaceutical ventures. That is why it is of keen importance to have the right partners to enable sufficient funds to keep the business going until it becomes self-sufficient. Not only leveraging on cash means, but as well as accessing to this stakeholder's knowledge for advice and its vast network of contacts. This network can bring other partners to the table that could help our company develop and thrive, accessing new opportunities.

There is a synergetic effect for value creation from both sides. In exchange for means to an end, the investing partner will get ROI. Our company as a valuable partner for profit and purpose generation. The investing partner can capitalize while having a sense of mission accomplishment by relieving human ailment.

Examples of investing partners can be VCs, Corporate Investors, Patient Advocacy Foundations and Family Foundations.

The cost of capital also needs to be considered, since choosing between these types of partners will increase or decrease this cost: VCs ultimate goal is usually having returns of more than 4 or 5 orders of magnitude the cash invested (in a short period of time), by either buying shares, ask for "x" percent of future profits and/or ask for royalties, however, they do not typically want to control the company by owning more than half of its value; Corporate investors usually have a future agenda despite financing another firm, whether being by buying stocks and investing great amounts of capital every year, the key interest is to control or acquire the other company in the end; Patient Advocacy Foundations and Family Foundations are philanthropy institutions dedicated to a specific cause, usually interested in the sense of mission accomplished, these non-profits apply their funds in solving societal issues, valuing impact above financial returns.

We underline our will of having a good relationship with our chosen partner, enabling us to achieve a loyal, long-term shareholder board as well as being held as a credible source for investing.

The absence of this stakeholder would halt the project completely. This business is known for its high barriers of entry, specially (but noy only) due to cash-intensive needs, without funding, the embryonic Deca Pharmaceuticals ceases functions;

- **Insurance Companies:**

These companies' main service is providing financial coverage to people that are not able to afford medical treatments or medication. Depending on the subscription plan, covered customers have more or less benefits. Insurance companies work in parallel ways to eachother, with variations between countries and law systems. For instance, in the US, for substantial amounts of healthcare expenses, patients are in charge for the payment of a fixed amount of cash, called "deductible", as a first installment of the total bill. Then, after the "deductible" is met, patients are up to pay the "co-insurance", which is a lower "x" percentage of an agreed second instalment limit, co-paid with the insurance company, that is responsible for the bigger remainder of that percentage. Hence thereafter, if the bill is not yet totally covered, the insurance company will cover the rest, which is named "out-of-pocket limit" until the annual coverage limit is met (EHealth 2011).

As per the information we gathered from André Rufino, MBA (See Interview notes section, in the Appendix), these companies run complex business structures with a network of partners. To be able to provide accessible healthcare to users, contracts are made with different partners – usually big private Hospital chains and Clinics, then contracts are also made to define how a treatment is provided to the patient and what kind of drugs are administered. It must be underlined

that private Hospitals and Clinics are free to contour what is agreed in the contract, however, Health Insurance companies will only finance the treatments in their terms, resulting in professional litigation and legal processes.

Usually, patients benefit from insurance companies the most when vast amounts of capital is needed to finance one's treatment, which is definitely not the case for a cheap to acquire drug (as the price projections remain loyal to our forecast). Albeit, in the case of Invasive Fungal Infections (IFIs), these firms will play a role on paying for the patient's ICU treatment and value surplus will be created in favor of this stakeholder. Moreover, by having a solution available in alternative to a 40% mortality rate, insurance companies do not have to pay copious amounts of cash to the deceased family, improving their profitability;

- **Wholesalers:**

As per Bruno Tubarão, MSc (See Interview notes section, in the Appendix), Pharmacies and Hospitals do not have inventory space to accumulate vast amounts of products, neither the logistics in the ecosystem work in the direction of pharmacies requesting directly to laboratories. Healthcare wholesalers are the intermediary between both. They possess large warehouses or hubs, with the necessary infrastructure to keep drugs stored safely.

These companies also provide other services to their customers such as logistics automation, fast shipping, returns, paying solutions, country-wide coverage, and product info and statistics.

Examples of these companies in Portugal are Alliance Healthcare and Empifarma, and in the US are Cardinal Health and McKesson Corporation.

This stakeholder is the equivalent of a distribution hub, it allows the innovation to reach far and wide within a country. The bridge between the lab or production facilities to sell points;

- **Patients:**

At the bottom of the stakeholder map, lies the main benefactor. The improvement of the Human effort to fight off diseases that jeopardize the safety of a human life constitutes an interest to us all.

Compromised immune systems can be a result of many things, auto-immune diseases, cancer treatments, certain medications, in-development immune systems of neonatal patienrs and old-age. By having a depleted defense system, opportunistic infections compromise the health of the patient.

Regarding not life-threatening fungal infections, and the pesky symptoms associated with them, it is becoming harder to clear the body of the infection, due to several years of these yeasts and molds species being developing resistance to antifungals. Hence, new developments on this field comes with great interest for these individuals. It is estimated that fungal infections of all types can affect 1 billion people worldwide, that is 12,5% of the world population (Bongomin et al. 2017) and some of these are a part of human microbiome, excessively multiplying when the immune system is weakened.

Not only value is being created to the patient, relieving itself of malaises caused by fungal infections, but also moral value is being returned to our company and its stakeholders. Having a sense of accomplishment by saving and illness reliving of human lives matters greatly and serves as fuel for our company to pursue more projects in the future;

- **NGOs (non-governmental organizations):**

These entities operate independently of any government, non-profits with a strong mission and sense of humanitarian aid. The common denominators of NGOs as a stakeholder to our project are; (1) the dissemination of information, known as awareness, (2) acting as a catalyst in the development of research, (3) as a force for good, ensuring equity and health for all, (4) improvement of health care systems, and (5) treatment access for the socially unfavored.

Organizations such as NGOs can contribute for the scaling of sought-after medications, that ensure a fair access to treatments world-wide.

Examples are WHO (World Health Organization), ISID (International Society for Infectious Diseases), and HIS (Healthcare Infections Society).

The presence of this stakeholder serves as a small catalyst for scalability, for example, the African continent holds the highest rates of AIDS in the world, the bearers of the condition have depleted immune systems, which makes them at risk of having an invasive fungal infection. Healthcare NGOs can help our company to expand and access this market, saving limitless amounts of lives and contributing with success case-studies.

To better understand where each of the interest parts fit together, a map was developed to better aid in understanding the ecosystem from a "bird's eye view" (see figure 16 below).

As already aforementioned, from viability studies (before drug inception) to market launch, without major setbacks, usually the length mean of this process takes anywhere from 10 to 15 years. Of course, this length, depends on many variables, some being: the medicine field, stakeholders involved, cash available, setbacks and bureaucracy. In our case, based on our projections, the development roadmap serves as guidance from the *in vitro* pre-clinical stage where

we are today, to market release. It is forecasted to take us just below 10 years, because other of the therapeutic are in question – the anti-infectives.

To enable our innovation to fast-track and bypass regulation difficulties, as well as procedures to perform trials in humans, a contract with a CDMO or CRO will pose an advantage, timely and cost wise. The research will continue and guided accordingly, based on expertise.

Along this way, far from being the only partner in early stages, we also count with VC funds, corporate funds, and foundations from funding rounds to enable our cash-burning R&D efforts. Deca Pharmaceuticals will apply to funding, as necessary, to build strong evidence foundations, allowing our innovation to be attractive for the fulfillment of the next step described below.

The main objective of the project is the exit strategy at the end of phase II - being acquired by a pharmaceutical company. This outcome will ensure maximum ROI for our investors, as well as healthy profits for the effort of developing a novel antifungal through a new method. Mission accomplishment is also achieved, since well-established pharmaceutical companies have the necessary means to guarantee that the innovation sees the light of the market, relieving the healthcare burden.

However, since there is a certain level of uncertainty with this outcome, further planning was developed. The end of phase II timing is strategically emplaced due to the valley of death or "translational gap" overtaking, which is precisely when the drugs at this stage show evidence that they can cure people with the target disease, and with acceptable safety levels, meaning that the risk of failing here henceforward is substantially reduced in comparison with stages before. (Calza et al. 2021, 1186-1187). This does not necessarily unable an M&A to take place further on the map. Being this the most attractive scenario, we will consider this a priority over market rollout.

In the eventual situation where we need to carry on forward, more funding will be needed. At the end of phase III, when the drug possesses sufficient long-term information regarding its effect on the pathogen, human body, pharmacodynamics and pharmacokinetics, safety levels, efficiency and efficacy, side effects, administration and combined drugs therapy effects, an NDA will be submitted to the Health Regulator to review and authorize the mass production and commercialization of the medicine.

With CDMO or CMO as a service provider, the mass production of drugs is assured via outsourcing since the facilities that allow scaling to be reached are too costly to acquire at this point.

In the aftermath, a market strategy is needed for customers to know about the existence of the drug. Forms of marketing in this field include ads, commercials, posters in the pharmacy, and promotion via medical information delegate, which is a person whom responsibility is to ethically disclose drugs and healthcare products to Hospitals, Pharmacies, Clinics, Seminars, Webinars, etc. The latter being the suited marketing strategy for prescription drugs or for ICU usage.

Afterwards, Healthcare providers that know about the treatment potential of the drug that want to extend their shelfs, can place orders under a health wholesaler.

Sale points will be Pharmacies - patients will be able to buy via doctor prescription, and Hospitals - where doctors will administer as a part of the treatment in ICUs.

By participating in co-paying drugs and treatments there are three main investors of a Healthcare System: (1) Government, (2) Health sub-systems (held by public institutions, hence, under Government supervision), and (3) Health Insurances. Since the innovation’s final price projection is to be kept cheap, they will not constitute a main buyer (contrasting with the case of oncology and some orphan drugs, where these three entities act as main buyers).

Finally, NGOs, although not connected to the purposed pipeline, they serve as a force-for-good instigator, contributing to healthcare awareness world-wide, access and overall right to health, and positive healthcare system changes, thus included on how far our innovation can impact a patient's life in our value chain.

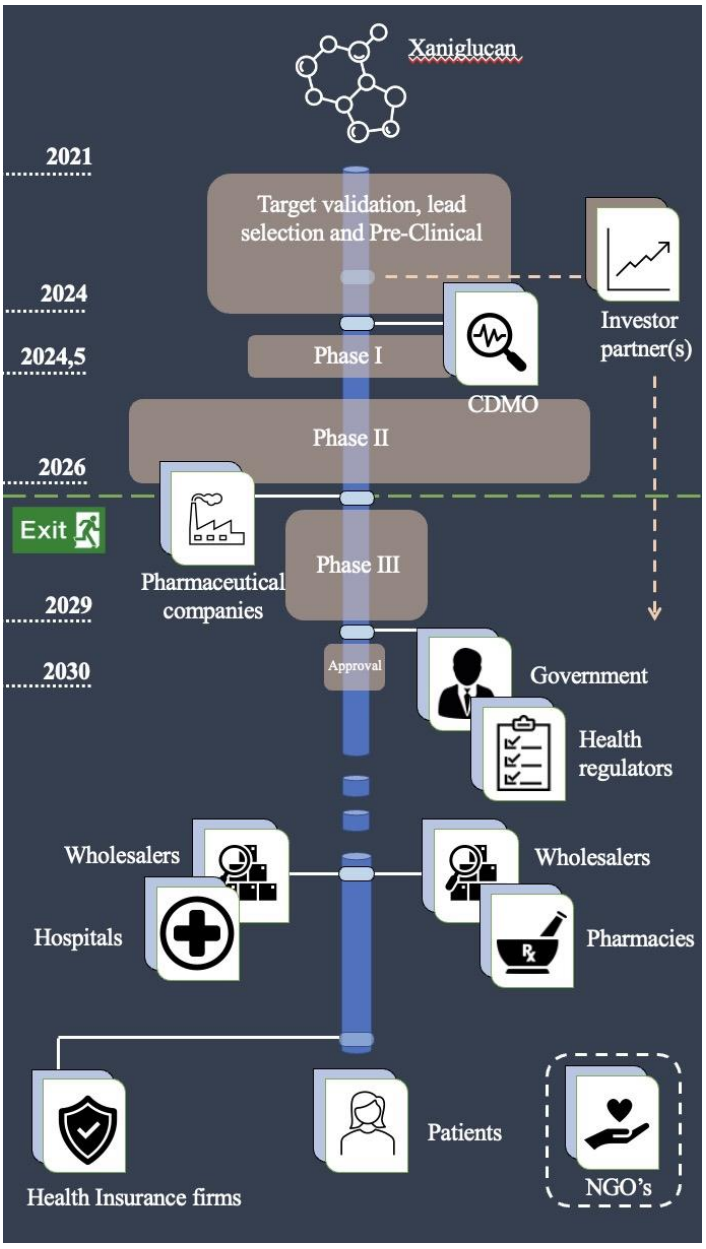

Figure 2 - Stakeholder map: the wideness of the rectangles represents greater associated risk of failing and the dotted green line, where the exit strategy is placed, divides the valley of death above. Most drug innovations fail to progress below this line (Zurdo 2013, 30) (Sun et al. 2022, 3050)

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APPENDIX

Interview notes

<u>Filipe Assoreira, MBA – Biotech Entrepreneur and Consultant</u>

In your point of view, since we are very early stage, what follows next?

New drug application to get to clinical stages

Considering our project and the early stage, what would be more appealing to pitch to investors?

Unique selling point, our competitive advantages

Strong points – low cost and unique in terms of fungi resistance

How should we get funded, and in what stages? Do you know ideal venture capital firms that would be suitable to our project?

EU Grants, VC or Business Angels.

VC, if they believe in the results, they'll only enter in Phase I.

There are Private Equity firms that invest in Pre-Clinical, if the patent is robust, followed with a need in the market.

Investival (https://www.lsxleaders.com/investival-showcase/our-story)

Depending on the innovation, you may have fast-track approval (cancer, orphan drug designation - big deals)

Antifungals and Antibiotic are not very attractive at the moment

Welcome foundation, Bill and Linda Gates foundation – for low-income countries

Given the nature and stage of our investigation, from your experience, what would you say could be the best? Continue to the market or sell the company at the end of 2nd stage?

Crunchbase and pitchbook for public information on exits

Regarding the Business model? Should we have different mock-ups along the phases? More alternative for each phase of development? Is it to early to draw a business model canvas?

Characterize the patient journey, how does the patient reach this point, and how he's treated. Then assume a percentage of the money, by simulating how many patients will be cured, how much money will come back in

What are the needs of Big Pharma? How should we get visibility to sell to Pfizer, or how should we approach? or should we focus small?

Needs proof that is adjuvant of Fluconazole.

Instead of Pfizer, since it is generic already, why not test the molecule to Fluconazole solely, to be defined a path after the Pre-Clinical

Other notes from the interview:

EIC it's a good set of money that would fit our situation. These grants you apply for them, and then if the project is good enough and there is market, they will give the grant à these grants will cover like 70% of the cash needed, the resting 30% should be private (VC or angel investors)

VC (check investivalia) might decide to enter already in Phase 1 if they are convinced about the results. Also, they would need the patent to be really robust and if there is a clear need. Orphan drug classifications is game changing (fast track (in some), longer time in the market, … other info that I had found already).

Antibiotics and anti-infectives are not very attractive currently.

Pharma directly or pharma VC (also other than VC, other foundations have programs we can apply to à but geographical distribution of the diseases? Crucial question in order to understand to which foundation applying).

How to be more appealing at this stage? Finding the USP

It's going to be cheaper (discuss the cost, not the price. It's also important in order to understand if low-medium countries could afford it), hopefully it will be more efficient.

CrunchBase and PitchBook databases

Testing the molecule already as a complementary molecule to fluconazole might be a good move, to have a proven value proposition for Pfizer in case it works.

1. Product for ambulatory (e.g.: aspirin)
2. Product exclusively sold in hospitals (e.g.: injectable paracetamol, many antibiotics) à these ones have generally a premium price

Business Model: probably unnecessary at this stage (in my opinion might be worth to show some business model canvas as we were planning to propose more than one way to develop this innovation and company)

Talking to doctors to have details about the patient journeys and see if it would makes sense to bundling with fluconazole.

André Rufino, MBA – Health Insurance Ecosystem Director at Medis

Does that work alike in Portugal somehow? Or is the Portuguese Government the only entity providing a co-payment to certain drugs?

Is true on US. However, in Portugal the insurance company pays in case of very expensive medicines used as a part of treatments in the Hospital.

If yes, how are medicines encompassed in the coverage?

The Portuguese Health system is comprised of 3 big investors: Health Insurance, Health Sub-Systems (ADSE, SAD-GNR, CAIXA, etc) and the Government.

Manage care (like US system) - Each insurance has a contracted network with "x" entities, and for each contract, the pricing is tabled (for every service and treatment).

In the ICU, a lot of things are in contract, which makes doctors follow a certain procedure since it's cheaper. Some drugs are in contracts (for instance oncology), however, general rule, the private hospital administers what they want, nonetheless, this will break the contract – professional litigation. Insurance only co-pay drugs that are also co-payed by the government.

Do you have in your knowledge, the inner workings of such a system, in different countries?

Doesn't know exactly.

How does the insurance network work? Money-flow wise

The business is like Spotify or Netflix. The client pays a subscription (according to characteristics, as age, etc.,) for services, they need to have a lot of people subscribed to be profitable. Margins are little, there is a calculation of the risk - average consumption per healthy individual.

How is the network chosen?

Big groups need to be in the portfolios, great amounts of money invested in big private Hospital chains, since it's where patients want to go to. Then the small clinics are managed with what's left.

Is the health insurance market influenced by a drug innovation?

Not at all. For example, when the Da Vinci surgical machine came out, there was a big commotion about it, but surgeries could be done all the same, so scientifically, there wasn't any reason for Health Insurances to abide to new innovations. They would lose money, or make the price per subscription more expensive.

Do you see Health Insurance as a partner to a new drug development? (If yes, how?)

It doesn't improve the Health Insurance companies.

André agrees to be apart of the Special Thanks section?

Yes, to be notified

<u>Dr. Cristina Toscano – Clinical Pathologist at Hospital Egas Moniz's Microbiology Lab</u>

A patient comes in, how does a Dr prescribe one type of antifungal? It obeys certain insurance company criteria? The doctor prescribes the same medicine due to force of habit?

By experience and pass knowledge basically

What about in the case of nosocomial invasive fungal infections, when the patient is immunosuppressed?

Past experience/ knowledge, or may contact other colleagues. In the case of new drugs, they may be not ready to use on the Hospital Pharmacy, they need to be ordered.

Do you see an increasing resistance of invasive fungal infections to its traditional treatment?

Yes, a greater record particularly in *Candida* and *Aspergillus*. We have a good capacity to detect and a good repertoire of antifungals. However, the number of resistant isolates is low. The existent drugs cover the need. But it's always good to have more molecules available, so we have different minimum inhibitory concentrations (MICs), absorption levels, being administered orally (easier) or intravenous (IV).

In the case of onychomycosis, drugs success rate is lower.

How does it come to your knowledge that a new drug is on the market?

Scientifical meetings, then the laboratory or pharmaceutical company markets the drug through ads, webinar, or delegate of medical information.

When and how is a combination therapy prescribed?

Only in despair/ when everything else fails that combine therapy is a choice. A benefit of this treatment is in patients with myelodysplastic syndrome and acute myeloid leukemia.

If an antifungal circumvents the resistance mechanism of the fungus, where all others had failed, would you hold a new medicine to be best-in-class?

If it works then yes, sure!

Extra info:

- New antifungals are very expensive.
- Fluconazole successor: Isavuconazole (Pfizer)
- Fluconazole no good for aspergillus
- EUCAST – European committee on antimicrobial susceptibility testing

- Medscape – panel web meeting about new drugs on the market

Dr. Ana Rita Domingues da Silva - Infectiologist at Hospital Beatriz Ângelo

A patient comes in and he has a fungal infection, how does a Dr prescribe one type of antifungal? Which criteria do you abide to make a prescription?

In Portugal, depends on the fungal infection, depends on the patient (common for old people, woman, immunosuppressed patients).

What about in the case of nosocomial invasive fungal infections, when the patient is immunosuppressed?

Depending on what you suspect, you'll be prescribed an indicated one. If it is resistant, you need to talk to the chief pharmacist at the Hospital, to know what's available for prescription. The infectious diseases committee also has a word on it. If nothing works, the hospital can borrow from another hospital. If not approved by Health Authority, but by European Medicines Agency (EMA), and expensive, it obeys to special criteria (everyone meets, doctors, head pharmacist, board of the Hospital and comitee).

Do you see an increasing resistance of invasive fungal infections to its traditional treatment?

Yes, over the years this has become common. Not a lot of IFIs, but past patients come back to the hospital, still on the drug to get rid of the fungal pathogen.

Is it true that Fluconazole is the most prescribed drug? Why?

Deals with most common infections, such as C. albicans, it's also cheap (very important factor) Also used as a combined therapy, in extreme cases (cryptococcus meningitis).

How does it come to your knowledge that a new drug is on the market?

Through a big pharma representative, it shows the scientific data. Also, through congresses. Googling it as well – metanalysis, clinical cases.

When and how is a combination therapy prescribed?

Not very common on candidemia.

If an antifungal circumvents the resistance mechanism of the fungus, where all others had failed, would you hold a new medicine to be best-in-class?

Yes of course, they'll have to see about the price, because it's a very important factor.

New MOA, would you be excited to know more?

Of course, the Comissão de Controlo Hospitalar would be interested to know more about that. If is effective and saves people, then there will be interest

How much time until resistance would be developed?

Depends on a lot of things, not easily answered, the more the fungi is exposed the faster it will gain resistance.

What do you have to say about *C. glabrata*?

We are seeing more and more, especially in the ICU. The drug resistance is increasing in neutropenic patients (lower neutrophile count).

A great number of antifungal drugs have a tool on the liver (hepatic function) and kidneys (Amphotericin B).

C. glabrata is part of our digestive track, so any case of rupture, since they're opportunistic by nature, if you have an imunosuppressed condition, most likely it will cause Candidemia.

Tratements need to start with a high (normal dose), then it's lower. Otherwise, if it is exposed to a small amount, we open a chance for resistance to be acquired. Some cases, bacteria switch genes with each other.

Bruno Tubarão, MSc – Pharmacist

Personal friend of Miguel was interviewed by means informal conversation about how the journey about from study proposal to selling points, pharmacy and hospital works. New info gathered about INFARMED procedures and unknown stakeholder – the wholesaler, and how the drugs are marketed from lab/ pharmaceutical company (via delegate of medical information).

Abbreviation Index

AIFA – Italian Medicines Agency

BfArM – The Federal Institute for Drugs and Medical Devices

C. – *Candida*

CMO – Contract Manufacturing Organization

CRO – Contract Research Organization

EMA – European Medicines Agency

EU – European Union

FDA – US Food and Drug Administration

ICU – Intensive Care Unit

IFI – Invasive Fungal Infection

IPO – Initial Public Offering

IV – Intervenus

M&A – Mergers and Acquisitions

MIC – Minimal Inhibitory Concentration

MOA – Mode of Action

NDA – Non-Disclosure Agreement

PCT – Patent Cooperation Treaty

R&D – Research and Development

ROI – Return on Investment

SDG – Sustainable Development Goals

Spp. – Species

UN – United Nations

VC – Venture Capital

Limitations

Within every project, there are always mishaps. Agendas that once idealized, upon realization, everything would be perfect. Unfortunately, in reality, that is not the case. Several companies from other stakeholders were contacted via LinkedIn, Web-site email, and friends' referrals, but

regretfully, denials and no replies limited our validation of assumptions, despite several tries. Nonetheless, all our efforts were channeled, as best we could, to come with the most solid case, with the resources that we possess.

Special thanks

I would like to humbly give my appreciation to the people that have contributed directly to the development of this thesis, them being: Professor Nuno Arantes-Oliveira, for his availability, wisdom and kindness. The researchers Ana Petronilho, PhD and Catarina Pimentel, PhD, and expert Pedro Pedrosa, PhD, for their patience and trust, explaining us (management and entrepreneurship students) core aspects of fungal infections, chemistry, and intellectual property protection. Filipe Assoreira, MBA, for is brilliant insights in life sciences investing and ecosystem. André Rufino, MBA, for his clarification and wisdom on how the 3 main healthcare systems cover part of medical expenses, and their importance in the ecosystem. Dr. Cristina Toscano on her solid knowledge on infectious diseases in the laboratory. Dr. Ana Rita Domingues da Silva for her insightful version of the facts, on how infectious diseases are treated, from a customer journey point of view. Bruno Tubarão, MSc, for is availability to help, showcasing how does the ecosystem works from a pharmacist point of view and extra information on Infarmed processes to approve new drugs. Special thanks also to friends, family and acquaintances that are always ready to motivate and insight us to keep on going.

To everybody, my special and profound: “thank you!”