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Bachelor in Micro and Nanotechnology Engineering

From Lab to Industry: a Scale-up Framework for a Medtech Startup

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Innovation is taking two things that already exist and putting them together in a new way. – Tom Freston

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Abstract

An important step forward for every startup company is to formulate a step-by-step plan that will help them to navigate in the next years. Within the medical technology industry (Medtech), the success of an emerging product is highly influenced by having a solid innovation strategy. According to new updates in the Medtech regulatory system, this thesis addresses what can be done to overcome the challenges and risks to cross the bridge between lab and industry. Our research is deducting from already existing academic and general knowledge. Therefore, a critical review of the literature on both Medtech and innovation processes is provided. From data collection to data analysis, relationships between concepts and variables are proposed, thus creating a comprehensive guide to fulfil a specific research gap. As a result, a fully integrated next-generation Stage-Gate® system is presented as a conceptual framework. Then, nearly every aspect of medical technologies lifecycle is revised and updated into the new framework. The newer process was aimed for more innovative and bolder projects targeted at less well defined but growing markets and relying on newer technology with technology risks. To demonstrate its applicability, case-study research was conducted with a real Medtech startup - RUBYnanomed. Throughout the development stages of its new in-vitro medical device product - a microfluidic cartridge aimed for liquid biopsy -, RUBYnanomed provides the relevance and applicability needed for the proposed model.

Keywords: Innovation, Strategy, New Product Development, Medtech

Resumo

Um marco importante na criação de uma empresa consiste na formulação de um plano detalhado para mais tarde funcionar como guia estratégico. Na indústria de tecnologias médicas (*Medtech*), o grau de sucesso de um produto emergente está altamente associado à adoção de medidas estratégicas de inovação. Tendo em conta as últimas atualizações das normativas regulamentares na área das *Medtech*, este trabalho incide sobre os procedimentos a adotar na superação de riscos e desafios consequentes do desenvolvimento de novas tecnologias. Com base no método de investigação dedutivo, uma revisão crítica da literatura é apresentada em relação à indústria e aos processos de inovação. Da pesquisa à análise de dados, relações entre vários conceitos e/ou variáveis são propostos, formulando assim um suporte prático no preenchimento daquela que é considerada uma lacuna na investigação científica – a passagem, do laboratório para a indústria, de tecnologias *high-tech*. Como resultado, obtêm-se um sistema *Stage-Gate*® mais contemporâneo que será implementado enquanto *framework* conceptual. Aqui, as atividades principais do ciclo de vida das tecnologias médicas são revistas e adotadas no novo sistema. Esta *framework* visa projetos inovadores que pretendam penetrar novos mercados em crescimento, e cujo produto contenha elevados riscos tecnológicos. De forma a demonstrar a aplicabilidade da mesma, propôs-se um estudo de caso com uma *startup* real. A RUBYnanomed, por meio do seu novo dispositivo médico *in vitro* - um cartucho de microfluídica destinado à biópsia líquida – apresenta aqui um papel de extrema relevância no processo de avaliação do modelo proposto.

Palavras-chave: Inovação, Estratégia, Desenvolvimento de Novos Produtos, Medtech

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Acronyms

CDHR	Center for Devices and Radiological Health
CE Mark	*Conformité Européenne* mark
CEO	Chief Executive Officer
CTCs	Circulating Tumour Cells
DFM	Design for manufacturing
Ec Rep	Authorized Representative
EPO	European Patent Office
EU	European Union
FDA	USA Food and Drug Administration
FD&C	Federal Food, Drug, and Cosmetic Act
GMP	Good Manufacturing Practices
ICC	Immunocytochemistry
IDE	Investigational Device Exemption
IF	Immunofluorescence (IF
IFU	Instructions for use
INL	International Iberian Nanotechnology Laboratory
IP	Intellectual Property
IPO	Initial Public Offering
IPR	IP review
IVD	In-vitro diagnostic
IVDD	IVD Directive
IVDR	IVD regulation

KOL	Key opinion leaders
Medtech	Medical technologies
MD	Medical device
MDD	MD Directive
MDR	MD Regulation
M&O	Manufacturing and operations
MRI	MRI magnetic resonance imaging
NB	Notified Body
NPD	New product development
OEM	Original equipment manufacturer
PDMS	*Polydimethylsiloxane*
PMA	Premarket approval
PMCF	Post-Market Clinical Follow-up
PMPF	Post-Market Performance Follow-up
PMS	Post-Market Surveillance
PoC	Proof-of-concept
PPMF	Product-Project management framework
QMS	Quality Management System
QSR	Quality System Regulation
R&D	Research and development
ROI	Return of investment
RUO	Research use only
SAM	Serviceable available market
SME	Small and medium enterprises
SOPs	Standard operating procedures
TRL	Technology readiness level

UDI	Unique Device Identifier
USA	United States of America
VP	Value proposition
V&V	Verification and validation

Motivation

A major step in the development of any high technology is the scale-up process from lab to pilot production towards commercialisation. Moreover, when the technology is at the front-end of innovation, this transition implies big challenges. Still, the risks associated can be predicted using innovation strategies that aid the systematic management of promising technologies and, thus, facilitate the generation of future commercial income[1].

Apart from the digital-based technologies, the scalability phase remains unresolved for high-tech/high-growth projects in other sectors, mainly when referring to early-stage companies[2][3]. This issue is even more noticeable for those operating in a conservative and highly regulated industry - as in the case of the medical technologies industry (Medtech)[4].

Through the characterisation of such specialised market, a management framework is often required by stakeholders to understand and support the scale-up strategy of a Medtech business[5]. Not only product/market fit specifications are needed but also external factors affecting healthcare industry, such as regulatory constraints, must be taken into consideration.

In this sense, the main goal of this project is to develop a step-by-step guide on how to bring emerging medical devices towards commercialisation based on existing theory and knowledge acquired from experts in the field.

This project aims to answer the following research question: which tools are more suitable to use in the development of medical devices? And accordingly:

1. How should a conceptual framework be developed?
2. How should the new design be implemented in practice?

For this purpose, the work was divided into three main research phases:

- Collection and analysis of the current tools to elaborate a product/project development plan in the niche segment, though critical literature review;
- Exploration and implementation of the best practices to support the development of a generic framework, considering empirical data analysis related to regulatory systems, reimbursement and risk strategy;
- Test and evaluation of proposed scale-up management methodology, through a real case study.

Ultimately, the work contained in this thesis aims to help Medtech small and medium-sized enterprises (SMEs) to fulfil the gap between lab and industry by using an innovative conceptual methodology. Such methodology is expected to contribute to speed up the adoption and diffusion of medical technologies among early adopters in both Europe and the United States of America (USA).

1

Introduction

1. Background

Less than 50 years ago, only five proteins from genetically engineered cells had been approved as drugs by the United States Food and Drug Administration (FDA). However, by the end of the 1990s, 125 more genetically engineered drugs would be approved[6]. This growth only increased with the arrival of the 2000s and the so-called *Biotechnology Era*[7], due to rapid advances in the exploitation of biological processes for industrial applications that would completely revolutionise many aspects of life in the coming decades.

Unlike most of the established pharmaceutical companies, biotechnology ones introduced a whole new approach to drug development that did not easily integrate into the chemically focused approach. This shift in focus precipitated a rash of potential biotechnology products coming out of the lab[8]. Similar to biotechnology, nanotechnology applied to biological processes also aroused recently, exploiting the physical, chemical, and biological properties of materials at the nano level, to create new biomedical research tools, diagnostic tests, and drug-delivery systems[9].

For the first time, a big wave of initial public offerings (IPOs) of young biotechnology firms emerged, starting with the founding of Cetus (now part of Novartis Diagnostics), Genentech, Chiron, Biogen and Amgen[10]. In the first nine months of 2018 alone, 47 biotechnology IPOs raised $4.6 billion in venture capital - which is already more than 2015 and 2016 together. In the biggest biotechnology IPO of the year, the anti-cancer drug maker Allogene, brought in $324 million in a public offering that valued the company at $2.2 billion[8]. Lately, the dynamic has changed, and big pharma not only acquires biotechnology-based startups but, also, they pursue biotechnology either in-house (e.g. biotechnology divisions) or using an in-licensing strategy[11][12].

Under the umbrella of biotechnology, the medical technologies segment (Medtech) has also witnessed a remarkable growth, with a broad spectrum of available physical devices used in

every stage of healthcare, from diagnosis to treatment. Despite its massive impact in society, only a few Medtech startups made it from the lab to large scale production, and finally to the market. Tech-innovators behind them have to deal with a very complex, conservative and heavily regulated industry. In this sector, tech/digital strategies do not apply, and the lack of available information among real cases is scarce, mainly due to confidentiality concerns.
In 40 years, the whole healthcare industry is thriving. The promise is great for medical technologies, but in such a complex and fast-moving universe, the need for a more efficient and partnered collaboration has risen. A well-structured methodology contributes to speed up new product entry into the market, lowering costs and risks.

2. The Medtech landscape

International investors in the healthcare sector were used to high risk operations and long waits for return on investment (ROI). In contrast with the past, Medtech is increasingly seen as a safe bet to fund products or services that can reach the market comparatively quickly. With Medtech as a growing promise in a world of possibilities, the European Union (EU) and the United States of America (USA) remain the global market leaders.

In the European Union

The European market (EU28, Norway and Switzerland) is regulated under the *Conformité Européenne* mark (CE mark)[1]. This regulatory framework plays a significant role in the clinical market (and clinical practice), as well as in Research and Development (R&D) and manufacturing. The European regulatory system is considered by most as innovation-friendly and the statistics prove it: the number of Medtech filings within the European Patent Office (EPO) has doubled in the past decade[13]. But unstructured or decentralised processes still exist for regulatory and reimbursement approval, which can be burdensome to most companies. Further, recent financial crises led to reducing/slowing expenditure on healthcare.

In United States of America

The USA Food and Drug Administration (FDA) is, by statute, responsible for regulating the safety and effectiveness of new medical innovations in the United States[14]. Within FDA, the Center for Devices and Radiological Health (CDRH) has primary regulatory responsibility for medical technologies (solely known as medical devices in the USA). However, over the past years, representatives from the Medtech industry have reported that the FDA is becoming less predictable, transparent, and reasonable. At the same time, its requirements for demonstrating the safety and effectiveness of new devices continue to increase, slowing their response to inquiries and regulatory submissions.

Pathway from EU to USA

Under the EU structure, the focus relies on the demonstration of safety and performance, as opposed to safety and clinical effectiveness in the United States. Due mainly to the different clinical data requirements, innovative devices are often commercialised in Europe first. By receiving CE regulatory clearance years ahead of FDA approval, there is a real delay in the introduction of Medtech products in the USA market [1]. An early market entry is however important for entrepreneurs and investors to gain commercial exposure and potential first revenues.

3. Medical technologies

Nowadays, through innovative medical devices, non-invasive tests or digital health solutions, Medtech is already saving lives and improving people's health. So, in its many forms, the medical technologies are capable of preventing, diagnosing, monitoring, treating or caring for every disease or condition that can affects USA.

In the European Union

Currently, the European Medtech sector is transitioning from being regulated under the medical devices directive 93/42/EEC (MDD) or the *in-vitro* diagnostic medical devices directive 98/79/EC (IVDD) in to two new regulations: the medical device regulation (MDR) and the *in-vitro* diagnostic medical device regulation (IVDR). Within the new structure, medical technology definitions include:

- A medical device (MD) is an instrument, apparatus, appliance, software, implant, reagent, material or other article, intended to perform one or a series of roles, from prevention to cure. Examples range from syringes and wheelchairs to cardiac pacemakers and medical imaging technologies (such as MRI, CT and X-ray machines).
- *In-Vitro* diagnostic medical devices (IVD) provide medically useful diagnostic information, by examination of a specimen derived from the human body. Their role is to enable patients and healthcare professionals to make healthcare decisions. Some examples are pregnancy tests, blood glucose monitors and urine test strips.

In United States of America

Both the new European definitions (MD and IVD) fit in the one stated by the Federal Food, Drug, and Cosmetic Act (FD&C) as medical devices[1]. Such a broadly defined specification permits a wide range of medical technologies to fall under FDA regulation[15].

4. Innovation

Innovation is the process of translating an idea or invention into a good or service that generates value or for which customers will pay. R&D and new product development (NPD) are often branded as innovation. Instead, they should be seen as inputs to the innovation process.
Traditionally, R&D processes are expected to bring long-term value but most of the time they focus on invention. Only after the idea has evolved is when it is shared with other functional groups. This process slows down the chances of actual implementation. Commercialisation and customer acquisition start after the R&D process and is done by different people from the ones who came up with the idea, introducing a significant barrier to the flow.
Often, NPD comes up with a new product and then the search of the company is on to see which market to connect it to. The core of this problem is the fact that NPD focuses on reducing technical risk, where market risk still is an afterthought.
In the startup world, technologists who come up with an idea work hand in hand with the business people who market and commercialise it. Successful startup founders, even ones coming from a technical background, have a vision for actual commercialization.
While R&D works as a functional group that lives within the innovation process, strategies from NPD can be incorporated as a phase before commercialisation.

5. New product development

In many organisations, the budding ‘product management’ concept often becomes confused with ‘project management’. Using a clear definition and a proper alignment of each activity needed for the transition of a product to the market, helps to setup appropriate goals, expectations and results, being an imperative process in a high-performance organisation.

[1] For the sake of clarity in this project, when referring to a generic medical technology, it includes both medical devices and *in-vitro* diagnostic medical devices.

Product management

A product is commonly defined as a piece of goods, services or knowledge that can be sold and that integrate a bundle of attributes such as features, functions, benefits and users[16].
A product manager has the responsibility to ensure, over time, that a product profitably meets the need of customers. To achieve this goal, continuous monitoring and adaptation of the product attributes, communication strategy, distribution channels, go-to-market strategy, product roadmap and price are necessary.
Typically, a product lifecycle starts with its NPD phase (from conception to qualification), and then goes through launch and delivery, before finally declining and being removed[17][18].

Project management

A project is a temporary endeavour undertaken with the aim to create a unique product or result. The application of knowledge, skills, tools, and techniques to meet project requirements is defined as project management. The person responsible for achieving the project objectives and outcomes is the project manager[16].
A typical project starts with initiation and goes through planning, execution, and control, with the final phase being the closure of the project[17][18].

Framework integration

An integrated framework can be used to guide the activities contained within the various phases of a product lifetime, especially during a new product development (NPD) phase and support the decision-making process.
When integrating both, a product-project management framework (PPMF) is created, being possible to understand that multiple project executions living within the product lifecycle (Figure 1)[19].

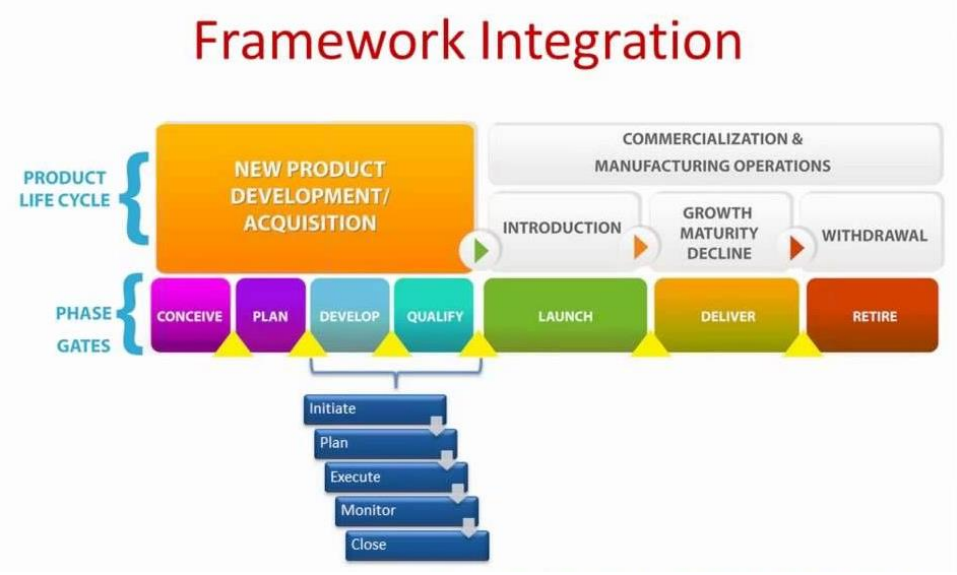

Figure 1 | Project management activities integrated in the product lifecycle (adapted from [20]).

6. The Stage-Gate® approach

Understanding the factors responsible for new high-tech products to succeed has been the focus of both academic research and managerial concern. A modern concept for new product development, known as Stage-Gate®, divides project managements tasks into different stages, separated by decision points, also known as gates [12].
Such approach was primarily designed to assist in decision-making processes about investments in large-scale products for mechanical and chemical engineering. The idea-to-launch model developed by Robert G. Cooper (Figure 2) consists of:

- A series of stages – where the project team undertakes the work, obtains the needed information, and does the subsequent data integration and analysis;
- Followed by gates – where Go/Kill decisions are made to continue to invest in the project.

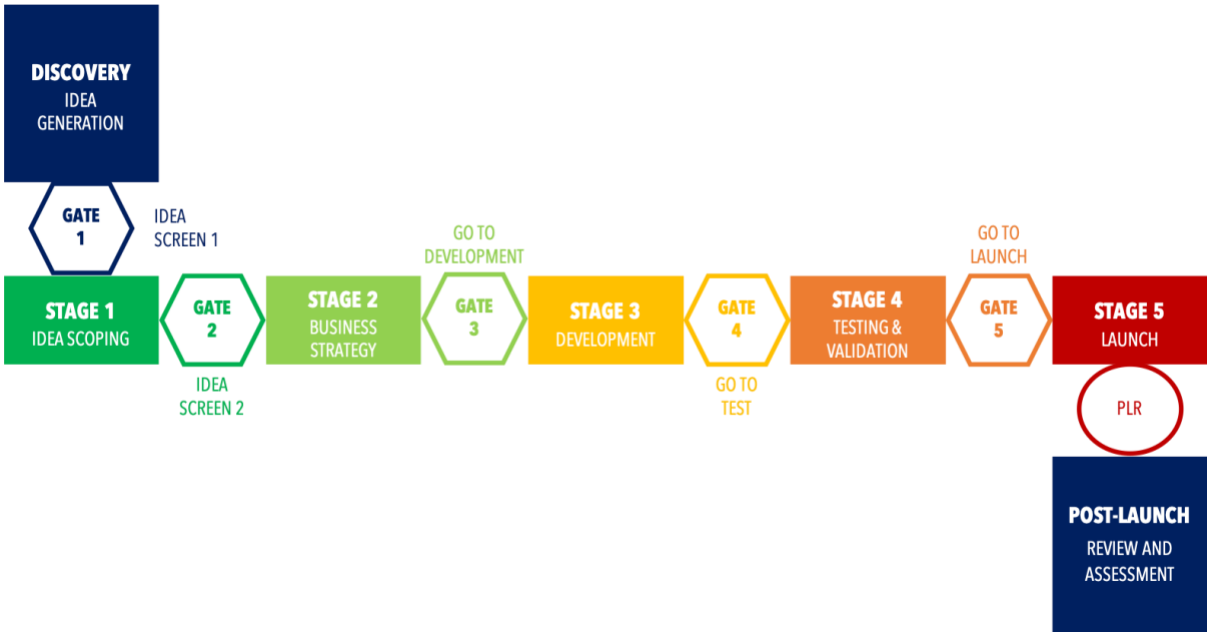

Figure 2 | An overview of a typical Stage-Gate® system for major new product developments (adapted from [12]).

Next-generation system

The Stage-Gate® author presented, in 2014, an essay redefining and updating his previous concept. Cooper studied new practices acquired by the most progressive companies in the world and integrated them with Stage-Gate® resulting in a next-generation system[21].
The new system named as Triple A (A1: Adaptive and Flexible; A2: Agile; A3: Accelerated) consist of:

A1.

i. The new approach promotes experimentation and iteration based on stakeholder's involvement. A series of spirals (build, test, feedback and revise) were included within stages (Figure 3-A);

ii. In addition to the full five-stage process to handle high-risk development, there is a lighter version for moderate risk and an express version for smalls developments or changes in technologies capabilities (Figure 3-B);

iii. Implementation of risk-based contingency models. Opposed to SOPs, which uses standardised prescriptions, the entire process (its activities, deliverables, decisions and portfolio) is now designed to gather information in need to be validated;

iv. With flexible gates, instead of a set of mandatory decisions following a stage, decisions rely more on strategic criteria rather than financial and are executed according to new key findings along the framework. Portfolio management will occur periodically in each gate to review the entire set of key activities (i.e. check if milestones are aligned with the strategic vision);

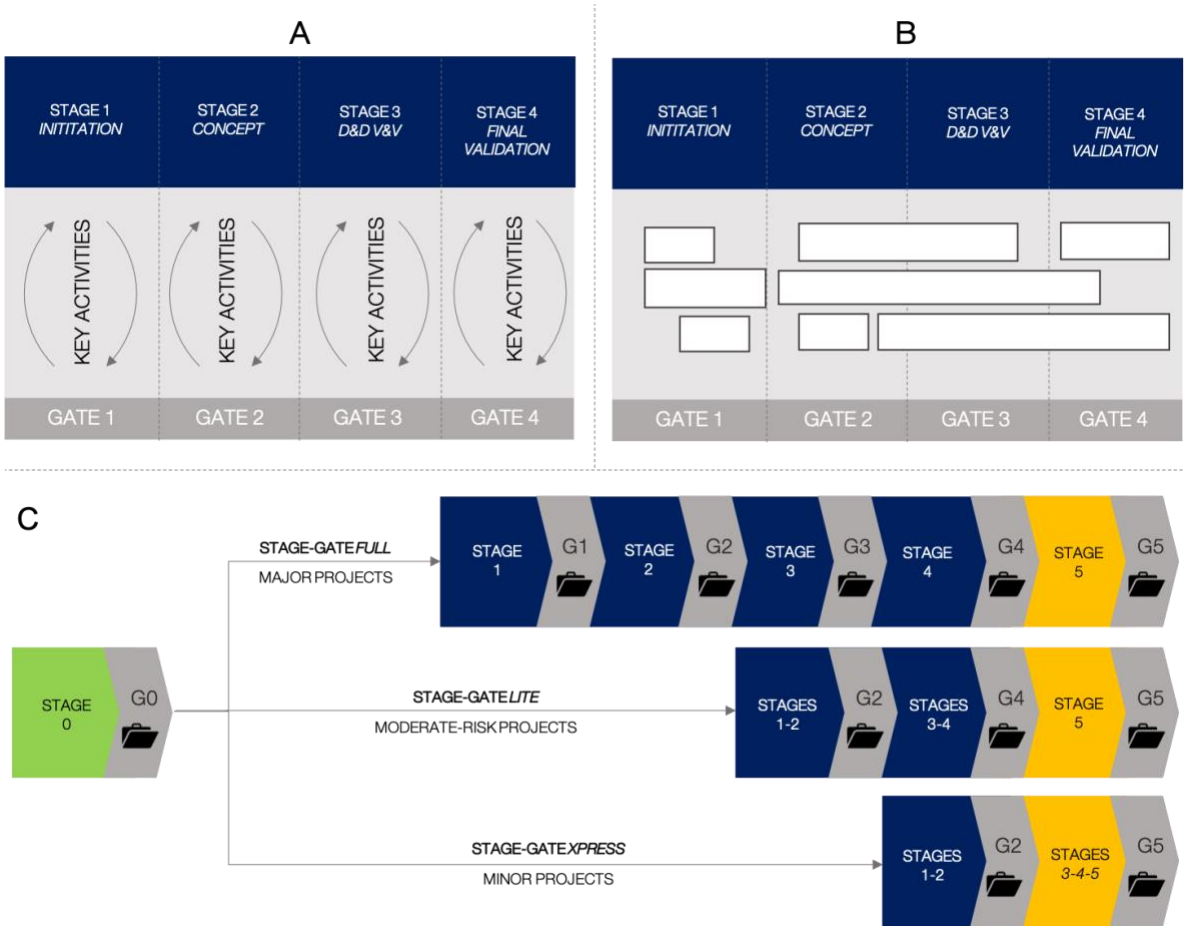

Figure 3 | Next generation Stage-Gate® system (adapted from [21]). A: series of spiral/iterative development cycles; B: Three risk-based fast-track versions; C: Accelerated.

A2.

i. Some practices here are adapted from the Agile Development for software, a rapid development system that relies on short time-boxed projects designed by the software industry. A detailed discussion of the various elements of Agile is beyond the scope of this thesis (additional background and information on this topic can be found in pertinent textbooks[22][23]);
ii. In this next-gen system, Agile also calls for responsiveness to change or agility, so no bureaucracy, unnecessary activities or documentation will be added;

A3.

i. For a maximum speed to market, activities overlap in time within and between stages (Figure 3-C);
ii. Properly resourced projects with dedicated teams focused on product innovation to maximize speed;
iii. Sharpening the fuzzy front-end of innovation by anticipate challenges, needs, risks and solutions in advance;
iv. Automated software to decrease the burden with administrative tasks and to decrease the time needed to complete activities and deliverables.

Integration

Stage-Gate® incorporates decision-making practices including success criteria, self-managed gates and integration with portfolio management. Progressive companies around the world are reinventing Stage-Gate® for use with open innovation, while others are applying its principles to adapt to other realities. Although practical data is scarce in the Medtech, previous concepts regarding new product development comply with rules, standard or directives in the field.
Under the scope of this project, one crucial factor is to recognise valuable information to support a framework integration within the Medtech context. By doing this, key milestones, major deliverables, requirements, assumptions and constraints in the case of medical technologies need to be identified.

7. Startup case study

RUBYnanomed is a spin-off company from the International Iberian Nanotechnology Laboratory (INL) aiming to commercialise medical technologies[24]. This early-stage startup developed the RUBYchip™, an *in-vitro* diagnostic medical device intended for pathologists in the cancer diagnostic and monitoring field.

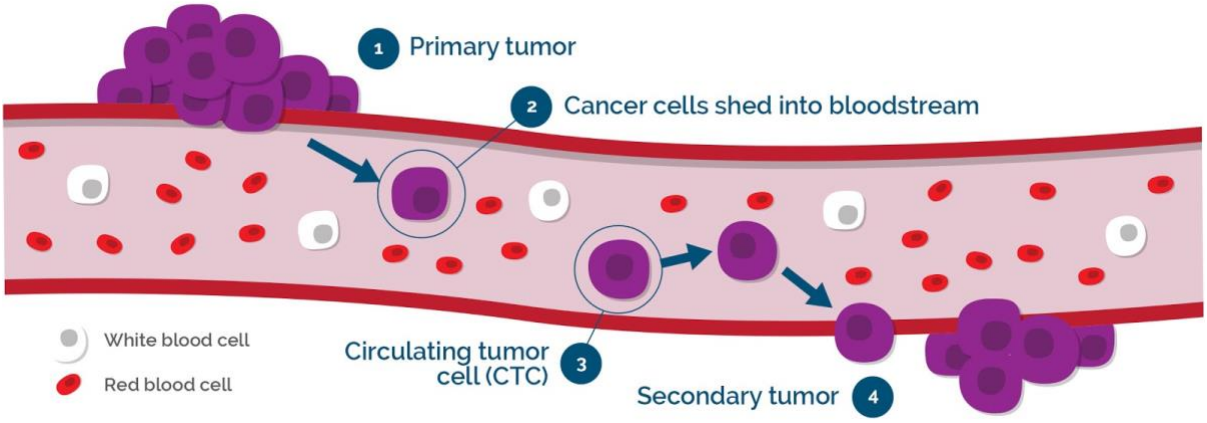

Figure 4 | Illustration of circulating tumour cells (CTCs) forming tumour metastasis (adapted from [25]).

The patented technology[26] consists of a microfluidic cartridge, which can isolate and identify a cancer biomarker - the circulating tumour cells (CTCs).
These are extremely rare cancer cells that escape from the primary and/or distant tumours and disseminate through the bloodstream. During this process, CTCs can invade other organs and cause metastasis, a mechanism that is responsible for the vast majority of cancer-related deaths (Figure 4). The process of analysing cancer biomarkers in body fluids is called liquid biopsy. Instead of analysing tumour material from invasive tissue biopsies, the RUBYchip™ performs liquid biopsies by retaining CTCs based on their morphology. By using a microfluidic filter fabricated in a polymeric substrate (Figure 5), CTCs are unable to escape and get entrapped. Then, within the chip, they are stained using fluorescently labelled antibodies to identify specific phenotypes and enumerated.

Figure 5 | Illustration of circulating tumour cells isolation cartridge and equipment (adapted from RUBYnanomed Business Plan).

In contrast with other technologies that use immunological isolation techniques, the RUBYchip™ captures CTCs based on their size and deformability, meaning that cell selection is not biased by molecular characteristics. These intact and viable cells provide the clinician

direct access to cancer biology, thus providing a remarkable advance towards personalised medicine[27].

RUBYnanomed plays an essential role when answering the second research question (how should the new design be implemented in practice?). By applying the new framework to RUBYnanomed, a real startup case scenario is exemplified here, and thus, the practical value of this project can be demonstrated as intended.

2

Methods

1. Research strategy

Deductive research is characterised by starting from specific findings based on available theories. Research that follows deductive reasoning, processes general knowledge into a more refined and specific theoretical or conceptual framework, and subsequently tests it using strategies for data analysis. The research performed in this thesis is based on deducting information from already existing academic and general knowledge, creating a step-by-step guide to fulfil a specific research gap in the commercialisation of medical technologies.
The project follows a list of procedures based on Robson's five sequential stages for deductive approach[28]:

1. Deducing a hypothesis (a testable proposition about the relationship between two or more concepts or variables) from the theory;
2. Expressing the hypothesis in operational terms (by indicating exactly how the concepts or variables are to be measured), which propose a relationship between two specific concepts or variables;
3. Testing this operational hypothesis (this will involve a single case study strategy);
4. Examining the specific outcome of the inquiry (it will either tend to confirm the theory or indicate the need for its modification);
5. If necessary, modifying the theory in the light of the findings.

2. Data collection

Mostly, the information used in this thesis refers to all non-numeric data that ranges from a shortlist of responses or results from empirical studies to more complex data such as interview transcripts or entire policy documents.

Data was collected in relation to the concepts and stablished theories that later would make up the hypothesis[29]. Most searches were conducted in the World Wide Web using the search engine Google to identify books, standards, and publications from governments and regulatory authorities. Some keywords used in the research include:

- Medical technologies + commercialisation
- Medical device + product development
- New product development + methodology
- Other variations

The first activity involves collecting and classifying data into meaningful categories. The publications found through this study are indicated in Table 1, including a summary of each publication, and categorised into three different topics:

- Maturity stage of the new product:
  - Ideation: from basic principles to proof-of-concept
  - Development: from proof-of-concept to pilot
  - Commercialisation: from pilot to production
- Functional Groups: the main set of activities in the development phase can be organised into major groups. In the Medtech context, several were identified, namely marketing, R&D, legal, regulatory, reimbursement, manufacturing & operations, quality, clinical strategy and sales).
- Format: whether valuable information is delivered via text only or if it adapts itself in the form of a graph and interactive presentation.

3. Building a new conceptual framework

Based on the deductive research strategy, a conceptual framework should be developed out of patterns and connections through data[30]. Once there is no of quantitative data to analyse, this framework will assist our understanding of the causal or correlational patterns of interconnections across ideas, observations, concepts and other parts of the experience in a predictable way[31].

For the first research question (how might a conceptual framework be developed in theory?), the research strategy is first to bring together concepts from various existing theories in NPD (PPMF, Stage-Gate® and next-generation system) and compare them. Following such approach[32], a skeleton of the upcoming methodology can be developed.

Then, by doing a good critical data analysis review, data related to the Medtech functional groups must be analysed. Relationships between concepts, good practices based on real experience or the latest trend in the field are considered an intuitive foundation for developing a conceptual methodology.

Finally, by integrating them into the framework, a new and updated conceptual methodology to scale-up medical technologies should be considered an outcome. The new model aims to be comprehensive and easy to apply to support managers scaling-up their products [33].

Table 1 | Data collected regarding new product development and/or Medtech main activities.

				Maturity			**Functional Groups**											**Format**	
#	**Authors**	**Title**	**Summary**	Ideation Phase	Development Phase	Commercialization Phase	Marketing	Research & Development	Legal	Regulatory Affairs		Reimbursement	Manufacturing & Operations	Quality Management	Clinical Strategy	Sales	Text	Graphical representations
										USA	EU							
1	Pietzsch et al. (2009) [34]	Stage-Gate Process for the Development of Medical Devices	This paper presents a model for the development of medical devices based on best-practices of USA's companies.	x	x	x	x	x	x	x		x	x	x	x	x	x	x
2	Pietzsch et al. (2009) [35]	The Iterative Nature of Medical Device Design	This paper examines variations to the linear MD development model through six case studies.		x		x	x	x	x		x	x	x			x	x
3	Zenios et al. (2010) [1]	Biodesign: the process of innovating medical technologies	This book describes the medical device development process.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
4	Kelvin K. L. Wong et al (2013) [36]	Methods in R&D of Biomedical Devices	This book presents a roadmap from the conceptualization to the testing stage	x	x	x		x					x				x	x

			of new medical technologies.																				
				Maturity			Functional Groups													Format			
#	Authors	Title	Summary	Ideation Phase	Development Phase	Commercialization Phase	Marketing	Research & Development	Legal	Regulatory Affairs		Reimbursement	Manufacturing & Operations	Quality Management	Clinical Strategy	Sales	Text	Graphical representations					
										USA	EU												
5	Linda Rochford; William Rudelius (1997) [5]	New Product Development: Stages and Successes in the Medical Device Industry	This article presents a model to compare new product successes and analysis in the USA medical device manufacturer industry		x		x	x					x				x						
6	Douglas J. Pisano; David S. Mantus (2008) [37]	FDA Regulatory Affairs: A Guide for Prescription Drugs, Medical Devices, and Biologics	This report provides guidance to manufacturers regarding the requirements of the FDA's quality systems.		x		x		x	x			x				x	x					
7	Jesús Martínez de la Fuente (2018) [38]	EU Horizon 2020 - Call: H2020-NMBP-TO-IND-2018-2020	This project aims to establish an open innovation test bed to enable industry and users to develop and test novel MD and IVD technologies.		x			x			x		x		x		x	x					
8	The European Parliament	[MDR] Regulation (EU) 2017/745 of the	This Regulation lays down rules concerning the	x	x	x	x	x			x		x	x	x	x	x						

	and the Council of the EU (2017) [39]	European Parliament and of the Council	commercialization of medical devices in the EU.																				
				Maturity						Functional Groups												Format	
#	Authors	Title	Summary	Ideation Phase	Development Phase	Commercialization Phase	Marketing	Research & Development	Legal	Regulatory Affairs		Reimbursement	Manufacturing & Operations	Quality Management	Clinical Strategy	Sales	Text	Graphical representations
										USA	EU							
9	The European Parliament and the Council of the EU (2017) [40]	[IVDR] Regulation (EU) 2017/746 of the European Parliament and of the Council	This Regulation lays down rules concerning the commercialization of *in vitro* diagnostic medical devices in the EU.	x	x	x	x	x			x		x	x	x	x	x	
10	Robert G. Cooper (2008) [12]	Perspective: The Stage-Gate® Idea-to-Launch Process - Update, What's New and NexGen Systems	This article reviews the Stage-Gate system and its principles and applicability.	x	x	x											x	x
11	Isa C. T. Santos (2013) [4]	Product Development Methodologies: The Case of Medical Devices	This PhD thesis proposes a product development methodology modeled to the medical device system.	x	x	x	x		x	x	x	x	x	x	x		x	x
12	Greg Geracie; Steven D.	The Guide to the Product Management and Marketing	This book provides the most comprehensive view of product	x	x	x	x									x	x	x

	Eppinger (2013) [18]	Body of Knowledge: ProdBOK(R) Guide	management and marketing.

#	Authors	Title	Summary	Maturity			Functional Groups											Format	
				Ideation Phase	Development Phase	Commercialization Phase	Marketing	Research & Development	Legal	Regulatory Affairs: USA	Regulatory Affairs: EU	Reimbursement	Manufacturing & Operations	Quality Management	Clinical Strategy	Sales		Text	Graphical representations
13	Travis G. Maak (2016) [41]	Medical Device Regulation: A Comparison of the United States and the European Union	In this paper, a brief review of FDA's regulation of medical devices will be provided.	x	x	x				x	x							x	
14	Cooper, Robert G. (2014) [21]	What's Next? After Stage-Gate	This article looks at what leading firms are doing to move beyond their current idea-to-launch methodology and tries to integrate these practices into a next-generation system.	x	x	x												x	x

4. Applying the new methodology to a case study

The overall purpose of developing a conceptual framework is to make research findings meaningful and generalisable. So in order to answer the second research question of this thesis (how should the new design be implemented in practice?), the success of the new methodology is tested based on its applicability and repeatability in a case study[42]. RUBYnanomed was selected for this purpose, since it represents a critical, extreme and unique case in a specific environment, to prove the relevance and applicability of the new model.
First, data acquired about the startup were collected through primary and secondary information channels[43]. Primary data was directly collected from meetings with the Chief Executive Officer (CEO) and co-workers. Secondary data were obtained via available documentation, such as:

- Scientific papers;
- Standard operating procedures (SOPs);
- Patent and licensing agreements;
- Business model;
- Grant applications and other proposals (e.g. startup accelerator programs);
- Pre-pilot verification and validation (V&V) paperwork;

Such documentation supports the understanding of both technical and managerial concepts. By analysing them, a general overview of the actual stage of the company, its vision and strategy is obtained are revealed. Still, the hypothesis and assumptions drawn from the theories need to be verified.

The model of validation proposed focuses on observing how the new methodology meets the project objectives:

- Is it comprehensive?
- Is it easy to use?
- Ultimately, does it support the scale-up of new medical technologies?

3

Results and Discussion

1. Conceptual framework

Startups in the Medtech are looking for a repeatable and scalable model that can withstand the peculiarities of the industry. Unlike them, big companies can put more efforts and invest more resources on adapting attributes from existing models to their own reality. In this work, we are going to have a closer look at models focused on new product development activities and create a unique framework aiming to improve SMEs in the field.

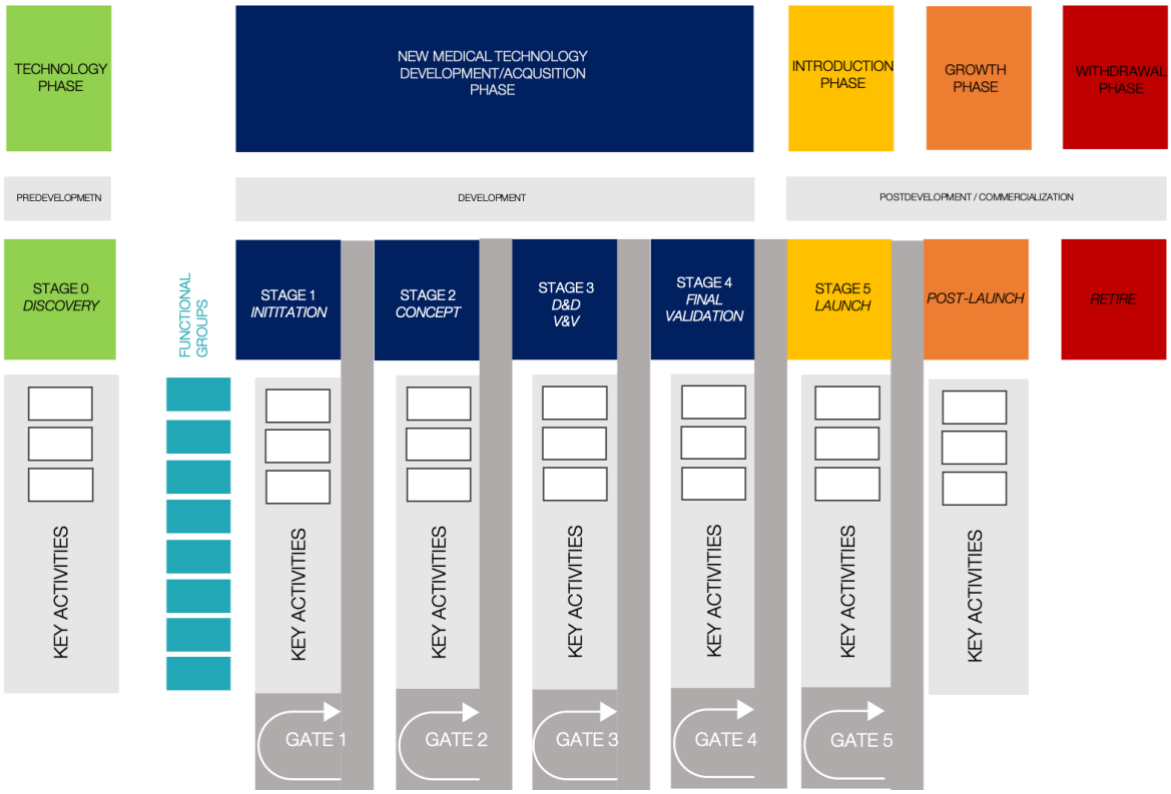

Figure 6 | Stage-Gate® process integrated with project development and new product life cycle structure (adapted from[12][18]).

There are many similarities between the PPMF and the Stage-Gate® process. For instance, phases in the PPFM are related to the stages in the Stage-Gate® process. At the same time, independent projects living within each phase are seen as the main set of activities for each stage. Following the completion of each project/activity, there is a checkpoint – a gate - where a decision should take place (whether it will be a Go/Kill/Hold/Recycle decision). Although both frameworks consider several steps of the NPD, the Stage-Gate® includes the Launch as a NPD stage while the PPMF refers to it as a Introduction (in the market). The PPMF misses the Discovery stage – a stage prior to NPD. In the case of medical products, predevelopment activities are critical before following stages[5]. The insights and information gained in the Discovery stage (e.g.: a preliminary market report or a technical analysis) may reduce costs and problems in the later, more expensive and risky development and post-development stages[34]. In short, both models can be applied to the Medtech scheme and be merged without overlapping issues (Figure 6). From now on, we consider three main phases (predevelopment, development and postdevelopment) divided by several stages (from Discovery to Retire) along the product lifecycle.

From the next generation Stage-Gate® system, we will adopt the following main attributes:

- Instead of prior project management steps (initiate, plan, execute, monitor and close) we use the new approach (build, test, feedback and revise) for activity loops and iterations (A1.i);
- Medical technologies are often classified according to the risks associated (more information on this subject in the section 3.2). Lower-risk technologies will be shrunk to decrease time-to-market and to fit into the lighter and express versions of the new model (A1.ii);

- For each stage, main activities, decisions and deliverables to portfolio management are defined. Decisions no longer belong to Gates, instead they are taken throughout the process and are strategy-based, i.e., through a clinical, regulatory or technical perspective (A1.iii-iv and A2.ii);
- Throughout the development phase, activities will often converge into loops, spirals or iterations. Overlaps occurs within and between stages, and also, functional groups (A3.i);
- Portfolio management updates shall be subject to the assessment of stakeholders and key opinion leaders. This mindset should be implemented from the Discovery stage on (A3.ii-iii)

By updating the framework with the attributes above, it is expected the overall look to become more flexible and able to support future customisations. Additionally, during the whole process, technical maturity can be estimated through the technology readiness level (TRL), a scale from 1 to 9, being 9 the most mature technology. The use of TRLs enables consistent, uniform discussions of technical maturity across different types of technology. An adaptation for the Medtech is presented in Figure 7, which includes 10 levels instead of 9, since it considers the postdevelopment phase.

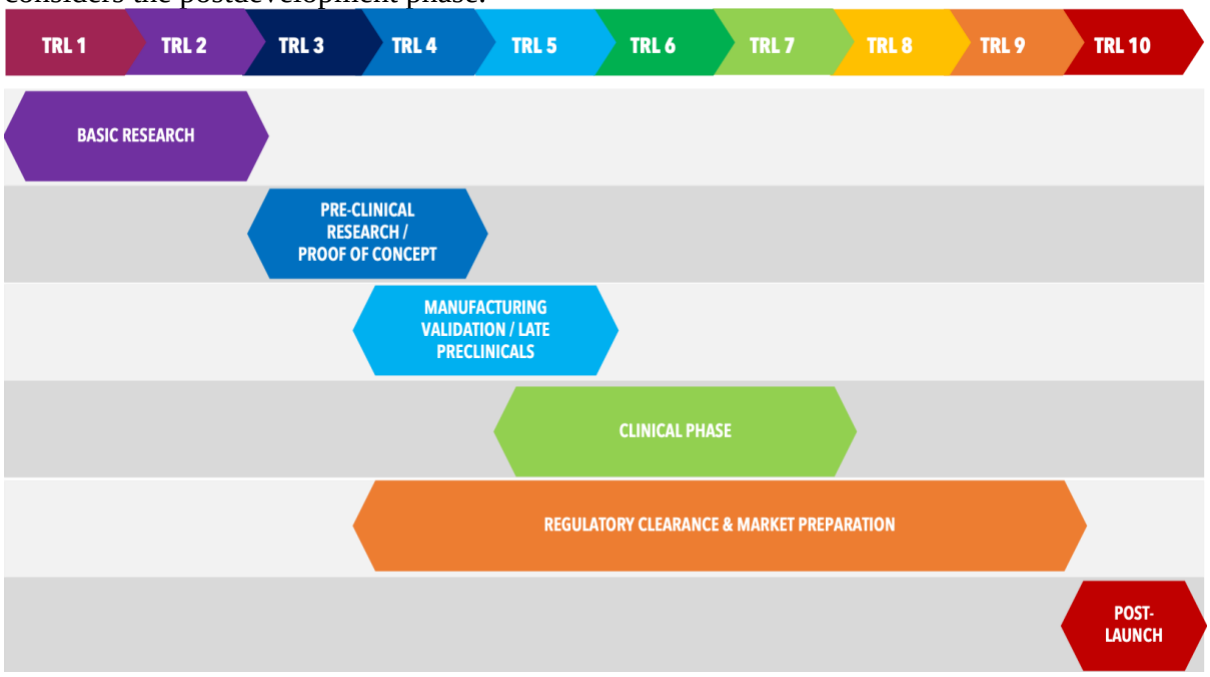

Figure 7 | Gantt of TRL using medical technologies development (adapted from[44]).

Bringing it all together, the base structure with the new add-ons, the final version of the framework is now ready. It provides guidance while being flexible to adapt to changing conditions or to be customized. Here, based on the previous connections, we present the solid base structure of our framework (Figure 8).

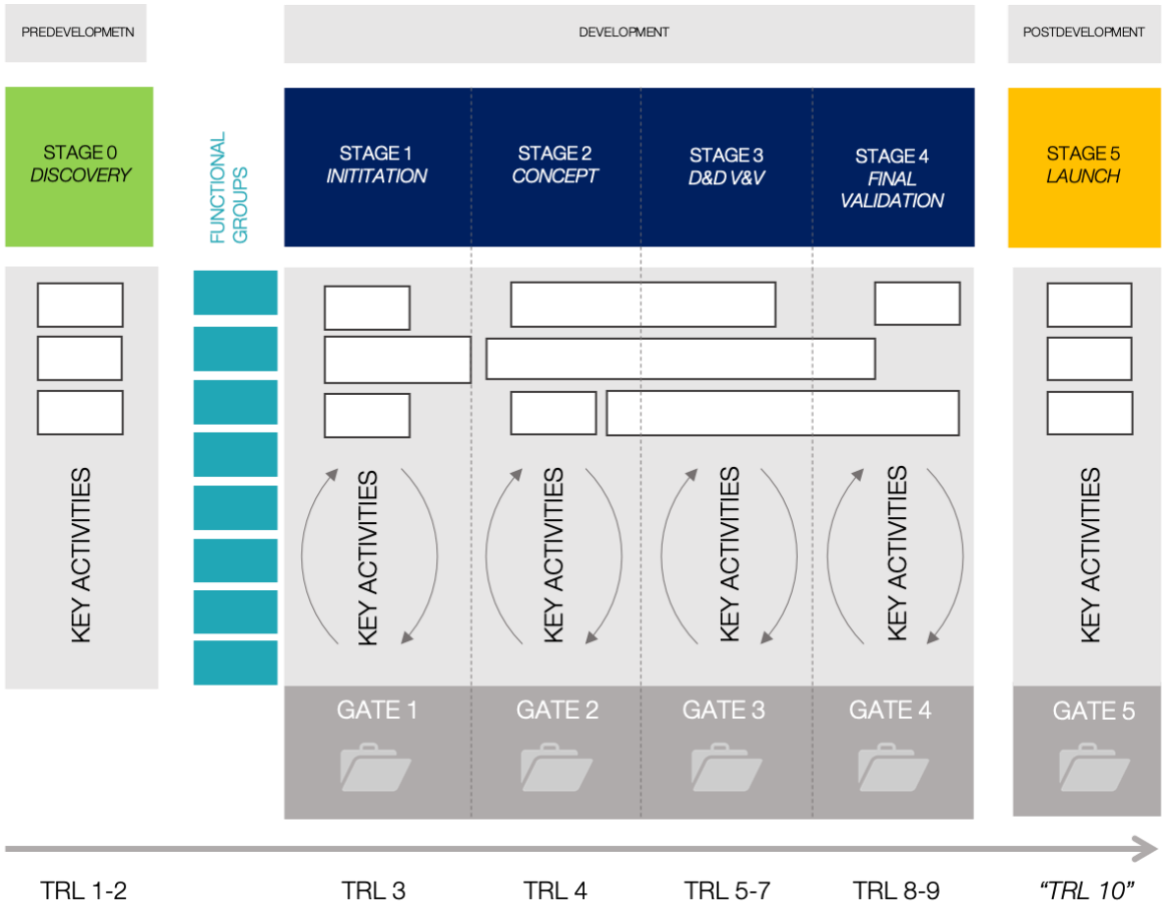

Figure 8 | A framework next generation Stage-Gate® system (adapted from [21]).

2. Conceptual methodology

Emerging medical technologies aiming to operate within the Medtech industry are the perfect target to put the previous concept into practice. Without being too rigid, the new framework works like the skeleton that will incorporate the main activities of development stages to scale-up new to the world Medtech products.

Predevelopment phase – Stage 0 - Discovery

Following the logic order of product life cycle, the first focus is the Discovery stage, where predevelopment activities take place. Predevelopment activities, such as preliminary market and technical analysis, are critical because the insight and information gained may reduce costs and problems in the later, more expensive and risky development and postdevelopment stages in product development[5].

Clinical needs screening

In order to create a new medical technology, inventors and device companies must focus on the how to solve an existing clinical need[45]. The main objective of Discovery stage is to develop a set of prioritised product concepts to match a clinical pull. The sourcing plan consists in:

- Site miner;
- Finding unmet needs;
- Scoping projects.

Solution to the problem

Although a challenging task, finding solutions process to a problem can be done by translating specific products features into technical capabilities, to meet a clinical need. This work can be done with the support of stakeholders (physicians, patients, and other healthcare providers), through personal experiences, user interviews, and by a review of the relevant clinical literature. Once a list of possible applications is identified, it is important to prioritize technology concepts.

SWOT analysis

A SWOT analysis must be developed to choose the best candidate among technologies. The main goal here is to exclude product ideas less suited to a specific need and to proceed with applications where assumptions were verified. To further narrow the list down, future barriers in the development phase from an intellectual property perspective should be identified. Additionally, a preliminary market analysis should be performed to ensure market opportunity and validate market needs. In the end, remaining technologies must get validated in terms of regulatory considerations and reimbursement strategy [34]. At this point, the team must be formalised to ensure they have the necessary skills to successfully commercialize the product.

Development phase – Stage 1 – Concept

In order to design a generic methodology for the development phase, an extensive field study was conducted based on the data previously collected (Table 1).
In what follows, each phase of the framework is described, and major responsibilities of selected functional groups are discussed in an integrated framework for both EU and USA markets. The whole development process is expected to take anywhere from 15 months to 32 months, depending on the device classification and quality of the work done.
The first stage in the development phase is considered a more detailed and narrowed extension of the predevelopment activities. The main activities of this stage are summarised below. A compact look inside key activities, decisions and portfolio reviews can be found in Annex I.

Market analysis and competitive landscape

A preliminary business plan must be drafted including analysis of the market/clinical need, technology selection, key opinion leaders (KOL) feedback, information regarding competitive technologies and market segmentation and size. At this stage, the company shall be

incorporated, and seed funds secured (i.e. through grants or acceleration program prizes) for the early stage expenses.

Design feasibility

In order to test usability with potential end-users, the key ingredient is to research and iteratively brainstorm models using tools such as visual and digital cards, development kits or 3D-printings. All the work developed in this stage is crucial to support the filling of the documentation and traceability requirements from regulations and certifications (e.g.: Design History File (DHF)).

Financial review

A critical financial review must include sales projections, projected gross margins and often includes proposed royalty breakout for those who contributed to the primary device concept.
A projected inventory analysis must be performed to assess the number of units that would be necessary to develop to satisfy market demand.

Legal/IP analysis

An IP review shall be conducted including a throughout evaluation of the technology concepts previously identified, also called prior art. For this purpose, scientific literature, granted patents and patent applications should be analysed not only in EU and USA, but worldwide.
In order to avoid IP violations, licensing agreements may be considered at this point if existing IP was generated from third parties.

Regulatory and clinical path

An international regulatory assessment should be performed to identify the requirements in order to commercialise the product within different markets. In this study, the focus is the exploitation of both EU and USA markets.
Although the Medtech regulatory structure is a controversial topic worldwide, for both EU and USA systems, classification is based on risk[41]: the risk class determines whether or not a conformity assessment would be required in terms of safety and effectiveness.
In the USA, the FDA regulates device approval and surveillance under one umbrella, allowing technologies to be marketed in all EU states. Within the new EU structure, a specific notified body (NB), which is a for-profit company, is contracted by the manufacturer to ensure device approval. For a NB to grant a CE mark, the medical technology must comply either with European Commission Regulation (EU) No. 2017/745, commonly known as the Medical Device Regulation (MDR) or European Commission Regulation (EU) No. 2017/746, commonly known as the In Vitro Diagnostic Regulation (IVDR).
For both systems, manufacturers need to demonstrate that their product meets the requirements during the development phase by carrying out a conformity assessment[46].
A regulatory risk analysis identifies the preferred regulatory path, based on its type (i.e. medical device, *in-vitro* diagnosis medical device, other), risks and classification and market entry point (for instance, breakthrough products with significant risks have a more complex path comparing to the ones in compliance with recognized standards). A preliminary clinical plan assesses whether or not the approval process will require clinical trials.

In the USA, the classification of a medical device or In Vitro Diagnostic (IVD) device can be determined by searching the *FDA classification database* using relevant search terms, or by identifying another (predicate) device with the same intended use and technology. It is important to pay special attention to the three letter Product Code and seven-digit Regulation Number associated with the predicate devices identified. If the classification cannot be determined, the *513(g)* process can be used to request classification from the FDA[37].
For the EU system, the first step recommended is to appoint a person as responsible for regulatory compliance. Then, the classification of the device can be determined using the Classification Rules in Annex VIII of both the MDR or IVDR.
In stage 1, a regulatory assessment must have been performed in order to identify information needed to obtain a CE marking and/or FDA 510(k) clearance and Premarket Approval (PMA). In the same sense, whether or not the process will require clinical trials must have been revealed.

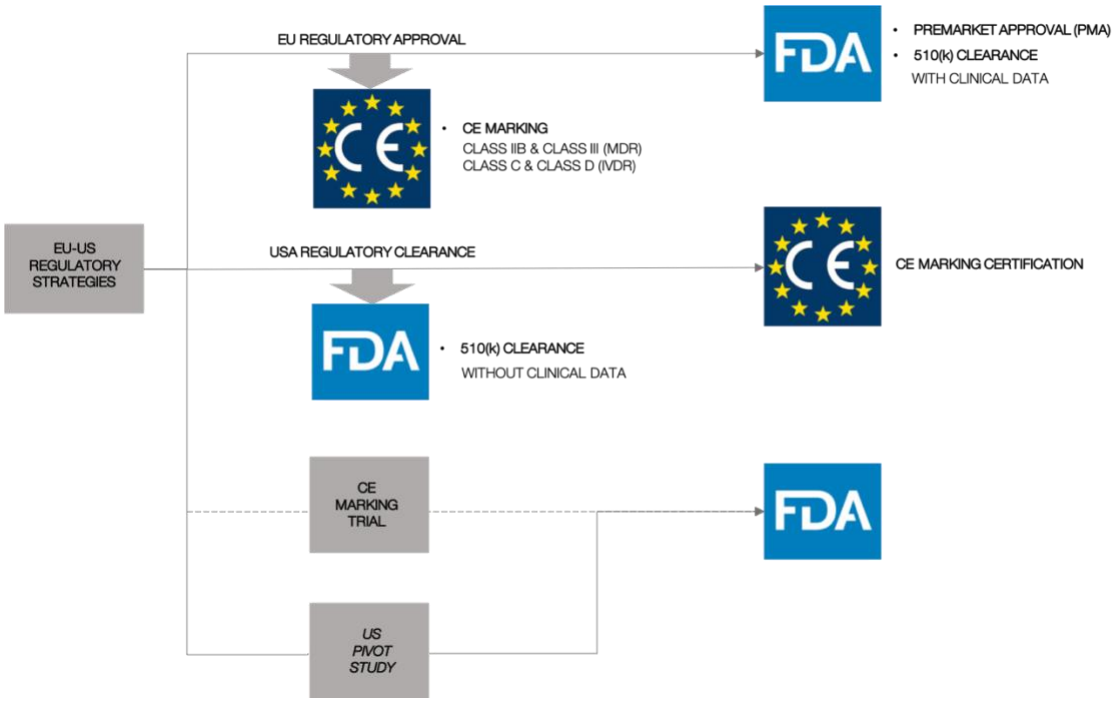

Figure 9 | Integrating EU-USA regulatory strategies path (adapted by [1]).

In Figure 9, three common strategies to obtain early regulatory approval were identified:

1. While pursuing a PMA approval or 510(k) clearance (with clinical data requirements), innovators may shorten time to market by obtaining a CE Mark in advance of USA approval.
2. Conversely, a second pathway may be used when a device is headed for 510(k) clearance (no clinical data) before entering the EU market, and then the company seek reimbursement abroad, through USA preclinical data.
3. Another strategy consists in usage of pre- and post-CE Marking trials in lieu of a USA pilot study, enabling the company to start a USA pivotal trial earlier.

Reimbursement strategy

A reimbursement analysis addresses whether there can be adequate payment for the physicians who would deliver the solution and for the facilities where patients would be treated. A reimbursement strategy is often the first step that companies formulate in determining how to successfully market their products. In the Medtech industry, lifecycles from concept to launch are relatively short, comparing to biotechnology and pharmaceutical ones. Here, early planning is crucial, and innovators must decide whether or not to get a reimbursement and, if so, develop a plan to obtain reimbursement coverage prior to market entry. Reimbursement and payment are key factors in determining sales growth and market adoption in later stages.

Development phase – Stages 2-4

The next series of stages (from concept to launch preparation) are nothing but very iterative due to roadblocks encountered along the process, which often results in re-designs and re-evaluations. Following the Agile accelerated concept developed during framework conceptualisation, activities in stages 2-to-4 are mostly overlapped.

Verification and validation (V&V)

This across-stage iteration is composed by several loops within marketing and R&D functional groups. After product conceptualisation (stage 2-concept), a functional or working prototype must be presented to the final user for feedback (stage 3-Design and development). This process (Figure 10) should be repeated until user needs and functionality requirements are fully satisfied (stage 4-Final Validation).

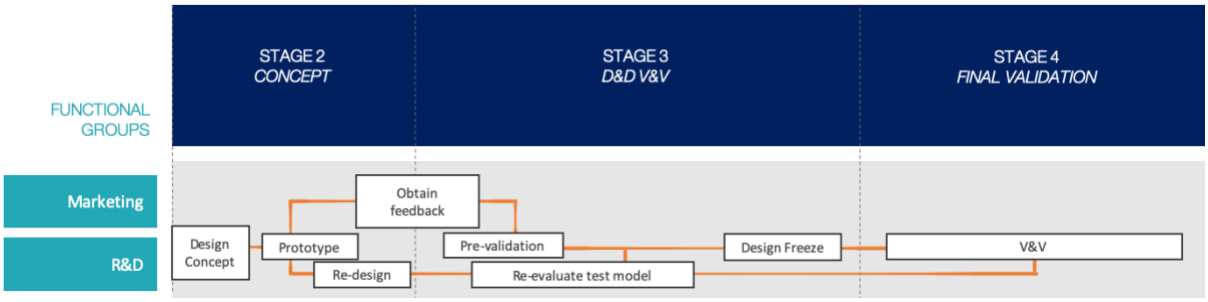

Figure 10 | Performance, feedback and V&V loop (adapted by [35]).

In stage 3, in order to prove technical feasibility and to assess design performance, the device undergoes a pre-validation test in laboratory. Design freeze occurs during stage 3 of development, once the product has successfully delivered proof-of-concept studies. In the next stage, formal verification and validation testing begins in a clinical setting. Verifications assures that the product performance meets the design requirements, whereas validation assures that the device meet user needs.

Legal/IP analysis

The preliminary IP review (IPR) can be used to establish design boundaries. Once the IP has been filled, it is necessary to keep ensuring that design features are in agreement with existing patents. This process should be monitored until stage 3 or 4, where freedom to operate (FTO) and patent clearance is expected to occur (Figure 11).

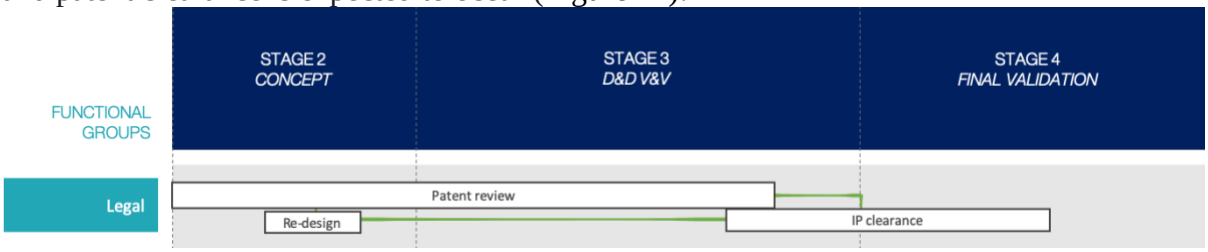

Figure 11 | Intellectual Property loop (adapted by [35]).

Risk management and process validation

This across-stage loop involves collaboration among a cross-functional team, with a particular emphasis on the quality, (R&D), and M&O functional groups.
Under the FDA, risk management is a critical part of design controls (Annex II). The FDA expects companies to have risk analysis (identification and quantification) and management in compliance with testing standards (ISO 14971). Design for Manufacturing (DFM) efforts begin in Stage 2 in parallel with device concept and prototyping. DFM is used to ensure the success of manufacturing process/production of a safe and effective device. Additionally, the Design Failure Modes, Effects and Criticality Analysis (DFMECA) tool is used to avoid technical failure. A process validation plan is developed in stage 3 ensuring compliance with Good Manufacturing Practices (GMP), through the IQ/OQ/PQ/PPQ qualifications protocols (installation, operational, performance and product performance, respectively)[47]. In stage 4, after design freeze, the process validation plan is executed. Figure 12 summarises the whole process.

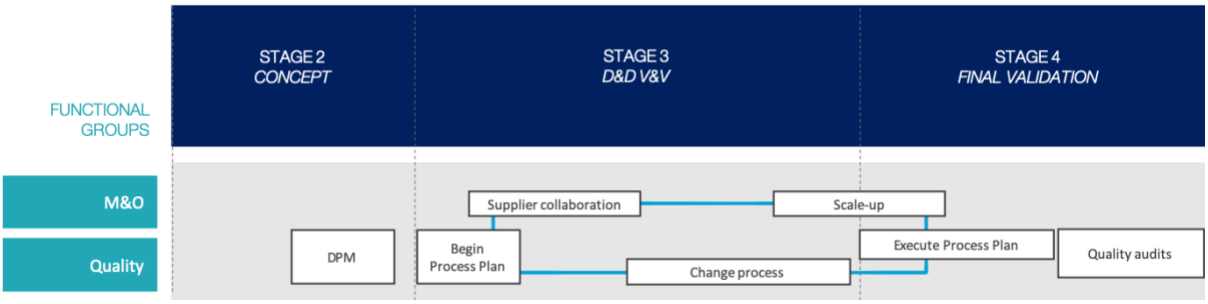

Figure 12 | Process validation loop (adapted by [35]).

In the EU, companies must implement a Quality Management System (QMS) in accordance with the MDR[48] or IVDR[49]. The QMS plan must include Clinical (MDR) or Performance (IVDR) Evaluation, Post-Market Surveillance (PMS) and Post Market Clinical (MDR) or

Performance (IVDR) Follow-up (PMCF/PMPF) plans. It is also necessary to make arrangements with suppliers about unannounced audits from NB.

Regulatory

The regulatory process shall be performed closely with other functional groups, namely clinical, R&D, quality and the regulatory itself.

Stage 2 in both systems is likely to prepare the documentation to submit together with other groups. In the USA, innovative Class II and all Class III devices will likely require clinical studies, a "Pre-Submission (Pre-Sub)" feedback from the FDA should be required.

In the USA, the Stage 3 in device development includes regulatory activities, such as submitting an application to the FDA for review (which includes a fee). FDA submission is considered a major milestone in the Medtech development process. If clinical studies are required, it is recommended to apply for an Investigational Device Exemption (IDE), which allows the device to be used in clinical study to collect safety and effectiveness data. At this stage, it is necessary to develop a clinical trial protocol and to conduct the respective study. For Class III devices, the FDA conducts inspections at the manufacturer facility and at all major suppliers involved in the design and production of the device. All parties must be compliant with FDA Quality System Regulation (QSR) found in 21 CFR Part 820[1].

For the EU system, in accordance with Annex II and III of both MDR[39] and IVDR[40], the team must prepare a CE Technical File or Design Dossier providing information about the device and its intended use plus testing reports, Clinical (for MDR) or Performance (for IVDR) Evaluation Plan and Report, risk management file, instructions for use (IFU), labelling, etc. It is also necessary to obtain a Unique Device Identifier (UDI) for the device. Also, ISO 13485 certification for QMS is required at all facilities involved to achieve success in the regulatory process.

An Authorized Representative (EC REP) located in the EU needs to be appointed, who is qualified to handle regulatory issues. The name and address of the EC REP needs to be included in the label of the device. Finally, a Single Registration Number is obtained from the regulatory authorities. With the exception of MDR Class I and IVDR Class A devices, the QMS and Technical File or Design Dossier (MDR Class III or IVDR Class D) must be audited by a NB, a third party accredited by a European Competent Authority to audit quality management systems and products.

Finally, in Stage 4 the regulatory process is finalised and the device is expected to obtain clearance or approval. The FDA issues 510(k) clearance or postmarket approval (PMA) letter and posts it online. At this time, the company must be in full compliance with FDA-QSRs. The FDA will not inspect Class I or II device manufacturers for compliance prior to device registration, but once registered, the FDA may conduct random inspections and can issue a Form 483 for non-compliance.

In the EU, the company will be issued a CE Marking certificate for the approved device and an ISO 13485 certificate for the facility, following successful completion of the Notified Body audit. The ISO 13485 certification must be renewed every year. CE Marking certificates are valid for a maximum of 5 years, but are typically reviewed during each annual surveillance audit. A Declaration of Conformity shall be prepared by the manufacturer, in accordance with Annex IV-MDR/IVDR, a legally binding document stating that the device is in compliance with applicable European requirements.

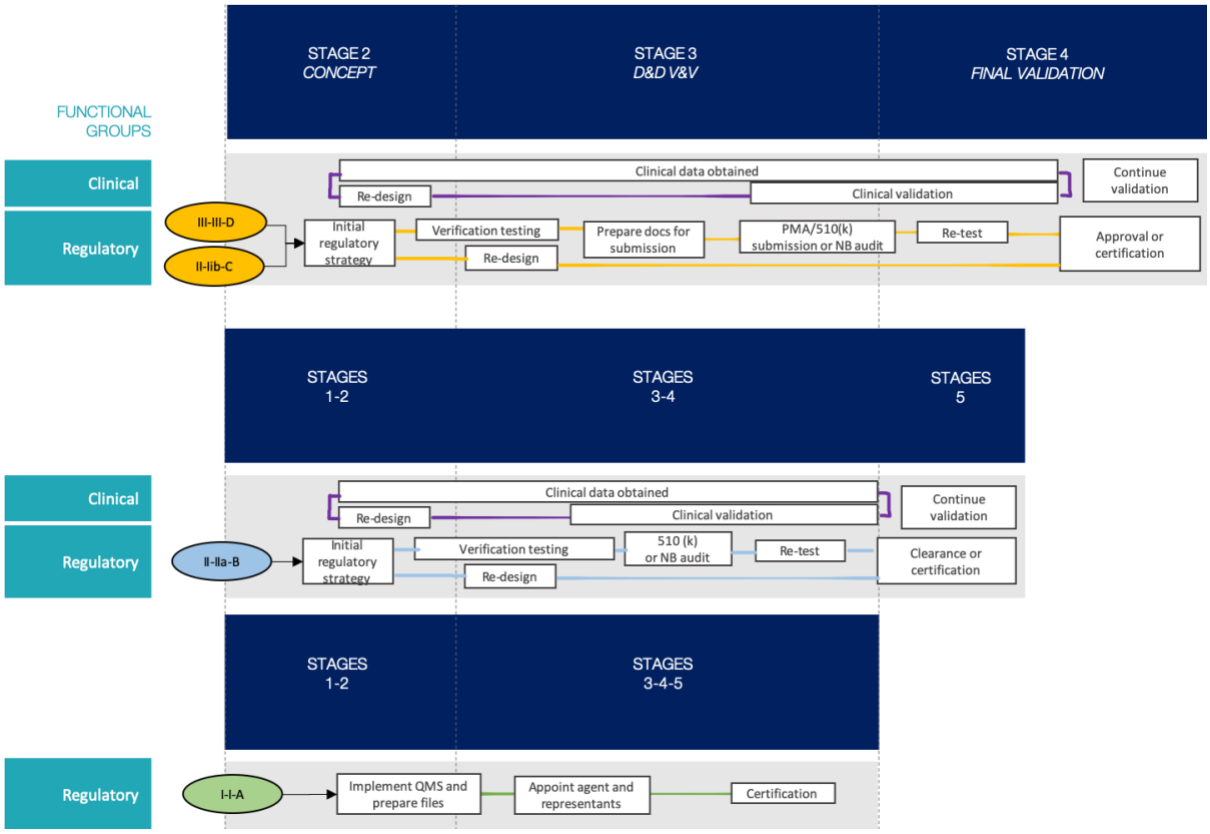

Figure 13 | Regulatory and clinical iterative loop divided per device classifications (adapted by [35]).

Clinical trials

Clinical trials are of major importance for the successful approval and later commercialisation of medical technologies, and thus need to be carefully planned and conducted. Clinical validation happens before and continues after the regulatory approval has been granted, in order to continue to monitor device performance.

Reimbursement

In phase 2, innovators must assess whether or not existing reimbursement codes (for the USA, EU and international markets) can be applied to a proposed device and, if so, the amount that insurers and users might be willing to pay for the medical technology (Figure 14). In phase 3, reimbursement strategy is further established as codes and part numbers are assigned to the new device. The reimbursement strategy must be ended before sales (stage 5) with coverage and payment results.

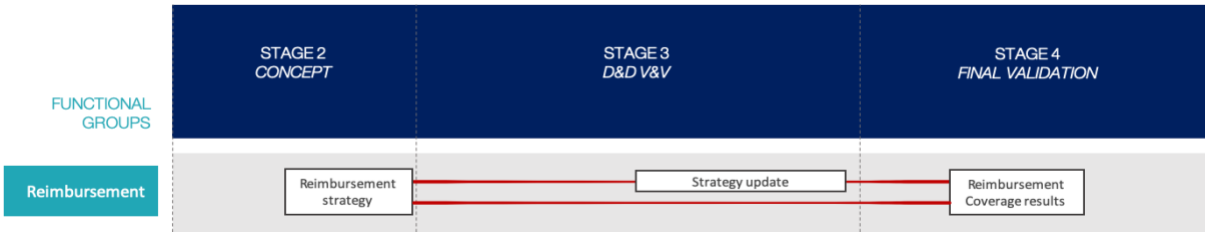

Figure 14 | Reimbursement landscape (adapted by [35]).

Market release

In the USA, the device should be listed and the company registered using the FDA Unified Registration and Listing System (FURLS) on the FDA website; upon the payment of fees for Establishment Registration and Listing, which must be renewed each year.
In the EU, the CE Marking should be added to the product name and registered in the EUDAMED database, together with its Unique Device Identifier (UDI). UDI must be on the label and associated with the regulatory documents.
The sales activities start in stage 4, where the team must choose the appropriate distribution channels and define marketing items. Examples include end-user technical guides that explain how the device performs (i.e. sample kits, promotional illustrations and videos), advertisements in journal papers and showcasing in medical conferences and fairs.
Along with the M&O team, it is necessary to ensure that product inventory and launch quantities will be available to fulfil sales forecasts.

Postdevelopment phase – Stage 5

The company is now able to sell the device in the USA. Both company and device registration status will be listed on the FDA website. Device's marketing authorization does not expire as long as no changes are made to the device design, intended use, etc. While reporting by manufacturers and healthcare institutions to FDA is mandatory, reporting by healthcare professionals and consumers is a voluntary act through the FDA MedWatch reporting program. FDA investigations based on these reporting systems can lead to public health advisories, safety alerts and product suspensions and withdrawals.
EU countries have their own competent authorities or governmental agencies in charge of postmarket surveillance of safety. All adverse events are mandatory to be submitted by manufacturers in the European Databank on Medical Devices (EUDAMED). In the EU, each year, a Notified Body will audit the company to ensure ongoing compliance with the MDR/IVDR. Failure to pass the audit will invalidate the CE Marking certificate. Innovators must perform Clinical/Performance Evaluation, Postmarket Surveillance and Postmarket Clinical/Performance Follow-up (MD/IVD, respectively) activities to maintain certification. If the long-term safety of the device in unknown, post-market studies are part of the CE mark certification.

Framework integration

The whole development process can be visualised through the four figures in Annex III. Note that FIGURE X1 is intended for most FDA Class I devices (the ones that are exempt from most QSR requirements), MDR Class I self-certified medical devices and IVDR Class A non-sterile

devices. FIGURE X2 is meant for FDA Class II devices (no clinical data required), MDR Class II-a and IVDR Class B. Following the same approach, FIGURE X3 is intended for FDA Class II devices (clinical data required), MDR Class II-b and IVDR Class C. Ultimately, FIGURE X4 is made for FDA Class III devices, MDR Class III and IVDR Class D devices.

3. Case study

Background

Researchers from the International Iberian Nanotechnology Laboratory (INL) have developed a microfluidic cartridge for low cost, biomarker-free, automated, fast and sensitive circulating cancer cell analysis. A phenotypic and/or molecular characterization of the isolated cells is achieved using a panel of biomarkers, indicative of cancer progression and correlated with the success of targeted therapies. The system, patent pending, has been licensed to RUBYnanomed. Several preclinical trials were successfully completed, and validation has been obtained. The technology has reached TRL 6. More information about RUBYnanomed in Annex IV.

It is time to proceed to the test of feasibility and applicability of proposed scale-up management framework, through RUBYnanomed case study.

Predevelopment phase – Stage 0

Based on the Discovery stage, main specifications of technology were identified and linked with clinical need or user benefits and assessed by a market analysis. The results for RUBYnanomed are compiled above:

Clinical needs screening

To healthcare providers in the cancer diagnosis field (i.e. pathologists, oncologists), current needs are:

- Current tools to analyse tumor subtype are invasive and cannot be used regularly.
- Current tools for patient monitoring have low sensitivity and do not provide phenotypic information on the disease progression.
- CTCs are extremely rare (1 to 10 cells per a billion of blood cells) and current liquid biopsy techniques rely on the expression of the EpCAM protein on cell membrane, losing aggressive cells that undergo Epithelial to Mesenchymal transition

It offers unique opportunities for low invasive sampling in cancer patients, constituting the so-called liquid biopsy, aimed for therapy monitoring, accurate prognosis and personalized treatment through a companion diagnostic strategy.

Solution to the problem

Several applications exist for different needs. Included among them are:

- Prevention: screening of population at risk and patient stratification.

- Diagnosis and monitoring: counting and phenotypic characterisation of CTCs to predict therapeutic resistance and to find cancer origin
- Treatment: as companion diagnostic: finding therapeutic targets; i.e. assessing ER, PR and HER2 in breast cancer

A preliminary state-of-the-art analysis about market needs and opportunities was taken in consideration:
Cancer is a heterogeneous and dynamic disease and 60% of patients diagnosed with a primary tumour, will relapse having other tumours spread in their body. For instance, a mid-size non-specialized in cancer hospital performs around 30,000 solid biopsies per year, each of them having an average cost of €2,000-10,000. When the tissue biopsy is not possible, due to the localization of the tumour, or for monitoring, imaging techniques such as magnetic resonance imaging (MRI) have to be applied. MRI cost, depending on the tumour, accounts for €500-13,000, and it is performed every 3 months for the first two years after primary tumour removal, every 6 months from year 2-5, and once a year after year 5, for each cancer patient. Further, the MRI equipment alone costs around €1M. Cancer treatments can range from €100/month to €56,000/month for the most specialized drugs.
To find metastasis early, there is an obvious need for continuous cancer progression monitoring, but current tools used in the clinic (tissue biopsy and imaging technologies) are not able to be performed regularly on the metastatic site and often miss early spreading. Also, the frequency at which these check-ups are done decreases as time goes by. Once RUBYnanomed uses the so-called liquid biopsy, a simple blood draw can provide real-time information about the tumour burden. For example, a liquid biopsy using the RUBYnanomed approach, apart from being non-invasive, has an embedded cost of around €300-500 per patient. The major competitor in the liquid biopsy field is CellSearch®, a phenotype dependent system, the first and only liquid biopsy system approved by FDA for metastatic breast, prostate and colorectal cancer.

Table 2 | SWOT analysis of RUBYnanomed.

Strengths	Weaknesses
CTCs provide valuable information for the clinical management of cancer patients since they provide a real-time snapshot of the current tumour burden. The presence of proteins in the CTCs can be used for patient stratification and accordingly to design an updated therapeutic strategy.	Scale-up production of materials. Technology readiness level (below 7).
Opportunities	Threats
The technology can also be used to isolate cancer cells from other body fluids (by adding a sample preparation step). Potentially, this technology can also be used for the isolation of rare cells in circulation related to other diseases.	Two major competitors with regulatory approval.

Bearing in mind the problem assessed above, the most desired product application is the one used for diagnosis/monitoring/therapy. Based on Table 2, a value proposition for the proposed solution – now called RUBYchip™ - has been formulated:
For pathologists/oncologists in the cancer diagnosis field who require an unbiased result, the RUBYchip™ is a liquid biopsy microfluidic device that isolates all types of CTCs from 7,5 mL whole blood sample based on size and deformability. Unlike standard tissue biopsy or CellSearch®, our solution provides a non-invasive procedure and a biomarker-free isolation, recovering 70% of viable CTCs (40x higher sensitivity). Also, no sample preparation is required enabling time/cost-saving for therapy monitoring. Moreover, this technology enables accurate prognosis and personalized medicine due to its capacity to stratify patients for successful targeted therapy.

Development phase – Stage 1

Design feasibility

RUBYnanomed has already demonstrated its improved performance against CellSearch® (Ribeiro-Samy et al, SciRep 2019), which is the only FDA approved system for enumeration of CTCs used in the clinic. The sensitivity is 40 times higher, which is crucial for the oncologist to make the most appropriate therapeutic decision (more information below, in Regulatory and clinical path).
The solution is a disposable unit for cell isolation and enumeration form the blood of cancer patients (fully developed).

Figure 15 | RUBYchip™ (retrieved from RUBYnanomed business case).

For the RUBYchip™, some unit operations about the fabrication and operations processes include (Figure 16):

- Microfluidic isolation platform – Mask CAD design and fabrication; DWL + DRIE; PDMS substrate fabrication; device bonding; channel functionalization; plug & play system;
- Whole blood sample processing inside the microfluidic device – setup preparation; air bubbles removal; set up the syringe pump parameters (flow rate, volume, syringe diameter, viscosity, shear force); cell capture and storage;

- Cell staining (immunocytochemistry (ICC) and Immunofluorescence (IF)) – membrane permeability process; cell incubation with antibodies (pan-CK FITC, CD45 Cy5, Vimentin TRITC and DAPI); characterization (with a 20x magnification objective) and enumeration.

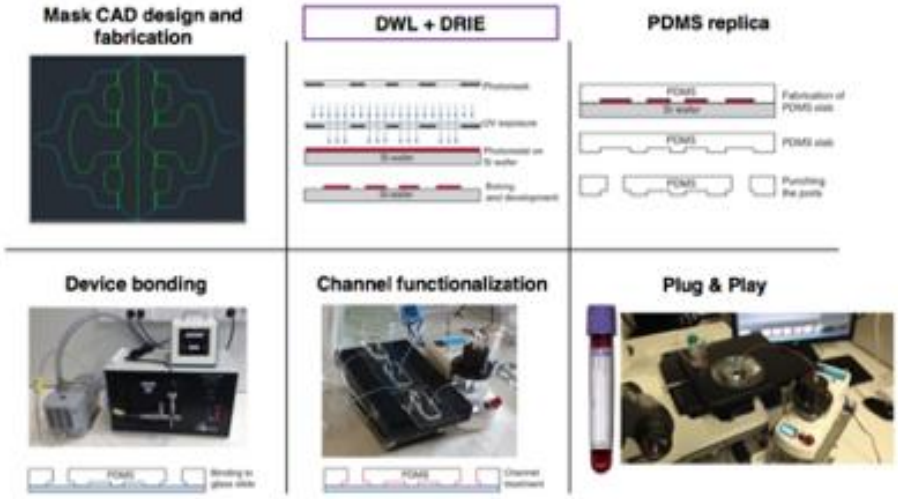

Figure 16 | Microfluidic cell design and isolation, staining, imaging and analysis system (retrieved from RUBYnanomed SOPs).

Regulatory and clinical path

A first preliminary clinical test was conducted, where RUBYchip™ demonstrated its higher efficiency and sensitivity against the reference CellSearch® equipment in a small pool of 9 metastatic colorectal cancer patients (Figure 17). It was possible to isolate a higher number of CTCs from unprocessed whole blood samples and showed the potential to provide improved correlation with clinical prognostic information (Ribeiro-Samy et al., Scientific Reports).
In a second pre-clinical study, it was demonstrated the ability for the cartridge to assess the aggressiveness of metastatic bladder cancer by correlating the phenotype of the CTCs isolated from 6 patients with that of their metastatic lesion. RUBYnanomed also demonstrated the potential toward patient-tailored precision medicine, by the ability to identify proteins in CTCs, as potential targeted therapies (Lima et al., Urologic Oncology 2017; Neves et al., New Biotechnology 2019).

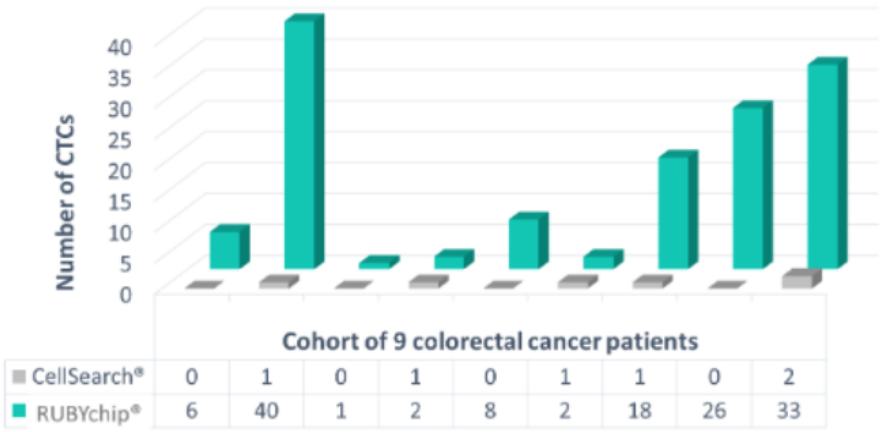

Figure 17 | Preclinical trials RUBYchip™ VS Cellsearch® (retrieved from RUBYnanomed business case).

Ongoing work demonstrates the ability to isolate tumour cells from the urine of early diagnosed bladder cancer patients. Current studies are being performed in a larger cohort of metastatic breast, colorectal and prostate cancer patients.

In addition, some Key Opinion Leaders were identified that are currently in collaboration with RUBYnanomed:

- Dr. Manuel Cirne de Carvalho (Pathology Advisor) holds a PhD in the area of clinical pathology. He is the vice-president of the scientific committee for the National Association of Clinical Laboratories in Portugal.
- Prof. Luis Costa (Oncology Advisor) is currently the director of the Oncology Division at Hospital de Santa María and professor of medicine & Biology cancer at the Faculty of Medicine in Lisbon. Also, he runs a research group at the Institute of Molecular Medicine (IMM) as well as being the director of the clinical research centre at CAML (Academic Medicine Centre of Lisbon). Professor Luis Costa is an expert in cancer metastasis (bone, breast, prostate, and other solid tumours) and he has been involved in 12 clinical trials for new drugs as principal investigator. He is also member of different medical and scientific committees and societies in Portugal. Currently, Prof. Luis Costa and RUBYnanomed are collaborating in a BioBanking project analysing the blood of 170 cancer patients with the RUBYchip™ in the context of breast, prostate, colorectal and melanoma cancer.

According to existing definitions, the RUBYchip™ belongs to the *in-vitro* diagnostics medical device category, in both the EU and the USA markets.
RUBYnanomed is very well positioned in the race for a CE Mark, due to its involvement in several preclinical trials. Under the EU legislation, processes are dictated by the IVDR.
Based on technology-associated risks, the IVDR placed a set of rules to define the classification of any IVD device. A graphical representation can be found in Annex V, where the RUBYchip™ is defined as Class C device.
Although the RUBYchip™ already has preclinical data that demonstrates its performance for its indented function, in the USA it is also required clinical efficacy data, meaning a premarket authorization (PMA). If proved to be substantially equivalent to a predicate device, it can also be approved by a premarket notification requirement, known as 510(k) clearance.

As research use only (RUO), RUBYnanomed can begin to provide the device to physicians and building this market. Moreover, this is an important milestone to enhance the clinical needs approach, gain market traction and customer trust (for further reimbursement approach).
Furthermore, clinical data generated in the EU may subsequently be used to build markets in other geographies.
Taking this into account, the best route for RUBYnanomed might be a RUO strategy, and then pursuing a CE Marking in advance of a USA approval (see Figure 9).

Legal/IP analysis

The geometry and design of the chip and microfilter are the core of this technology. The IP should be protected by filing a PCT patent worldwide[2].

Market analysis and competitive landscape

The study of cancer cells in circulation was valued worldwide at $10 billion in 2017 and has an expected annual growth rate of 13.8%. Among the different sub-markets, RUBYnanomed can address the RUO, as well as private healthcare (pathology labs) and public healthcare (hospitals). Among a list of >60 competitors in liquid biopsy, CellSearch® was the first FDA approved system for enumeration of CTCs used in the clinics. Besides, most direct competitors still in the RUO market (Figure 18).

CTC isolation system	Efficiency
RUBY nanomed	**70 %**
Vortex BIOSCIENCES	37 %
PARSORTIX	62.5 %

Figure 18 | RUO competitors in the market (retrieved from RUBYnanomed competition analysis).

[2] RUBYnanomed PCT patent was filled in 2016. Currently this patent is undergoing national phase in EU, USA and China.

Financial review

The current business plan will allow the company to reach the break-even in their fourth year and pay-back at year 6. This projection has been performed considering a moderate and conservative investment, as well as a medium market share for RUBYnanomed. However, with a higher investment, this numbers can be further pulled down.
The company plans to create 4 positions in the first year (once funding is raised), and 2 more in year 2. It is expected to partner with an automated analysis system manufacturer in year 2, and subcontract services of regulatory experts from year 3.

RUBYnanomed expects a production cost of 10 € and a selling value of 50 € per RUBYchip™ for the RUO market. The IVD costs are calculated considering the production cost of the chip plus necessary reagents and amortization of a full reader in a 3-year renting contract, adding up to 66.82 € the kit, and a selling value of 300 €. Regarding sales, RUBYnanomed considered a minimum of 30 chips per RUO client, and a minimum of 730 tests using the IVD system per hospital per year. Taking this into account, the company calculated an annual *serviceable available market* (SAM) of 716550€ for the RUBYchip™ as a RUO consumable, and an annual SAM of 3,5M€ for the IVD system.

Reimbursement strategy

The purpose of a reimbursement analysis is to understand the reimbursement landscape in the early phases of developing a new medical technology. The whole process can be burdensome for RUBYnanomed, as it is for most Medtech startups. As soon as possible, a clear strategy focused on clinical and cost evidence is often required to win a favourable reimbursement decision.

Although innovation-friendly, decisions related to reimbursement and payment in the EU system can be challenging. The first step should be addressing the three major countries in the Medtech industry (Germany, France and UK), since the process in those countries is structured and centralised. In other countries it can be more diffused, and negotiations are handled in a less formal way (e.g. Italy). Later in the USA, this process can be handled by healthcare insurance programs - for instance, the largest public one is Medicare. Due to its large scale, the USA private payers closely follow its system (coding, coverage and payment). In short, oncologists and hospitals (RUBYnanomed's major customers) must submit claims using standardised codes to get paid. For that, coverage of the technology must be obtained, which determines if the RUBYchip™ will be reimbursed and under what conditions, and payment describes who is being paid and how much.

Development phase – Stages 2-4

Verification and Validation

The RUBYchip™ (Figure 19) consists in a disposable cartridge that performs isolation of cancer cells in circulation. A blood sample from the cancer patient is flowed through the RUBYchip™ and in less than one-hour cancer cells have been isolated without the need of sample pre-processing. Cancer cells are trapped in microfilter system, and the cartridge can be imaged and analysed in any laboratory microscope. The RUBYchip™ has been designed and

is being fabricated in PDMS – a transparent material that allows easy imaging. When scale-up occurs the cost per chip is expected to be 10 €.

The RUBYreader is a full analysis system in which the RUBYchip™ is analysed automatically and provides a full report to the oncologist, with prognostic indications. The RUBYreader will be composed of an automatic station holding the RUBYchip™ and blood samples will be automatically injected in each cartridge and analysed by an embedded fluorescence imaging microscope. As a result of the clinical trials a set of biomarkers will be imaged and a snapshot in real-time will be converted into a report for the clinician to support therapeutic decisions and help in personalised therapy follow-up.

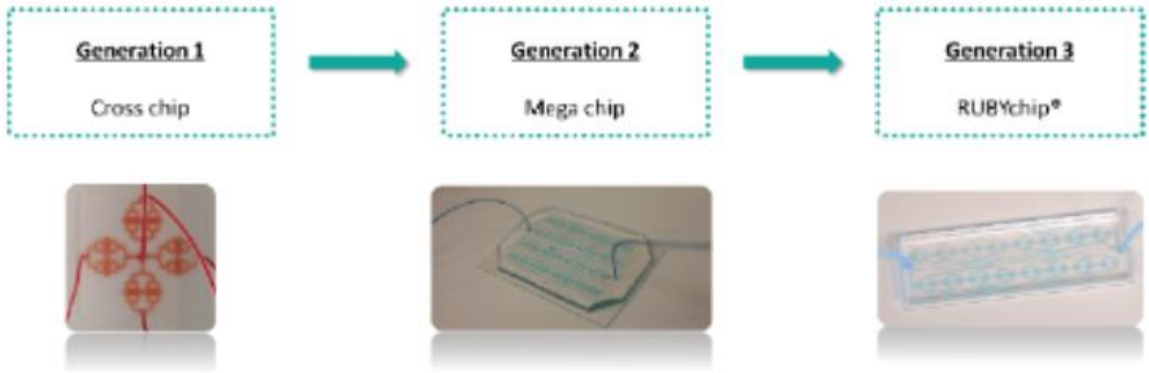

Figure 19 | Prototype evolution of RUBYchip™ (retrieved from RUBYnanomed slide deck).

The RUBYreader () is a full analysis system in which the RUBYchip™ is analysed automatically and provides a full report to the oncologist, with prognostic indications. The RUBYreader will be composed of an automatic station holding the RUBYchip™ and blood samples will be automatically injected in each cartridge and analysed by an embedded fluorescence imaging microscope. As a result of the clinical trials a set of biomarkers will be imaged and a snapshot in real-time will be converted into a report for the clinician to support therapeutic decisions and help in personalised therapy follow-up.

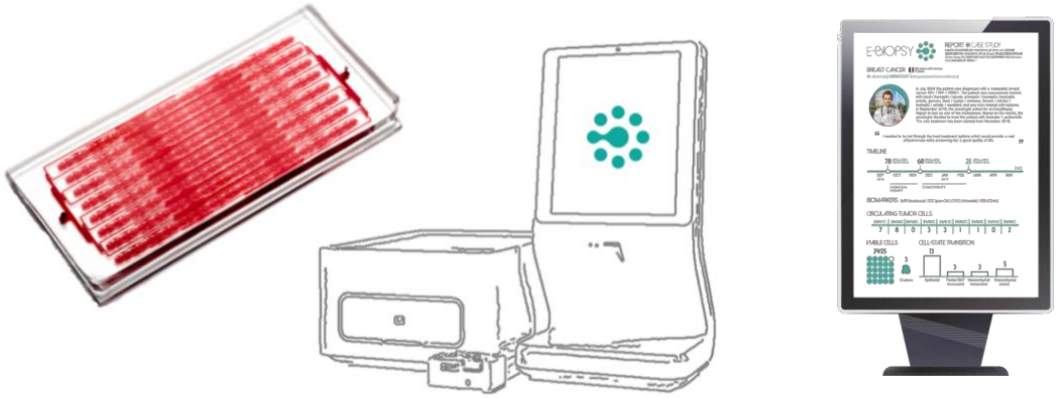

Figure 20 | Fully automated system for the analysis of RUBYchip™, providing report for personalized medicine (retrieved from RUBYnanomed pitch deck).

A set of several risks were identified, namely:

- M&O: A failed scale-up production;
- V&V: The chip material for scale-up not working at the same efficiency than current prototype material – polydimethylsiloxane (PMDS);
- M&O: Automated full system development requires higher funding and integration;
- Clinical: Clinical trials extend above 2 years;

Strategy to mitigate risks:

- RUBYnanomed will outsource the fabrication of the first test batch to two different companies (already identified) to minimize the risk. In the meantime, RUBYchip™ prototype can also be developed in house to bootstrap the economy and save funds;
- Several materials are being taken into account for the scale-up and preliminary checks will be done before test batch;
- RUBYnanomed will partner with an original equipment manufacturer (OEM) company or alternatively co-develop the technology with industrial partners;
- At the time of this risk, RUBYnanomed would have already been selling the RUBYchip™ for R&D for at least 2 years, which will provide steady income to the company. RUBYnanomed will ensure that the funds available can cover for extended clinical trials. Further, the hospitals where the clinical trial are developed, are very likely to support the extension in time, if the result will have such an impact in the clinic.

Regulatory

In order to be able to enter the clinical market in Europe, a CE Mark for IVD will be needed as well as a scale-up production of the cartridges. In order to achieve those milestones, there is a need to certify the laboratories (and manufacturing partner facilities) following quality standards ISO 13485. The company is incubated at INL that has been ISO 9001 certified, and recently got a laboratory compliant with ISO 13485.

Clinical trials

The company has already successfully completed several preclinical trials, while others are still undergoing in collaboration with different reference hospitals and clinicians. As next steps, a scale-up production for a test batch of RUBYchip™ with different companies must be planned as well as the search for value chain partners: technology developers, regulatory experts, clinical trial designers, and hospitals must be selected to conduct the clinical trial in a regulatory framework.

IP

The main IP relies on the characteristics of the RUBYchip™, which have been protected in an international patent application (national phases pending in EU, USA and China - PCT/EP2016/078406) and licensed exclusively to RUBYnanomed. Eight months after the PCT

submission, a search report was received from the European Patent Office that did not highlight any significant findings that could hinder our freedom to operate.
In terms of commercial exploitation, with the help of IP rights experts and patent attorneys, a patent search was performed which confirmed the novelty of the technology. Further IP is expected in the following steps of development.

Risk management and process validation

At this time, RUBYnanomed has accomplished the following technical challenges:

- Preclinical trial for colorectal cancer completed
- Benchmarking vs only clinical FDA approved system completed
- Preclinical trials for breast cancer ongoing with the RUBYchip™
- Test samples for certified RUBYchip™ material received
- RUBYchip™ 4th generation designed and prototyped

For process validation:

- Starting the process for CE mark as IVD (complete system and qualified, TRL 5);
- Scale-up mass production, for a test batch of RUBYchip™, enabling to demonstrate the clinic (TRL 5&6);
- Developing with the right partners the automated prototype (enabling inter-user and inter-laboratory reproducibility, TRL 5-6);
- Starting clinical trials (complete system demonstrated TRL 6&7);
- System certified (TRL 8);
- System enter into the clinical market (TRL 9&10).

Some requirements need to be met for a conformity assessment (for more information, see Annex IX, X and XI of IVDR).

1. General Safety and Performance Requirements (Annex I of the IVDR): benefits must outweigh risks and achieve the claimed performance (must be proven with supporting clinical evidence); chemical, physical and biological properties; performance characteristics; and information supplied by the manufacturer with the device (i.e.: instructions for use (IFU));
2. Technical documentation (Annex II of the IVDR) to start conversations with NBs;
3. Harmonised standards / common specifications (Articles 8 and 9 of the IVDR);

Reimbursement

For IVDs, the D&D-V&V stage of the product already includes several studies that capture clinical and analytical information. RUBYnanomed should be assessing and publishing such results. Additionally, comparisons between prototypes and device evolution are useful and can be used to highlight benefits when comparing to direct competition. Such information plays a critical role in the reimbursement strategy. An early focus is necessary to appreciate and collect the clinical and cost evidence that is required to win a favourable reimbursement decision.
Within the EU, coverage must be negotiated separately with payers in each country. The biggest Medtech markets have more structured and centralised processes (Germany, France and UK). In the USA, for instance, a 510(k) clearance can open the door to reimbursement since it is often a prerequisite to be considered for coverage. FDA does not hold any function towards reimbursement decisions.

Market release

RUBYnanomed will devote approximately 10% of the budget to gain traction in the market, namely conferences, roadshows, biomedical fairs and technological fairs. Early adopters from RUO and KOL that already work in close relationship with the company will spread the word about how RUBYnanomed can change the status quo of cancer monitoring. Oncologists believe that such tool would be very valuable to stratify patients and to personalize the therapeutic selection to ensure the best possible outcome for patients.

Postdevelopment activities – Stage 5

In order to comply with the requirements established, following steps in product commercialisation include:

- Marketing and communication actions
- RUBYchip™ scale-up production
- RUBYreader system automation
- Laboratory certification
- Clinical trial planning and communication with NBs
- 510(k) clearance with CE Marking trial data
- Postmarket surveillance
- Postmarket performance

4. Framework implementation

The implementation of the model is tested in an academic setting as part of the workplan of the master thesis, where a RUBYnanomed shared valuable knowledge and information. Annex VI summarises the functional groups, stages and main activities for the development of the RUBYchip™, from lab towards commercialization.

5. Discussion

Usually, most descriptive information about tech transfer in the Medtech sector comes from dense books or from free and short versions of white papers sold by big companies in the field, so finding relevant guidelines can be an exhausting process. On the other hand, most graphical documentation available fits in one of the two extremes: very complex visual data (e.g.: the FDA regulatory pathway) or simplistic schematic versions of the reality that miss a lot of details. Additionally, both graphical and text formats usually address only one field of study, missing the connections between dots on the multiple activities needed in the development phase. In this thesis, through a twofold approach, phases, stages, functional groups and their main activities are explained accompanied by an intuitive graphical summary.
A deep knowledge of the multiple activities involved in the development of new medical technologies and their interrelations is essential to support the development of an efficient go-to-market strategy. However, currently such knowledge is insufficient and not easily found in existing literature. In order to investigate those activities, already existing methodologies in new product development, especially in the case of medical technologies, were scrutinized. As

a result, a generic conceptual framework was adapted from older versions, updated with new innovation and regulatory constraints, and implemented using RUBYnanomed as a case study. Medtech innovators work in a field dominated by science entrepreneurs but, when it comes to developing strategies for a successful implementation, they are asked to make countless assumptions. In a highly competitive sector, the founders get used to keep technical information secret, and when moving to the business side of the technology, the mindset hardly changes. Although its differences from pharmaceutical and biotechnology fields, the Medtech still is considered a conservative industry with lots of traditional corporate research labs. Consequently, due to intellectual property and confidentiality reasons, very few other studies were found involving a case study implementation, and none as immersive as this one. With a global mindset of collaboration, we truly believe that being exposed to open innovation offers several benefits for Medtech companies to achieve their success.

The development of medical technologies should always start with the user in mind. Although it may seem intuitive, it is surprising how often the user's needs get lost in the process of developing a new product. Besides the initial user requirements, also understanding the clinical and user environments are crucial. The definition of the user problem culminates in the formulation of the intended use, which specifies the initial device classification. With the RUBYnanomed example, we enhance the importance of preliminary work done before the development phase.

Up to now, there is no other framework contemplating an in-depth strategy for both the EU and USA, the two global leaders in the medical technology innovation. For early-stage companies aiming to have a global market entry, such work can be burdensome. In this study, innovations are encouraged to make an explicit global consideration when choosing a strategic focus, mainly when exploring market needs, regulatory and reimbursement opportunities. Moreover, in this thesis, the newly created (2017) European regulatory pathway has already been adopted, prior to its official date of application (MDR in 26th May 2020; IVDR in 26th May 2022).

Companies seeking to place a new product in the EU market can look to the USA model to find the type(s) of data that are necessary to demonstrate sufficient clinical performance and, more important, key building blocks for what a good clinical trial looks like.

The commercial success of any medical technology depends not only on regulatory approval but also on the company's ability to secure payment for providing it to final customers. The reimbursement landscape is complex and challenging across the world, once companies must prove, not just the clinical value of their technologies, but also the economic value. Any delays may affect negatively the Medtech company, especially startups, by decreasing changes of product adoption rate.

The global harmonisation of the development and regulatory processes is important to help improve the adoption of medical technologies, avoiding product redundancy and focusing in the needs of the community. These efforts are expected to enhance a global integration of medical device safety and process quality.

One of the most general reviews to date was developed in 2007 and served as the skeleton, both descriptive and graphical, to answer our first research question ("how should a conceptual framework for medical technologies be developed?"). Although it is one of the most accurate methodologies in the field, providing a summary of the many concepts related to medical device regulation and a discussion of contemporary issues such as combination products, it is intended for USA companies alone. This thesis addresses both the USA and the on-going process associated with the EU near future regulatory scheme, which can be noticed by the usage of both FDA and MDR/IVDR terminology, processes and activities along the way.

The Biodesign book is considered by most as the 'Bible' for medical technology innovations, deeply describing the elements needed to support Medtech startups, in a practical and comprehensive way. However, this book is very fragmented, and no conceptual graphic representations are shown summarising the big picture scenario. The graphical integrations proposed in this thesis ensure a visual correlation between stages and functional groups, thus enhancing the effective communication about Medtech strategy and its main activities.
In this thesis, we applied some methods outlined in the next-generation Stage-Gate® system, which was developed in 2015 by Robert G. Cooper, the Stage-Gate® creator himself. As a result, the new context-based model: 1) can handle and be adapted to the various medical technology risk classifications (i.e.: tested with an EU IVD Class C device); 2) contains agile spirals within its stages and flexible decision criteria with a strategic focus; and 3) is less rigid and more accelerated, where functional groups and stages overlap.

To date, no Medtech company has yet implemented a strategy based in this modern approach, making RUBYnanomed the first real case. As a first objective, RUBYnanomed helps to answer our second research question ("how should the new design be implemented?"), and secondly can serve as a practical guide for others in the field.
The new methodology is, in short, adaptive and flexible, agile and accelerated. Tasks move quickly from milestone to milestone and engage in frequent experiments or spirals, with the evolving product regularly exposed to stakeholders in a series of build-test-revise iterations.

4

Conclusion

This study presents a validated model for the medical product design process, as a conceptual tool and a visualisation approach for Medtech innovators. There is extensive research on the development processes for new medical technologies, mainly in separate areas, such as regulatory structure or prototyping. The proposed model is unique since, in contrast with any of the previous models, it provides a comprehensive, practical and updated representation of the whole development phase in the Medtech landscape.

Considering the new regulations, especially from the EU Medtech landscape, nearly every aspect of the device production lifecycle is expected to be amplified and likely to require considerable time and cost to implement. In order to support Medtech innovators in this constantly changing ecosystem, the proposed framework is adaptive and flexible, agile and accelerated. In this sense, the presented framework aims at accelerating the entry of Medtech into the market.

The proposed methodology includes the fundamental information that innovators should grasp to initiate the development of a medical technology. It supports innovators in multiple forms, providing: (1) training material for startup companies, first time innovators and experienced designers new to the field of medical devices, (2) solid framework for process improvement, (3) process guideline for implementing medical technologies and (4) assistance for regulatory compliance.

At the same time, the model supports potential research efforts towards identifying critical success factors in device development by providing a clearer view of the domain's overall landscape. The proposed model was primarily validated against the literature, through document analysis and content validation, which justified the concepts and their significance. A secondary validation was sought, after explaining the importance and implementation of the different concepts in the model, applying the proposed model in a real case study. Both, practical observations and theoretical documentation demonstrated that the model serves its purpose of usability and guiding the development and implementation of new devices.

Despite the results of the case study verified the applicability of the proposed framework, a biased mindset may have influenced our results due to prior assumptions or unintended exclusion or selection of criteria to fit the original hypothesis. To solve this issue and improve on the results contained in this thesis, future research should address the limitations of this work by considering: 1) specific focus in EU and USA markets; 2) major focus on startups or early-stage companies, not corporative research innovations; 3) focus on generic medical

devices, not including medical software cases or the exceptions in device regulation (e.g.: drug-device combinations, sterile vs non-sterile Class I devices, etc.); and 4) challenges to enhance the use and applicability of the model.

A global harmonisation has a broader impact on society by speeding up patient's access to the latest technological advances worldwide. Although this study integrates the global two biggest realities, future work on the subject should address others geographic areas namely: Canada, Australia, Japan, China, India, Latin America and Africa, among other regions.

This project was conceived to respond to the current and future needs and challenges that the Medtech innovators, in the EU and USA markets, face in the development of new medical products. Although not being the main target, innovators from established firms in these areas can look at the proposed methodology and develop it further by proposing new concepts within their well-defined structures.

The complexity of the device classification is a challenge that each project team needs to overcome in order to move forward with their project. For projects involving types of devices not mentioned in this study, an extra preliminary work is required, to complement this framework with relevant information, following the observation and analysis scheme of the model proposed here. Meanwhile, the involvement of stakeholders and key opinion leaders helps to understand the product and the requirements for re-design. In addition, the involvement of the customer is important in design reviews and verification to make sure that the requirements were met.

Meanwhile to motivate the exploitation of the model and to increase its credibility, the application of the model to a product in development was performed through a case study. The case study presented promising results, however, additional case studies are necessary to further increase the model's exposure and use. To accomplish this goal, the case study presented in this thesis can be used as a pilot to facilitate the implementation and optimisation of future case studies. Evaluation tools to maintain consistency should be developed.

A benefit but also a limitation of the model is that it is very agile and flexible and hence it requires that the users adapt it into their own reality. Given the complexity of the regulatory scheme, a four-picture result based on classification had to be used for the integration of the overall process. To overcome this challenge, the model should be converted to a software tool where innovators can zoom in and zoom out of the model and choose from the beginning the correct path. Converting the model to software will provide additional benefits and further development of this study.

Despite above-mentioned constraints, the assessment of the model showed its utility from the point of view of the innovator, ranging from the initial planning and understanding of the whole process, to the implementation of specific model concepts.

The Medtech industry is a dynamic field providing thousands of products to the market every year with the aim to enhance people's lives. In such a complex and fast-moving universe, the need for a more efficient, partnered Research & Development & Innovation & Regulatory System (R&D&I&RS) for device evaluation has risen. The risks associated to the development phase can be mitigated using new product development methodologies to systematically manage promising technologies in order to shorten the time to market. Bearing in mind the inherent need for understanding overall processes in the field, this study was intended to raise awareness for the practical knowledge and experience in device development. Thus, this model contributes to increase societal benefits by speeding up device entry into the market (lowering costs, saving time and overcoming potential risks).

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ANNEX I-1

Key activities, decisions and portfolio review for stage 0-Discovery

	DISCOVERY		GATE 0
Functional Groups	Key Activities	Decisions (Go/Kill)	Portfolio Updates
Clinical Strategy	Assess clinical needs with stakeholders.	Market/Clinical problems and solutions. Reject or retain T-P-M products for further development Decide which product application is worth to pursue based on risks and market opportunity.	Stakeholders worksheet Technical worksheet (disease state fundamentals included) Preliminary market analysis Needs exploration and selection Product requirements
Legal	Keep protecting IP. Determine IP barriers of each product.		
R&D	Preliminary product concept.		
Business	Assess market opportunity for each need Competitors and market assessment		
Regulatory	Draft regulatory considerations		
Reimbursement	Draft reimbursement strategy		
Marketing	Showcase your technology		

ANNEX I-2

Key activities, decisions and portfolio review for stage I-Initiation

	INITIATION		GATE 1
Functional Groups	Key Activities	Decisions (Go/Kill)	Portfolio Updates
Clinical Strategy		Obtain validation in laboratory environment. Determine if existing healthcare payment infrastructures will accommodate the solution.	Stakeholders worksheet (e.g.: KOL, customers, etc) Technical and risk analysis worksheet Preliminary Market Analysis Legal, regulatory and clinical path
Legal	IP analysis and fillings		
R&D	Risk assessment Create industrial design controls concepts Use rapid prototyping to define product requirements		
Business	Financial analysis Form your company Secure funding (e.g. grants) Identify KOL Market analysis draft Competitive assessment		
Regulatory	Develop regulatory strategy (worldwide coverage, FDA, CE Mark)		
Reimbursement	Develop reimbursement strategy		
Marketing	Showcase your product concepts		

ANNEX I-3

Key activities, decisions and portfolio review for stages II-Concept

	CONCEPT		GATE 2
Functional Groups	Key Activities	Decisions (Go/Kill)	Portfolio Updates
Clinical Strategy	Identify procedures and methods for trials. Demonstrate PoC in a laboratory model (safety, animal tests)	Prove technical feasibility (performance, functionality, usability) in relevant environment Manufacturing and value chain confidence assessed	Stakeholders worksheet Design History File (results of laboratory findings of PoC) Preliminary Market Analysis Risks assessment documentation Legal, regulatory and clinical path Manufacturing plan
Legal	IP filling reviews		
R&D	Design specifications (…) Maintain DHF. Final risk analysis		
Business	Project core team selected Produce a general timeline plan Target price requirements		
Regulatory	Initiate regulatory strategy; Contact FDA		
Reimbursement	Validate reimbursement strategy		
Marketing	Prepare prototype for customer evaluation		
Manufacturing & Operations	Industrial design		

ANNEX I-4

Key activities, decisions and portfolio review for stage III-D&D-V&V

	D&D-V&V		GATE 3
Functional Groups	Key Activities	Decisions (Go/Kill)	Portfolio Updates
Clinical Strategy	Pre-validation in clinical/operational conditions. Study feasibility and human safety.	Design freeze Risk mitigation confirmed Define supply chain	Stakeholders worksheet Design History File (results of pre-clinical findings of prototype) Market Analysis Legal, regulatory and clinical path Manufacturing plan Quality validation plan
Legal	Patent reviews		
R&D	Develop test protocols and reports along specs Verify design and risk analysis		
Business	Hire cross-team		
Regulatory	Update and prepare submission		
Reimbursement	Update reimbursement considerations		
Marketing	Customer validation		
Manufacturing & Operations	Supplier collaboration Producibility analysis Design packaging, labelling		
Quality	Begin process IQ/OQ/PQ/PPQ		

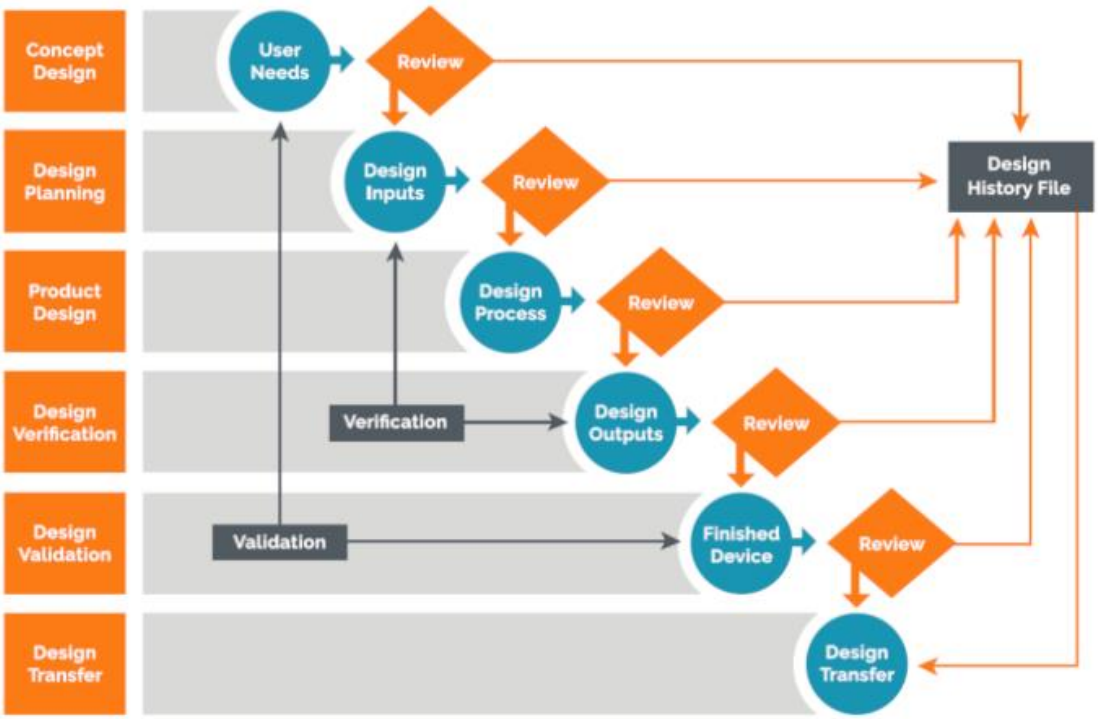
ANNEX I-5

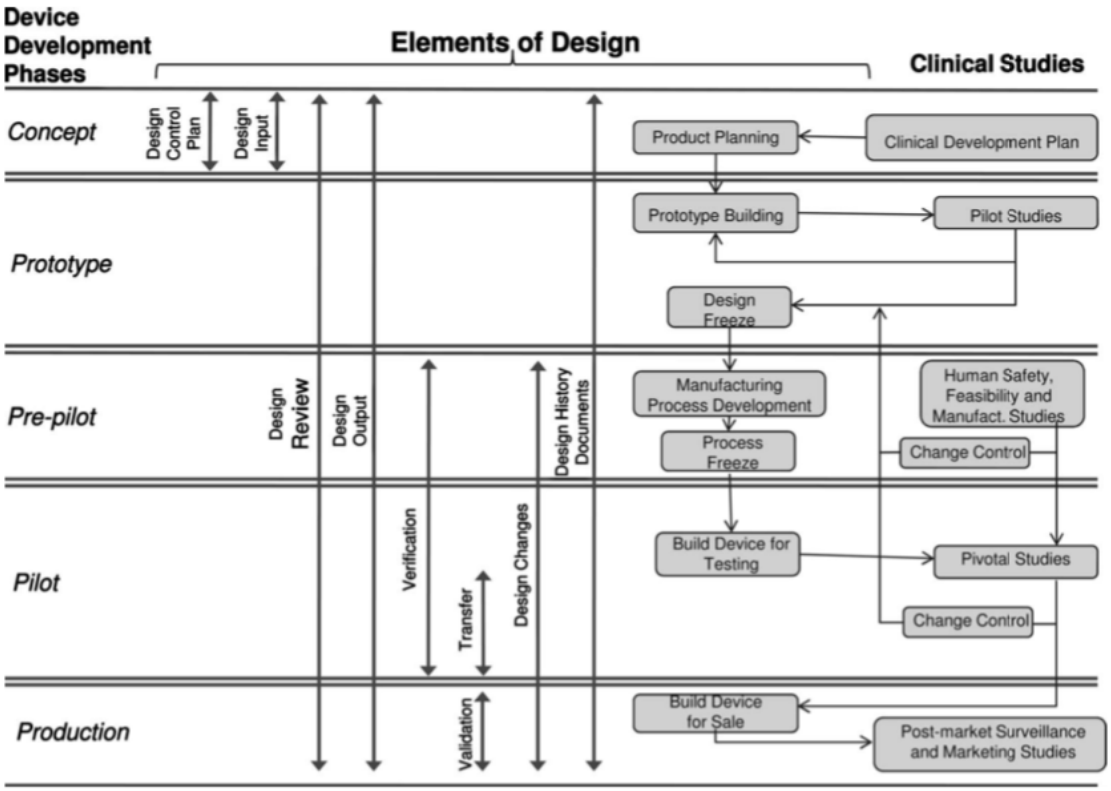
Key activities, decisions and portfolio review for stage IV-Final Validation

	LAUNCH PREPARATION		GATE 4
Functional Groups	Key Activities	Decisions (Go/Kill)	Portfolio Updates
Clinical Strategy	Implementation of clinical trials	Verify if design outputs satisfy design inputs. Prepare sales launch Stable manufacturing process Business launch plan Approve suppliers Prepare FDA visit	Stakeholders worksheet Design validation completed Risk analysis completed Preliminary Market Analysis Legal path Regulatory path Clinical path Manufacturing plan Quality validation plan Product branding and sales launch optimised
Legal	Final patent review Legal clearance obtained		
R&D	Establish and validate process. Launch SOP. Setup pilot production		
Business			
Regulatory	Register with FDA/NB. Obtain regulatory approval/clearance		
Reimbursement	Finalise reimbursement strategy		
Marketing	Catalog numbers assigned Market launch plan		
Manufacturing & Operations	Supplier qualification Scale up preparation Train operators		
Quality	Finalise process QMS and setup postmarket		
Sales	Sales and marketing team training		

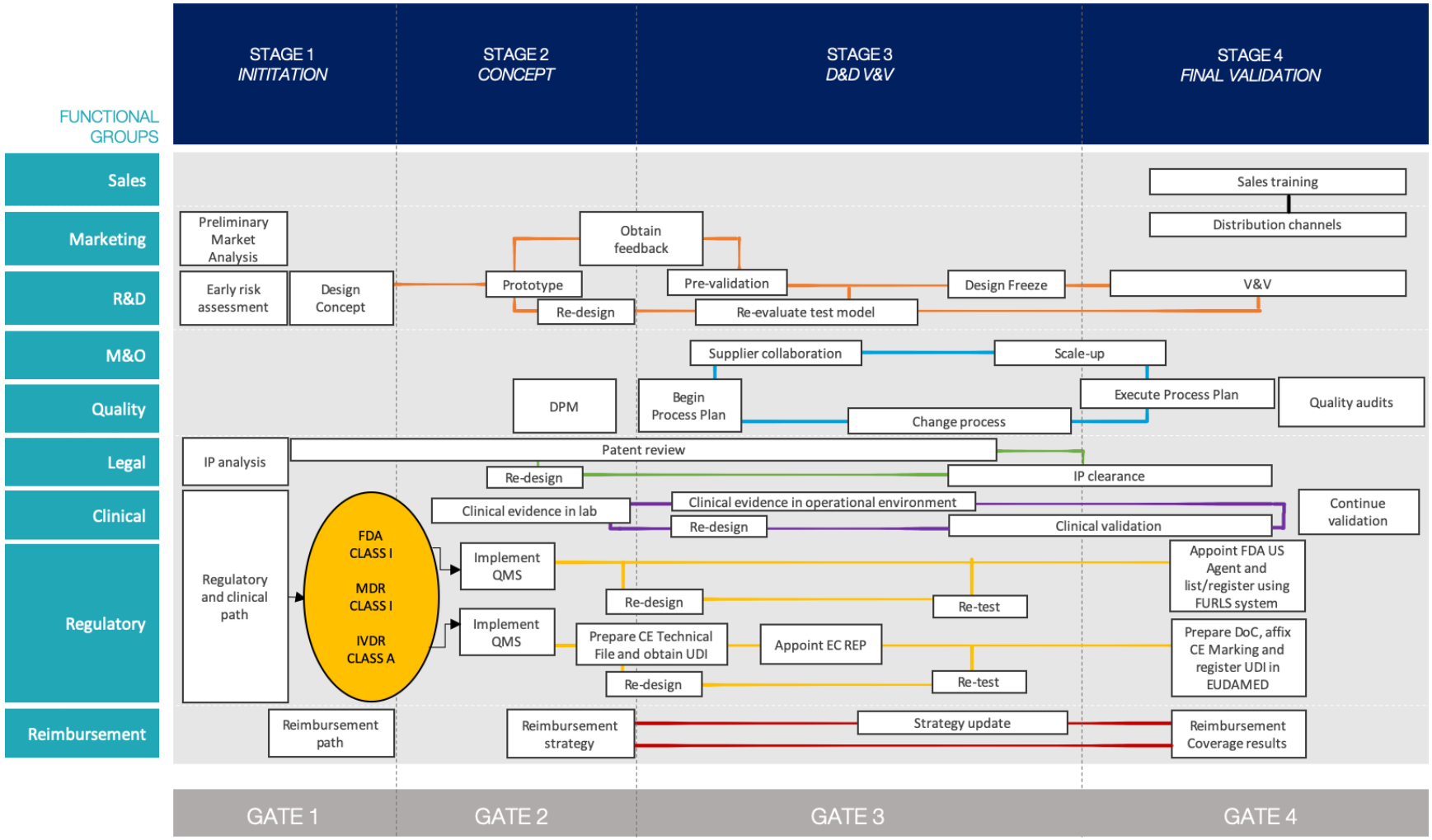
ANNEX II

Device design controls

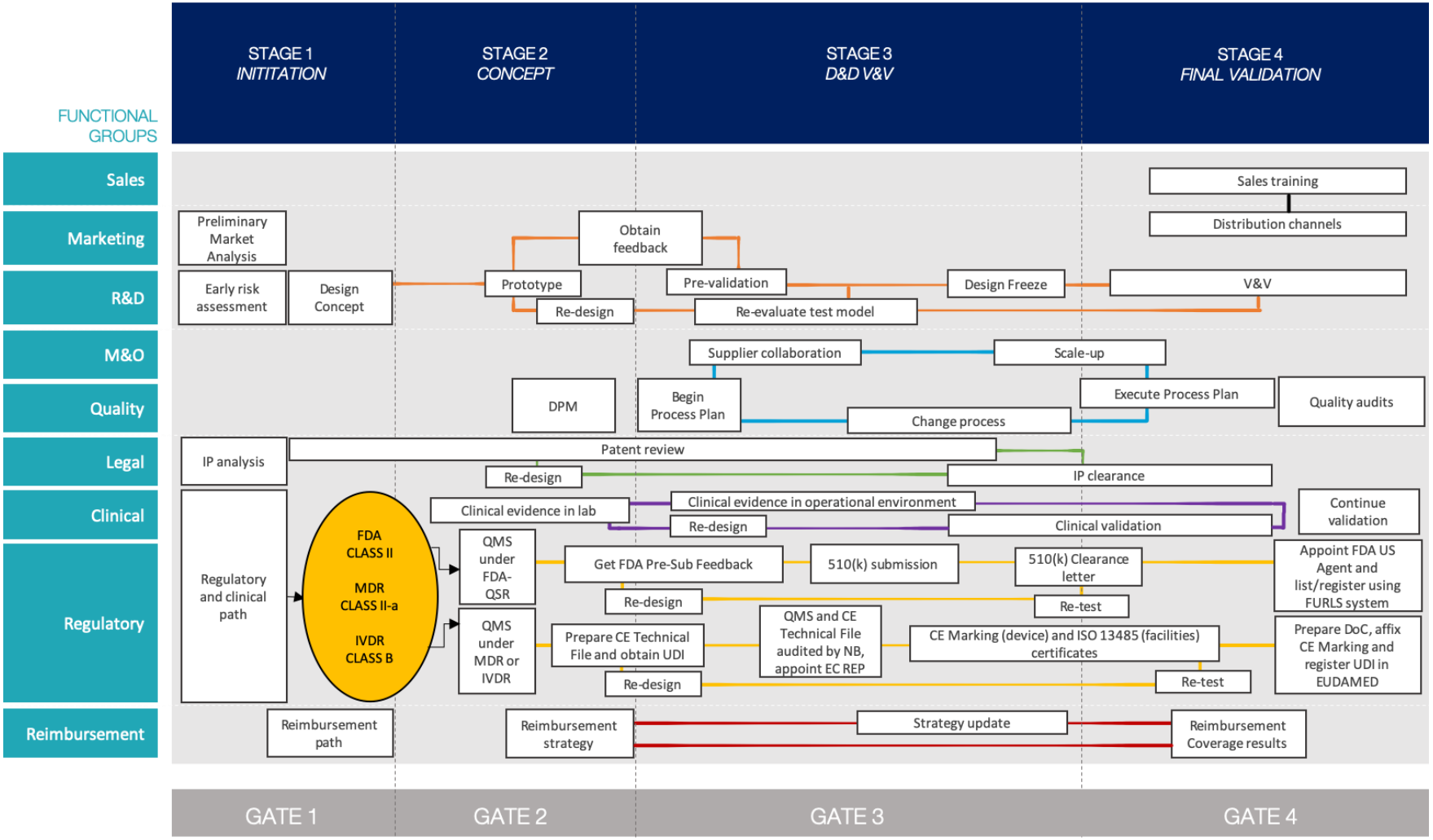




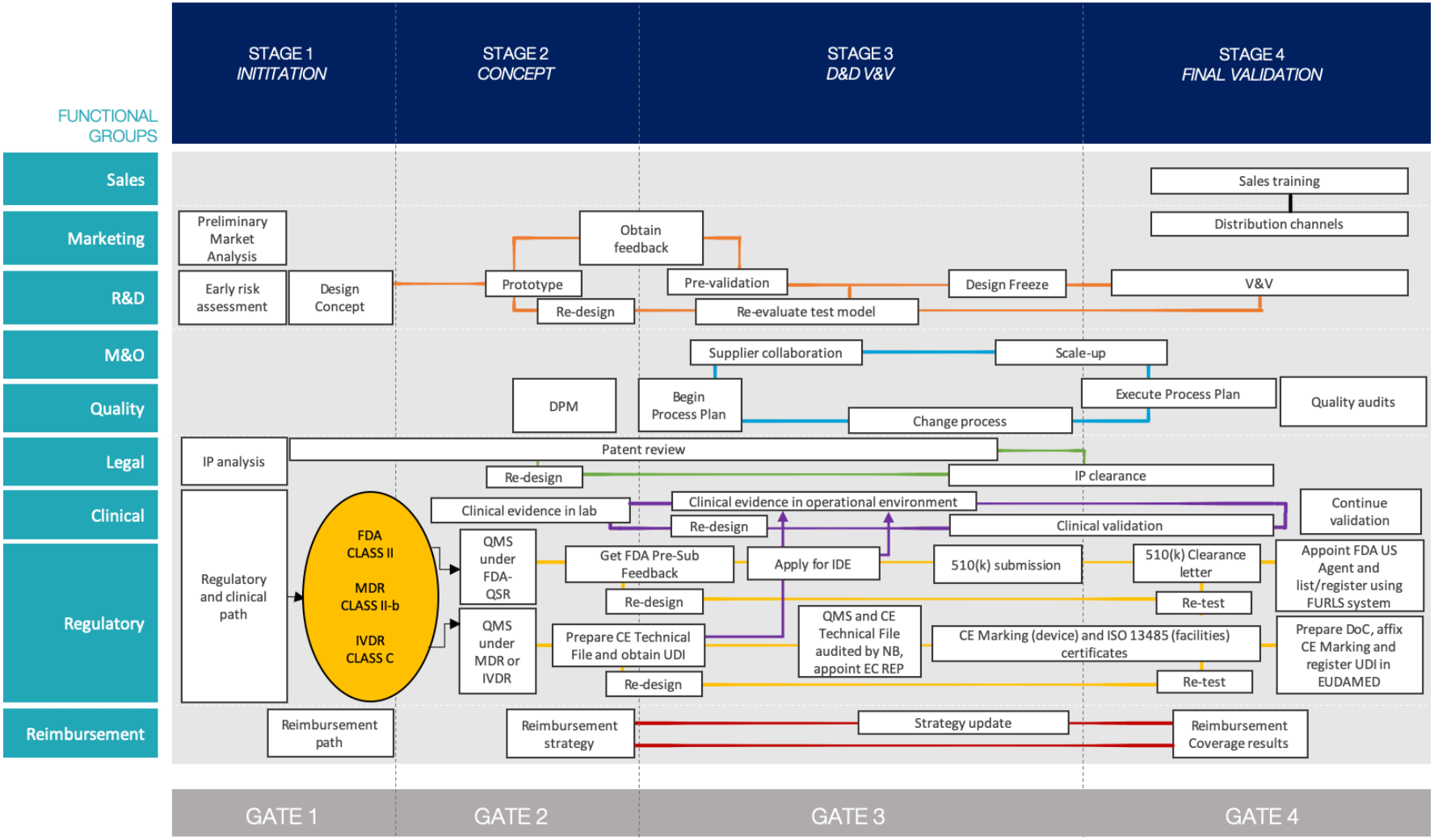
ANNEX III-1 *Framework implementation Class I-I-A (FDA-MDR-IVDR)*



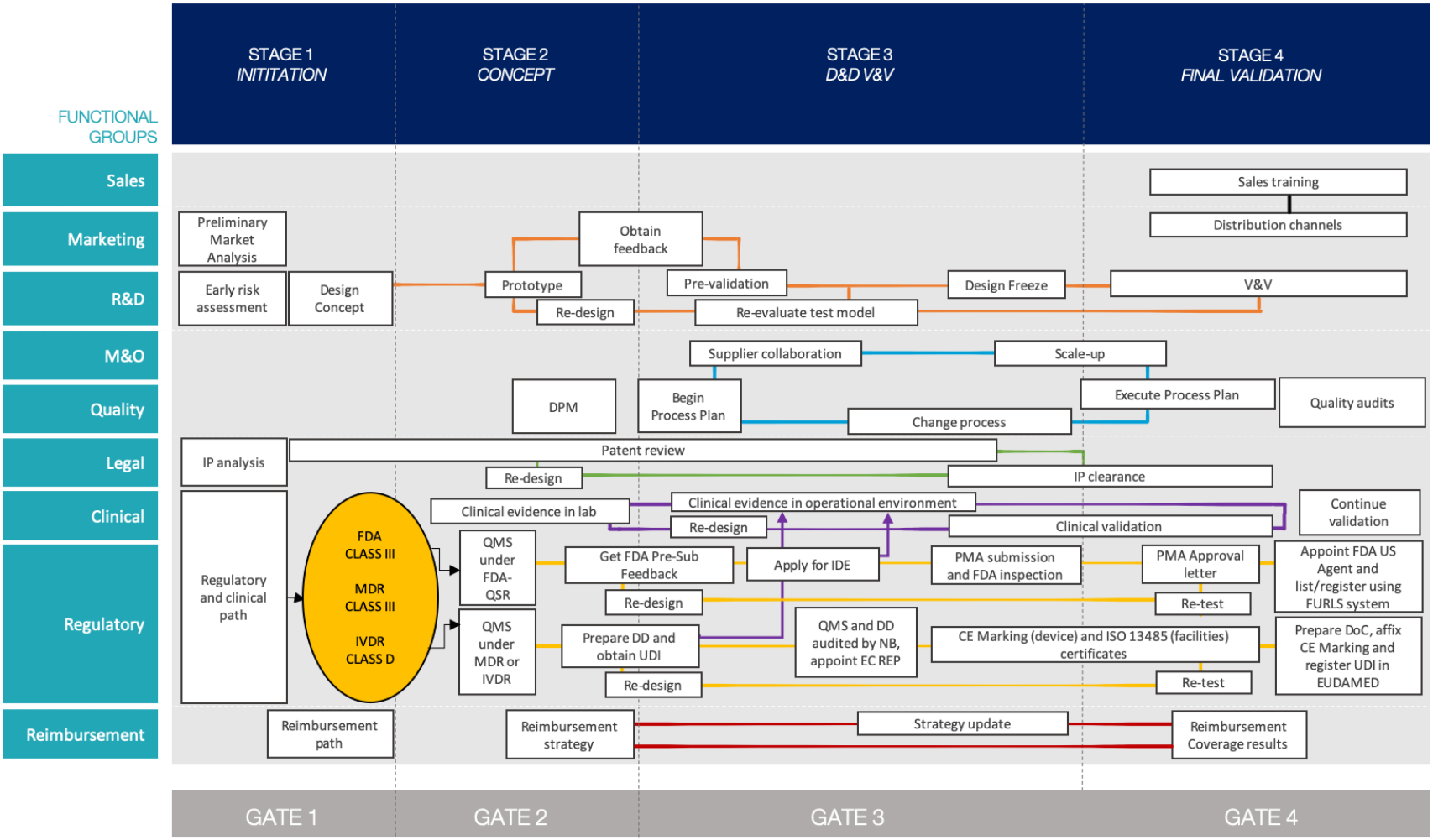
ANNEX III-2 *Framework implementation Class II-IIa-B (FDA-MDR-IVDR)*



ANNEX III-3 *Framework implementation Class II-IIb-C (FDA-MDR-IVDR)*


STAGE 1
INITITATION
STAGE 2
CONCEPT
STAGE 3
D&D V&V
STAGE 4
FINAL VALIDATION
FUNCTIONAL GROUPS
Sales
Marketing
R&D
M&O
Quality
Legal
Clinical
Regulatory
Reimbursement
Sales training
Distribution channels
Preliminary Market Analysis
Obtain feedback
Early risk assessment
Design Concept
Prototype
Pre-validation
Design Freeze
V&V
Re-design
Re-evaluate test model
Supplier collaboration
Scale-up
DPM
Begin Process Plan
Execute Process Plan
Quality audits
Change process
IP analysis
Patent review
Re-design
IP clearance
Clinical evidence in lab
Clinical evidence in operational environment
Continue validation
Re-design
Clinical validation
Regulatory and clinical path
FDA CLASS II
MDR CLASS II-b
IVDR CLASS C
QMS under FDA-QSR
QMS under MDR or IVDR
Get FDA Pre-Sub Feedback
Apply for IDE
510(k) submission
510(k) Clearance letter
Appoint FDA US Agent and list/register using FURLS system
Re-design
Re-test
Prepare CE Technical File and obtain UDI
QMS and CE Technical File audited by NB, appoint EC REP
CE Marking (device) and ISO 13485 (facilities) certificates
Prepare DoC, affix CE Marking and register UDI in EUDAMED
Re-design
Re-test
Reimbursement path
Reimbursement strategy
Strategy update
Reimbursement Coverage results
GATE 1
GATE 2
GATE 3
GATE 4

ANNEX III-4 *Framework implementation Class III-III-D (FDA-MDR-IVDR)*



ANNEX IV

Company overview

1. Description of the legal entity

RUBYnanomed is a recently founded startup devoting its activities to non- invasive progression monitoring of cancer. RUBYnanomed has developed and can manufacture the RUBYchip, a microfluidic device for isolating all types of CTCs (epithelial and mesenchymal). This device has demonstrated the ability to isolate a higher number of CTCs comparing with the reference CellSearch® equipment and the potential to provide improved correlation with clinical prognostic information. During 2016 and 2017 this innovation project (formerly called EasyBiopsy) started its path participating in several innovation and technology transfer programs at European and national level. In 2017, RUBYnanomed received the first prize of the innovation contest StartupNano and, as a result was accelerated in Startup Braga and participated in a USA roadshow in preparation for a first investment round. RUBYnanomed also received support by the RESOLVE program to achieve further pre-clinical validation of the technology. Currently, mentorship is obtained through the HealthTech Translation Advisory Board program (HealthTechTAB), funded by the EC through the NOBEL project. RUBYnanomed will participate in Case Study 3 for the market validation of their technology.

2. Description of technology

The main goal of this thesis is to develop a conceptual framework for a Medtech startup and validate it through a case study in the field. RUBYnanomed has an innovative microfluidic system for Non-invasivE monitoring of cAnceR progression (EARly). This disposable microfluidic cartridge, the RUBYchip™, enables low cost, biomarker-free, automated, fast and sensitive circulating tumor cell (CTC) analysis, isolated from the peripheral blood of cancer patients based on their size and deformability. With an automated analysis platform, the RUBYreader, a phenotypic and/or molecular characterization of the isolated cells is then achieved, using a panel of biomarkers, indicative of cancer progression. With the information obtained, doctors can evaluate the status of the disease in real time and take updated and personalized therapeutic decisions. Cancer progression monitoring is not well managed nowadays as the available techniques (tissue biopsy and imaging technologies) are either invasive, not sensitive enough, slow or at a high economic cost. In this way, doctors are forced to take therapeutic decisions on outdated information. However, there is a method able to provide updated prognostic information, so-called liquid biopsy, which relies on the analysis of the number of CTCs using just a blood sample from the patient, thus minimally invasive. In this way, the clinical management of cancer patients is based on a real-time snapshot of the tumour burden and biomarker profile. RUBYnanomed's technology is based on the use of microfluidics and nanotechnology to isolate the very scarce circulating tumour cells (CTCs) in a 7.5 mL blood sample of a cancer patient. The isolation with RUBYchip™ is

done based on the size and deformability of the cancer cells. RUBYnanomed has designed a microfilter integrated in a microfluidic device that can process blood without any sample pre-treatment in less than one hour, and separates, with a remarkable efficiency, the cancer cells from the healthy cells in circulation. The geometry and design of the chip and microfilter are the core of this technology, and this intellectual property has been protected by filing an international patent (PCT/EP2016/078406). Once isolated, the user is able to enumerate and characterise the cancer cells in circulation, which has a tremendous impact to the oncologists' decision making, as the therapeutic strategy can be better adapted depending on the cancer status of each patient. Opposite to other CTC isolation systems that base their cell selection on the expression of epithelial proteins in the cell membrane, RUBYnanomed and INL have developed a microfluidic device for isolating all types of CTCs, regardless of their phenotype (epithelial, mesenchymal or intermediate epithelial-mesenchymal EMT states). This is of remarkable importance, since the mesenchymal and EMT cells are the ultimate responsible of the metastatic process. In comparison to other CTC isolation technologies that rely also on the size of CTCs, we demonstrate increased efficiency and purity (70% and 10%, respectively). Moreover, isolation is performed from unprocessed whole blood samples in only 47 minutes and yielding unfixed CTCs that can be recovered in a small volume for further phenotypic, genotypic or functional studies. Ongoing work demonstrates the ability to isolate tumour cells from the urine of early diagnosed bladder cancer patients. Current studies are being performed in a larger cohort of metastatic breast, colorectal, prostate and melanoma cancer patients. The company expects that by introducing the RUBY IVD system in the clinic, they could achieve: 1) Earlier diagnosis of metastasis: 6 months to 1 year earlier compared to current imaging tools; 2) Accurate prognosis of patients: real time snapshot of cancer progression; 3) Enable personalised treatment and tracking of cancer origin: according to the biomarkers analysed; and 4) Longer progression-free survival and overall survival.

3. CEO CV and description

Lorena Diéguez (female) is a physicist, with masters in optoelectronics and PhD in nanoscience. She started working in INL in 2014 as a Staff Researcher focusing in the development of biomicrofluidic devices for Translational Medical Research in close collaboration with Hospitals. Since 2018 she is the Leader of Medical Devices research group in the Nano4Health Unit. Her research activities are currently devoted to the development of integrated nanobioengineered systems for the isolation and characterization of Tumor biomarkers from body fluids of cancer patients, as well as their integration in ex vivo organ-on-a-chip 3D models. At INL she manages the Microfluidics laboratory and the microfluidic fabrication station at the cleanroom and she supervises the work of 7 postdoctoral researchers, 3 PhD students, 3 Master students and 1 research assistant. Previously, she has co-supervised 2 PhD, 3 master, 1 honours and 6 Summer students.

List of relevant publication and/or products, services or other achievements

1. PCT/PT2018/050019, 25 May 2018
2. PCT/EP2017/189246, 04 September 2017.
3. PT 20171000035347, 25 May 2017.
4. PCT/EP2016/078406, 22 November 2016.
5. Fast and efficient microfluidic cell filter for isolation of circulating tumor cells from unprocessed whole blood of colorectal cancer patients. S. Ribeiro-Samy, M. Oliveira, T. Pereira, L. Muinelo, J. Gaspar, P. Freitas, R. López, C. Costa, L. Diéguez. *Scientific Reports 9, 1-12 (2019)*
6. Exploring sialyl-Tn expression in microfluidic-isolated circulating tumour cells: a novel biomarker for precision oncology applications. Neves, M.; Azevedo, R.; Lima, L.; Oliveira, M.; Peixoto, A.; Ferreira, D.; Soares, J.; Fernandes, E.; Gaiteiro, C.; Palmeira, C.; Cotton, S.; Santos, M.; Mereiter, S.; Campos, D.; Afonso, L.; Ribeiro, R.; Fraga, A.; Tavares, A.; Mansinho, H.; Monteiro, E.; Videira, P.; Freitas, P.; Celso, R.G.; Santos, L.; Diéguez, L.; Ferreira, J. A. *New Biotechnology, 2019, 49, 77-87*
7. The significance of Circulating Tumor Cells in the Clinic. S. Abalde-Cela, P. Piairo, L. Diéguez. *Acta Cytologica, 2019 DOI: 10.1159/000495417*
8. Sialyl-Tn identifies muscle-invasive bladder cancer basal and luminal subtypes facing decreased survival, being expressed by circulating tumour cells and metastases. L. Lima, M. Neves, M. I. Oliveira, L. Dieguez, R. Freitas, R. Azevedo, C. Gaiteiro, J. Soares, D. Ferreira, A. Peixoto, E. Fernandes, D. Montezuma, A. Tavares, R. Ribeiro, A. Castro, M. Oliveira, A. Fraga, C. A. Reis, L. Lara Santos, J. A. Ferreira. *Urologic Oncology: Seminars and Original Investigations 35 (12), 675, (2017).*

4. List of relevant projects or activities

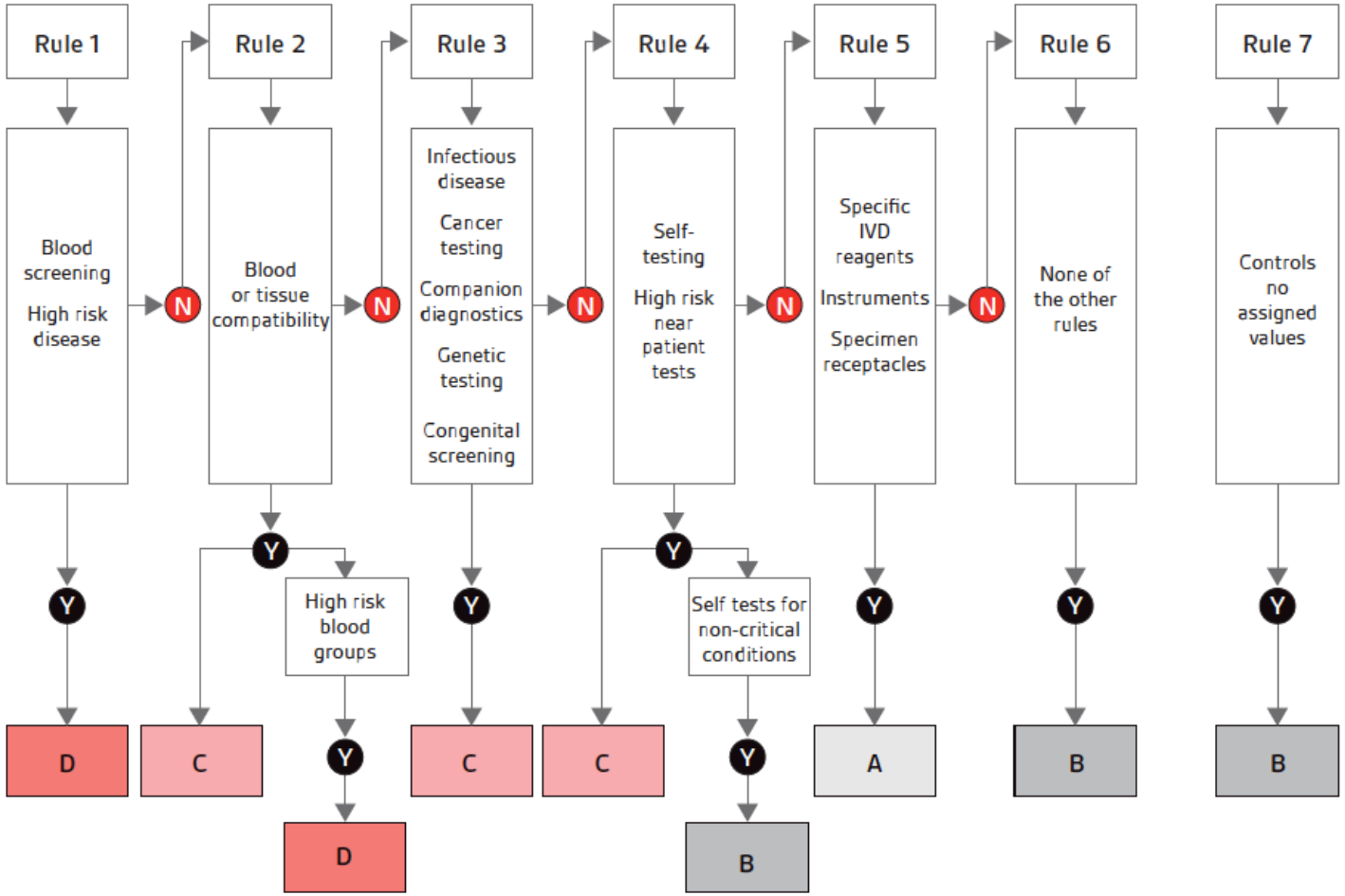
NanomedTAB, StartupNano (5000 € + incubation + inkind access to facilities and equipment), StartupBraga, RESOLVE (35000 €), NanoTechNorte (2500 €), AdMaCoM (12000 €). OncoDynamicsBiobanking project (ODB) at Hospital de Santa Maria and IMM-Lisbon.

5. Description of infrastructures and/or technical equipment

This spin-off company arising from INL is incubated in its premises and has access to its facilities, providing access to over 30 M€ worth of equipment. These include state of the art cleanroom and characterisation facilities, as well as microfluidic, cell culture, molecular biology and engineering labs. All included in one of a kind innovation-based ecosystem focused in nanotechnology.

ANNEX V

EU-IVDR Device classification



ANNEX VI – *RUBYnanomed case study*