PROJECT REPORT

Group 3

MALE CONTRACEPTIVE IMPLANT

USE OF ARTIFICIAL INTELLIGENCE IN THE PROJECT REPORT

Artificial intelligence applications have been used in this report:

☒ YES

☐ NO

According to our statement, we have used the following artificial intelligence applications in our report during the report process:

AI application names and versions:

ChatGPT 4o mini, 4o

Perplexity

SciSpace

List here all AI applications and their versions that you have used during the report process.

Purpose:

AI tools were used for the purpose of understanding concepts, brainstorming, internet research, literature search, report structure and linguistic aspects.

Sections where AI has been used:

Throughout the report

We are aware that we are fully responsible for the content of our report, including parts that have utilized artificial intelligence, and we accept responsibility for any violations of the Code of Ethics.

Change History

Version	Date	Author	Brief summary of changes
0.1	12.09.2024	*Vilhelmiina Hännikäinen*	Chapters 1, and 2.1.
0.2	14.09.2024	*Siiri Parviainen*	Changes to chapter 2.1
0.3	14.09.2024	*Elisa Sipola*	First draft of chapter 5, information about current knowledge to chapter 2.1
0.4	23.09.2024	*Vilhelmiina Hännikäinen*	Text to chapters 3.1, 3.2, 3.3.
0.5	24.09.2024	*Fizra Khan*	Text to chapter 2.1
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0.9	29.09.2024	*Elisa Sipola*	Chapter 5
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0.27	24.11.2024	*Elisa Sipola*	Finalizing executive summary
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Dates and Signatures

Performed by

Name and Title	Signature
Role	

Reviewed and approved by

Name and Title	Signature
Role	

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Executive summary

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Unintended pregnancies place a burden to society by causing healthcare costs and neglecting sustainable population growth. Annually over 120 million women face an unintended pregnancy globally. Nowadays, the responsibility of contraception falls usually to women due the lack of reliable long-term and effective solutions for male contraception.

Solution

To improve the sustainable population growth, we offer a male contraceptive solution which enables reduction of unintended pregnancies and therefore saves costs from healthcare. The savings can be done by causing azoospermia with natural polymer-based hydrogels implemented into vas deferens.

Plan

Step 1: Identify the design of the product, identify project group and do project plan

Step 2: Determine the purpose of the device, State-of-art, patent research (FTO) and product details. Provide a market analysis by utilizing current literature, patents and other relevant data.

Step 3: Create a regulatory strategy to fulfill the requirements of the device by searching for relevant standards and guidelines to ensure compliance.

Step 4: Analyze product and its safety by providing verification and validation through clinical evaluation and risk assessment.

Step 5: Provide a go-to-market plan by assessing knowledge for key opinion holders and industry experts, exploring potential partnerships in institutions and organizations and contributing training programs.

Risks

Men can be uninterested about the product because of other contraceptives intended to be used for women. We aim to create long-term yet reversible solution for men that are interested to impact their reproductive autonomy. We will encourage men to evolve the safety of their contraceptive by using novel non-hormonal long-term solution.

The initial costs of research and development of the product are significant. However, the product starts to produce capital after launching.

Recommendations

We need approval for 2MEUR in funding to provide prototyping, regulatory compliance and initial clinical trials. The solution will pave the way for scalable, innovative contraceptive which align with sustainability in family planning and healthcare goals.

1 Introduction

This report goes through the project development process of a long-term male contraceptive method, DEFLEXA. We will introduce the project team and the device and its design as well as the different marketing, regulatory and validation aspects that have been assessed. The report will include risk management and assessment as well as an insight into the schedule and budget of the project. The more detailed information about risk analysis, schedule and budget can be found in the attachment files, with links to the files found in their own sections.

The device is an implantable long-term contraceptive method aimed for males. The contraceptive implant is made of metacrylated gellan gum hydrogel and it is implanted into both vas deferens. The implanted hydrogel will block the semen from entering the ejaculate. The implant is designed to degrade inside the body after two years, but it is possible to start the degradation process earlier by using enzymes.

2 Project

2.1 Team

The project team consists of five people, the project manager, market and sales manager, quality and regulations manager and two research and development engineers.

The project manager is Vilhelmiina Hännikäinen who is responsible for the overall project and the risk assessment. The project manager must have good leadership and communication skills and knowledge in resource allocation, time management, and risk mitigation. The project manager also needs to understand the basics of technical, regulatory, and market aspects of the project. Vilhelmiina has overseen many larger scout projects in the past and thus has a good understanding of what different things need to be considered in any project. Vilhelmiina has also gained some leadership and communication skills from her past projects.

Our team member, Fizra Khan, is responsible for marketing and sales, including market analysis of the product. Fizra has a bachelor’s degree in biomedical engineering and is currently pursuing master’s degree in Health Technology and Informatics. She has previously worked as a Research Associate in the Lung Health Department where she was responsible for multiple tasks such as clinical data analysis, stakeholder communication and leading different events like ambassadorship program for youth to advocate against tobacco hazards. Her educational and professional experience has equipped her with understanding related to medical, technical, analytical, research, industry and communication, all relevant skills required for scientific communication, market research, analyzing trends to develop targeting marketing and sales strategies as well as conducting market analysis.

The quality and regulations manager Elisa Sipola oversees the regulatory strategy and the validation of our product. The Q and RA manager needs to have a good knowledge of the different relevant regulations like the MDR as well as different quality control processes and testing methodologies. Elisa has over 5 years' work experience in MD/IVD companies. She graduated from Turku university of applied sciences in 2022, and her topic of thesis was "usability engineering of medical devices" in which she created two user specification documents for class IIb medical devices by utilizing MDR and involved standards. After graduation she has been involved in expanding the market area to USA and participated in validation, change management, risk assessment and development processes. During educational leave, she has been deepening her expertise in regulations.

The research and development engineers Susanna Kaukoranta and Siiri Parviainen are together in charge of the product development and design. The R and D engineers must have deep knowledge on biomedical materials and human anatomy as well as good technical testing and problem-solving skills. Susanna has Bachelor of Technology in biotechnology from Tampere University and has continued her studies in the field of hydrogel biomaterials and their applications. Susanna has expertise related to hydrogel material production and testing. Siiri has a wide knowledge about medical device manufacturing and quality control. She has studied cell biology and bioinformatics and works with medical device and pharmaceutical industry. She has seen R&D processes from up-close and this will benefit her in this position.

2.2 Schedule and milestones

DEFLEXA is planned to be able to enter the market during year 5 after registration and validation is completed. The pre-project phase and phase 1 are planned to take the whole first year of the project and the phases have five critical milestones, patent search (FTO) and regulatory strategy at M2/Y1, literature search 1 as well as design inputs, business strategy and securing initial funding at M7/Y1. The research and development engineers are responsible for the patent search and design inputs whereas the project manager oversees securing the funding. The business strategy is overseen by the marketing and sales manager. Once these 3 milestones have been achieved phase 2 can commence with pre-clinical testing. Preclinical testing is taking up the whole year 2 and if all pre-clinical tests, including animal testing have promising results by Q4 of year 2, clinical testing can commence. Design freeze is done at M6/Y2 and animal testing is finalized by the end of year 2. The R&D engineers oversee the pre-clinical studies, and the quality and regulations manager takes charge of the clinical testing.

Year 3 consists of clinical studies that need to be finalized to be able to fill the registrations and finalize risk assessment. Registration needs to be completed by the end of year 4, for DEFLEXA to be able to enter markets by Q3 of year 5. The Q&RA manager is leading the registration process. For large scale start of production to happen, production capabilities will be scaled up during the first two quartiles of year 5 which is led by the project manager. For the launch to be successful the M&S manager plans and

executes sales and marketing activities in Q1 and Q2 of year 5. During the whole year 5, the M&S manager gives training and support to healthcare providers leading up to and after product launch.
A more in depth schedule can be found in the scheduling and budgeting file in teams, from this link Scheduling and Budgeting_Group3.xlsx.

2.3 Budget and funding

The total five-year budget for DEFLEXA is going to be around 15,8 million euros, that is further divided into 1,8 million € in employee costs and 14 million € in materials and services. This budget is further divided into yearly budgets that can be seen in figure 1. Most of the materials and services budget will be used during years 2 and 3, during which pre-clinical and clinical testing is conducted. Overall, clinical studies are the biggest expenditure and will take an estimate of 10 million €. Scaling up the production is another big expense that will be done during the first two quartiles of year 5 and will total up to 1,7 million €.

When looking at the employee costs, years 1 and 3 will have the largest costs. During year 1, the pre-project phase and phase 1 are partially overlapping, which will require more work hours for all tasks to be completed. Year 3 will have the clinical testing which will require more manpower and workhours. Otherwise, employee costs will be around 200k to 250k a year. A more in depth budget can be found in the scheduling and budgeting -file in teams, from this link Scheduling and Budgeting_Group3.xlsx.

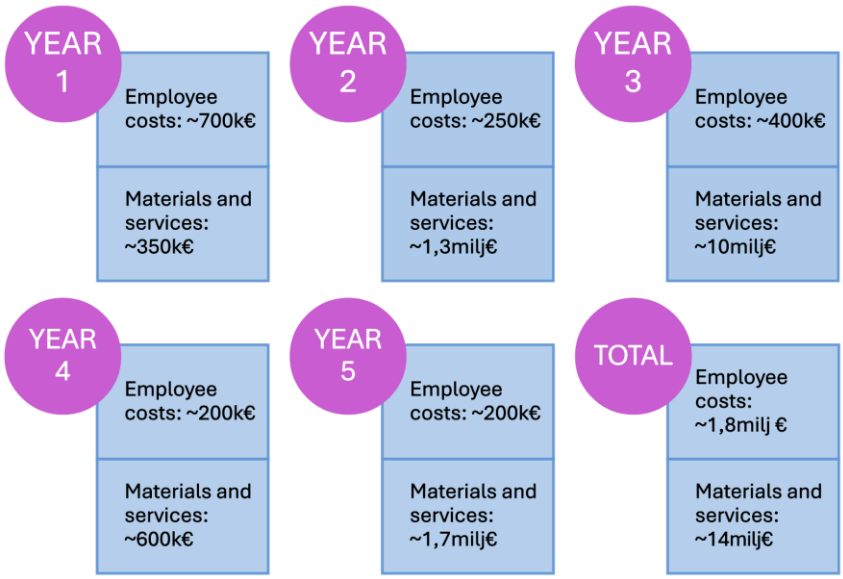

Figure 1: A breakdown of the yearly budget for DEFLEXA.

To obtain funding for this project, the DEFLEXA team will be asking for funding from different government and public funding as well as philanthropic and nonprofit organizations. Different government and public funding sources in Finland include Business Finland that offers grants and loans for innovation, research and development projects [1] as well as Finnish Innovation Fund Sitra that supports projects that are

addressing societal challenges such as reproductive health [2] and Research Council of Finland that offers grants for scientific research in health and medicine [3]. Funding will also be applied from Male Contraceptive Initiative [4].

DEFLEXA team is also researching the possibility of academic and research collaboration in form of a university partnership to get access to a well-equipped lab during the first few years of the project. Possible universities to partner with include the University of Tampere and the University of Turku, both of which are hubs for medical research. If gained, this partnership will strengthen the project's credibility and open doors for further funding opportunities. Finnish philanthropic foundations such as Emil Aaltonen Foundation [5], Jane and Aatos Erkko Foundation [6] and Sigrid Jusélius Foundation [7] may also offer funding for our project.

2.4 Risk management

Risk management is an ongoing and iterative process that will be integrated into all stages of the project. To ensure good risk management risks are anticipated prior to them occurring, and they are updated and reassessed as the project moves forward. Good collaboration between all team members is crucial for gaining a comprehensive insight into the risks. Both qualitative and quantitative risk assessment methods will be used to ensure a good overall assessment.

We will follow the ISO 14971:2019 – Risk Management for Medical Devices -standard in our risk management as it is applicable to our product. According to ISO 14971:2019 the risk management framework includes the following steps: Risk analysis, evaluation and control as well as post-market surveillance. A risk management file will be maintained, documenting all risk management activities. [8] As risk controls, DEFLEXA will at least have inherent design safety with the use of biocompatible and stable hydrogels, precise insertion and removal guidelines as protective measures and clear instructions and user education materials for proper safety information.

During pre-project phase a risk management plan will be developed, and high-level risks are identified. The high-level risks for DEFLEXA include funding challenges, regulatory hurdles and technical feasibility. These risks are further discussed in chapter 7.2. Business risks. During phase one of the project risk analysis is conducted to evaluate possible hazards around the hydrogels design and properties. The risk analysis assesses the hazards, evaluates the acceptability of said hazards and presents mitigation methods. The base of the analysis can be found in ISO 14971:2019. [8] The risk analysis can be found in Teams from this link risk analysis_group 3.xlsx. Biocompatibility risks will be assessed per ISO 10993 standards [9].

During animal studies and clinical evaluation, a clinical risk analysis is done to identify risk with animal studies and early human trials such as long-term reversibility and adverse reactions. Also risks related to clinical trial design including ethical considerations and informed consent are evaluated. When starting

manufacturing phase, risks related to production such as batch to batch consistency and batch contamination are assessed and quality controls are implemented to ensure compliance with ISO 13485. During manufacturing validated risk control methods need to be implemented, such as material testing protocols. [8], [10]

A good time before regulatory submission, a Regulatory Gap Analysis will be performed to identify risks of non-compliance with EMA regulatory standards. Regulatory gap analysis is a review of internal procedures compared against a standard, good practice or regulation and can help identify areas of MDR compliance [11]. The gap analysis helps to address risks of having incomplete or misinterpreted submission data. The ISO 14971 standard requires to implement a post-market surveillance plan to monitor usage for new of unforeseen risks and to collect and analyze data on product performance and adverse effects. [8]

2.5 Key Partners

DEFLEXA is manufactured using services and materials provided by third-party companies. These services and materials are presented in a Table 1. This table also tells the nature of partnership between third-party company and DEFLEXA.

Table 1: List of key partners and what product or service they provide

Product/Service	***Company***	***Partnership***
Raw materials other essential chemical and humidity maintaining bags	VWR International Oy	DEFLEXA buys raw materials for hydrogel from VWR International Oy
Catheters	Freudenberg Medical	DEFLEXA buys manufactured catheters from Freudenberg Medical
Packaging materials (labels, cardboard box, IFU papers)	Jaakkoo-Taaraa Oy	Jaakkoo-Taaraa Oy makes packaging materials according to our mock-up and we buy the finished products
Laboratory analysis and testing	Eurofins Scientific	DEFLEXA provides samples for Eurofins Scientific, and they do analysis according to standards. DEFLEXA will buy laboratory services from Eurofins Scientific
Facilities	Depends on the place where DEFELXA operates	We rent manufacturing facilities from company/person that owns the property
Patent applications, IPR consulting and other legal consulting	Berggren Oy and Berggren Legal Oy	Berggren Oy will be employed to do patent application and legal consultation for DEFLEXA. We pay according to used working hours
Syringes	SeaskyMedical	DELEXA will buy sterile syringes from SeaskyMedical
Consultation from medical professionals (urologist and general doctors)	Medical professionals from Tampere area	Professionals will be employed to do consultation about DEFLEXA usability and development. We pay according to used working hours
Consultation for MDR and FDA requirements	AKM Consulting Oy	Consultation from AKM Consulting to apply for CE-mark and for expanding market to USA. Professionals will be paid according to the working hours

3 Product

3.1 Device description

DEFLEXA is a natural polymer-based implant that is intended for healthcare professionals use to prevent the sperm of men in reproductive age from travelling outside of vas deferens. The product is a biocompatible, long-term alternative to traditional male contraceptive methods for males that wish to prevent unexpected pregnancy. The product is a pair of metacrylated gellan gum hydrogels injected into the vas deferens that degrades to the human body in approximately two years. The hydrogels are injected to both vas deferens with a long and flexible syringe via the urethra. The hydrogel degrades in situ after 1,5- 2 years and it can also be removed enzymatically prior to that.

3.2 Intended purpose of the device

Intended Use	*The natural polymer-based implant is intended for use by healthcare professionals to prevent sperm from traveling outside the vas deferens in men of reproductive age. It serves as a long-term male contraceptive option. The hydrogel can be removed with predetermined specific enzymes.*
Indications for Use	*This product is indicated for use in men of reproductive age as a biocompatible, non-permanent contraceptive method. The product offers an alternative to traditional male contraceptive methods to prevent unintended pregnancy. The implant is designed to be injected into the vas deferens, where it functions for up to two years before degrading naturally within the body.*
Contraindications	*The implant should not be used in patients with a history of hypersensitivity to gellan gum or those with anatomical abnormalities in the vas deferens, infection, or inflammation in the reproductive tract.*
Patient population	*Men of reproductive age seeking a temporary, long-term contraceptive method to prevent unintended pregnancy.*
Body contact and duration	*The product involves contact with the internal tissues of the vas deferens for two years, after which it degrades and is absorbed by the body.*
Single use / reusable	*The implants are single use only. Once injected, it cannot be reused as it degrades within the body. The contents of the kit are also single use only.*
Precautions and Warnings	• *The implant must only be placed into the vas deferens by a healthcare professional.* • *The implant offers contraception for up to two years; after this period, fertility may return as the hydrogel degrades.* • *Patients must be told of the temporary nature of this contraceptive method and that the contraceptive method does not prevent sexually transmitted diseases.* • *The implantation must not be performed if there is infection, active inflammation, or trauma in the reproductive tract.* • *Risks of complications such as infection, inflammation, or discomfort following the injection can be possible.*

3.3 State-of-the-Art Review

Novel contraceptive methods aimed for men have faced many challenges that are scientific, regulatory as well as cultural. The scientific challenges mainly involve the complex male reproductive biology as well as reversibility and efficacy. Men can produce millions of spermatozoa daily, which poses difficulties in controlling or stopping spermatogenesis. The complexity of male contraceptive is clear when compared to female contraceptives that focus on blocking the release of a single egg per cycle. [12] Also the discussion of reversibility is important to consider, as the contraceptive method should be reversible

which would ensure that once the treatment is stopped, fertility is regained. Regulatory wise, rigorous clinical trials are required for the approval of new contraceptive products. In male contraceptives in particular, a lack of participants for clinical trials has been a prevalent problem. [13], [14]

Traditionally there has been only a few options contraceptive options for men. These methods have often included condoms, vasectomy and withdrawal. Methods for male contraceptive can be classified according to their working principle. These principles can be divided into five categories: methods that inhibit spermatogenesis, methods that make spermatozoa lose the ability to fertilize, methods that physically prevent sperm from going to the site of fertilization, methods that interfere with the sperm in the female genital tract and methods that interfere with functions that are necessary for fertile spermatozoa [15].

Condoms are one of the oldest contraceptive methods available today. They aim to act as a barrier between semen and the opposite genitalia to reduce the probability of pregnancy as long as it is used correctly [16]. Condoms also give protection against sexually transmitted diseases and this feature is connected to the popularity of condoms [16], [17]. However, condoms are not 100% safe contraceptive method because there is always a possibility of breakage or slippage. Many factors contribute to the risk of breakage and slippage for example man's level of experience with condoms and the material of condom [18].

Another traditional contraceptive method for male contraceptive is a vasectomy where the vas deferens is dissected and the ends are sealed with electrocoagulation. After this procedure, male hormones are produced normally and the volume of ejaculate remains normal, but ejaculate will not contain any sperm [15]. The working principle of vasectomy makes it the most effective form of long term contraception for men [19] but the main disadvantage of vasectomy is the poor reversibility [15].

Besides the so-called traditional methods for male contraception, there are also hormonal methods available for men. These methods are mostly based on the administration of testosterone which suppresses secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). When LH and FSH production is suppressed, the testes does not receive necessary signals for spermatogenesis [15]. Currently there are many (pre-)clinical trials ongoing for hormonal based male contraceptives for example Nestorone [20] and DMAU [21]. There are also drug development aiming to suppress other hormones related to spermatogenesis for example GnRH [22].

In addition to hormonal methods there are mechanical methods developed to prevent the passage of sperm during ejaculation. One of the most promising mechanical methods is RISUG (reversible inhibition of sperm under guidance) where styrene maleic anhydride dissolved into dimethyl sulfoxide is injected in vas deferens [23]. RISUG has mild adverse effects (swelling without pain) making it very promising option for men [24]. There has also been many other development projects for mechanical contraception methods for example silicone plugs placed into vas deferens [25] and ADAM (proprietary hydrogel) [26].

Several hydrogel materials have been studied for the male contraceptive purpose but those have mainly been synthetic materials or alginate-based materials. Material for ADAM previously known as Vasgel hydrogel consist of synthetic styrene-alt-maleic acid (SMA) and is dissolved in dimethyl sulfoxide [27]. Wang et al. have studied hydrogel based on natural sodium alginate that has been conjugated with thioketals and mixed with titanium dioxide (TiO_2) and calcium chloride ($CaCl_2$) that allows the crosslinking of the material. Reversing of the contraceptive hydrogel is done by inducing ultrasound and then the reactive oxygen species created from TiO_2 disturb the hydrogel structure by cleaving the thioketals [28], [29]. Mid-term contraceptive consisting of calcium alginate hydrogels, PEG-Au nanoparticles and EDTA has also been studied [30].

Gellan gum is a natural polysaccharide produced by bacterium *Sphinomonas elodea*. It has gelling properties and is used as food additive accepted and evaluated as safe to use by FDA. Other application methods have been also defined [31]. Hydrogel properties have also increased interest towards the material in biomedical research [32]. Gellan gum can be chemically modified to gellan gum methacrylate (GGMA). This modification included addition of methacrylate groups to polysaccharide backbone in desired degree. GGMA has been studied for diverse applications in biomedical field including mucoadhesive agent for eye drops [33], tissue adhesive wound healing [34] and 3D printed bone scaffolds [35]. For male contraceptive application the discovery of thiol-methacrylate adhesion of GGMA [36] is supporting material selection of DEFLEXA as thiol groups are present in vas deference and they have active role for spermatogenesis at rodents [37], [38].

Several possibilities to crosslink GGMA for DEFLEXA have been identified. Crosslinking could be ultrasound mediated liposome break releasing Ca ions [39] or bioamines spermidine trihydrochloride or spermine tetrahydrocloride [40]. Light based methods have been also studied and several different types of photoinitiators and wavelengths are possible for methacrylated materials [41]. For the removal of the DEFLEXA before natural degradation possibility to inject gellan gum degrading enzymes like metalloproteinase 1 [42] or galactomannanase [43] needs to be evaluated. As a conclusion GGMA with possibility for various mechanical possibilities due to variety of crosslinking options, methacrylation degrees and mucoadhesive properties is promising material option for this application.

3.4 Freedom-to-operate (FTO)

Table 2: List of relevant patents to prove freedom to operate for DEFLEXA

Patents	Legal Status	Claims
Compositions and methods for sustained drug release from an injectable hydrogel WO2021035217A1 WIPO (PCT) - International US20220175672A1 - USA CA3183275A1 - Canada	Pending Pending Pending	This patent, filed by a US originated company Contraline Inc, makes claims regarding different aspects of the device. These claims include device properties (occlusion of vas deferens), hydrogel properties (expansion on body fluid contact), reversibility (absorption of the hydrogel), delivery of therapeutic agents (HIV drug, antibiotics etc), biocompatibility and method of use (injectable and minimally invasive), materials of hydrogel (multi-arm polyethylene glycol (PEG) -thiol, PEG-maleimide) The main claims to point out are the implantation procedure by injecting the hydrogel in vas deferens by make an incision and the synthetic polymer used to make the hydrogel.
Device for obtaining male contraception JP2020078582 (A) — Japan	Active	This patent, filed by a Japanese company Implantica Patent Ltd, claims that their device provides temporary contraception by clamping and constricting the vas deferens to obstruct the flow of semen.
Medical devices including medicaments and methods of making and using same including enhancing comfort, enhancing drug penetration, and treatment of myopia US11510869B - USA	Active	This patent, assigned to a US-based company Mediprint Ophthalmics Inc, outlines the use of gellan gum in the development of contact lenses. They claim to use gellan gum for gel formation in the lenses and to provide comfort. The primary claim is that this material facilitates the delivery of the medication in the eye.

Based on the above patents, we can say that DEFLEXA has freedom to operate in the market as it is novel from the available inventions in terms of materials used, its function and the method of administration of the product. Moreover, the application of gellan gum for male contraceptive implant has not been explored before however, the material has been used previously for biomedical applications indicating its effectiveness and high biocompatibility.

3.5 Product information

3.5.1 Design and Materials

DEFLEXA product includes injectable hydrogel precursor solution delivered in syringe and accessory catheter for the delivery to the vas deference. Figure 2 is presenting the planed implantation method. Main ingredients of the injectable hydrogel precursor solution are water, GGMA, crosslinking agent and pH buffering components. During the product development the degree of methacrylate modification is determined to have proper properties to be injectable solution and repeatedly reproduceable in a medical grade purity. Suitable concentration of material in solution is defined. Biocompatible pH buffering system is needed for injectable solution as gellan gum and GGMA are naturally acidic.

During the further development process most functional crosslinking option is defined. Experiments will include photocroslinking in visible light range with suitable photocroslinking agent usable in situ after implantation. Either light would be used from outside of the body or inserted light fiber would go through the catheter to initiate crosslinking to hydrogel. Another method tested in the development will be to blend lipid particles containing calcium ions or bioamines to the GGMA solution and crosslinking would then happen by breaking the lipid structure with ultrasound. During the development of the solution storage conditions and possibility of shelf-life enhancers need to be evaluated.

Injectable GGMA solution is packaged into sterile syringes. The required volume will be defined during the product development experiments, as the volume in syringe needs to cover the catheter volume as well as the injectable volume. Based on the previous studies 50µl or less of solution could be used for 1cm of vas deference [44]. Sterile syringes will be bought from a partner SeaskyMedical and during the development customized needs are defined and the functional syringe is developed in co-operation. The syringe must be easy to use for the clinician, most importantly ease in determining the volume injected.

For the injectable hydrogel there will be three layers of packaging. Primary layer is the syringe containing the solution. Secondary layer is bag that ensures the sterility of the outer layer of the syringe. And the tertiary layer of the product package is cardboard box with the name of the product and labeling as defined in regulations and standards. For ease-of-use cardboard inner structures might be used to have parts in right places. Initial idea of tertiary packaging designed with Pacdora is presented in figure 3.

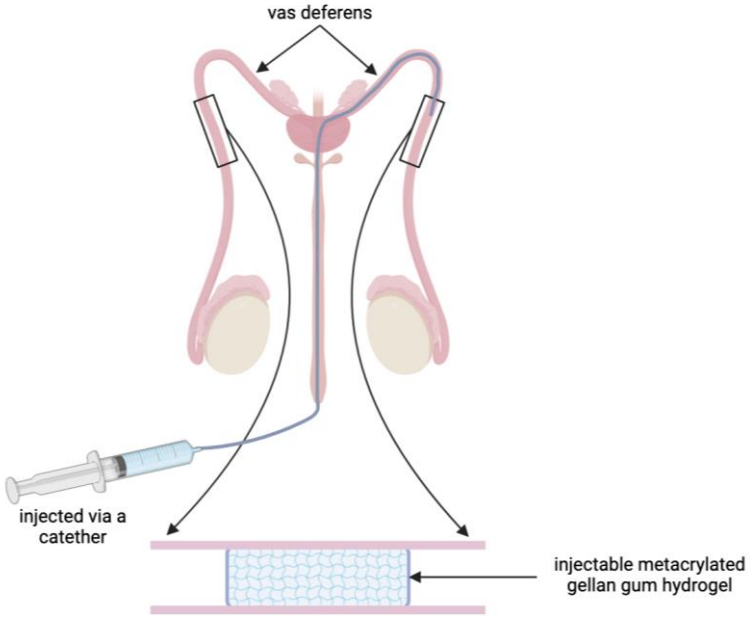

Figure 2: Implantation and principle function of DEFLEXA

Figure 3: Initial draft of the DEFLEXA tertiary packaging design

3.5.2 Manufacturing methods and production cost

DEFLEXA manufacturing starts with the methacrylation of gellan gum. This process includes steps of purchasing and checking the quality of medical grade gellan gum. Then in a clean room quality laboratory gellan gum is dissolved to buffer solution maintaining the pH at 8,5 in increased temperature. pH is checked to be at 8,5 and then methacrylic anhydride can be added. Typical protocols use 8ml per 1g of dissolved gellan gum, but this should vary depending on the wanted modification degree. Reaction is allowed to run till the end that happens in 12h after which pH is adjusted to 7. Dialysis of 7 days is used to purify GGMA from methacrylic acid and possible other small molecule residues. During product development the effective ways to remove the residues will be determined. Dialyzed solution can then be lipolyzed and stored at -20 °C and dark. Methacrylation modification success needs to be verified with the NMR-analysis for each patch. These phases can be done by people by hand in clean room but for clinical

trials with animals and mass production dialysis and modification states should be partly or fully automated.

After the material is prepared dissolving and blending components together can start. During the development process suitable water-based solvent is selected strong options are ultrapure water or buffer solution like DPBS without Mg and Ca. Next step is to dissolve selected crosslinker to solvent then GGMA is added, and homogeneity of solution is ensured. When the solution is ready, syringes can be filed with the material using aseptic techniques. During development and in vitro and animal testing these can be done by hand and later at least the syringe filling will be automated. Filed and closed syringes will be packed in a secondary bag with humidity controller to ensure the sterility of the syringe and the humidity environment of the material.

Work hours used for synthesis, modification, modification verification and solution preparation are estimated to be 15 and that in the beginning gives material for 25 devices equaling 0,6h/device with manual labor. Estimate for the packaging time is 0,4h/device. In total that would mean a employment cost of 23 euros per device in Finland. In table 3, are presented the other cost related to the product preparation. Overall manual production of one product cost 118 euros. When scaling production up and using automation and more efficient use of clean room facilities per device production cost can be cut to 70 euros. Sterility of our devices is ensured with aseptic working and buying hydrogel materials, syringes and catheters sterile.

Table 3: Production costs for one device and patch of 25 device with manual labour

		Cost in euros	
		per device	for 25 devices
Packaging materials and accessories	Syringe	0,50	12,50
	Catethers	1,50	37,50
	Labels and secondary packaging material	2,00	50,00
	Humidity control	0,50	12,50
Injectable precursor solution materials	Gellan gum	0,12	3,00
	methacrylic anhydride	0,06	1,57
	pH control solutions	0,02	0,50
	dialysis device	5,05	126,18
	crosslinker	1,00	25,00
Facilities	Clean room with type II water, basic lab equipments	75,00	1875,00
	Quality control	8,00	200,00
Personnel	Personal protective equipment	1,20	30,00
	Employee costs	22,75	568,75
	Total	117,70	2942,50

* Estimated mothly rent 15000 euros and that 8 patches of 25 devices can be produced in a month

3.5.3 Accessories

In addition to our hydrogel, the kit will include a catheter, instructions for use, a syringe and a humidifying bag. Catheters will be bought from third-party company, and we will use the smallest catheter size suitable with the precursor solution to minimize discomfort. The catheters will be sterilized using in-house method. Instructions for use and implant card will be provided with each device and these will be written by QA department. Printing will be done using third-party company and printed instructions and implant cards will be placed inside every package. Syringes are ordered from third-party company, and they will be sterilized using in-house method. Hydrogel will be filled into syringes using aseptic filling techniques.

4 Market analysis

4.1 Overview of current market status

In 2023, the valuation for overall contraceptive market was estimated to be between 29 billion and 33 billion dollars worldwide. [45] [46] The projected growth of the market size by 2033 is around 62 billion dollars. [46] In Europe, the contraception market is valued at 6.76 billion dollars and is estimated to increase up to 9.27 billion dollars by 2029. [47]

The contraceptive market can be segmented into two segments: drugs and devices. Devices such as condoms and intrauterine devices (IUDs) have the largest market share of about 67.98% revenue of the total market. [48] Out of this, condoms dominate and are estimated to be 13.13 billion dollars, 98% of the devices segment. [49] While the contraceptive drugs such as oral contraceptives, patches, injectables have the total market share of about 16.94 billion dollars. [50]

This suggests that the overall market of contraceptives and male contraceptives is substantial and has an opportunity for new products to be successful. It is also notable that the market is mainly dominated by one device, condoms, and oral hormonal contraceptives because safe, harmless and less permanent alternatives are not available on the market. This shows that there is a significant need for products such as DEFLEXA that can help both male and female make decisions about reproductive health and family planning safely.

4.2 Competitors

Products and companies listed in table 4 can be considered primary competitors of DEFLEXA.

Table 4: List and description of primary competitors

Product	***Company***	***Status***	***Description***
ADAM	Contraline Inc, USA	Clinical trials ongoing	A resorbable aqueous hydrogel based injectable implant to block the sperm in vas deferens that lasts up to one year.
Plan A	Next Life Sciences and Parsemus Foundation, USA	To be launched in 2026	An injectable material (Styrene-alt-maleic acid) in vas deferens to block sperm.
RISUG (Reversible Inhibition of Sperm Under Guidance)	Indian Institute of Technology, India	Late-stage clinical trials ongoing	A polymer gel implanted using incision to deactivate the sperms in vas deferens by coating the tissue walls. It lasts up to 10 years and can be reversed by flushing out with a solution.

Products or procedures listed in table 5 can be considered secondary competitors for DEFLEXA.

Table 5: List and description of secondary competitors

Product	***Company***	***Status***	***Description***
Condoms	Reckitt Benckiser Group PLC, Church & Dwight Co., Inc., Fuji Latex Co Ltd, LifeStyles Healthcare	Active	The main brands are Durex, SKYN and Trojan. All companies have a presence in global market
Dimethandrolone Undecanoate (DMAU)	Research mainly in USA	Clinical trials ongoing	This male hormonal contraceptive pill works by combining an androgen with a progestin to suppress sperm production.
NES/T	Research mainly in USA	Clinical trials ongoing	A topical gel combining Nestorone (a progestin) and testosterone to reduce the sperm production
Andro Switch	Theoreme	Not active, redoing the clinical trial	A ring made of platinum-catalysed silicone keeps the testicles close to the body, where body heat can reduce sperm production,
Vasectomy	Hospitals/clinics	Active	This procedure is effective and conducted by doctors. However, it is not always reversible.

4.3 Competitive advantage of your device

The first and foremost benefit of our product is that it provides long term, reversible and safe contraceptive method for men which is not currently available in the market. When compared to our competitors, our product is more beneficial for health and environment as it uses a natural polymer

instead of a synthetic polymer used by ADAM and Plan A, and rubber used in condoms that is not biodegradable, making it safer and sustainable option. The synthesis of our polymer, gellan gum, does not require any fossil fuel, degrades much more easily reducing environmental footprint and health complications, and has low toxicity for both humans and aquatic life when compared to synthetic materials that may introduce harmful chemicals in the environment. Moreover, unlike RISUG and vasectomies, our product offers flexible duration (up to 2 years) and reversibility for users seeking temporary, reversible solutions without committing to long-term effects. Our procedure to administering the product is less invasive compared to RISUG as it involves incision, allowing for quicker recovery and less discomfort.

5 Regulatory Strategy

5.1 Product type

The product is a long-term implantable medical device intended to be placed in vas deferens by a catheter. The device is hydrogel based male contraceptive intended to be used to prevent sperm of men in reproductive age from travelling outside of vas defenses. Device isn't intended diagnostic use or as a combination product with drugs. The design of the device does not include software. The device does not fulfill the determination of active implantable medical device.

5.2 Regulations must be followed

Medical devices must comply with the applicable regulatory requirements which are dependent on the market area. DEFLEXA is intended to be purchased in the EU. Thus, it must comply with Medical Device Regulation (MDR) 2017/745. Based on rule 15, the risk classification of the device is III. Therefore, the notified body involvement must be established. The notified body can be searched from NANDO. For DEFLEXA, suitable notified body would be Eurofins electric and electrics Finland Oy. Furthermore, the notified body must consult an expert panel before deciding about certification. EMA provides administrative, technical and scientific support for expert panels. Fimea will oversee the compliance with the regulations as the national competent authority [51], [52].

Medical Device Regulation Article 10 demands that manufacturers must hold a strategy for regulatory compliance which should include the following information:

1) Processes for identification of relevant legal requirements
2) Processes for the qualification of devices
3) Processes for the classification of devices
4) Processes for handling equivalence
5) The manufactures choice of and compliance with the conformity assessment procedure
6) Procedures for management of device modifications.

The information needed to regulatory compliance can be divided roughly into eight steps: determining intended purpose, identifying applicable legislations, classification of the device, identifying relevant

requirements, demonstrating conformity, declaration of conformity and CE-marking, device registration and compliance throughout the life cycle of the device [53].

The regulatory strategy for DEFLEXA is presented as follows:

STEP 1: DETERMINING INTENTED PURPOSE

The intended purpose of the device should describe the use of the device as accurately as possible. Use specification is a summary of important characteristics of the medical device. Medical device use specification is referred to by some authorities having jurisdiction as the statement of intended use. The use specification includes intended medical indication, intended patient population, intended part of the body or the type of tissue applied or to interact with, intended use profile and environment and operating principle [54]. The characteristics of DEFLEXA are illustrated in figure 4.

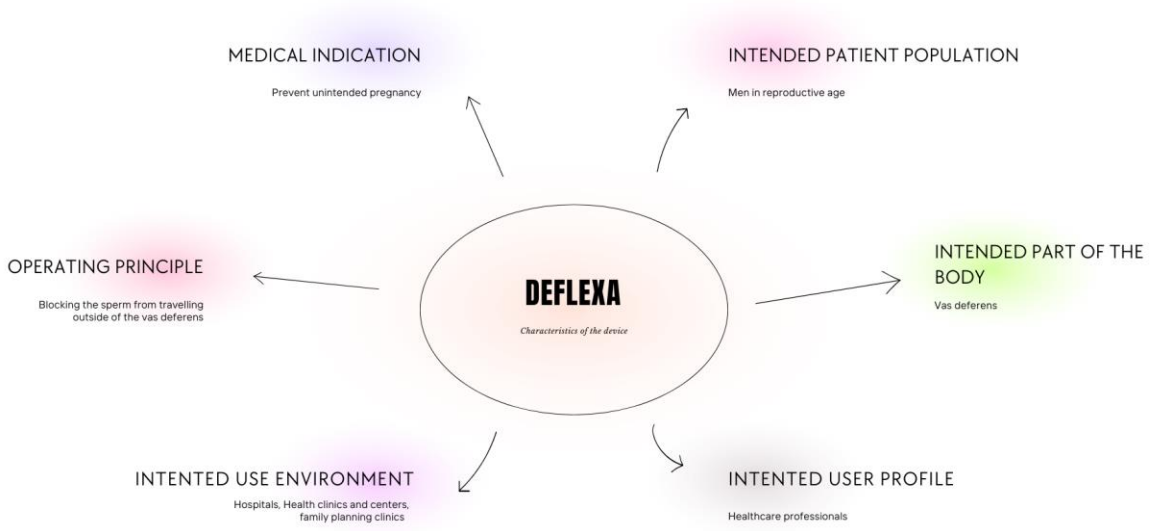

Figure 4: Use specification of DEFLEXA

STEP 2: IDENTIFYING APPLICABLE LEGISLATIONS

Identification of applicable legislations aren't only for indication whether the device is falling into MDR or IVDR but also for possibility for other relevant regulatory requirements that must be fulfilled. Since DEFLEXA is made of chemicals, it must fulfill the requirements of regulation No 1907/2006. Furthermore, MDR requires that manufacturers must provide implant cards (719/2021) that enables identification of the device and safe use of the device for the patient. Thus, the regulation of general data protection regulation must be fulfilled. MDR do not only consider the patient or user safety, but also the environmental safety of the process. Thus, it might be reasonable to fulfill the directive of 94/62/EC and

2008/98/EC. Furthermore, the manufacturer in Finland should follow the regulations of 24.6.210/629 [53], [55], [56], [57].

STEP 3: CLASSIFICATION OF THE DEVICE

MDR is divided into four risk classes: I, IIa, IIb and III. The high-risk devices fall into class III and the risks eases when approaching the risk class I[56]. MDR annex VIII includes the classification rules of the devices. Based on rule 15: “All devices used for contraception or prevention the transformation sexually transmitted diseases are classified as class IIb, unless they are implantable or long-term, in which case they are classified as class III” [56] DEFLEXA is both long-term and implantable device, which makes it class III medical device.

STEP 4: IDENTIFICATION OF RELEVANT REQUIREMENTS

This step is led by the intended purpose of the device and the risk classification of the device. Requirements focus on fulfilling general safety and performance requirements but are also related to QMS [53]. For DEFLEXA relevant requirements are identified by utilizing a check list which is available in Teams, Identification of regulatory requirements .docx.

STEP 5: DEMONSTRATING CONFORMITY

According to MDR, the device must meet general safety and performance requirements. The manufacturer must prepare technical documentation that demonstrates the fulfillment of the requirements. Technical documentation should include description of the device, materials and methods, risk management, clinical evaluation, labeling and symbols, IFUs, implant card, clinical measurements, manufacturing and quality control, post-market surveillance and demonstration of compliance. This can be established with an efficient quality management system that includes risk management, usability engineering and clinical evaluation procedures. For demonstration of conformity, there are harmonized standards and guidelines that can be utilized. The technical documentation is evaluated by notified body.

STEP 6: DECLARATION OF CONFORMITY AND CE-MARKING

Once the notified body has approved the technical documentation, the company can do the declaration of conformity to DEFLEXA. This document content is implemented in Table 1. Before placing the device into the markets it has to be affixed with CE-mark [53] .

Table 6: Document content for DoC [53]

Declaration of conformity	
1	The name, registered trade name/trademark,
2	A statement: The EU declaration of conformity is issued under the sole responsibility of the manufacturer
3	UDI-DI
4	Product code, cataloque number, intended purpose of the device (can be included in UDI)
5	Risk class of the device
6	A statement: The device is covered by present Declaration of conformity with the MDR
7	References to any common specifications used and in relation to which conformity is declared
8	Identification of Notified body
9	Additional information
10	Date, sign and initials

STEP 7: REGISTERATION

Lastly the device must be registered via EUDAMED [53].

STEP 8: COMPLIANCE THROUGH LIFE CYCLE OF THE DEVICE

Even though the market realize might be completed, the process of regulatory compliance isn't over. The manufacturer must ensure that possible training is planned beforehand. Furthermore, manufacturers must collect and analyze data after launching. Post market surveillance can bring valuable information about new risks and possible errors of device that must be reacted with corrective and preventive actions. Post market surveillance can also identify systematic misuse that can enable new target markets for technology or components of DEFLEXA [53], [56].

The product is intended to be placed to European markets and then expanded to USA. To expand the market area, the regulatory requirements that manufacturers must comply with are:

1) Establishment registration
2) Medical device listing
3) Premarket approval (Class III devices)
4) Investigational Device Exemption for clinical studies
5) Quality system regulation
6) Labeling requirements
7) Medical device reporting [58].

However, many countries outside of Europe allow the sales of the devices that have gained CE-mark that covers MDR. For that Fimea must be contacted [53].

5.3 Classification of the product

In the table below, list the product's risk classifications and justification for those.

Market	**Risk Classification**	**Justification**
EU	III	Based on rule 15: All devices used for contraception or prevention of the transmission sexually transmitted diseases are classified as class II b, unless they are implantable or long-term, in which case they are classified as class III [59].
USA	III	The device is placed to vas defenses. This implantable includes introducer but doesn't contain function by drug activity. Based on FDA database, this type of device is classified as class III MD [60].

5.4 Standards and guidelines must be followed

Due to the risk class of the device, there are many guidelines and standards that need to be utilized during the life cycle of the product for ensuring safety and efficiency of the device. Most relevant guidelines and standards are listed in the following table:

Table 7: Relevant guidelines/standards for ensuring competence [61], [62].

RELEVANT GUIDELINES/STANDARDS FOR ENSURING COMPETENCE OF THE DEVICE	
DESIGN AND MANUFACTURE OF THE DEVICE	
Intended use of the device	IEC 62366-1:2015 + A1:2020
Aseptic processing of healthcare products	ISO 13408-1:2024, ISO 13408-6:2021
QUALITY, RISK-MANAGEMENT AND CLINICAL EVALUATION	
Quality management system	ISO 13485:2016, ISO 13485:2016/AC:2018, ISO 13485:2016/A11:2021
Risk management and mitigation strategies	ISO 14971:2019+A11:2021
Preclinical testing data	ISO 14155:2020, ISO 10993- series, ISO 14791:2018, MDCG 2020-1
Clinical data or plans for clinical trials	ISO 14155:2020, ISO 10993- series ISO 14791:2018,
Clinical investigations	ISO 14155:2020, ISO 10993- series ((2019:9, -12:2021, -3:2014, -5:2009 and –10:2010), ISO 14791:2018,
Clinical investigation plan	MDCG 2024-3, MDCG 2024-3 ANNEX A,
Ethical Approval and Regulatory Authorization	ISO 14155:2020
Summary of safety and clinical performance	MDCG 2019-9
Post-market surveillance	MDCG 2020-7, MDCG 2020-8, ISO/TR 20416:2020
Implant card	MDCG 2021-11, MDCG 2018-1
PACKAGING	
Symbols to be used	ISO 17664-1:2021

5.5 Market approval and Quality Certificates

For market approval, technical documentation described in chapter 5.2 is assembled from gathered data. For this type of product clinical trials must be added to the technical documentation. Technical documentation is delivered to notified body Eurofins electrics and electronics Finland Oy (NB 0537). Notified body evaluates the technical documentation and might perform an audit to ensure that quality management system (QMS) and manufacturing process are valid. If deficiencies are found, changes to the process, QMS and technical documentation should be made. After approval, the manufacturer can issue declaration of conformity and affix CE-marking to the device. For implantable male contraceptive (class III) device, certificates needed or beneficial for sales are CE-mark, ISO 14971, ISO 10993 and ISO 13485 [61], [63].

Furthermore, if the market area is expanded outside of the EU, Certificate of free sales would be needed. That can be get by placing the request to Fimea [53].

6 Design Verification and Validation

6.1 Design Inputs and Outputs

Input source	**Specification of Design Input**	**Initial verification plan to verify the output**
User need	The device must provide contraception for up to 1.5 years	Long term clinical study to achieve 99% efficacy for up to 1.5 years
Patient safety	The device must be sterilized for healthcare professionals when opened for implantation	Standard sterility testing as per ISO 11737 to achieve no microbial growth after sterilization
Regulatory compliance	The device must meet the MDR regulations for medical devices	Identifying and documenting any gaps during QMS to ensure no major non-conformities exist
User need	The hydrogel must be dissolvable when required within one hour	Laboratory testing (dissolution time test) to ensure hydrogel is dissolvable within the desired time
Patient Safety and Regulatory compliance	The hydrogel must be biocompatible, non-toxic to the body and human tissue	Cytotoxicity, reproductive and development toxicity, sensitization and irritation testing to achieve 99% biocompatibility and hemocompatibility
User need	The hydrogel must be 99% effective in blocking sperm within 30 days of implantation	Clinical study to achieve desired efficacy within 30 days
User need	The implant must be visible under ultrasound guidance for accurate implantation. Experiments started with microbubles	Laboratory testing to achieve 90% visibility under ultrasound
User need	The hydrogel must not degrade prematurely	Long term study to ensure that hydrogel does not degrade less than 5% over 18 months
Regulatory Compliance	The device should have a shelf life for up to 2 years	Accelerated aging study to ensure the specifications are retained for 2 years.

User need	The procedure should be easy for healthcare professionals and achievable within 40 minutes.	Testing and developing the injectable solution and the crosslinking to approach this and then simulated procedure study to ensure 90% of procedures are completed within 40 mins
User need, Patient Safety and Regulatory Compliance	The cross-linking method used must be safe, easy to use and effective to form stable gel	Chemical analysis, cytotoxicity and biocompatibility testing to check stability of the gel and no harmful residues left by crosslinking.
Regulatory Compliance	The catheter must deliver the hydrogel effectively and safely without altering its properties	Laboratory testing to achieve more than 95% of properties intact after implantation

6.2 Preclinical testing and evaluation

Since DEFLEXA is a completely new medical device, extensive preclinical testing and evaluation is needed. During this stage, for example biocompatibility, usability and mechanical properties of DEFLEXA are tested. The aim of these tests is to make sure that design can be validated and frozen.

The biocompatibility testing plan of DEFLEXA will be done according to ISO 10993-1:2020. DEFLEXA uses unique hydrogel composition that is not yet sold on markets and due to that, there is a need for evaluation based on the chemical nature of materials (ISO 10993-18:2020, ISO 10993-18:2020/A1:2023) and duration of contact. Toxicity will be estimated using ISO 10993-17:2023. Tests that are needed for DEFLEXA will test cytotoxicity (ISO 10993-5:2009), sensitization (ISO 10993-10:2023), irritation (10993-23:2021), material mediated pyrogenicity (no single test can differentiate possible reaction), acute system toxicity (ISO 10993-11:2018), subacute toxicity (ISO 10993-11:2018), chronic toxicity (ISO 10993-11:2018), reproductive and developmental toxicity (ISO 10993-3:2014) and implantation effects (ISO 10993-6:2016). Testing of degradation of product will be done according to ISO 10993-15:2023. During testing samples should be prepared according to ISO 10993-12:2021.

DEFLEXA will have usability engineering according to IEC 62366-1:2015. The aim of usability tests is to identify and mitigate risks associated with correct use and use errors of the device. During this testing different simulated scenarios will be gone through, and the aim is to identify possible problems and hazards for user. In the end of this process the aim is that 90% of procedures with DEFLEXA are done within 40 minutes and user interface of the product is as clear as possible. This testing includes process of device application (includes visibility under ultrasound) and device removal (hydrogel dissolving testing).

The shelf-life of DEFLEXA will be tested and determined from many perspectives. The stability of the packaging system and its sterility will be tested according to ISO 11607-1:2020. The stability of hydrogel will be tested using accelerated and real-time stability tests. Stability testing can be done by applying testing strategies, for example from ASTM standard F2900-11 and other previous studies. Stability studies will consider device's intended use and expected storage conditions. Stability testing can be partially outsourced, for example sample storage in controlled environment can be done by third-party company Eurofins Scientific.

Sterilization testing will be done according to ISO 11737-2:2020. This standard determines how to define, validate and maintain a sterilization process. Sterilization testing will be done using direct immersion technique. This testing can be outsourced to third-party company Eurofins Scientific.

Mechanical testing will be done to ensure that all mechanical components work as expected. These components include the syringe and catheter. For catheters testing is done following ISO 10555-1:2023. Catheters will be tested for power injection, gauge length, tensile force, surface material (coating), simulated use to investigate kinks and freedom from leakage during pressurization. DEFLEXA will use a catheter and a syringe that has a small-bore connector. Testing of this will be done according to ISO 80369-7:2021. Syringes will be otherwise tested according to ISO 11608-1:2022. These tests will test dose accuracy, dry-heat and cold storage, free falling and functional stability. Mechanical tests can be outsourced from third-party companies, for example Eurofins Scientific.

6.3 Clinical evaluation

For clinical evaluation of DEFLEXA, data of performance, safety and clinical benefits must be collected. Medical device regulation that novel class III implantable medical device must undergo clinical investigations [64].

PERFORMANCE:

Since DEFLEXA is non-hormonal option for male contraceptive its technology is based on the products mechanical properties which includes injectability, gelation time, stability and reversibility testing. Furthermore, the material must be suitable to block the sperm cells. The injectability of Gellan Gum methacrylate-based hydrogels have shown promising results of injectability characteristics by exhibiting shear-thinning behavior. These hydrogels were suitable for injection with 16G needle which is common in clinical applications [65]. However, since DEFLEXA is intended to travel through the vas deferens via catheter the injectability must be further studied. Gelation time and stability are highly affected by modification rate of the used hydrogel. Thus, they are essential to study.

Mechanisms of sperm blocking male contraceptive have been studied with rabbits. According to these studies hydrogel used to block the sperm in vas deferens caused rapid onset of azoospermia with duration of 12 months. Reversibility studies were provided to this material and observed that while the concentration and motility was able to reach the baseline levels, the forward progression and acrosome

integrity was compromised [27], [66]. However, in these studies, the material differences critically from DEFLEXA, demanding performance of these studies.

SAFETY:

According to existing literature Gellan Gum methacrylate (GGMA) is a non-toxic biocompatible material providing promising features for tissue engineering applications. In short-term use (up to 18 days), GGMA based hydrogels have shown good tissue compatibility and non-toxicity after subcutaneous implantation in a rat model. In-vivo studies proved that there weren't any signs of infection, necrosis or calcification. During the studies, moderate infiltration of inflammatory cells was noted on 10. day. However, by 18 days, the cell infiltration decreased significantly which indicates that implants were adapted to the body. Furthermore, histological analysis showed that the body can accept GGMA implants without adverse reactions, which is crucial for long-term applications like DEFLEXA [67].

These findings support that the material has a potential to meet biocompatibility requirements under of ISO 10993-standard. However, this must be further studied by adapting toxicity and biocompatibility in long-term use.

CLINICAL BENEFITS:

The data collected to evaluate the clinical benefits of DEFLEXA should include comparison of current contraceptive methods compared to clinically proved claims of DEFLEXA. These include the reversibility when compared to vasectomy and duration of use when compared to condoms. Also, one clinical benefit would be that the contraception efficiency of the device isn't limited to user errors of lay person.

As a conclusion, while there is existing data of novel male contraceptives that can be used as literature data for DEFLEXA, the clinical investigations are still needed due the nature of the device and the material choice of the device. The stage of clinical investigations should be from I to III.
Stage I should focus on assessing the safety and injectability of DEFLEXA covering also the evaluation of materials biocompatibility and any potential immediate adverse effects following implementation. Stage II is intended to be conducted for larger scale to evaluate the safety and efficacy of DEFLEXA enabling monitoring of possible side effects and contraception effectiveness of wider target group. The final stage is to study long-term effects of DEFLEXA focusing on its durability, reversibility and safety during prolonged use.

7 Risk Assessment

7.1 Product risks

The most common risks associated with the product are roughly divided into material-based and user-error-based hazards. In the material-based hazards, the most severe risks are premature degradation and bad cytocompatibility, which can lead to unintended pregnancy and/or inflammatory conditions. On

the other hand, user-based errors can lead to unintended pregnancy or STIs, due to not reading or adhering to the precautions given. A common hazard is irritation of the urethra and vas deferens due to the implantation procedure, which can for example cause difficulties in peeing and discomfort for a week after implantation. Irritation is minor in severity nature, but frequent in probability, which makes it important to mention. ISO 14971 was used to identify risks, hazardous situation, possibility, risk class then designing mitigation strategies to lower the risk for suitable level.

Hazard (Known and foreseeable sources of harm and how the patient is exposed to the hazard)	**Harm** (Physical injury or damage to health)	**Risk Control / Mitigation** (Protective measures in medical devices or manufacturing process)
The device is not 100% effective the first few days	Unintended pregnancy	clinical studies of sperm concentration post implantation, proper precaution measures with information on using other contraceptive methods for a set time after implantation
The hydrogel degrades prematurely	Unintended pregnancy	stabile degradation of hydrogel, accelerated degradation tests annually, precaution on the temporary nature of device
Used against indicated use	STIs	Education of the device for healthcare professionals and lay persons. Precaution: Product do not prevent from STIs.
Irritation of the urethra and vas deference due to implantation procedure	Irritation, difficulties in peeing for about a week after implantation	Using the smallest catheter possible, using lube to cover the catheter, making syringe and hydrogel compatible with smallest catheter, patients warned about the probability of irritation
Biocompability of the device is not achieved	Tissue damage, inflammatory condition in vas deferens	cytocompatibility tests and post-market surveillance with batch-to-batch QC measurements
The material evaporates during storage or transportation	Unintended pregnancy	Identifying the limit values (min.-max.) of the material needed for working properly. Identifying the evaporation rate and utilizing it for determining expiry date.

7.2 Business risks

Business related risks are as important to assess as product-related risks. Business risks span across multiple different areas which makes it even more important to assess. The risks for the business can be divided into five categories: market acceptance, regulatory, financial, legal and competitive risks. Out of these the most likely risks are related to regulatory and market acceptance risks.

Medical devices are strictly regulated and meeting the requirements of EMA and/or FDA is obligatory for market approval. Delays or failures in gaining regulatory approvals can lead to significant financial loss, lengthened time to get the device to market and loss of trust from investors. To be able to get regulatory approval, the results from clinical trials need to be successful. If problems with safety or efficacy are noted, there is a risk of complete shelving of the product. Legal risks may arise if the DEFLEXA causes unforeseen side effects post-market. Product liability lawsuits could be raised causing financial damage and harm to the reputation.

As a novel medical device, the business idea, DEFLEXA, needs to be protected by creating patents for the manufacturing methods. The patents can be challenged by competitors and if intellectual property is not granted, the idea can be copied. To mitigate the risk of our intellectual property getting used by others, patents are done as soon as possible. Gaining market approval is one of the key things needed for larger success, because reluctancy from the target market can lead to loss of revenue. Detailed market analysis and Voice-of-Customer analysis need to be done to ensure acceptance. Successful educational campaigns can help gaining increased adoption of the device.

Competitive risks deal with other products that are under development. If for example our main competitor ADAM expands to global markets before DEFLEXA, the competitor will decrease the customer value of our product. Financial risks stem from failing to get investors for pre-clinical and clinical trials. This will lead to delays in entering the markets and may even cause the total abandonment of product idea.

8 Marketing and Sales

8.1 Customer segments

The overall contraceptive users can be further divided into male and female users. In 2019, World Health Organization (WHO) reported that around 922 million women of reproductive age use female contraception globally and around 50% of women in Europe use some form of contraception. [68] Total male users of condom are about 208 million worldwide and about 16 million male users rely on sterilization methods like vasectomy for contraception. [69] This number is increasing significantly every year as efforts are made to raise awareness and assistance with family planning and reproductive health worldwide, especially in under-developing countries.

As the women-oriented contraception dominate the market, male contraception account for only one-quarter of the overall contraceptive use worldwide. Moreover, only 13% of women in committed relationships rely on male contraception method. [70] In US, it is reported that out of 7 million women of reproductive age, 25% are unable to use contraception due to various chronic health conditions such as hypertension, diabetes, depression, and vascular disease. [71] Moreover, in a study conducted in Brazil,

Germany, Mexico, Spain, it was found that 60% of males have expressed their interest to participate equally in family planning.[72]

Our product is primarily used by healthcare professionals and targeted towards couples. The product is implanted in the male reproductive system and by a healthcare professional. DEFLEXA is made for men seeking less harmful and reversible contraceptive options that avoids daily reliance on products like condoms while the product can be administered by urologist, family planning specialists or general practitioners. The nature of the product can interest males in long term relationships while single males can also use it for long term contraception. Healthcare professionals will be responsible for recommending, explaining and administrating the product for product adoption.

Therefore, it is quite important to provide adequate training to healthcare professionals and education to the male users about the product. For this purpose, clear guidelines and materials need to be provided about the product for healthcare professionals to ensure successful implementation and patient care. It is also crucial that the product is clinically validated, safe to use and effective for men while regular support and market surveillance is provided to ensure that men understand the benefits, challenges and usage of the product.

8.2 Marketing claims

The following are some of the claims made DEFLEXA:

Claim 1: DEFLEXA is long term contraception and 99% effective in preventing pregnancy for up to 1.5 years

The efficacy of DEFLEXA will be demonstrated during clinical evaluation with azoospermia testing with at least 30 couples. The acceptability criteria will be at least 99% reduction in sperm motility count within 30 days. The sperm count and pregnancy rates will be monitored monthly. All data and processes will be documented for post study analysis, to ensure no severe side effects occur during the trial and to ensure that all requirements by MDR are addressed properly. Post-market surveillance will be conducted to track efficacy in the real world and any severe incidents to be immediately reported to the authorities.

Claim 2: DEFLEXA is reversible contraception method for men with a return to fertility within 3 months of removal

The non-permeance of DEFLEXA will be demonstrated by conducting reversibility studies during clinical evaluation that include the increase of the concentration of sperm cells after removal, viability and movement of the cells. We expect reversibility within 3 months for 95% of the participants. The sperm count and pregnancy rates will be monitored monthly. All data and processes will be documented for post study analysis, to ensure no severe side effects occur during the trial and to ensure that all requirements by MDR are addressed properly.

Claim 3: DEFLEXA offers non-hormonal contraception without affecting hormonal balance

The approach of DEFLEXA does not target any hormonal reduction/production for azoospermia. Biocompatibility with tissues will be demonstrated in clinical evaluation with different cytotoxicity and hemocompatibility testing. The biocompatible should be shown in 100% of the cases. Post market surveillance will ensure smooth adaptability in the market.

8.3 Go-to-market plan

The first step in the marketing strategy would be to engage with key opinion holders and industry experts in andrology, urology, reproductive health experts and family planning experts during the clinical investigation process to ensure that the efficacy and safety of DEFLEXA is well-established. This will help us develop credibility in the market and an avenue to facilitate product adoption.

We will also develop partnerships with institutions and organizations in Finland and Europe. Key organizations and institution for networking and collaboration would be European Society of Contraception and Reproductive Health (ESC), European Academy of Andrology (EAA), Male Contraceptive Initiative (MCI), and Helsinki University Hospital (HUS). We can conduct training programs for healthcare professionals with leading healthcare providers such as HUS and other clinics to introduce them to DEFLEXA. ESC and EEA will give us opportunities to do academic publications such as research articles, presenting at conferences and network with more industry experts to get them onboard with our product. We can also do pilot user testing of DEFELXA with MCI collaboration to get customer feedback in Finland.

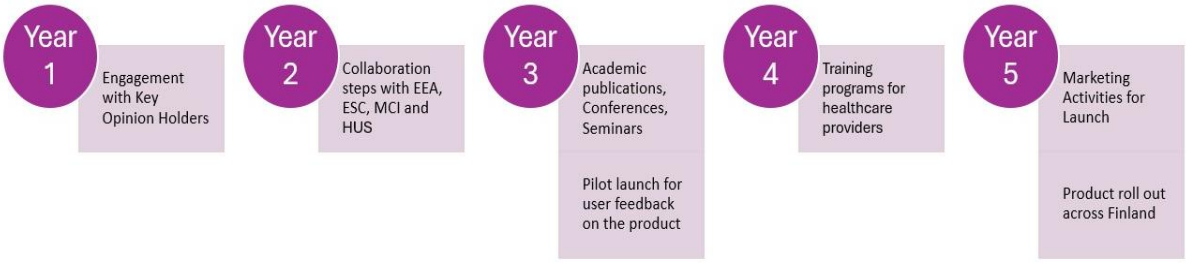

Figure 5: Yearly breakdown of marketing efforts

8.4 Sales Strategy and Revenue Stream

Our targeted customers purchasing our products would be healthcare providers, especially urologists and andrologists, fertility clinics, public health organizations promoting family planning. We will make direct partnerships with this segment. We will adopt two approaches, targeting direct sales to clinics and hospitals in bulk, and doing partnerships with pharmaceutical companies as a distributor in their network.

This will help us broaden our network in the targeted market. Moreover, marketing efforts, both digital and traditional to raise awareness about the product primarily among couples and male population that will encourage them to seek this solution from their healthcare provider. We will first launch the product in Finland (Phase I), then Norway, Iceland, Liechtenstein, (Phase II) then Australia, New Zealand, and Switzerland (Phase III) as MDR compliance gives market approval in these countries. They also have high adoption of innovative health solutions and established healthcare infrastructure.
The cost of our device would be 200 EUR where our gross margin is 33% and the rest in production cost, the breakdown of this is described in the above sections. Our aim would be to target 20 healthcare providers in the first year in Phase I countries. With scaling up, our production costs can go down and we will be able to increase our profits in 5 years.

In the first year, we will target 20 healthcare providers, and our target would be 50 devices per provider on average in Finland. This amount is realistic and manageable to do market penetration in the first year of launch. In the first year, our revenue will be low and may not cover initial investments but with our production cost going down and our efforts to push market adoption, we can achieve desirable results. In the later year, the devices per provider is on average and sales may fluctuate between the providers according to their needs.

Revenue in Phase I countries (Year 1):

$$20\ providers \cdot 50\ devices\ per\ provider \cdot 200\ EUR\ per\ device = 200{,}000\ EUR$$

Revenue in Phase I and Phase II countries (Year 2 and 3):

$$200\ providers \cdot 100\ devices\ per\ provider \cdot 200\ EUR\ per\ device = 4{,}000{,}000\ EUR$$

Revenue in Phase I and Phase II countries (Year 4):

$$250\ poviders \cdot 100\ devices\ per\ provider \cdot 200\ EUR\ per\ device = 5{,}000{,}000\ EUR$$

Revenue in Phase I, Phase II and Phase III countries (Year 5):

$$400\ providers \cdot 100\ devices\ per\ provider \cdot 200\ EUR\ per\ device = 8{,}000{,}000\ EUR$$

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