# Diaβiologics LLP

## Business Plan

THEBIGPIE

Beta cells In Gut Producing Insulin using E.coli

**Team IISER Bhopal 2020**

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# Table of Contents

# List of Figures & Tables

**List of Figures**



**List of Tables**

# Executive Summary

India, the diabetes capital of the world, is home to a whopping 77 million diabetics[1]. Diabetes can be treated either by oral hypoglycaemics or by using insulin injections with 4 in 10 diabetics in India and the Gulf using the latter[2]. Oral medications may lead to unexpected hypoglycaemia if the dose is not titrated while insulin injections have the added disadvantage of pain, scarring and rashes. With success stories on oral insulin far away from the horizon newer approaches are imperative. We present an out-of-the-box approach to tackle diabetes - **“iβeta”**.

iβeta is an affordable bio-therapeutic in capsule form that will reprogram the duodenal crypt cells by transdifferentiation into glucose-responsive β-islet-like cells. iβeta will facilitate the normal production of insulin by the body, in a glucose-responsive manner, overcoming unexpected hypoglycaemia associated with conventional therapies. It will help diabetic patients lead a normal life, without diet restrictions & is not likely to have adverse effects on long-term usage as seen in the current therapy.

iβeta is proposed as a capsule, requiring no special manufacturing facilities. The pricing being affordable it can cater to a large population and result in insulin substitution leading to enhanced quality of life over a period of time. The current Indian diabetes market is valued at INR 145 billion and is growing at a CAGR of 16.7%[3]. iβeta will enter the market in about 12 years when the estimated market size is likely to be INR 925 billion. In the first year of launch, we plan to achieve sales of INR 200 million followed by exponential growth. iβeta will bring about a disruptive change in diabetes treatment using the inestimable potential of synthetic biology. Irrespective of market growth, it will shift the market of insulin users towards a safe and easy-to-use alternative. Significantly, the poorer population of India will get an affordable alternative with most of them not adept at injecting themselves with insulin.

# Assumptions

The business plan has been drafted after making the following assumptions:

1. No drastic change in diabetes treatment methods likely to occur in the next 10-12 years
2. After evaluating the current market and the research trend as available in public domain, it is unlikely that a similar product may appear in the market during the next 15 years

# 1. Business

## 1.1 Company Description

The BIG-PIE is a brainchild of a team of inter-disciplinary students from the Indian Institute of Science Education and Research (IISER) Bhopal interested in improving the quality of life using synthetic biology. The team plans to set-up a start-up, Diaβiologics, as a Limited Liability Partnership (LLP) Company.

Diaβiologics LLP aims to develop novel, and affordable solutions for diabetes, related complications and other diseases. We are a product and Research & Development company based out of Bhopal, MP, India focused on harnessing the inestimable potential of synthetic biology to help the society at large.

Our flagship product is a therapeutic for diabetes, based on the principle of transdifferentiation. Our delivery vector, E. coli Nissle would be programmed to attach to crypt cells through expression of a crypt cell-specific antibody Lgr5 followed by injection of the three transcription factors - PDX1, MAFA & NGN3 - via the Type 3 Secretion System into the cells to convert them into glucose responsive beta-islet like cells. iβeta  provides us with a renewable income stream as customers must regularly purchase the same for treatment..

Our principal market is within the healthcare sector. Our first generation product will allow us to move into various markets over time. Next generation products will include therapeutics and early-diagnosis tools for various diabetes-related complications and other diseases.

We have taken an out-of-the-box approach to tackle and developed a technology with distinct advantages compared to competing products. The competitive advantage, particularly in this rapidly growing market segment has been elucidated in the later sections of the document.

## 1.2 Vision & Mission

Diaβiologics LLP envisions to become a leading provider of innovative, user-friendly and frugal solutions to treat diabetes, related complications and other diseases. We are guided by the conviction that such life-saving therapy must be made easily accessible to people from all economic strata in India and abroad.

### 1.3 Values

We strongly believe in and will abide by the following ethical and professional principles:

- **Service:** To find novel solutions to global problems
- **Efficiency:** Achieving affordable excellence without compromising on quality and providing goods and services to our customer at a competitive price
- **Responsibility:** We are responsible for the safety of our customers and our environment. We seek to build relationships with our stakeholders based on mutual trust

### 1.4 Location

Diaβiologics LLP will begin its journey at the Innovation and Incubation Centre for Entrepreneurship (IICE), IISER Bhopal. In a few years, the company will relocate its base of operations to the Mandideep Industrial Area in Bhopal, Madhya Pradesh, India

### 1.5 Registration

Diaβiologics will be registered as a LLP with the Ministry of Corporate Affairs (MCA), India. The registration process of an Indian LLP is summarised in the table below[4]:

**Table 1:** Procedure for registering an LLP in India

| Step | Task | Documents & Approvals |
|---|---|---|
| 1. | Application for Designated Partner Identification Number (DPIN) | **e-Form DIR-3** |
| 2. | Acquire/Register Digital Signature Certificate (DSC) | Approach the Certifying Authority with original supporting documents and self-attested copies of the same as specified by the MCA followed by registration on the MCA portal |
| 3. | New user registration | Register on the LLP portal as a New user to file the relevant forms |
| 4. | Incorporate a LLP | **Form 1**: Application for reservation or change of name; **Form 2**: Incorporation Document and Subscriber's statement. The approval of the form will be intimated through an email |
| 5. | File LLP Agreement | **Form 3**: Information with regard to LLP Agreement and changes, if any, made therein, should be filed within 30 days of incorporation |

### 1.6 Organization

All the members of the iGEM IISER Bhopal 2020 team will be partners in Diaβiologics LLP. The R&D team of our company will be headed by the Principal Investigator of our team. One of the partners of the company will be appointed as the CEO. The proposed administrative structure of Diaβiologics LLP is as shown below.

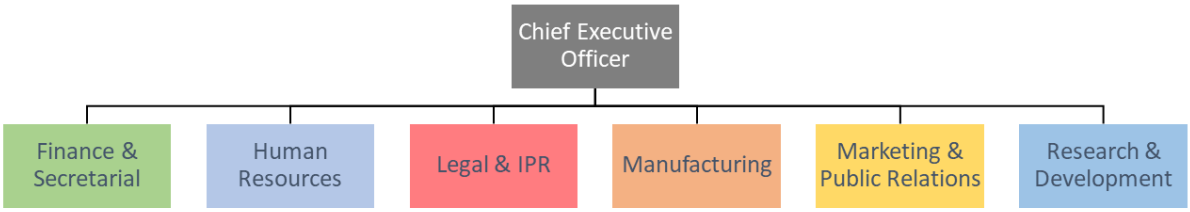


**Figure 1:** Organizational Structure of Diaβiologics LLP

### 1.7 Team

Our iGEM teams consists of undergraduates focussed on Biology, Chemistry, Physics and Engineering disciplines. Hence, our present group has a good scientific background and we lack expertise in the production, marketing, finance, legal, secretarial and HR aspects.

Keeping this in mind, we'd be looking for experts in the following divisions of our company in addition to other employees.

| Finance & Secretarial | Marketing & PR | R&D and Manufacturing |
|---|---|---|
| Chief Finance Officer<br>Company Secretary<br>Accountants | Medical Representative<br>Product Manager<br>Business Analyst<br>Market Experts | R&D Head<br>Scientists<br>• Synthetic Biology<br>• Biochemistry<br>• Cell Biology<br>• Genetics<br>• Human Physiology<br>Engineers<br>• Software<br>• Hardware<br>QC Manager<br>Operating Staff<br>Industrial Design Experts |
| **Human Resources** | **Legal & IPR** | |
| HR Manager | Patent Attorneys<br>Legal Executives | |

**Figure 2:** Diaβiologics LLP - Team

All the above positions will be inducted gradually into our company's framework. At the appropriate time the job specification for each heads will be decided

In case we are unable to attract the required skill set to our company, we will approach local and national institutes and offer internships to students with the necessary skillset along with a reasonable stipend or make the salary more competitive for the offered position.

# 2. Products and Services

Diaβiologics LLP aims to become a leading provider of diabetes solutions and presents its first product: **'iβeta' - a biotherapeutic**.
iβeta consists of genetically engineered *E.coli Nissle 1917*, an FDA approved probiotic that can reprogram duodenal crypt cells into glucose responsive β-islet-like cells. iβeta is an out-of-the-box product, positioned as a non-invasive alternative to insulin injections and oral hypoglycaemics.

### 2.1 Literature Support

Our proposition is primarily supported by existing evidence on the efficacy of cellular reprogramming mediated by PDX1, MAFA and NGN3 on our target niche along with the ability of Type III Secretion Systems (T3SSs) to deliver factors to the nuclei of target cells, including transcription factors intended to effect reprogramming.

The three transcription factors, when expressed in mice using a viral vector[5], were able to transform cells in the crypts of the duodenal and jejunal epithelium into cells resembling $\beta$-islet cells, capable of glucose-responsive, monohormonal insulin production. The effect of the factors was large enough to alleviate hyperglycaemia in STZ-treated mice. Similar results were observed in human intestinal organoids. More broadly, $\beta$-islet replacement therapy[6] has long been explored as a means to manage diabetes, with several independent lines of evidence demonstrating its effectiveness, both *in vitro* and *in vivo*.

Type III Secretion Systems[7] are rapidly emerging devices with the potential to deliver therapeutic factors *in vivo*. They have been explored as delivery vehicles for a variety of curative and preventive agents[8], including vaccines and anti-cancer factors. They have also, *in vitro*, proven to be able to deliver transcription factors for cellular reprogramming[9]. The T3SS of our choice[10], being derived from an enteric bacterium, is very likely to possess the ability to deliver to our cells of interest namely $Lgr5^{+}$ crypt base columnar cells[11].

### 2.2 Goals & Objectives

The goals and objectives that Diaβiologics LLP plans to achieve are:

- To create an innovative, non-invasive and viable alternative for diabetes treatment using synthetic biology
- Reduce or even eliminate the dependence on insulin
- To ensure safety of our product iβeta for human use
- To simplify and optimize the process of manufacture of iβeta

### 2.2 Action Plan

Diaβiologics LLP will complete preliminary research and development of iβeta at IICE, IISER Bhopal. The first prototype developed will be tested at the Animal and Fly facility at IISER Bhopal by taking appropriate ethics committee approvals. The drug will be manufactured in a Good Manufacturing Practices (GMP) laboratory[12], to ensure consistent high quality of the product. Stability and toxicity studies will be carried out according to International Conference for Harmonization (ICH) and Organisation for Economic Co-operation and Development (OECD) guidelines respectively. The pre-clinical data generated at IISER Bhopal will be used to make appropriate modifications and improvements to iβeta before proceeding towards Phase I clinical trials.

### 2.3 Proof of Scalability

Pilot batches of iβeta will be manufactured in GMP laboratories for clinical studies. Subsequently, large scale batches will be initially outsourced, followed by manufacturing in our own facility. The safety standards, as laid down by the Central Drugs Standard Control Organisation (CDSCO) in India and the respective drug control authorities abroad, will be adhered to very strictly. Multi-layered safety designs will be put in place to ensure patient safety.

### 2.4 Patents & Trademarks

The trade names Diaβiologics LLP (company) and iβeta (product), will be protected by trademarks to ensure exclusivity of their usage.

Diaβiologics LLP will file for a product patent for iβeta to maintain exclusivity of sales during the early marketing phase. This was discussed with an expert from the Institute of Chemical Technology, Mumbai who had suggested that we must also file a process patent if there is an inventive step involved in the final, optimized protocol for manufacture of iβeta.

The breakdown of the cost for filing and maintaining an Indian Patent (Natural person(s) and/or Start-up) as of October 2020 is as follows[13]:

**Table 2:** Fees for Indian Patent Application

| On What Payable | e-Filing (INR) | Physical filing (INR) |
|---|---|---|
| On application for a patent under sections 7, 54 or 135 and rule 20(1) accompanied by a provisional or complete specification | 1,600 | 1,750 |

| | | |
|---|---|---|
| On filing complete specification after provisional up to 30 pages having up to 10 claims | No Fee | No Fee |
| For each page of sequence listing of nucleotides and/ or amino acid sequences under sub-rule (3) of rule (9) | 160/page (max. 24,000) | Not allowed |
| **Renewal of Patent(s)** | | |
| Years 3, 4, 5 & 6 | 800 p.a. | 880 p.a. |
| Years 7, 8, 9 & 10 | 2,400 p.a. | 2,650 p.a. |
| Years 11, 12, 13, 14 & 15 | 4,800 p.a. | 5,300 p.a. |
| Years 16, 17, 18, 19 & 20 | 8,000 p.a. | 8,800 p.a. |

To protect iβeta upon international expansion, Diaβiologics LLP will also file for a PCT patent. The fees for a PCT application filed in India for a small entity are as follows[14]:

**Table 3:** Fees for PCT Patent Application

| On What Payable | e-Filing | Physical filing |
|---|---|---|
| Transmittal Fee | No fees | INR 17,600 |
| Search Fee | INR 10,000 | INR 10,000 |
| Preliminary Examination Fee | INR 10,000 | INR 10,000 |
| International Filing Fee | USD 1,337 | USD 1,337 |

### 2.5 Pricing

Initially, we had thought that iβeta could be marketed and sold as a probiotic. However, upon discussion with experts from CDSCO, we were informed that iβeta will be classified as a "New Drug" since it will have pharmacological effects. Furthermore, iβeta is classified as a "Schedule H Prescription Drug" and hence it's price will also be regulated by the Drugs Prices Control Order (DPCO). The sales price will vary based on the negotiated agreements established between Diaβiologics LLP and super-distributor. For further details, please refer to Sections 4. Sales and Distribution and 5. Finances.

### 2.6 Unique Selling Proposition

- **User-friendly:** An orally administered capsule containing freeze-dried bacteria with a kill switch
- **Low frequency of use:** Once every few days  as opposed to few times a day
- **Specific:** Specifically binds and modifies the duodenal crypt cells
- **Innovative:** An alternate, synthetic biology approach to tackle diabetes and improve patients' quality of life
- **Non-invasive:** No more scarring and rashes due to injections!
- **Self-sufficient:** Helps your body secrete insulin naturally in response to fluctuating glucose levels. Hence, no unexpected hypoglycaemia
- **Safe:** No adverse effects on long-term use

### 2.7 Minimum Viable Product

The minimum viable product for iβeta is an easy-to-use capsule containing genetically modified *E.coli Nissle* 1917 that can transform duodenal crypt cells into glucose-responsive β-islet-like cells. The bacteria will specifically bind to intestinal crypt cells and inject three transcription factors into them to bring about the above-mentioned transformation. Discussion with immunologists at IISER Bhopal has indicated that generation of an immune response as a result of the reprogramming of the duodenal crypt cell into a glucose-responsive β-islet like cell is highly unlikely.

### 2.8 SWOT Analysis

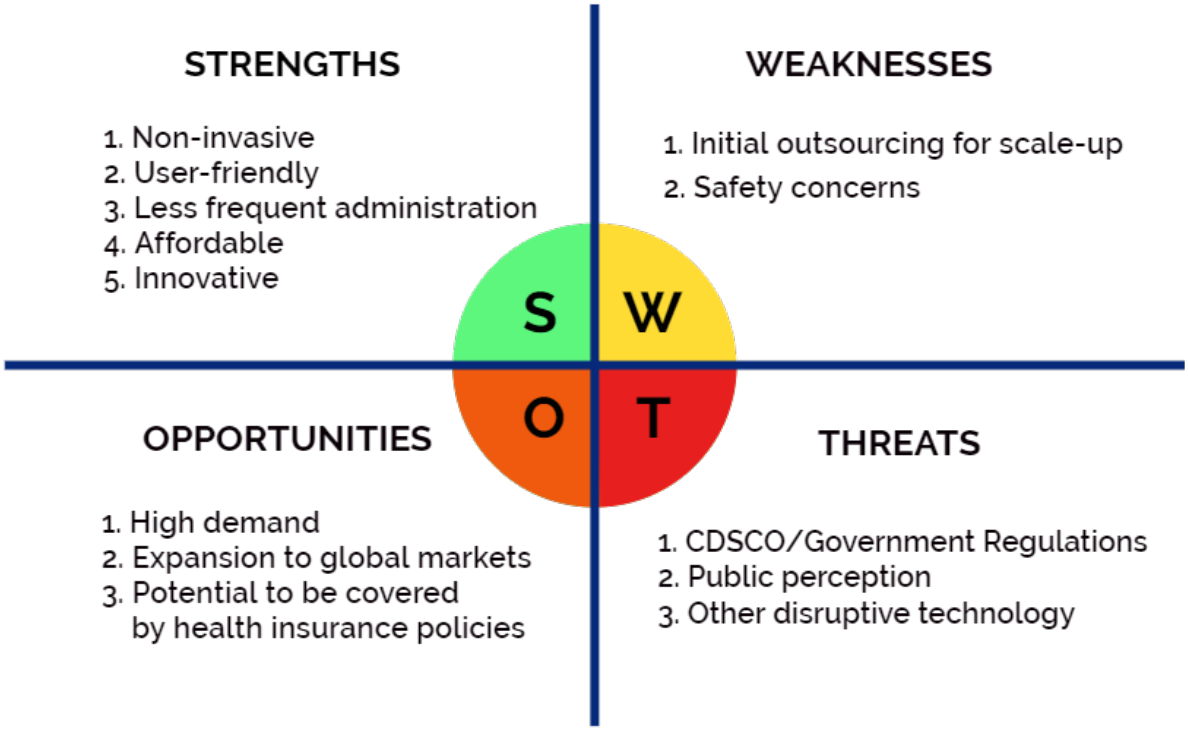


**Figure 3:** SWOT Analysis of iβeta

## 2.9 Risk Assessment

**Table 4:** Risk Assessment

| **Risk Factor** | **Likelihood*** ***Scale: 1-10*** | **How to avoid the risk?** |
|---|---|---|
| **External** | **5** | |
| Economic risk | 3 | The effect of any economic turmoil is likely to be low as iβeta will be an essential part of daily medicine to mitigate health risk. Public health programme may eventually approve iβeta as a part of national programme where economic risk will be negligible. |
| Policy Risk | 4 | Change in policy by the Government may result in lowering of import cost, increase in duties, levies etc which may affect competitive pricing and thereby sales. |
| Political risk | 5 | This manifests in the form of imports getting affected due to relationship between countries changing periodically. |
| Cultural risk | 8 | Educating the general public about synthetic biology to uproot the lingering fear regarding GMOs in their mind. A strong marketing campaign which highlights the benefits of iβeta over conventional therapy would be the key to success. |
| Technological risk | 5 | Keeping an eye out for disruptive technology in the field and advancement in the field of allopathy and alternative medicine and adapting iβeta to such changes are key mitigating factors. |
| Trade Treaty risk | 5 | The WTO being the fulcrum for major changes in multilateral treaties is currently seeing a significant amount of protectionism from member countries which could affect international marketing of iβeta. Bilateral treaties may mitigate the risk to some extent. |
| Currency Risk | 5 | Exports and imports will face currency risk which will be mitigated by careful hedging policy to minimise open positions. |
| Development of the industry | 4 | Diabetes is a lifestyle disease and the market shows a positive trend with an increase in urbanization, Although iβeta is a novel product, a strong market presence should help us maintain a competitive edge. |
| The market & customers | 1 | Diabetes is not geographically restricted and hence does not pose a huge threat to the market size. A gradual expansion to create a global presence will mitigate this issue. |
| Competition | 5 | Patenting our technology will ensure exclusivity of production rights giving us an edge over competitors. |
| **Internal** | **5** | |
| Organization & human resources | 4 | Team building seminars, positive reinforcement and leadership boot camps will be organised to foster healthy relationships among the employees and to create a sense of belonging. Flexible work timings |

| | | |
|---|---|---|
| | | and an option to work from home will also ensure increased productivity. |
| Production risk | 4 | We will develop optimal protocols that enable fast, economic and reliable production of iβeta, without compromising on quality. |
| Finance risk | 6 | Applying for Government funding opportunities for start-ups as well start-up expos. Developing a network of long-term investors and reallocating positive cash flow effectively to ensure sustainability. |
| **Product** | **3** | |
| Immune response | 3 | Generation of an immune response in response to reprogramming intestinal cells is a significant risk. Experts have indicated that this risk is minimum. This will be investigated and validated during clinical trials. |
| Oncogenesis | 4 | Activation of β-catenin to oncogenic state poses a risk of causing cancer due to the reprogramming. The design of iβeta has been modified accordingly to mitigate this risk. |
| Impact on intestinal function | 1 | There is a remote possibility of a direct impact on intestinal function. This risk is however very close to zero as tissue samples taken from animal models whose cells were transformed did not have any abnormalities |

# 3. Market Analysis

## 3.1 The Indian Market Scenario

### 3.1.1 Diabetes Market

The diabetes market in India was valued at about INR 145 billion in 2019 and is expected to grow at a rate of 16.5 % p.a. to reach INR 360 billion by 2025[3].At the current growth rate, in the next 12 years, the market will explode to a size of INR 925 billion.

There are approximately 77 million diabetics[1] in India with this number expected to exceed 100 million by 2030[1]. Type 2 diabetes accounts for over 95% of all diagnosed cases. Indians spend INR 35,000 to INR 75,000 per annum[15] for routine diabetes care and complications caused by the condition may increase the annual cost by up to 5.5x[15].

The major drivers of the industry include increasing awareness, population and incomes along with a decrease in manufacturing cost among many others[15]. Fuelled by a continuous increase in healthcare expenditures, the market for diabetes drugs and diagnostics is expanding robustly in the country.

### 3.1.2 Insulin Market

The Insulin market in India has seen a growth of 13.9% (CAGR) between financial years 2008 and 2013[17] and is valued at approximately INR 62 billion in 2019. The market is witnessing tremendous development and is yet to mature. With the second largest number of diabetics globally, it is estimated that only 25% of this population is receiving the necessary treatment[17]. Lack of awareness backed by low-affordability has marred the ambit of treatment and hence, left the major diabetic populace untreated. The astounding growth rate of the insulin market has made the Indian market bankable for multinationals.

### 3.1.3 Oral Anti-diabetes Drugs Market

The oral anti-diabetes drug market in India is valued at INR 83 billion and is growing at a CAGR of 11.21%[18]. In the Indian drug market, three oral anti-diabetes drugs had featured in the top 10 most selling drugs in 2016 with a total annual sales of INR 8.83 billion[19]. The oral anti-diabetes drug market in India is promising and growing at a good double-digit rate.

## 3.2 Market Segmentation

Our market segment initially focuses on India to analyse and understand product demand, price sensitivity, marketing and production cost, scalability and also the demand supply ratio. The launch in India will be followed by expansion to countries having a large diabetic populace (USA, China, etc.) and subsequent expansion to Europe & Australia. The demography being targeted is people above the age of 20 suffering from diabetes. The prevalence of diabetes is higher in urban areas as

compared to rural areas due to a sedentary lifestyle of majority of the working population, with the 40-59 years age group being the most affected. Hence, our focus will initially be on urban areas and we will ensure rapid expansion to rural areas to make iβeta widely available.

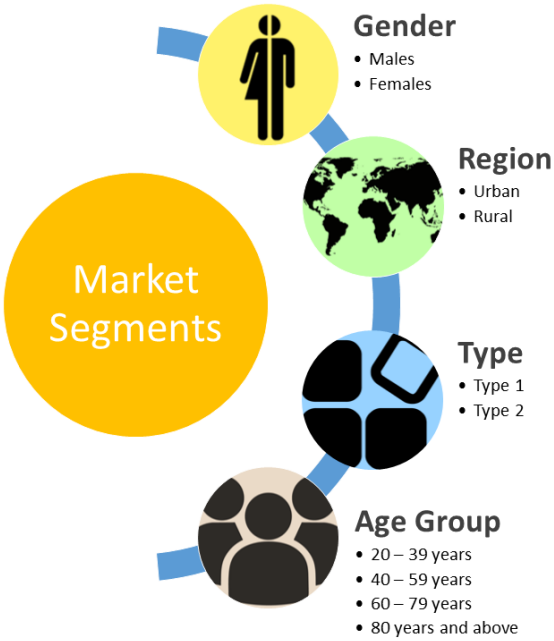


**Figure 4:** Market Segmentation

### 3.3 Customers & End-users

The targeted customers for iβeta are hospitals, clinics and pharmacies, the end-users being diabetes patients. iβeta will be classified as a 'Schedule H' prescription drug and can be sold to the end-users only with a doctor's prescription. The drug will be made available throughout the country by a dense network of distributors, stockists and retailers.

#### 3.3.1 Consumer Demographic

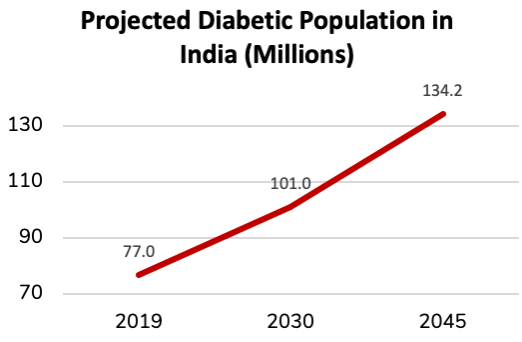


**Figure 5:** Diabetic Population in India[1].

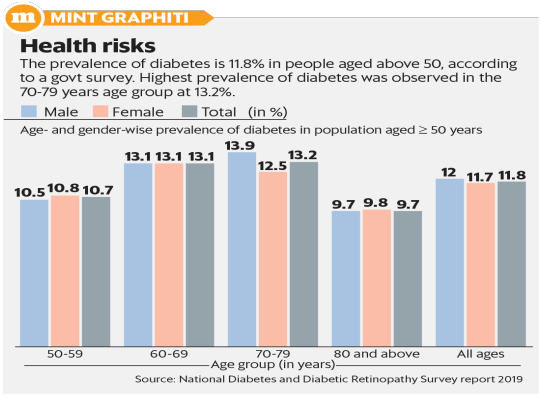


**Figure 6:** Diabetes Prevalence by Age Group[20]

Diabetes, a lifestyle disorder occurs as two major types: Type 1 and Type 2. The prevalence of diabetes is similar in both men and women with a slightly higher percentage of men affected[20]. A higher number of diabetics are found in urban areas as compared to rural areas[21] and this can be attributed to the changing

lifestyles of people. The diabetic populace also shows an increasing trend with age. A majority of the diabetes cases in India are of Type 2 Diabetes[22]

### 3.3.2 Geographical Distribution

In India, the prevalence of diabetes is significantly higher in the south(Figure 6(a)). With 77 million diabetics as of 2019[1], India serves as a great starting point for Diaβiologics LLP. Diabetes is not geographically restricted (Figure 6(b)) and hence we will gradually expand to other international markets.

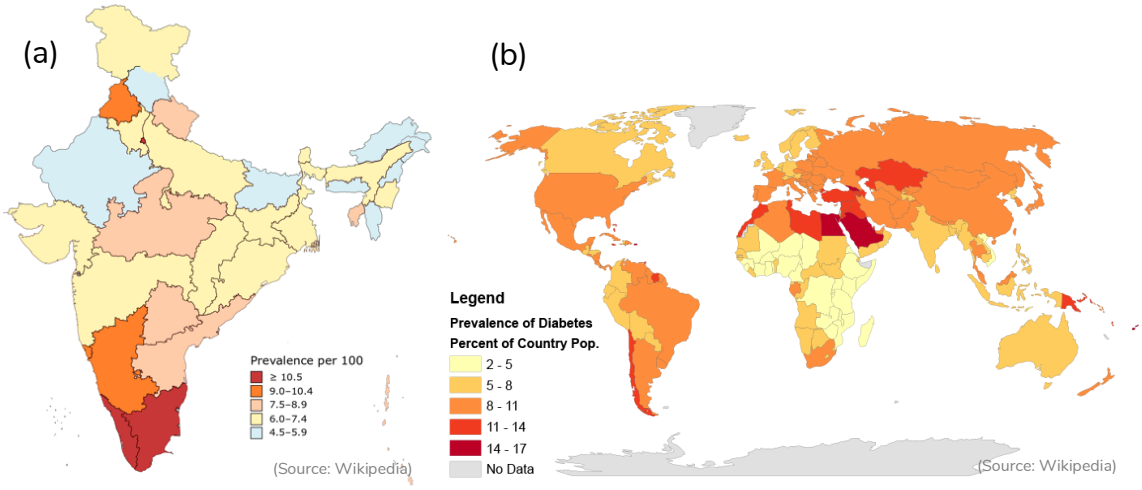


**Figure 7:** Geographic Distribution of Diabetes Patients in (a) India[27], (b) Global[27]

### 3.3.3 Socio-economic Distribution

iβeta is an out-of-the-box, novel and affordable alternative to insulin injections and other oral hypoglycaemics. Hence, the socio-economic status of the patient is not a crucial factor to ensure accessibility.

Lifestyle changes resulting from migration towards urban areas and industrialization along with other environmental and genetic factors are the main reasons for an increasing diabetic populace[23].

## 3.4 Survey Insights

We circulated a survey among people (*all iGEM and Institute guidelines were followed*) to understand their preferred dosage form and also the factors that they consider while choosing a medicine. We asked them to choose (one or more) between injection and oral formulations. From the 119 responses for the question, tablet/capsule emerged as the preferred dosage form. Based on this data obtained, we decided that iβeta will be designed as an orally administered capsule containing freeze-dried, genetically modified bacteria.

In the same survey, people were also asked the factors that they take into consideration while choosing a drug. Side effects, cost and ease of use were the top three followed by doctor's prescription and peer recommendations (n=119).

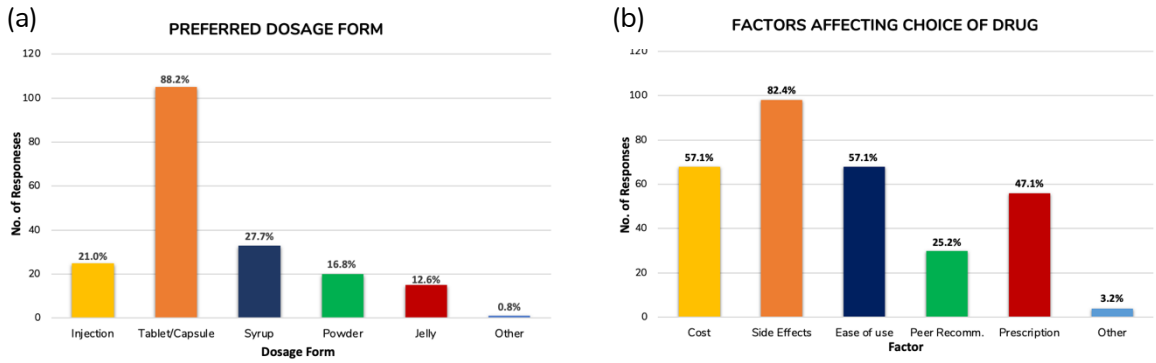


**Figure 8:** Survey Results (a) Preferred Dosage Form (b) Factors affecting choice of Drug

As stated earlier, iβeta is an easy-to-use, affordable capsule. However, to further increase affordability, Diaβiologics LLP will try to get iβeta under the ambit of national health programmes and insurance companies. Careful consideration has also been given to the design of iβeta to minimize the probability of side-effects.

iβeta has been carefully designed for patient compatibility and the highest priority has been given to safety and patient needs.

### 3.5 Stakeholder Analysis

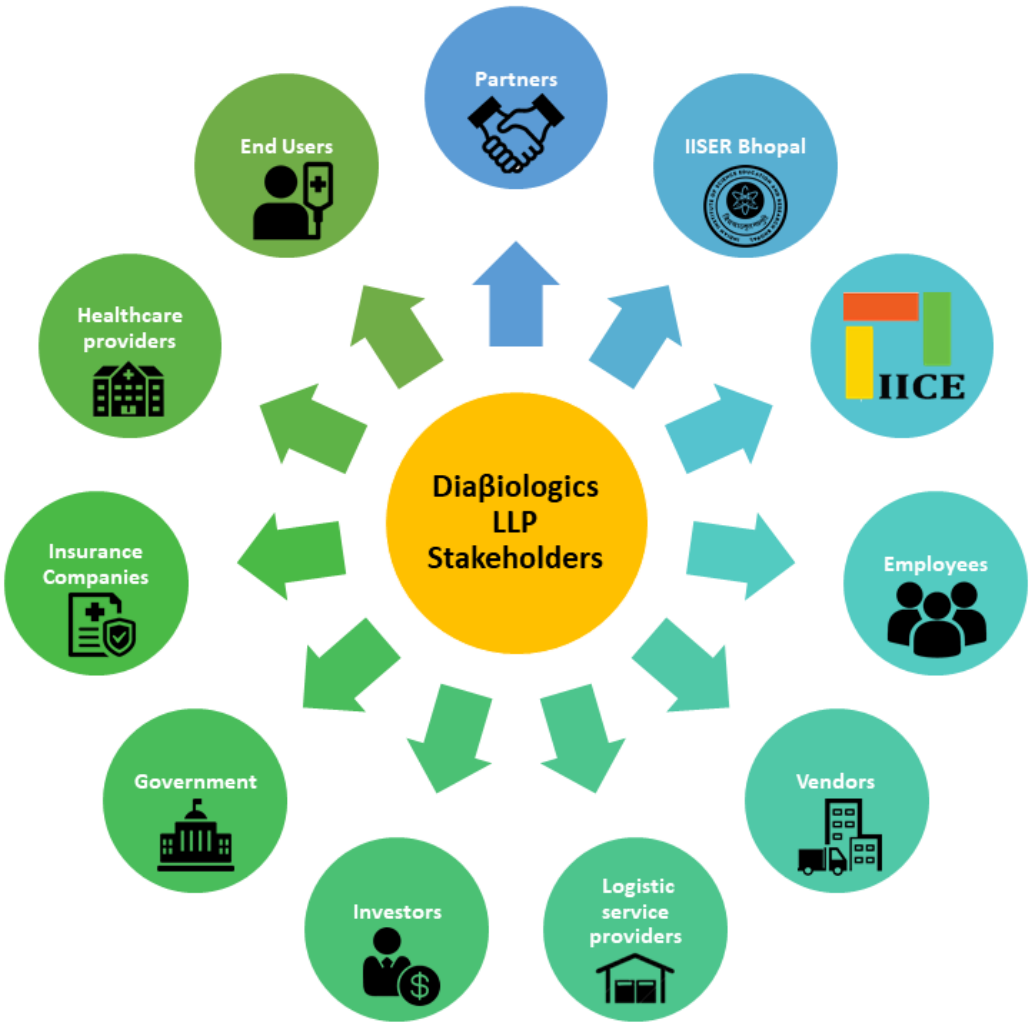


**Figure 9:** Stake holders for Diaβiologics LLP

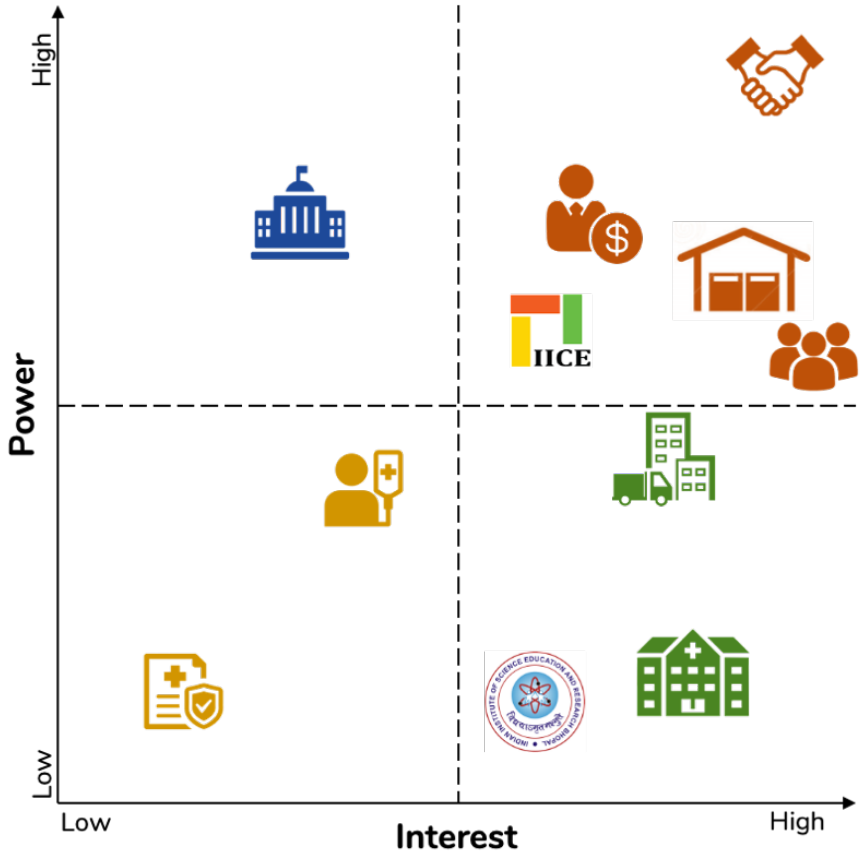


**Figure 10:** Power-Interest Matrix

All stakeholders will play an important role in ensuring the success of Diaβiologics LLP. Every stake holder is extremely important to us and all opinions will be taken into consideration before taking any major decisions.

### 3.6 Competition Analysis

There are well established national and multinational companies in the diabetes market in India. Although they are competitors, they will not significantly affect business as their areas of focus are different and Diaβiologics LLP's iβeta is very different from currently available products.

**Table 5:** Competition Analysis

| Competitor Name | Est. Year | Global presence | Product Description | Product Price | Strengths | Weakness |
|---|---|---|---|---|---|---|
| **Novo Nordisk** | 1923 | 180 countries | Insulin vials, cartridges, pens and pumps | ₹150 to ₹5,500 | Best therapeutic available | Scarring and rashes at the site of injection, hypoglycaemia |
| | | | Oral anti-diabetic: Repaglinide | ₹13 to ₹25 per tablet | Can treat T2 diabetes without other medicine | Side effects, dietary restrictions, interacts with other medicine |
| **Sanofi S. A.** | 1973 | 170+ countries | Insulin vials, cartridges & pens | ₹140 to ₹3,000 | Best therapeutic available | Scarring and rashes at the site of injection, hypoglycaemia |
| | | | Oral anti-diabetic: Amaryl | ₹4 to ₹20 per tablet | Decreases insulin absorption and glycogenolysis | Many side effects and interacts with other medicines |
| | | | Daonil | ₹25 to ₹50 per tablet | Stimulates the release of insulin from the pancreas | Depends on functional beta cells |
| **Eli Lilly & Co.** | 1876 | 125 countries | Insulin pens and cartridges | ₹650 to ₹2,500 | Best therapeutic available | Scarring and rashes at the site of injection, hypoglycaemia |
| | | | Nasal Powder: BAQSIMI | ₹20,500 per pack | Nasal glucagon delivery to treat hypoglycaemia | Nausea, Nosebleed, watery eyes, etc. |
| **Biocon** | 1978 | 120+ countries | Insulin vials, cartridges & pens | ₹150 to ₹1,000 | Best therapeutic available | Scarring and rashes at the site of injection, hypoglycaemia |
| | | | Oral anti-diabetic: BLISTO | ₹5 to ₹15 per tablet | Stimulates the release of insulin from the pancreas | May trigger allergy, other side effects include light-headedness |
| **Wockhardt** | 1960 s | 20 countries | Insulin vials, cartridges & pens | ₹150 to ₹500 | Best therapeutic available | Scarring and rashes at the site of injection, hypoglycaemia |

The diagram below allows easy visualization of the market niche the Diaβiologics LLP plans to create in the diabetes market.

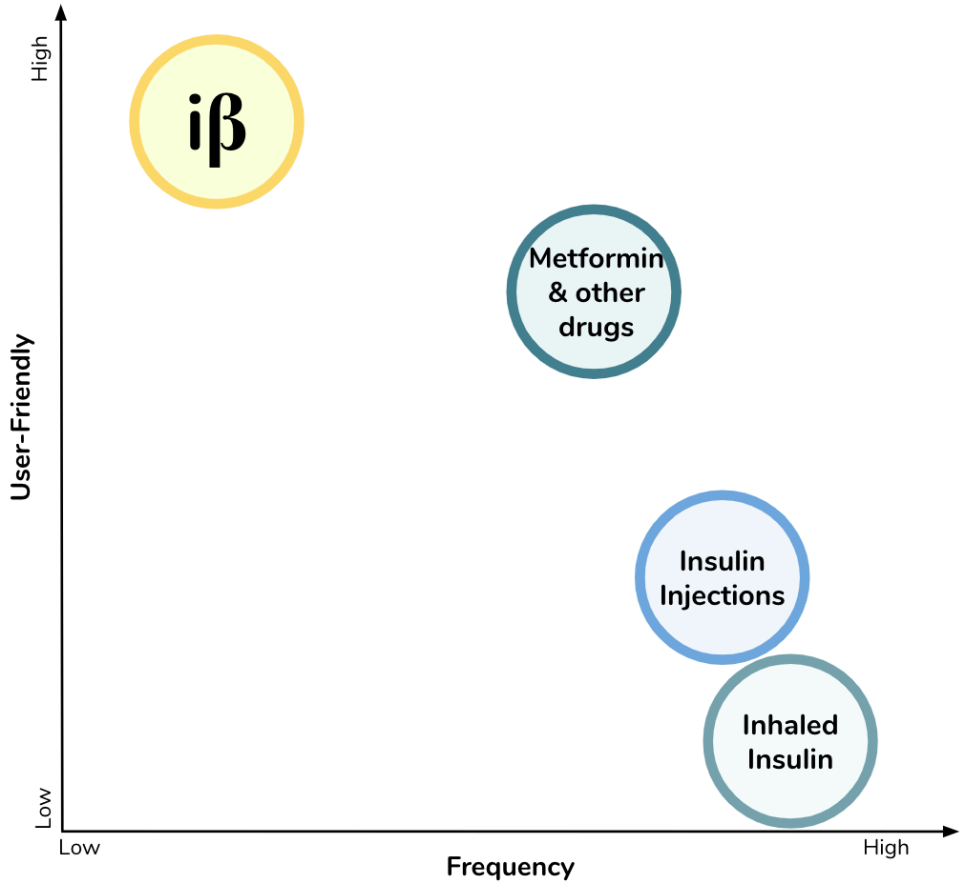


**Figure 11:** iβeta - Comparison with Conventional Therapies

iβeta will be a low-frequency, high user-friendly drug. iβeta reprograms cells in the intestinal epithelium which are replaced once every 3 to 4 days. Hence, the frequency of administration of iβeta will be drastically lower as compared to current alternatives - once in a few days instead of a few times a day.

# 4. Sales and Distribution

## 4.1 Supply Chain

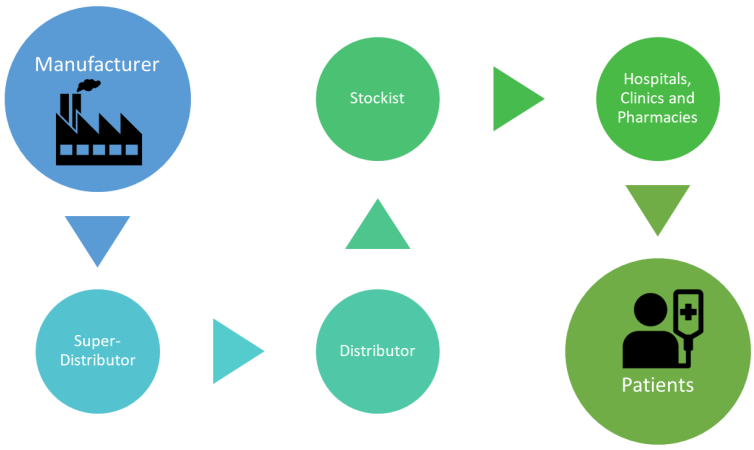


**Figure 12:** Supply chain for iβeta

iβeta will be distributed into the market as depicted in the schematic above. Diaβiologics LLP (the manufacturer) will sell the product to a super-distributor. The super distributor, through his wide network of distributors, stockists and sub-stockists will deliver it to the hospitals, clinics and pharmacies where they will be sold to diabetes patients upon prescription.

## 4.2 Technology Readiness Plan

Due to the COVID-19 pandemic, currently, iβeta is at TRL 2[24] and aims to be at TRL 5 by October 2023 and TRL 9 (ready for sale) by 2032.

**Table 6:** TRL Level Analysis

| TRL | Definition |
|---|---|
| TRL 1 | Basic Scientific Principles observed and reported: Need for iβeta identified and Basic principles on which iβeta is based have been observed and reported. |
| **TRL 2** | **Technology Concept and/or Application Formulated: Research ideas developed, the hypothesis formulated and protocols developed** |
| TRL 3 | Experimental proof of concept: Hypothesis testing and initial proof of concept (POC) is demonstrated in a limited number of in-vitro and ex-vivo models and limited in-vivo efficacy studies |
| TRL 4 | Technology validated in the lab: Efficacy & safety of candidate drug formulation is demonstrated in a defined animal model including formulation studies, pharmacokinetic studies & ADME, PD, the safety of candidate formulations at a preliminary level and efficacy in in-vivo disease models |
| TRL 5 | Technology validated in the relevant environment: Pre-clinical studies for acute and chronic toxicity to generate sufficient data to apply for clinical trials |

| | |
|---|---|
| TRL 6 | Technology demonstrated in a relevant environment: iβeta produced in a GLP facility for clinical trials. Phase-I clinical trials completed |
| TRL 7 | System prototype demonstration in an operational environment: Phase-II Clinical trials completed |
| TRL 8 | System complete and qualified: Phase-III Clinical trials completed successfully. iβeta approved and commercial marketing license obtained |
| TRL 9 | Commercialization: Commercial launch of iβeta, post-marketing studies and surveillance |

### 4.3 Sales

The only route for iβeta, a prescription drug, to enter the market is creating awareness of the drug via a Pharmaceutical Sales Representative (PSR). The PSRs will visit hospitals, clinics and pharmacies to educate the doctors on the features, advantages and difference of iβeta over other available treatment options. The PSRs will serve as a medium of communication to increase product awareness, provide advice, answer queries and introduce iβeta in the market. We would also conduct meetings and presentation with representatives from hospitals, clinics and pharmacies to achieve the same. Wherever tenders are floated, Diaβiologics LLP would contest for it and if we succeed, the product will be shipped to that place via the super-distributor.

In addition, Diaβiologics LLP will offer promotional discounts, bulk-purchase discounts and also offer subsidies for patients from low-income backgrounds.

### 4.4 Packaging

The capsules will be packaged in an ALU-ALU strip pack with the label prominently displaying the text *"Rx"* and *"Schedule H drug. Warning: To be sold by retail on the prescription of a Registered Medical practitioner only"*, in accordance with the prescribed norms. The advantages of ALU-ALU strip packaging is that it provides a 100% barrier against water vapour, gases & light, has excellent thermoformability and thermostability, is malleable and enables effective anti-counterfeit packaging. All other necessary guidelines as specified by the Central Drugs Standard Control Organisation (CDSCO) shall also be followed for sale in India. Packaging & Label shall be modified to comply with the country of sale upon expansion.

### 4.5 Distribution

Diaβiologics LLP will employ an authorised logistic supplier to distribute iβeta within the country. The super-distributor chosen will further supply the product to distributors across the country followed by distribution through stockists to hospitals, clinics and pharmacies, to be sold as prescription medicine. Contracts with international distributors will be signed upon expansion. Figure 11 is a simplified depiction of the supply chain for iβeta.

# 5. Finances

## 5.1 Funding

There are numerous funding opportunities, both government and private, for biotech start-ups in India. This will be a major source of funds for Diaβiologics LLP. Being incubated at IICE, IISER Bhopal would place us in a position of strength to secure funds. Some funding opportunities are listed below:

- DBT-BIRAC Biotechnology Ignition Grant (BIG)
- DBT-BIRAC Small Business Innovation Research Initiative (SBIRI)
- DBT-BIRAC Promoting Academic Research Conversion to Enterprise (PACE)
- DBT-BIRAC in partnership with Wellcome Trust
- DBT-BIRAC Product Commercialization Program Fund (PCP Fund)
- Grand Challenges India (DBT-Gates Foundation)
- DBT-BIRAC under Biopharmaceuticals Innovate in India (i3)

As students, we are also eligible to apply for the BIRAC-SITARE Gandhian Young Technological Innovation Award (GYTI) for funding.

Other funding opportunities include the National Bio-Entrepreneurship Challenge (NBEC) organised by the BIRAC Regional Entrepreneurship Centre (BREC) to nurture bio-entrepreneurs. Winning start-ups and individuals are funded and mentored by leading entrepreneurs in India. In addition, Diaβiologics LLP would also seek investment from angel investors and venture capitalists to fund its activities.

## 5.2 Infrastructure & Equipment Cost

A biotech-based start-up company requires a lot of investment to initiate business. While, initially outsourcing will be the model, in due course the necessary infrastructure would be created. The details are in Table 7 summarizes the proposed infrastructure.

**Table 7:** Proposed Infrastructure

| **Provisions** | **Area (sq.m)** |
|---|---|
| Production Area | 300 |
| Quality Control Area | 100 |
| Raw Material and Equipment Stores | 200 |
| Finished Product Stores | 200 |
| Library | 50 |
| Linen, Washroom, Medical Centre & Recreation | 100 |
| Office and Reception | 150 |
| Cafeteria (for Employees) | 100 |
| Electric Substation | 100 |
| Car park and Security | 200 |
| **Total** | **1500** |

The finances involved under various heads are depicted the following Tables 8 to 11.

**Table 8:** Estimation of Infrastructure Cost

| Item | Cost/unit (INR) | No. of Units | Cost (INR) | ~Cost (USD) |
|---|---|---|---|---|
| Land and Development Charges, MPIDC* | 1,500/sq.m | 3,000 | 4,500,000 | 60,000 |
| Class 100 Manufacturing Area (Production) | 10,000/sq.ft | 3,000 | 30,000,000 | 540,000 |
| Class 100000 Manufacturing Area (Q.C.) | 6,000/sq.ft | 1,000 | 6,000,000 | 80,000 |
| Building Cost (including all services like water, electricity, etc.) | 2,000/sq.ft | 15,000 | 30,000,000 | 400,000 |

*(*Since the required Floor Space Index in the Mandideep Industrial Area is 0.5, Diaβiologics LLP will have to purchase twice the amount of land. MPIDC stands for Madhya Pradesh Industrial Development Corporation)*[25][26]

**Table 9:** Estimation of Laboratory Equipment Cost

| Item | Cost Apiece (INR) | Qty | Cost (INR) | ~Cost (USD) |
|---|---|---|---|---|
| Biosafety Cabinet Class II | 1,000,000 | 2 | 2,000,000 | 27,000 |
| Refrigerated Micro-Centrifuge | 500,000 | 1 | 500,000 | 6,650 |
| Micro-Centrifuge | 400,000 | 2 | 800,000 | 10,650 |
| Thermal Cycler | 1,000,000 | 1 | 1,000,000 | 13,350 |
| Oven | 200,000 | 2 | 400,000 | 5,350 |
| Refrigerator (4°C) | 75,000 | 1 | 75,000 | 1,000 |
| Refrigerator (-20°C) | 400,000 | 1 | 400,000 | 5,350 |
| Refrigerator (-40°C) | 500,000 | 1 | 500,000 | 6,650 |
| Refrigerator (-80°C) | 600,000 | 1 | 600,000 | 8,000 |
| Gel Electrophoresis Apparatus | 40,000 | 2 | 80,000 | 1,100 |
| Microwave Oven | 13,000 | 1 | 13,000 | 200 |
| Autoclave | 50,000 | 2 | 100,000 | 1,350 |
| Nanodrop | 800,000 | 1 | 800,000 | 10,650 |
| UV/Vis Spectrophotometer | 750,000 | 1 | 750,000 | 10,000 |
| SDS-PAGE Apparatus | 20,000 | 2 | 40,000 | 550 |
| Orbital Platform Shakers | 900,000 | 2 | 1,800,000 | 24,000 |
| Gel Doc System | 900,000 | 1 | 900,000 | 12,000 |

| | | | | |
|---|---|---|---|---|
| Weighing Scale | 550,000 | 2 | 1,100,000 | 14,350 |
| Water Bath | 75,000 | 2 | 150,000 | 2,000 |
| Micropipettes | 25,000 | 4 | 100,000 | 1,350 |
| Densitometer | 100,000 | 1 | 100,000 | 1,350 |
| **Total (L)** | | | **12,208,000** | **162,900** |
| Installation Cost | 20% of Total | | 2,441,600 | 32,550 |
| **Total Cost** | | | **14,649,600** | **195,450** |

**Table 10:** Estimation of Manufacturing Equipment Cost

| Item | Cost Apiece (INR) | Qty | Cost (INR) | ~Cost (USD) |
|---|---|---|---|---|
| 50 L bioreactor | 300,000 | 2 | 600,000 | 8,000 |
| Capsule Filling Machine (25k-50k capsules per hour) | 1,000,000 | 2 | 2,000,000 | 27,000 |
| Freeze-Dryer | 2,500,000 | 1 | 2,500,000 | 33,500 |
| **Total (M)** | | | **5,100,000** | **68,500** |
| Installation Cost | 20% of total | | 1,020,000 | 13,700 |
| **Total Cost** | | | **6,120,000** | **82,200** |

### 5.3 Total Capital Investment

**Table 11:** Total Capital Investment

| Particulars | Cost in millions (INR) | ~Cost (USD) |
|---|---|---|
| **Total Installed Equipment Cost (TEC)** | | |
| Purchased Equipment Cost (PEC) (i.e. L+M) | 20.769 | 231,400 |
| Installation & Erection Cost (20% of PEC) | 3.461 | 46,250 |
| **Total (A)** | **24.230** | **277,650** |
| **Cost of Auxiliary Items** | | |
| Land & Yard Improvement | 4.500 | 60,000 |
| Building (Bld.) | 30.000 | 400,000 |
| Electrical Facilities (10% of PEC) | 2.076 | 23,140 |
| Repair & Maintenance (10% of PEC) | 2.076 | 23,140 |
| Piping (2% of PEC) | 0.415 | 4,628 |
| **Total (B)** | **39.068** | **510,098** |
| **Fixed Capital Investment (FCI) i.e. A+B** | **63.298** | **788,558** |
| **Working Capital** | | |
| Raw Material (R. M.)* | | |

| | |
|---|---|
| Salary/Wages | |
| Packaging Material (2% of R. M.) | |
| Transport Charges (2% of R. M.) | |
| **Total (C)** | |
| **Total Capital Investment (A+B+C)** | |

*(*The cost estimate for Raw Material cannot be made due to lack of data from experiments and clinical trials. The table has been completed to the best extent possible)*

### 5.4 Product Cost and Retail

The cost of iβeta can be determined accurately only after the dosage has been optimised in the Phase II clinical trials. The materials and expenses to be considered for a batch of 200,000 capsules are tabulated below:

**Table 12:** Estimation of Manufacturing Cost

| **Particulars** | **Cost in millions (INR)** | **~Cost (USD)** |
|---|---|---|
| **Fixed Cost** | | |
| Depreciation on Equipment (15% of PEC) | 3.115 | 34,710 |
| Depreciation on Building (3.5% of Bld.) | 1.050 | 14,000 |
| Insurance (2% of FCI) | 1.266 | 15,771 |
| Repair & Maintenance (M) (5% of FCI) | 3.165 | 39,428 |
| Interest (12% of FCI) | 7.596 | 94,627 |
| Property Tax (5% of FCI) | 3.165 | 39,428 |
| **Total (A)** | **19.461** | **237,964** |
| **Direct Production Cost** | | |
| Raw Materials* | | |
| Utilities | | |
| Packaging Material | | |
| Labour and Salary/Wages (W) | | |
| **Total (B)** | | |
| **Plant Overheads** | | |
| Medical, safety, canteen, recreation, etc. (50% of (W+M)) | | |
| **Total (C)** | | |
| **General Expenses** | | |
| Administration (15% of (W+M)) | | |
| Distribution and Marketing (15% of (W+M)) | | |
| **Total (D)** | | |

**Total Manufacturing Cost (A+B+C+D)**

*(*The cost estimate for Raw Material cannot be made due to lack of data from experiments and clinical trials. The table has been completed to the best extent possible)*

During cost calculations, the following points would be taken into consideration:

- 2% units will be made in excess to account for losses in manufacturing process
- 2% cost of raw materials will be added to account for loss of raw material due to defects
- Corporate Tax will be deducted from Profit Before Tax to calculate net profit

### 5.5 Cost of Project

**Table 13:** Cost of Project

| Activity | Cost in INR (millions) | | | | | | | | | | | | Total in INR (millions) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Y1 | Y2 | Y3 | Y4 | Y5 | Y6 | Y7 | Y8 | Y9 | Y10 | Y11 | Y12 | |
| Proof Of Concept | 1.0 | | | | | | | | | | | | 1.0 |
| Pre-Clinical Studies | | 3.0 | | | | | | | | | | | 3.0 |
| Clinical Trials | | | | 20.0 | 50.0 | | 70.0 | | | | | | 140.0 |
| Process Dev. | | | | | | | | 5.0 | | | | | 5.0 |
| Mfg. Set-up | | | | | | | | | | 39.1 | 12.1 | 12.1 | 63.3 |
| Margin for Working Capital | | | | | | | | | | 15.0 | | | 15.0 |
| Education | | | 0.2 | 0.2 | 0.5 | 0.5 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | | 6.4 |
| Marketing | | | | | | | | | | 20.0 | 20.0 | 15.0 | 55.0 |
| Cloud Services | | | | | | | | | | 30.0 | | | 30.0 |
| | | | | | | | | | | **Grand Total** | | | **318.7** |

Note:

1. All estimates are based on current costs
2. These are broad estimates of cost. Will require detailed working at the time of actual implementation
3. Working Capital computed as INR 6 million is based on annual sales of 200 million in the first year

### 5.6 Means of Finance

**Table 14:** Means of Finance

| Means of Finance | Funding in INR (millions) | | | | | | | | | | | | Total in INR (millions) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Y1 | Y2 | Y3 | Y4 | Y5 | Y6 | Y7 | Y8 | Y9 | Y10 | Y11 | Y12 | |
| Govt. Grant 1 | 1.0 | | | | | | | | | | | | 1.0 |
| Govt. Grant 2 | | 5.0 | | | | | | | | | | | 5.0 |
| Angel Investors | | | 20.0 | | | | | | | | | | 20.0 |
| Venture Capitalist | | | | 45.0 | | 65.0 | | | | | | | 110.0 |
| Private Equity | | | | | | | 50.0 | | | | | | 50.0 |
| Promoters' Contribution | | | | 5.0 | | 5.0 | 10.0 | | 27.2 | | | | 47.2 |
| Term Loan | | | | | | | | | 85.5 | | | | 85.5 |
| | | | | | | | | | | **Grand Total** | | | **318.7** |

### 5.7 Conceptual P&L Account

**Table 15:** Conceptual Profit and Loss Accounts

| **Particulars** | **Amount** |
|---|---|
| **Sales** | |
| Sales | 100 |
| **Total Sales (A)** | **100** |
| **Expenditure (% of Sales)** | |
| Raw Materials | 30 |
| Packaging Material | 8 |
| Manufacturing Overheads | 4 |
| Repair & Maintenance | 2 |
| Insurance | 1 |
| Salary & Wages | 8 |
| Sales and Distribution expenditure | 10 |
| Promotional expenditure | 10 |
| **Total Expenditure (B)** | **73** |
| **EBIDTA (A-B)** | **27** |
| **Deductions** | |
| Interest | 2 |
| Depreciation | 5 |
| **Total Deductions (C)** | **7** |
| **Profit Before Tax (PBT) (EBIDTA - C)** | **20** |
| Tax (30%) | **6** |
| **Net Profit (PBT - Tax)** | **14** |

**Note:** Based on actual sales the profitability will vary to reflect economies of scale

# 6. Future Plans

## 6.1 Product Development Plan

Figure 12 is a schematic representation of our product development plan from proof of concept to market entry, including Phase IV clinical trials.

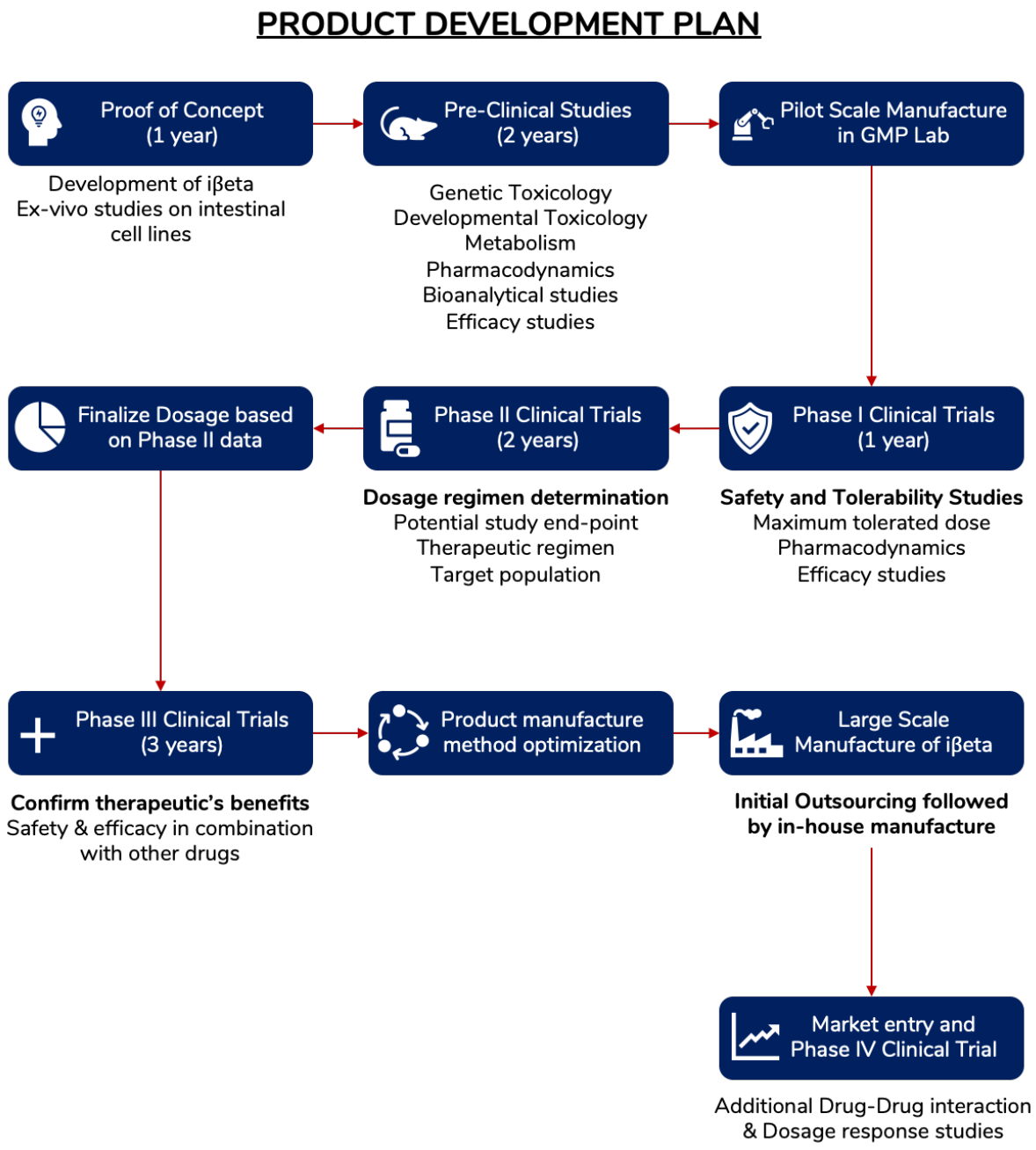


**Figure 13:** Product Development Plan

### 6.2 Milestones & Timeline

In the 20-year period of exclusivity conferred by the patent, pre-clinical and clinical-trials will be conducted as per the guidelines laid down by 'Schedule Y'. At the same time, we would be consistently sourcing funding to carry out the trials. Process development and optimization will begin towards the end of Phase III clinical trials prior to Phase IV. Towards the end of the clinical trial phase, we will also begin the development of an encrypted patient data cloud storage system to keep family doctors up-to-date. Spreading awareness about genetically modified organisms (GMOs) would be taken up from the start as it is critical to ensure that iβeta is well accepted upon market entry.

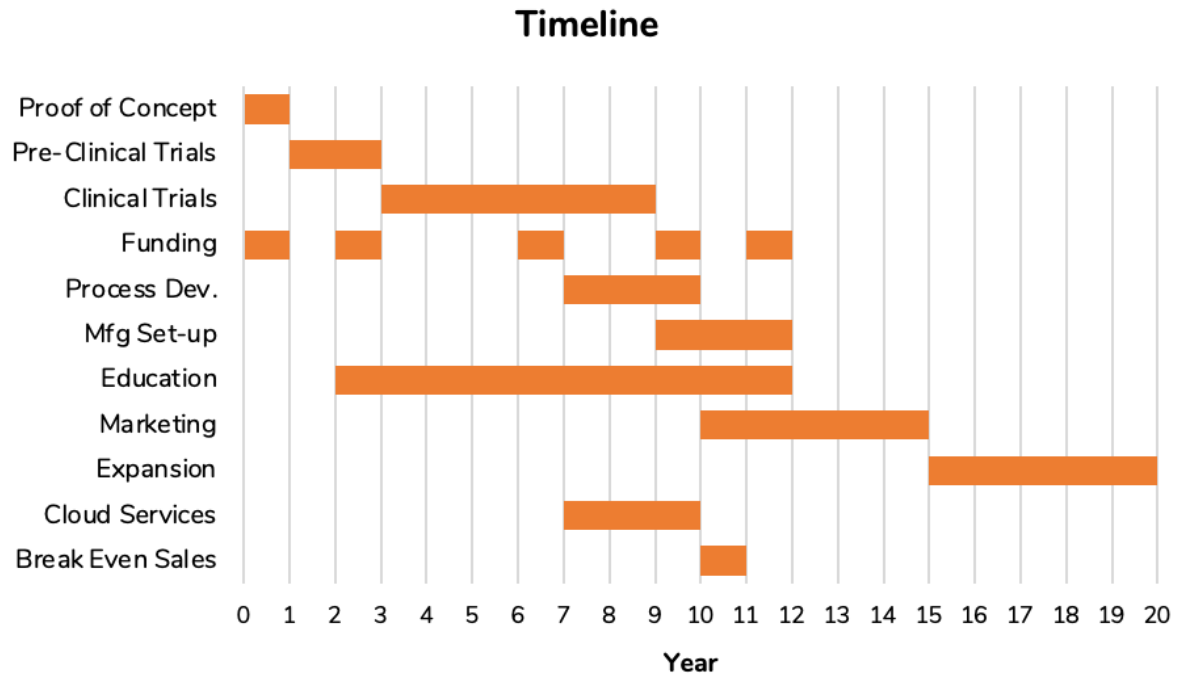


**Figure 14:** Gantt Chart - Tentative Timeline

### 6.3 Expansion

Diaβiologics LLP will introduce an IT division in the near future to create a cloud-based platform to store customizable and tailored patient information and share it with family doctors. This will allow the doctor to stay up-to-date with patient data. The data will be protected with industrial standard encryption protocol ensuring safety and confidentiality. Artificial intelligence will be used to analyse patient data (excluding personal information) to detect any medical issues, epidemics/endemics, etc.

Diaβiologics LLP will also expand its horizons to treatment and diagnosis of diabetes related complications by harnessing the inestimable power of synthetic biology. Each product developed and released into the market will be continually improved to enhance user experience and augment consumer satisfaction.

Finally, Diaβiologics LLP aims to tap into potential international markets like China and the United States among many others to make its revolutionary solutions to global problems available in every corner of the world.

### 6.4 Business Goals

The short term goal of Diaβiologics LLP would be to establish proof of concept and complete pre-clinical and clinical trials to enter into the market within the next 10 – 12 years. Diaβiologics LLP will also pro-actively be involved in educating the public about GMOs to destigmatise their use. This will increase acceptance and allow smoother entry of our products in the market. The company will also participate in seminars, conferences, conventions, etc. to improve public perception and brand reputation.

Diaβiologics LLP aims to become a million-dollar company within the first three years of market entry followed by crossing the 100-million dollar mark within 20 years. The company also intends to be debt free by the end of 10 years and would reallocate funds efficiently to ensure smooth functioning of all branches of the company.

The end-goal of Diaβiologics LLP is to become a leading provider of diabetes solutions worldwide.

# 7. Acknowledgements

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- Dr. Himanshu Kumar, Department of Biological Sciences, IISER Bhopal for his expert guidance on the immunological implications of iβeta
- Mr. Sunil Kulshrestha, Public Relations Officer at CDSCO for his valuable advice regarding the classification of our drug

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