ISCTE Business School
Instituto Universitário de Lisboa

DEOXY TECHNOLOGIES – A MEDICAL TECHNOLOGY STARTUP PROJECT

Business plan for UK market

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List of abbreviations

AAMI – Association for the advancement of medical instrumentation

AGO – Arbeitsgemeinschaft gynäkologische onkologie (German Gynecological Oncology Group)

APV – Adjusted present value

ARS – Analyte specific reagent

BC –Breast cancer

BRCA1 – Gene Breast cancer early onset 1 / 2

CA – Competent authority

CAGR – Compound annual growth rate

CE – *"Conformité Européene"* (french word for European conformity)

CED – Coverage with evidence development

CDx – Companion diagnostic

CDRH – Centers for Device and Radiological Health (FDA)

CHT – Chemotherapy

CLIA – Clinical Laboratory Improvement Amendments

CTA – Constructive technology assessment

DHF – Design history file

DNA – Deoxyribonucleic acid

EDMA – European Diagnostic Manufacturers Association

EEA – European Economic Area

EFTA – European free trade association

ER – Estrogen receptor

EU – European Union

FDA – Food and Drug Administration

FFPE – Formalin-fixed paraffin-embedded

FISH – Fluorescence in situ hybridization

FD&C – Federal Food Drug & Cosmetic

FMEA – Failure modes and effects analysis

FMECA – Failure modes, effects analysis and Critically Analysis

FTE – Full-time employee

GDP – Gross domestic product

GEP – Gene expression profiling

GHTF – Global Harmonization Task Force

GMP – Good manufacturing practices

HDE – Human device exemption

HR – Human resources

HTA – Health technology assessment

HTS – High-throughput sequencing technologies

IHC – Immunohistochemistry

IDE - Investigational device exemption

IMDRF - International Medical Device Regulators Forum

IP – Intellectual property

IQ – Installation qualification

IRR – Internal rate of return

ISH – *In situ* hybridization

ISO – International Organization for Standardization

IT – Information technology

IVD – *In vitro* diagnostic

IVDMIA - *in vitro* diagnostic multivariate assays

KOL – Key opinion leader

LDT – Laboratory developed test

M&A – Mergers and acquisitions

MDx – Molecular Diagnostics

MedTech – Medical technology

MLU – Ludwig-Maximilians-Universität München

MPI – Max Planck Institute

mRNA – messenger ribonucleic acid

MTEP – NICE's medical technologies evaluation program

NANDO -New Approach Notified and Designated Organizations

NB – Notified body

NGS – Next-generation sequencing

NHS – National Health System

NICE – National Institute for Health and Excellence Care

NPD – New product development

NPV – Net present value

OECD - Organization for Economic Co-operation and Development

OIVD – Office of in Vitro Diagnostic Device Evaluation and Safety

OQ – Operational qualification

PCR – Polymerase chain reaction

PCT – Patent Cooperation Treaty

PM – Personalized medicine

PMA – Pre-market approval

PR – Progesterone receptor

PMSIG - Personalized Medicine Special Interest Group

PQ – Performance qualification (PQ)

PPQ – Product performance qualification

QS – Quality system

QMS – Quality management system

RCT – Randomized clinical trial

R&D – Research and development

RNA – Ribonucleic acid

RUO – Research use only

SEER – Surveillance, epidemiology, and end results

SME – Small to medium enterprise

TAT – Turn-around-time

TNBC – Triple-negative breast cancer

VC – Venture Capital

V&V – Verification and validation

WHO – World Health Organization

3TG – Tin, tantalum, tungsten and gold

List of main definitions

Analyte specific reagents (ASRs) - ASRs are defined as "antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reactions with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens." ASRs are medical devices regulated by FDA and subject Good Manufacturing Practices (GMPs) controls (FDA, 2015).

Assay - Any laboratory test used to test or measure a biomarker.

Biomarker – Biomarker is a portmanteau of "biological marker", it refers to medical signs that are objective indications of a medical state and which can be measured accurately and reproducibly (Strimbu and Tavel, 2010). Biomarkers are used as an indicator of normal biological process, pathologic process, or pharmacologic response to a therapeutic intervention.

Chemotherapy (CHT) – Type of cancer treatment based on chemical substances - chemotherapeutic agents. Agents are administered as part of a standardized chemotherapy regimen, almost always involves combinations of drugs.

- **Adjuvant Chemotherapy –** Chemotherapeutic regimen administered after surgical treatment;
- **Neo-adjuvant Chemotherapy –** Chemotherapeutic regimen administered before surgical treatment.

Clinical Trial – A research study that involves people/patients and tests a new way to prevent, detect, diagnose, or treat a disease. Clinical trials have a protocol that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The clinical trial guideline ensures that trials are conducted according to established scientific and ethical principles.

Clinical Validation – Is the context of IVDs, a clinical validation is a research study involving samples from a large set of patients. Clinical validation studies are performed to confirm and thereby ''validate'' results that have been observed in earlier phase clinical studies.

Companion diagnostic (CDx) – According to FDA (2014, pp. 7), a CDx is "a medical device, often an *in vitro* device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product. The test helps a health care professional determine whether a particular therapeutic product's benefits to patients will outweigh any potential serious side effects or risks".

Eucomed – The association that represents the European medical devices industry.

EDMA – European diagnostic manufacturers association. Represents the European *in vitro* diagnostics industry.

FDA - FDA is an agency within the U.S. Department of Health and Human Services and is responsible for protecting the U.S. public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, food supply, cosmetics, and radiation emitting products.

Gene expression profiling (GEP) – Gene expression refers to the relative levels of expression and the pattern of a gene expression in a cell or tissue. The expression of a gene may be measured at the level of transcription (cDNA, mRNA). "Gene expression profile" refers to the levels of expression of multiple different genes measured for the same sample.

Gene Signature - Group of genes whose combined expression is unique characteristic of a specific condition or disease.

HER2 – Cell membrane receptor tyrosine-protein kinase, also known as ERBB2. A transmembrane protein encoded by the ERBB2 gene, which is also frequently called HER2 (from human epidermal growth factor receptor 2) or HER2/neu. Amplification or over-expression of this oncogene is known to promote development and progression of certain subtypes breast cancer, defined as HER2 positive breast cancers.

High-throughput sequencing technologies – see next-generation sequencing.

***In situ* hybridization** (**ISH)** – A molecular biology technique. This technique unfolds DNA strands and uses a probe, e.g. a labeled (with fluorescent (FISH) or silver SISH)) DNA strand that hybridizes with the target, complementary sequence and thereby identifies and quantifies the target sequence in the cell nuclei of interest in the tumor sample.

Immunohistochemistry (IHC) – *In vitro* diagnostic technique that uses antibodies to identify specific molecules in tissues. Combines anatomical, immunological and biochemical semi-quantitative assessment in a cheap and partially automated technique.

In vitro - The term "in vitro," meaning in glass, refers to testing that is carried out outside of the body. In contrast, "in vivo" testing is carried out in a living organism.

In vitro **diagnostic (IVD) device** - *In vitro* diagnostic medical devices are tests and related instrumentation used to test human samples to assist clinical diagnosis or decisions concerning clinical management.

MedTech Europe - An alliance of EDMA and Eucomed (MedTech Europe, 2016).

Multiplex assay (test with multiplexing capability) – An assay that simultaneously measures biomarkers in a single run or "cycle" of the assay.

Nanomaterials – According to European Commission "Recommendation on the definition of a nanomaterial (2011/696/EU), nanomaterial is "A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm." This definition is under review (European Commission, 2011).

Next Generation Sequencing (NGS) - Next-generation sequencing technologies, also known as **high-throughput sequencing technologies** or massively parallel sequencing, represent a revolution in the capacity to characterize biologic samples at the genomic, transcriptomic and epigenetic levels, from single cell samples to tissues. NGS technologies make possible to catalogue all mutations, copy number aberrations and somatic rearrangements in an entire cancer genome at base pair resolution in days or weeks.

Oncology - A branch of medicine that specializes in the diagnosis and treatment of cancer. It includes medical oncology (the use of chemotherapy, hormone therapy, and other drugs to treat cancer), radiation oncology (the use of radiation therapy to treat cancer), and surgical oncology (the use of surgery and other procedures to treat cancer).

Pathology – Is a branch of medicine that specializes in the histologic diagnosis based on examination of all types of tissue specimens resulting from all other medical specialties. This is usually performed by a combination of gross (i.e., macroscopic)

and histologic (i.e., microscopic) examination of the tissue, and may involve evaluation of molecular properties of the tissue by IHC, ISH, PCR or other laboratory molecular tests.

Platform (GEP) - (valid to this document only) The platform refers to the "reading technology" for biomarker detection and quantification. The GEP platform in combination with software and report writing technology form the GEP machine.

Polymerase chain reaction (PCR) – A molecular biology technique used for both research and diagnostic purposes. The technique consists on amplification of a single copy or a few copies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence.

Personalized medicine (PM) – According to the Personalized Medicine Special Interest Group (PM SIG) of the International Society for Pharmacogenomics and Outcomes Research (ISPOR), personalized medicine is "the use of genetic and other biomarker information to improve the safety, effectiveness, and health outcomes of patients via more efficiently targeted risk stratification, prevention, and tailored medication and treatment management approaches" (Faulkner, 2012).

Pre-market approval (PMA) – According to FDA, a PMA is "the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices".

Targeted therapies - A new generation of cancer treatment which uses pharmacological agents that inhibit growth, increase cell death and restrict the spread of cancer by interfering with specific proteins involved in tumorigenesis. Instead of using broad base cancer treatments, targeted therapies focus on specific molecular changes which are unique to a particular cancer, targeted cancer therapies may be more therapeutically beneficial for many cancer types and allow a patient-tailored treatment.

Turn-around-time – Time needed from sample collection until the diagnostic report is available for clinical decisions. Includes time spend with ancillary and molecular tests.

3TG - Tin, tantalum, tungsten and gold (3TG) are minerals potential originating from conflict-affected and high-risk areas. On May 20th, 2015, the European Parliament voted in favor of law that requires companies operating in the EU who are importers of 3TG, or

products containing those minerals, to certify that their supply chains are not supporting violence and conflicts.

510 (k) - The 510(k) is a submission process to FDA, which consists on a comparison of the submitted IVD with a legally marketed substantially similar IVD device already approved. The new IVD is than “cleared by 510(k)”.

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ABSTRACT

DEOXY Technologies is a seed-stage medical technology project whose future core business will be based on an innovative Gene Expression profiling (GEP) nanotechnology, developed and patented at Harvard University. The project is located at Ludwig-Maximilian University (Germany) and its goal is to develop diagnostic tests for clinical market where price, speed and automation are competitive advantages.

DEOXY Technologies intends to become a global and *lean* company focused on development and manufacturing of molecular tests (*in vitro* medical devices). This is a strategic analysis and a feasibility study for the breast cancer market. Breast cancer is the most frequent female cancer affecting 12% of women, worldwide and is seen as a paradigm of precision medicine success. The promoter identifies a clinical application for the GEP technology and proposes an alliance with an USA biomarker-focused company whose assets are complementary to the technology.

The strategic analysis was based on a macroenvironmental analysis for the entrance market: United Kingdom, where regulatory and reimbursement contexts were systematized, and for Germany the country of development and manufacturing, where the impact of governmental support and the integration in a biotechnology cluster are critical favorable factors. In the microenvironmental analysis the high barriers to entrance and the importance of planning an exit strategy were underlined.

The economic and financial viability analysis revealed that governmental funding is a critical success factor, as demonstrated by the positivity of the APV and emphasized the importance of a market expansion plan before starting operations. The scenario analysis explored how reimbursement and healthcare policies may impact the economic and financial viability of the project.

JEL classification: L26, O32

Keywords: Medical Devices, Innovation, Strategy, Lean startup.

RESUMO

A DEOXY Technologies é um projeto, baseado numa nanotecnologia inovadora de análise perfis de expressão genética (APEG), descoberta e patenteada na Universidade de Harvard. O projeto está integrado na Universidade de Ludwig-Maximilians, (Alemanha) e é candidato a fundos de investimento governamentais. A DEOXY Technologies acredita que por possuir uma tecnologia inovadora pode desenvolver máquinas de APEG e testes moleculares para o mercado clínico, onde o preço, automatização e rapidez serão vantagens competitivas.

A DEOXY Technologies planeia tornar-se uma empresa global e *lean*, focada no desenvolvimento e produção de testes moleculares *in vitro*. Este plano de negócios contém a análise estratégica e económico-financeira para o mercado do cancro da mama, em Inglaterra (Reino Unido). O cancro da mama é o cancro mais frequente na mulher, afetando 12% desta população, e é paradigmático do sucesso da medicina de precisão.

O promotor identifica uma necessidade clínica e para sua concretização propõe uma aliança com uma empresa biotecnológica detentora de ativos intelectuais complementares aos da DEOXY Technologies.

A estratégia proposta baseia-se na análise PEST para o Reino Unido, contendo a regulamentação e etapas-chave para obter reembolso, e análise PEST para Alemanha, destacando-se a relevância do apoio governamental e da inserção num cluster biotecnológico como fatores críticos de sucesso. Da análise micro-ambiental salientam-se as barreiras à entrada e a importância da estratégia de saída nesta indústria.

O estudo de viabilidade económico-financeira revelou que os fundos governamentais são um fator critico para a exequibilidade e viabilidade económico-financeira do projeto, sendo o valor atualizado ajustado o único indicador positivo. A análise de cenários demonstra como as políticas de cuidados de saúde influenciam a estratégia e a viabilidade económico-financeira do projeto.

Classificação de JEL: L26, O32

Palavras-chave: Medical Devices, Innovation, Strategy, Lean startup.

EXECUTIVE SUMMARY

Breast cancer is the 2nd leading cause of cancer worldwide with 1,67 million new cases, only in 2012. Among the breast cancer patients, a subgroup, defined as "triple-negatives" is recognized to have a poorer prognosis, affecting younger patients and do not have any validated personalized treatments available. A literature review revealed how intensively pharmaceutical companies are investing in developing and validating personalized drugs for "triples-negatives" (170 clinical trials in 2015). Since the personalized therapeutic decisions are based on molecular tests, the need of diagnostic tests to guide "triple-negatives" therapy decisions is expectable in the near future.

DEOXY Technologies, Munich, Germany, is a seed-stage medical technology project developing an innovative Gene Expression Profiling (GEP) nanotechnology able to diagnose and subtype any cancer according to its biomarkers of response to therapy. DEOXY Technologies is currently developing "minimum viable products" based on the nanotechnology, which are the foundation of the future GEP platform to be sold to molecular tests providers and, simultaneously, validating the nanoreporting system to be used with biologic samples (breast cancer). The proof-of-concept stage is expected to end in the beginning of 2019, when DEOXY Technologies intends to become a GmbH company. As a long-term goal DEOXY Technologies intends to become a global company focused on molecular diagnostic test development.

This business plan is a development strategy, from proof-of-concept phase to product launch, of a molecular test for the "triple-negatives" subgroup of breast cancer, in the English (United Kingdom) market.

The Medical Technology sector includes all industries related to medical devices and, in Europe, is regulated by the European Directives published by the European Commission, and applied by each European country through its competent authority agencies, a process defined as CE marking. In UK the competent authority is the MHRA. Molecular diagnostic tests are considered *in vitro* medical devices (IVDs), and a specific European Directive for IVDs was recently published where an increase in the required evidence for clinical validation has been noted. In USA IVDs are regulated by FDA and CLIA, depending on the type of test.

Aware of the impact of the regulations during product development, the Cooper's stage-gate model is presented as a management tool complemented with the FDA requirements and the perceived barriers, as shown in a reference study. Moreover, by analyzing its technology readiness level, DEOXY Technologies can analyze its technologic maturity, as seen by investors (Chapter 4).

As a molecular diagnostic developer, DEOXY Technologies must consider how the type of IVD (Chapter 3) influences its future business model and scalability. In line with our long-term goals, a decentralized model (selling machines and test kits to be performed by service providers) was the strategy chosen, based on the scalability of these model.

For medical devices industry, UK is a monopsony market since more than 80% of total healthcare services are provided by governmental funded hospitals, that belong to the NHS. To focus on the English market, is based on the independent and innovative character of the England's regulatory agency – NICE, despite the lower bargaining power expectable. The appraisal by NICE is the last milestone stablished in this business plan and failure of reimbursement acquisition can impede effective market entrance. UK has a growing population, with high education level and a favorable economic performance, factors expected to drive the market growth.

DEOXY Technologies intends to maintain its development and future manufacturing activities in Munich. An analysis on how the location in Germany affects the project expectations underlined how the proximity with complementary industry and the integration in a biotechnology cluster represents an advantage, by providing a complete value chain from research to product launch. Remarkably, the availability of governmental seed-stage funding for high-tech projects was identified as a critical success factor, as corroborated by the economic and financial viability analysis.

As a strategy to reduce the time to market, the author proposes a strategic alliance with a USA based company – Insight Genetics, who has licensed the patent for "triple-negatives" biomarkers of sensitivity to drugs, currently under validation. The alliance proposed is based on the complementarity of assets.

DEOXY Technologies projects to negotiate the alliance throughout 2019. Between 2019 and 2023, the "triple-negatives" test will be developed in collaboration with Insight Genetics. The NICE appraisal marks the effective market entrance and is projected to occur by the end of year 2023.The total investment was estimated in 6 229 110 €. Four years of market were considered, between 2023 and 2026. The economic and financial

viability indicators, considering only revenue from England, were all negative. When considered the effect of the governmental funding (projected to round 3 000 000€, between 2017 and 2020), the adjusted present value was positive.

This result demonstrates that the funding strategy is a critical success factor, particularly the governmental funding has a significant impact in the viability of the project. The impact of the governmental policies and the healthcare unsustainability was explored using a 3-case scenario analysis.

This study has multiple limitations: the intrinsic technologic risk related to its immaturity and the uncertainty of the funding sources can significantly change the projected milestones. Other processes, such as the CE marking (under MHRA) and the approval for clinical trial enrollment might introduce additional delays in market license. Ultimately, failure of NICE appraisal can impede the effective market entrance. In the scenario analysis, scenario 3 explores the impact of the lack of reimbursement in the business model and viability. The revenue estimations are limited to the English market, and potential revenues from USA (royalties from Insight Genetics) and other European private costumers are not included.

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2. PROMOTER AND PROJECT IDENTIFICATION

DEOXY Technologies is a medical technology startup project, in seed-stage, applying for governmental and other funding sources. The core team elements are Johannes B. Woehrstein (J.B.W.), Dr. Heinrich Grabmayr (H.G.) and Dr. Robert Grummt (R.G.). Currently, the project is supported by Dr. Ralf Jungmann who allows the use of his laboratorial space and equipment at Ludwig Maximilian University (LMU), Martinsried, Munich, Germany, where he is a Professor.

DEOXY Technologies goal is to develop an innovative Gene Expression Profiling (GEP) platform based on its main asset, a fluorescent nanotechnology detection system, that was invented by J.B.W., among other researchers, who filed a patent, at the Harvard University, in 2014, currently under the PCT phase. The nanotechnology detection system and the platform are under development by J.B.W. and H.G. and a new patent was filed in 2016, increasing the capabilities of the nanoreporter system.

The DEOXY Technologies nanoreporter system has potential competitive advantages compared to the currently available GEP platform technologies, namely speed, fully automation and very low production costs. Based on those technologic competitive advantages, DEOXY Technology strategy is to develop an automated GEP machine and test to become a global medical technology company focused on development of GEP-based *in vitro* medical devices (IVDs), primarily for Oncology, and potentially for other clinical conditions.

The promoter of this project joined the DEOXY Technology team as Medical Adviser and Master of Business Administration student, in 2015, and is currently receiving medical training in Anatomic Pathology, which includes training in cancer diagnosis, molecular biology, clinical Oncology and Oncobiology.

This thesis has the format of a business plan and was written as partial requirement for the conferral of Master in Business Administration. The business plan intends to construct a development strategy for DEOXY Technologies, identify a targetable market need and to analyze its financial and economic viability.

The first part of the document (Chapters 3 and 4) is a characterization of the medical technology industry, its legal definitions, the market and the technologic development process.

Being one of the most frequent cancers worldwide, breast cancer has been considered a good candidate as the first target market. A brief characterization of the breast cancer state of art and how research and drug development are creating new and unsolved clinical needs is presented in Chapter 5.

This business plan analyses how the location in the Munich Biotechnology cluster, Germany, influences its development strategy (Chapter 6.1). For strategic reasons, the promoter establishes England, UK as the entrance market, based on the reference nation's reimbursement and regulatory processes (Chapter 6.2). For simplification purposes, no other markets or revenues will be included in this business plan.

Currently, the market predictability is affected by two main factors: the European Directives for Medical Devices are under review, and the new regulations, expected to be included in the law on effect by 2021, have been claimed to require higher levels of clinical evidence for approval; trading and economic relationships between UK and Europe are under negotiation, and ultimately may have impact in the trading between Germany and UK.

For DEOXY Technologies, the product development cycle and the time to market are critical. The promoter proposes an alliance with an USA-based molecular diagnosis company as a strategy for the acquisition of necessary complementary assets to enter in the market (Chapter 8).

3. MEDICAL TECHNOLOGY SECTOR

3.1 Biotechnology industry

Biotechnology is "the application of science and technology to living organisms, well as parts, products and models thereof, to alter living or non-living materials to produce knowledge, goods and services" (OECD).

Nanobiotechnology is the application of nanotechnology to the life sciences. The technology encompasses precision engineering, electronics, and biomedical applications in areas as diverse as gene therapy, drug delivery and novel drug discovery techniques (Nanomedicine: Nanotechnology, Biology, and Medicine, accessed on 13 August 2016). Nanomedicine is the application of nanotechnologies in a healthcare setting (British Society of Nanomedicine, accessed on 13 August 2016).

Biotechnology application areas are wide and a color code was developed to aggregate segments by application field. Red biotechnology is the application of biotechnology to the medical area (Mietzner and Reger, 2009). Red biotechnology aggregates the largest segments of the life science industry: pharmaceutical, medical biotechnology, generics and biosimilars, and medical technology (Deloite, 2016). In general, the red biotechnology industry has a distinct profile characterized by Santos (2012) as:

- Long period of product development;
- High complexity and multi-disciplinary teams required for product development;
- High level of technological uncertainty until the final stages of development;
- Intense research and development (R&D) activities;
- Expensive development trajectory with high up-front investment;
- Dependent on continuous intellectual property (IP) production and IP rights protection;
- Multiple funding cycles depending on the phase of product development;
- Establishment of partnerships and alliances to gather necessary resources;
- Stringent and geographically heterogeneous regulations for clinical market.

3.2 Medical technology sector

The medical technology industry is defined as the development, manufacture, and distribution of medical devices as defined by European Union Medical Devices Directive (93/42/ ECC), *in vitro* Diagnostic Medical Devices Directive (98/79/EU), and Active Implantable Medical Devices Directive (90/385/EEC) (European Commission, medical devices directives, accessed on 13 August, 2016).

In Europe, there is an association that represents the medical technology industry - the MedTech Europe. MedTech Europe is a non-profit organization resulting from the alliance of EDMA (European *in vitro* diagnostics Manufacturers Association) and Eucomed (Association of the European Medical Devices industry). MedTech Europe scope is to support health care policies that promote the use of medical devices in Europe, as a strategy to overcome the increasing need to healthcare innovation and sustainability (Medtech Europe, accessed on 13 August, 2016).

Medical devices are considered central for high quality healthcare services. Innovative medical devices also have the potential to improve cost-effectiveness and productivity in health care facilities (Schmitt, 2002).

3.2.1 Medical devices

Medical devices have been receiving definitions by the main regulatory agencies across the world, namely:

- European Medical Devices Directive 93/42/EEC, developed in the MEDDEV documents. However, this regulation will be replaced in 2021, by a new regulatory statement, based on the Global Harmonization Task Force proposition documents;
- Section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act, under regulation by the FDA;
- Global Harmonization Task Force (GHTF).

Definitions of medical devices according to each agency are presented on Table 1.

Table 1: Definitions of medical devices according to European Directives, USA and GHTF.

EU	**Medical Devices Directive 93/42/EEC** "Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories or software for its proper functioning, intended by the manufacturer to be used for human beings in the: - diagnosis, prevention, monitoring, treatment or alleviation of disease; - diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; - investigation, replacement or modification of the anatomy or of a physiological process; - control of conception; and which does not achieve its principal intended action in or on the human body by pharmaceuticalcological, immunological or metabolic means, but which may be assisted in its function by such means".
USA	**Section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act** "Any instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: - recognized in the official National Formulary, or the United States Pharmaceutical, or any supplement to them, - intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or - intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."
GHTF	**GHTF proposed document /SG1/N71 in 16th May, 2012 - Definition of the Terms Medical Device' and *in vitro* Diagnostic (IVD) Medical Device** "Any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of: - diagnosis, prevention, monitoring, treatment or alleviation of disease, - diagnosis, monitoring, treatment, alleviation of or compensation for an injury, - investigation, replacement, modification, or support of the anatomy or of a physiological process, - supporting or sustaining life, - control of conception, - disinfection of medical devices, - providing information by means of in vitro examination of specimens derived from the human body; and does not achieve its primary intended action by pharmaceuticalcological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means. "
Software as a complement, accessory or standalone, is also considered a medical device by GHTF (GHTF, 2013), as well as by FDA (FDA, 2002)	

3.2.2 *In vitro* diagnostic Medical Devices (IVDs)

3.2.2.1 – Definition of IVDs

IVDs are considered a subgroup of medical devices. They are intended to be used in the analysis of human samples, outside of the human body. In Europe, those tests are under regulatory guidance of the Council Directive 98/79/EC on *in vitro* Diagnostic Medical Devices (European Commission, accessed on 12 June, 2016). European Directives are the foundation of the single European market: each nation transposes the law into its national law and nations mutually recognize the CE mark registration. Each country is responsible for market surveillance and vigilance. In Table 2 definitions of IVDs according to European Commission, USA and GHTF are presented.

Table 2: Definitions of in vitro diagnostic tests in Europe, USA and by GHTF.

EU	**Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices** "Any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information concerning a physiological or pathological process or state, concerning a congenital abnormality; to determine the safety and compatibility with potential recipients, or to monitor therapeutic measures."
USA	**IVDs as defined in section 210(h) of the Federal Food, Drug, and Cosmetic Act, biologic products observed in section 351 of the Public Health Service Act** *"In vitro* diagnostic products are those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body."
GHTF	**GHTF proposed document /SG1/N71 in 16th May, 2012 - Definition of the Terms Medical Device' and *in vitro* Diagnostic (IVD) Medical Device** "a medical device, whether used alone or in combination, intended by the manufacturer for the *in vitro* examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes." **Note 1:** IVD medical devices include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles and are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status. **Note2:** In some jurisdictions, certain IVD medical devices may be covered by other regulations.

3.2.2.2 – Types of IVD tests

IVDs are available as different types of tests: IVDs test kits (Kits), Laboratory developed tests (LDTs), *in vitro* diagnostic multivariate assays (IVDMIA), and Companion diagnostic tests (CDx). The type of test determines the commercialization strategies, scalability and regulatory barriers, and thereof should be considered in early in IVDs development process. In Europe, all IVDs tests should receive CE marking before being sold or put into practice. In USA, IVDs regulatory oversight depends on the commercialization model of the test. Both the FDA Office of *in vitro* Diagnostic Device Evaluation and Safety (OIVD), part of the FDA's Centers for Device and Radiological Health (CDRH), or Clinical Laboratory Improvement Amendments (CLIA '88) of 1988 (CLIA) are IVDs regulators (Sarata, 2014). Detailed information about FDA regulatory framework available on Annex I.

Kits - The concept of an IVD kit refers to a complete set of reagents, which is sold as a commercial product, typically a box containing pre-prepared reagents ready to be used in a standardized laboratory procedure, including all the instructions needed. A definition of kit was included in the proposal for a regulation of the European Parliament and of the Council of the European Union on *in vitro* diagnostic medical devices, on 12 June 2015, based on the definition provided by the norm ISO 18113-1:2011: an IVD kit is "a set of reactive components that are packaged together and intended to be used to perform a specific IVD examination" (EDMA, 2015).
Historically, the FDA oversight on IVDs has been focused on tests sold as kits, which can be marketed globally to laboratories or directly to the public (Sarata, 2014).

LDTs - Opposed to kits, LDTs are developed and validated by a proprietary laboratory or "in-house", and are sold as a service to hospitals or directly to patients. The majority of IVD tests in the market are LDTs. The regulatory classification and assessment of LDTs is different from kits. In the USA, LDTs regulation is performed by the Center for Medicare and Medicaid Services by authority of the Clinical Laboratory Improvement Amendments (CLIA) of 1988, and not by FDA. CLIA and FDA regulations differ significantly. CLIA regulates the testing process itself, mostly by assessing the quality of the clinical laboratory, and performance of the test itself, thereby focus on analytical validity. On the other hand, FDA premarket review requirements assess both test analytical validity, but also its clinical utility and validity (Sarata, 2014).

Until recently, FDA did not require premarket clearance and approval of LDTs if the test was performed under the CLIA regulations and not marketed for distribution. However, in 2014, the FDA released a draft guidance document: "Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" with a proposal to oversight LDTs, based on a risk assessment principle like the risk-based tests sold as kits (FDA, 2014).

***In vitro* diagnostic multivariate assays (IVDMIA) –** In a draft guidance published in 2007, FDA considers IVDMIAs as a device that "combines the values of multiple variables using an interpretation function to yield a single, patient-specific result (e.g., a "classification," "score," "index," etc.), that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, and 2) Provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user" (FDA, 2007).

Examples of IVDMIAs already approved for commercialization in Europe are Mammaprint® and OncotypeDx; both are LDTs, based on gene expression profiling (GEP) assays, intended to be used for breast cancer prognostic assessment (CAP, 2009). In Europe, IVDMIA tests have been required to comply with Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices. It has been recognized that the current directive is not adequate to the profile of those new IVD tests, an issue expected to be solved with the new risk/based classification CE Mark system that will be introduced by 2021 (Emergo Group, www.emergo.com).

Companion diagnostic (CDx) – The last decades witnessed a growing knowledge of the pathologic mechanisms that underlie and drive diseases. The formulation of therapeutic strategies that specifically target disease drivers is the foundation of the Personalized Medicine or Precision Medicine, which is already revolutionizing the Oncology clinical practice. Diagnostic tests have been developed to identify eligible patients for a specific treatment by identifying those with specific targetable mutations (Desiere, 2013). This test-drug model requires a new type of IVD, the CDx. The use of CDx, means that a drug is only prescribed if the corresponding CDx test detects responsivity to the target therapy. The breast cancer CDx "trastuzumab-HER2 amplification", is the paradigm for CDx application in oncologic treatment (Olsen and Jørgensen, 2014).

According to FDA (2014), an IVD CDx device is "an *in vitro* diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, including the labeling of any generic equivalents of the therapeutic product. An IVD companion diagnostic device could be essential for the safe and effective use of a corresponding therapeutic product to:

- Identify patients who are most likely to benefit from the therapeutic product;
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product;
- Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness;
- Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population".

Despite recommending concurrent drug and test approval or clearance, FDA (2014) extends its definition to cases where "contemporaneous development of drug and device are not possible. An IVD CDx device may be a novel IVD device, a new version of an existing device developed by a different manufacturer, or an existing device that has already been approved or cleared for another purpose." (FDA, 2014).

The current European Directive on IVD has no definition of "companion diagnostic test". The European Council proposed CDx definition significantly overlaps the FDA definition (European Council, accessed on 14 August, 2016).

3.2.2.3 Kits versus LDTs: Implications for business models and marketing strategy

Despite the evidence of growing regulatory involvement in LDT tests by FDA, the LDT route to market, currently under CLIA oversight, is still viewed as a favorable way to commercialization, and more importantly, a venture capital funding facilitator for SMEs dedicated to IVD development. The LDT pathway to market is shorter and cheaper because it avoids the complex FDA regulations. IVD manufacturers who decide to develop commercial test kits, which are required to go through FDA premarket approval (PMA), are therefore seen

as being in a competitive disadvantage compared to LDT manufacturers (Sarata, 2014). However, while opting for LDT development, to bypass FDA rigorous regulatory scrutiny, may seem to overcome most of the barriers to market, it can translate into higher difficulties in effectively and globally marketing the test, firstly LDTs are not scalable and second, lower evidence of clinical utility leads to lower adoption rate by clinicians. Meeting the high standards of FDA is a strategy to convince clinicians and payers of a test's validity and clinical utility. The number of medical technology firms choosing the FDA PMA pathway increased in the period 2014-2015, from 25 to 51 (Ernst &Young, 2015; EvaluateMedtech, 2015). Moreover, the type of test, not only influences the regulatory requirements, but also determines the business model as explained on Figure 1. Because LDTs are sold as services provided by central laboratories (centralized model) they are not scalable, while tests sold as kits are distributed to service providers who run the test "in house" (decentralized model), (Agarwal, 2015).

Centralized model – selling of tests as services

1 – The diagnostic developer establishes a laboratory waived by CLIA;

2 – All diagnostic samples must be shipped to the central laboratory;

3 – Results are sent back to the physician or patient.

Decentralized model – selling of test kits and instruments:

1 – Develop kits, obtain 510(k)/PMA approval (USA) or CE mark (EU);

2 – Develop and sale the platform machines;

3 – Scale sales of machines and kits to clinical laboratories.

Figure 1: Business model relationship with IVD type of test.

3.3 Medical technology market and drivers

Medical technology is an extraordinarily diverse industry whose existing classifications and taxonomies are inconsistent, creating difficulties in industry trends analyzes (Ernst & Young, 2015; Carlson, 2016). Moreover, the market for health services and products is different from other markets in several ways: i) the demand for services and products is not directly coupled to prices and customer preferences; ii) coverage and reimbursement decisions by public healthcare or private insurers determinate market access and adoption of new technologies (Wahlster, 2015).

3.3.1 Personalized Medicine is the main IVD market driver

IVDs are recognized to play a central role in Personalized Medicine (PM). PM has been defined as the medicine based on personnel characteristics of the patient and requires identification of genetic variations to define the right drug, for the right patient, in the right dose. This model is disrupting the still prevalent one-size-fits-all model or a one-drug-for all model, as seen on Figure 2.

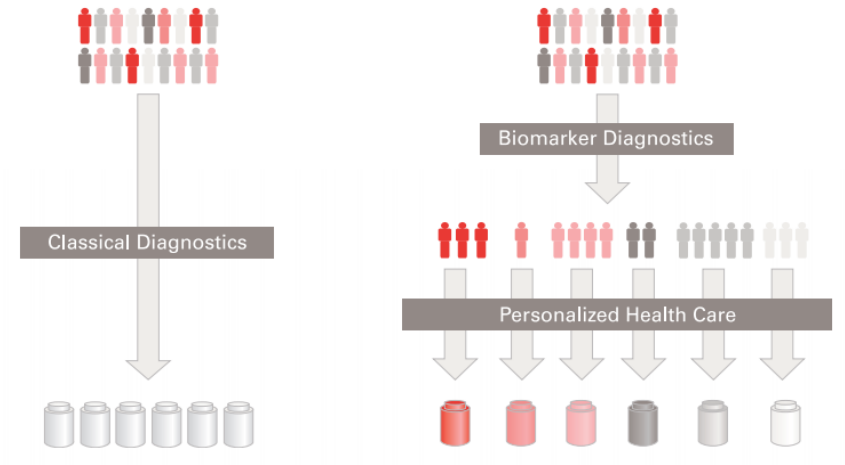

Figure 2: Precision Medicine (PM).

Source: Bio^{M4} (Munich Biotechnology cluster).

PM relies on Molecular Diagnostics tests (MDx) to inform, diagnosis, therapeutic and monitoring decisions, as shown on Figure 2. MDx is a diagnostic test able to detect and measure molecular structures, such as deoxyribonucleic acid (DNA), ribonucleic acid (RNA) or expressed proteins (AdvaMedDx, 2013). The rise of MDx is being driven by the rapid dwindle of genome sequencing costs, which are claimed to have outpaced the Moore's Law: a whole genome sequencing cost of $14 million by 2001 drop to $4000 in 2015 (Pant, 2014; Deloitte, 2014; National Institutes of Health, UK government).

The extensive use of gene sequencing platforms, in research activities, is driving a fast and continuous discovery of new biomarkers at the research level, which feeds the continuous design of new treatments to target these biomarkers. In 2015, 87% of the oncology pipeline drugs in late phases of clinical validation were therapies designed to target biomarkers, most of those will require a MDx test to be prescribed (IMS, 2016).

Despite being only 2% of total healthcare expenditure, IVDs, including MDx tests, create value all over the clinical pathway and for all types of health care services, see Figure 3 (Krishnamoorthy, 2015).

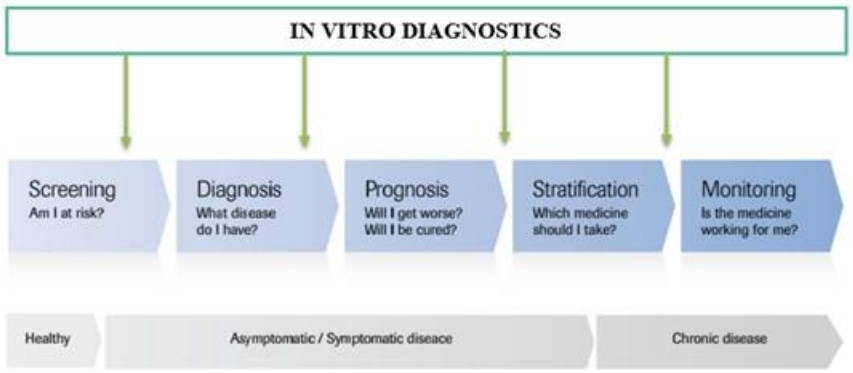

Figure 3: IVDs integrate the entire continuum of healthcare.

Adapted from Roche (2014).

Among MDx tests, those based on high-throughput (HTP) technologies, such as GEP and NGS, are specially promising for diseases that have a highly complex and heterogeneous genetic composition, as is cancer (Collins and Hamburg, 2013). Both cancer initiation and progression are driven by disruptions in cellular regulation networks set by hundreds of genes. Therefore, technologies with capacity to generate a gene signature or a "tumor signature" are the most promising technologies allowing the identification of the relevant genomic aberrations among hundreds of potentially affected genes (Alexandrov, 2013; Stephens, 2012).

The use of multiple gene (DNA) or transcript (RNA) panels, including all relevant biomarkers for different drugs also holds the potential to change the current companion diagnostic paradigm: "one test-one drug" to "one test-multiple drugs" and to become more appealing from the payer's perspective. With multiple therapeutic agents approved for subsets of patients with the same clinical condition, payers need to know what is the best therapeutic option each patient using the minimum number of tests. A test able to provide information about multiple targets/biomarkers, in a single run is defined as a multiplex assay (Agarwal, 2015; Pant, 2014). This scenario anticipates that MDx developers who hold the capacity to design multiplex assays, detecting a myriad of biomarkers required for the set drugs already approved in the clinical market, will be able to seek FDA clearance and CE mark independently of the pharmaceutical companies who developed those drugs. Multiplexing technology is also able to reduce the impact of an important limiting factor: the small size of tumor samples. CDx tests based on current techniques (IHC and ISH) require new sections per test and, not uncommonly,

there is not enough material to perform all necessary tests (Pant, 2014). However, the translation of multiplexing technology into clinical practice, is recognized to require significant improvements mainly on usability and affordability (Stelzer, 2015).

3.3.2 Market size and trends

Most of the medical technology industry leaders are concentrated in USA. Revenues concentration in medical technology industry leaders, occurs both in USA and Europe: the 40 largest USA medical technology companies hold 90% of the revenues and 86% of the market share; the European 18 market leaders hold 89% of the European revenues, 90% of the EU market capitalization, and 10% of its net income (Ernst &Young, 2015).

"Diagnostics" is a segment of medical technology industry, and it is usually split in two main areas: *in vivo* imaging and *in vitro* or non-imaging diagnostics (IVDs) (AdvaMedDx, 2013). Among medical technology companies, IVDs had the highest growth rate, in 2014, reaching 6%. This growth was mainly due to the genomic analysis equipment revenues, whose leader is Illumina, a USA based company whose revenues increased by 31% (Ernst &Young, 2015).

IVDs tests industry has been divided in non-consensual **segments by application** field: clinical chemistry; blood glucose testing; microbiology; hematology and flow cytometry; molecular diagnostics; immunoassay, point-of-care, and tissue diagnostic; **by technologies**: PCR, microarrays, immunohistochemistry, NGS, and nanotechnology-based techniques; also **by end-users**: hospital laboratories, independent laboratories, patients and others; and on the basis of **products or services**: instruments, reagents, and services, and software (MedTech Europe, 2015; Ernst &Young, 2015).

Collectively, IVDs are the fastest growing segment in the medical technology area with global sales estimated to reach 67.3 billion US$, in 2020, assuming a 14,1% of the market share. IVDs are also expected to be the fastest growing area with a compound annual growth rate (CAGR) of 5,1% between 2014 and 2020, with the top ten companies concentrating almost three quarters of the worldwide market share (EvaluateMedtech, 2015). The IVD segment leader – Roche Diagnostics - presented a revenue growth of 4%, in 2014 (Ernst &Young, 2015).

In Europe, the 2014 IVD industry revenues were stagnant in the four largest European IVD markets, whose market share in presented in brackets: Germany (20%), France (17%), Italy (16%), Spain (9%), and UK (8%) (Medtech Europe, 2015). Besides budget restrictions, in European countries a greater centralization of laboratory sectors led to increased bargaining power of purchasing organizations. Molecular diagnostics (MDx) is a subset of IVDs market.

New and improved NGS platforms, and the discovery of new targetable biomarkers, are driving the growing adoption of MDx by the clinical market (AdvaMedDx, 2013). The global market for MDx was evaluated at $45.6 billion in 2012. It is expected to keep an annual grow at about 7% and to reach a market size of $64.6 billion in 2017, with USA and EU holding 60% of the market share (AdvaMedDx, 2013).

Considering that 87% of the 586-late phase oncologic therapies are targeted therapies, which are likely to require a diagnostic test, a parallel increase in the MDx segment market size and share is expectable (IMS, 2016). For drugs already approved for marketing, the development of new diagnostic tests that can improve the use and expand indications of those drugs is another growth driver (AdvaMedDx, 2013).

Although the CDx model holds a great promise for all the stakeholders involved (patients, physicians, insurers, hospitals and governments), the 2013 European CDx market share was less than 5% of the total IVD market (€10,5 billion), and only less than 0,04% of the total spending on healthcare (Akhmetov, 2015). The main pointed reasons for this lower market penetrance are the higher complexity of development, commercialization, and regulatory compliance, as well as, underdeveloped reimbursement policies, with non-value-based public sector pricing; lack of evidence of clinical utility, provided by clinical trials, dissonant clinical guidelines and low public awareness (Akhmetov, 2015; Agarwal, 2015). The value-based decisions on reimbursement of new diagnostic tests, contrary to drugs, is difficult to apply to diagnostic and prognostic tests, due to lack of evidence of directly improvement in patient outcome. Diagnostic tests rather improve physician's decisions on therapeutic strategies (Akhmetov, 2015a).

For a deeper analysis of the companion diagnostic (CDx) market, it should be divided in sales of kits/reagents and LDTs services. The test/kits reagents market size was of 405 million US$, while the LDTs sales reached the $1.17 billion, in the year 2011 making up to a global market of $1.57 billion. Despite this accounted for only 3% of the global IVD market of that year, represented one of the fastest growing segments (Agarwal, 2015).

The number of first time FDA pre-market approval (PMA) and human device exemption (HDE) approvals have increased by 43% between 2013 and 2014 and continue to increase in 2015 (Ernst & Young, 2015; EvaluateMedtech®, 2015). Simultaneously, the time from drug patent filing to approval dropped since the introduction of the FDA Breakthrough Therapy program, in 2012. Some drugs based of the CDx paradigm were approved within 4 years (e. g. Dabrefenib for BRAF-mutated melanoma) (IMS, 2016). Despite this trend, the access to new drugs is not universal, and in Europe, it is mainly limited by reimbursement decisions that vary considerable

on a national level. Ultimately, reimbursements decisions are decisive for market growth (IMS, 2016).

4. MEDICAL DEVICES DEVELOPMENT

4.1 Technology readiness level

Technology readiness level (TLRs) is a classification system developed by the National Aeronautics and Space Administration (NASA). The system was created to analyze the risks of projects based on innovative technologies (Mankins, 1995). Technology maturity steps are classified through 9 levels, the lower the maturity (lower level) of the technology the higher the risk of a project.

TRLs 1-3 are the concept stage: technology moves from basic to applied research and feasibility studies are conducted. For commercial purposes, technologies are considered unviable until they reach at least the TRL 3.

TRLs 4-5 are the validation stage: technology is developed and validated in a laboratorial setting.

TRLs 6-7 are the prototype demonstration phase: technology is tested in operational environments. This phase ends with a functional prototype tested in a relevant environment.

TRLs 8-9 are the testing, evaluation, and application phase: When the final system verification and validation takes place, technology is at TRL 9.

The US Department of Defense adapted the NASA TRLs system to technology-based medical devices. The medical devices TRLs integrate the FDA regulatory process steps (explained on ANNEX I), allowing comparisons between medical devices in developing process (Department of Defense, U.S.A, 2003):

- **TRL 1** - Initial Market Surveys are initiated and assessed. Potential scientific application to defined problems is articulated.
- **TRL 2** - Hypothesis are generated. Research plans and/or protocols are developed, peer reviewed, and approved.
- **TRL 3** - Initial proof-of-concept for device candidates is demonstrated in a limited number of laboratory models.
- **TRL 4** - Laboratory research to refine hypothesis and identify relevant parametric data required for technological assessment in a rigorous experimental design. Exploratory study of candidate devices or systems. The design history file, design review, and when required a master device record, are initiated to support either a Premarket Notification (510(k)) or PMA for Medical Devices (more information available on Annex I).

- **TRL 5 -** All critical system components are audited for current Good Manufacturing Practices (cGMP) (or ISO) and Quality System Inspection Technique (QSR) compliance. The design history file, design review, and any other device record are verified. Pre-Investigational Device Exemption (IDE) meeting held with CDRH for proposed Class III devices, and the IDE is prepared and submitted to CDRH. For a 510(k) application, identification of substantially equivalent devices and their classification is necessary. Validation of data and readiness for the cGMP inspection.
- **TRL 6 -** Clinical trials are conducted to demonstrate effectiveness of the Class III candidate medical device. Production technology demonstrated through production-scale cGMP plant qualification is developed. Manufacturing facilities should be ready for cGMP inspection. For 510(k), all documents should be updated and verified. The data from the initial clinical investigation demonstrating that the Class III device meets safety requirements and supports proceeding to clinical safety and effectiveness trials.
- **TRL 7 -** Clinical safety and effectiveness trials are conducted with a completely integrated Class III medical device prototype, in an operational environment. Functional testing is completed and confirmed. Clinical safety and effectiveness trials completed. Final product design validated, and final prototype and/or initial commercial scale device are produced. Data collected, presented, and discussed with CDRH in support of continued device development. For a 510(k), final prototype and/or initial commercial-scale device are produced and tested in an operational environment.
- **TRL 8 -** Implementation of clinical trial to evaluation of risk-benefit of using the device and to gather information for product labeling. Confirmation of QSR compliance, the design history file, design review, and other records, are completed and validated.
- 510(k) or PMA application submission and pre-PMA meeting with CDRH.
- **TRL 9 -** The medical device may be distributed and marketed. Post marketing studies continue and are designed after agreement with the FDA. Post marketing surveillance.
- The US Department of Defense (2003), emphasizes that for medical technologies, the risk reduction rate is not linear along the progression in the TRLs. Technology based projects risk remains high until very late stages of TRL, because FDA-seeking medical devices do not achieve significant risk reduction until clinical evidence is provided by clinical trials.

4.2 Technology development – "the Valley of Death"

To move small, R&D-intensive, technology-based projects to the market, entrepreneurs usually need to apply for several funding rounds (Fleming, 2015). Usually in the first phase, the most uncertain one – The Seed Stage (proof-of-concept construction) - the funding is provided by business angels, grants and subsidies from governmental and non-governmental institutions supporting technology development. As the project progresses, the next phase – The Early or Startup Stage (product development) – is characterized by a decrease in technological uncertainty, however a still high uncertainty about commercialization persists, mainly due to regulatory issues. In this phase venture capital is the most common source of funding (OECD, 2011).

The costs of advancing through the TRLs don't follow a linear scale. Advancing technologies beyond TRL 3-4 is referred to as the technology "valley of death" (red line in Figure 4), a period characterized by high technologic uncertainty, high developing costs and consequent lack of funding (Bauer and Millar, 2015).

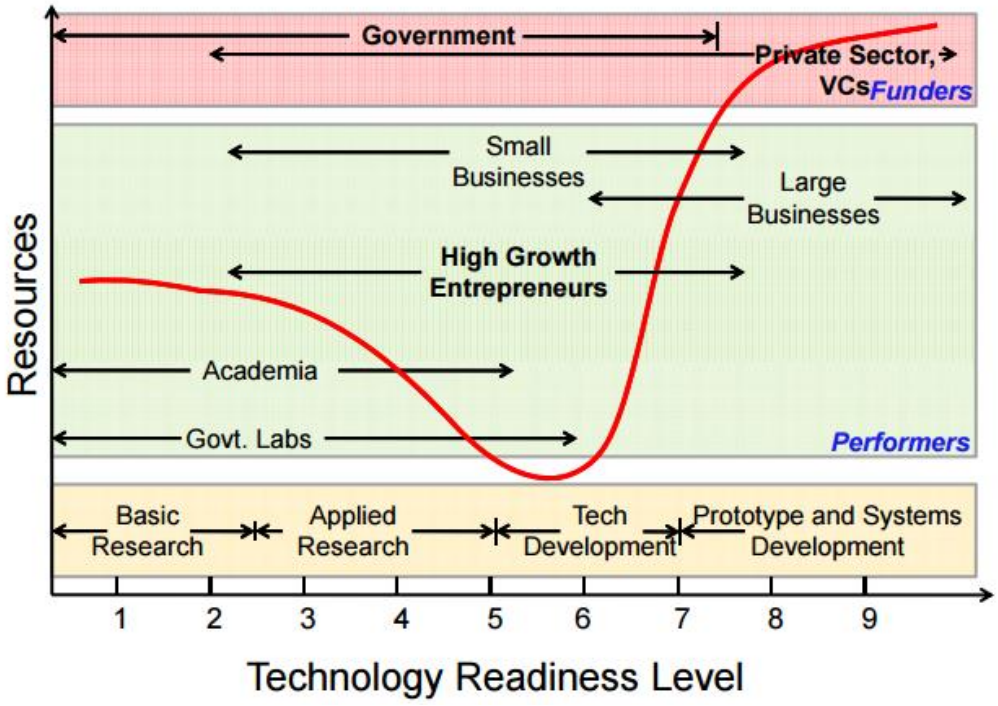

Figure 4: Technological and funding "Valley of Death".

Source: NASA, accessed on 21 September, 2016.

4.3 Modeling medical devices development

4.3.1 The Stage-Gate System

In 1990, Robert Cooper developed a tool for new product development management, the Stage-Gate System, claiming that the rate of innovation and shorter development cycle periods would be the key to keep or gain a competitive position in the market (Cooper, 1990).

The Stage-Gate System is a conceptual and an operational method that recognizes the new product development as a manageable process which is composed of a series of stages. Each stage has a set of recommended activities that can be used to collect information in order to reduce uncertainty about the new product. The stages are cross-functional and correspond to periods where teams develop parallel activities. Each stage is followed by a gate (Figure 5). Gates are decision points and quality checkpoints and where go or no go criteria is assessed. Gates should contain deliverables (results of the previous stage) to judge the project, and the output is a decision (Cooper, 2008).

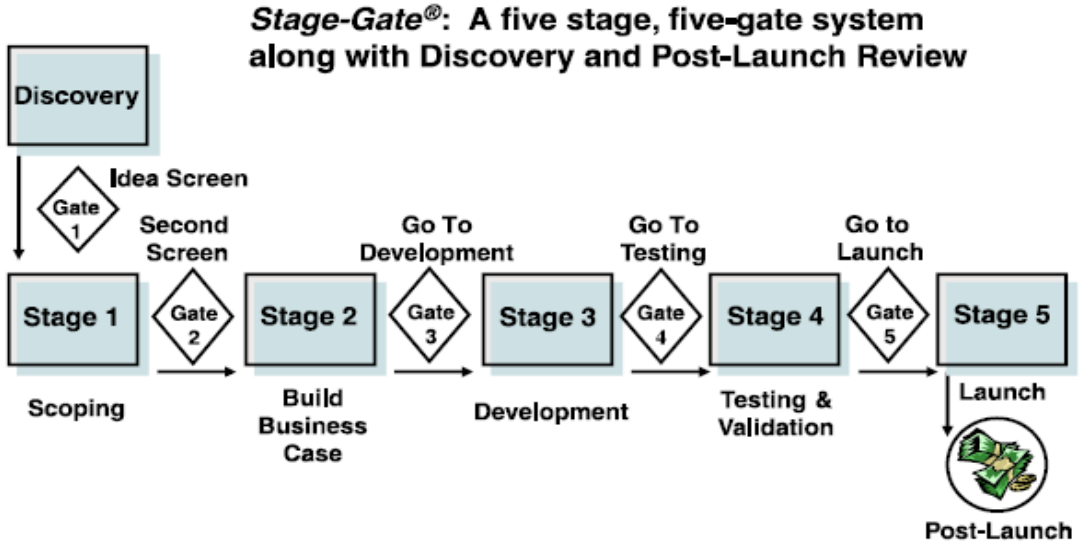

Figure 5: Cooper Stage-Gate System.

Source: Cooper (2008).

The Stage-gate System was adapted to medical devices development by Pietzsch *et al.* (2009), using FDA regulatory requirements to set stages and gates, applicable to medical devices with medium to high risk, e.g. that require a PMA application or 510 (k) clearance (See Annex I). Gate decisions for medical devices developers are suggested on Table 3.

The application of the Cooper's stage-gate system to the medical devices development gave rise to five major stages:

- **Stage 1: Initiation, opportunity, and risk analysis.**

- Analysis of market size, drivers, targetable clinical needs, product description, financial and development milestones, including regulatory and reimbursement strategies, manufacturing, distribution, sales and supply chain plans.

- **Stage 2: Formulation, concept, and feasibility.**

- Assemble of a multidisciplinary team and creation of a design plan (according to 21 CFR 820.30, FDA) and risk management plan, using Failure Modes, Effects, and Critically Analysis (FMEA/FMECA). Initiate design manufacturing.

- **Stage 3: Design, development, verification, and validation.**

- Verification and validation (V&V) tests results are documented for regulatory approval;

- Integration of user's input through the V&V;

- GMPs are fully integrated. Creation of a process validation plan: installation qualification (IQ), operational qualification (OQ), performance qualification (PQ), and product performance qualification (PPQ);

- Regulatory submission for investigational device exemption (IDE).

- **Stage 4: Final validation and product launch preparation.**

- Risk management system enters practice;

- Manufacturing and scaling activities are prepared;

- Sales preparation, including distribution channels;

- Product presentation in congresses and scientific publications (branding);

- Early adopters prepared for "limited market release";

- Regulatory and reimbursement plans completion;

- **Stage 5: Product launch and post-launch assessment.**

- Post-launch activities include post market surveillance and physician education.

Table 3: Decisions and achievements at gates.

Decisions at gates	
Gate 1	1) There is a market opportunity; 2) The market impact is determined; 3) Project risk from a regulatory and IP perspective is acceptable; 4) The device has an intended regulatory class defined; 5) The device is ready to transfer from concept to and active project (TRL3); 6) The device fits the company strategy.
Gate 2	1) Product development is ready to begin, based on user needs and design inputs; 2) The product offers costumer value; it is a viable sustainable product; 3) Technical feasibility is proven and optimized; 4) Manufacturing and value chain confidence has been assessed.
Gate 3	1) Design outputs satisfy requirements from design inputs; 2) Device has an acceptable design risk level; 3) Device can be developed from an IP perspective; there are no IP violations; 4) Design is frozen; 5) Device is ready for regulatory submission.
Gate 4	1) Validation testing shows that the device conforms to user needs & requirements; 2) Verification testing shows that design outputs satisfy design inputs; 3) device is ready and cleared for launch, from IP and regulatory perspective; 4) Design transfer complete: manufacturing specifications designed; 5) Process and design risk are acceptable (FMECA/FMEA); 6) Sales representatives equipped to sell product and LMR sites are defined; 7) Inventory levels are acceptable and launch quantities available.

Source: Pietzsch (2009).

4.3.2 Impact of regulations in medical devices development

Medical Technology is known as an industry where regulations are a major barrier to technologic innovation and successful market launch, and that the complexity of regulations has been compared to sectors like air space aviation (Santos, 2012; Medina, 2012; Engberg and Altman, 2015). Regulators, particularly FDA, is considered the first external factor affecting and influencing a company's ability to develop new products (Medina, 2012).

An in-depth case study of a large multinational medical device company evaluated the impact of regulations by each Pietzsch stage of product development, which are concentrated in phases II to III, shown on Figure 6 (Engberg and Altman, 2015).

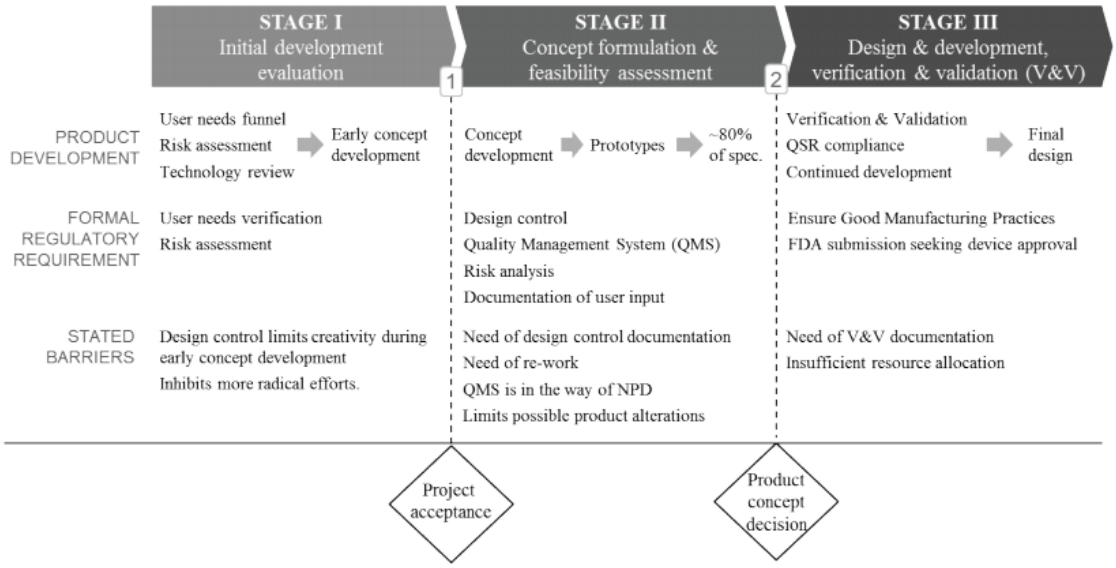

Figure 6: Regulatory requirements and stated barriers in medical devices development.

Source: Engberg and Altman, 2015.

Engberg and Altman (2015) identified four causes for the stated regulatory barriers and provided recommendations for managers, shown on Table 4.

User engagement in medical devices development cycle has the potential to reduce the time to market period and modifications required for approval (Ram, 2007). Human factors engineering processes are requirements of both European and FDA regulations (IEC 62366) and have been studied as an assisting method for manufacturers concerning usability and identification of medical needs (Martin and Barnett, 2012; Ram, 2007, Lissy, 2015, Jenkins and Draper, 2016).

Table 4: Perceived regulatory barriers to product development.

Cause 1: Impacting activities (mainly in stages II and III).
Recommendations: - continuous internal audits of regulatory compliance status and project documentation with presentation of the results to all projects members. This measure will detect early any lack of documentation, and avoid additional costs and rewriting later in the process; - avoid to let projects pass a decision point without the required regulatory groundwork; - ensure that only and all applicable QMS procedures as well as the design plan are compliant with regulations, until into Stage III. The development team should review design plans and relevant QMS procedures during development.
Cause 2: Limiting design choices (mainly impacts Stages I and II).
Recommendations: - developers should decide on the regulatory path only at the end of Stage I. - avoid limiting design choices.
Cause 3: Knowledge requirements (impact all stages).
Recommendations: - training and development of employees: development-oriented staff should acquire knowledge in terms of regulatory compliance; the regulatory and quality assurance staff should receive training in terms of technology innovation processes. - detail procedures that comply with regulations, being as lean as possible. - deep knowledge of the boundaries is necessary to avoid stricter than necessary control practices; this especially relevant during the development and implementation of the QMS. - build cross-functional teams able to view regulatory requirements as common sense practices.
Cause 4: Role assumptions and attitudes (impacts all stages).
Recommendations: - promote a quality culture, where employees accept regulations as a means to ensure safe and high-quality products. Everyone should know that quality is key and incentives are aligned accordingly. - build cross-functional teams with quality and development personnel in order to promote the quality culture. Be aware of shared assumptions formed during the low knowledge period.

Source: Engberg and Altman (2015).

Other authors (e.g., Santos, 2012; Mehta, 2008; Medina, 2012; Songkajorn and Thawesaengskulthai, 2014) developed comparable multiphase models for medical devices development, however, more visually complex and mostly without integration of regulations.

4.4 Lean strategies for startups

The Lean approach has its origins in the Toyota manufacturing environment in the 1940. Its main principle focus on elimination of any waste and to build a process flow restricted to what creates value for costumers (Jasti and Kodali, 2015; Khan, 2013). The ever-increasing pressure from customers and competitors drove the integration of lean principles across the whole value chain, starting from suppliers to the costumer delivering. This gave rise to the concept of Lean Enterprise (Jasti and Kodali, 2015). In recent years, there has been a growing interest on how lean principles could improve new product development and the lean concept evolved towards a higher focus on continuous and organizational learning. Kennedy (2008), introduced the "knowledge value stream", a concept that emphasizes how the knowledge acquired through the development process is used to develop products faster and efficiently (Kennedy, 2008; Lindlof, 2013).

The lean startup

Ries (2011) describes a startup as a team in search for a business model, by other words, a competitive way to create value for its future costumers, in uncertain conditions. For Ries (2011), waste is anything that delays or inhibits the team from learning about how to deliver value to its customers. The goal of a startup is to figure out their business model: what is the product that customers want and will pay for, in the faster way possible (Blank, 2013). It is well known that between 7 to 9 in each 10 startups fail into enter the market, in 42% of the cases, due to failure in developing a marketable product (Kiznyte, 2016; Blank, 2013).

According to Ries (2011), startups inherent risk results from:

- Costs incurred before establishment of the first customers and the risk of developing inadequate products;
- Long technology development cycles;
- The limited number of venture capitalist accepting the risks of a startup;
- Lack of specialized expertise in how to build and manage startups.

The lean approach was created to make startups less risky by focusing on costumers needs and by modeling the new product development to shorter and reduced cost of development cycle (Ries, 2011).

In practical terms, to build a lean startup is the introduction of simple concepts and tools in management practices (Blank, 2013; Ries, 2011):

- **The Business model on canvas** (available on Annex III) is a visual representation of the project that facilities intra and inter communication and problem diagnosis;
- **Costumer development.** By launching sequential “minimum viable products” (MVP), which is a simplified version of the product under development, which is made available for early adopters and will produce a continuous customer feedback. Continuous customer feedback is introduced in the development of pivot new alternatives and improvements;
- **Agile development**. Requirements and solutions evolve iteratively through the collaboration of cross-functional teams.
- **Validated learning.** This is the progress measure unit for lean startups. Validated learning means that only learning that translates into better company metrics are valid, since they create value for costumers.

5. BREAST CANCER

5.1 Breast cancer epidemiology

Breast cancer (BC) is the 2nd most common cancer in the world and the most frequent cancer among women both in developed and less developed regions (Globocan 2012).

Globocan 2012, estimates that 1,67 million new breast cancer cases were diagnosed in 2012, representing 25% of all cancer diagnosis. World incidence rates are increasing with estimated 1,98 million new cases in 2020.

The BC estimated age-adjusted incidence in European Union (27) is of 106,6 per 100 000 in 2012 (EUCAN, accessed on 14 August, 2016). In USA, in 2015, there were 231 840 new invasive BC cases and 40 290 women died from BC (American Cancer Society, 2015). European and USA incidence rates are still increasing mainly due to mammographic screening and population ageing. In 2020, the number of new cases is expected to reach 388 893 in Europe and 266 358 in USA (SEER, assessed on 14 April, 2016).

In the western world, effective screening programs and therapeutic innovation lead to improved outcomes that significantly reduced the mortality rates (5-year survival above 85%). Higher incidence and lower mortality, in turn, led to higher prevalence of the disease. In 2012, there were an estimated 2 975 314 women living with breast cancer, in the USA (American Cancer Society, 2015). The estimated 5-year prevalence of breast cancer in Europe in 2012 was 1 814 572 cases (EUCAN, accessed on 14 April, 2016).

5.2 Clinical pathway and diagnostic test performance

Clinical pathways are descriptions of the most consensual process of treatment and monitoring of a medical condition, and are supported by evidence. The clinical pathway is a roadmap that links tests to health and other outcomes. The clinical pathway therefore plays a central role when evaluating a new test impact in a medical condition (NICE).

The clinical pathway for BC, in UK, is defined by NICE and is globally taken as a reference for clinical practice (NICE, accessed on 13 August, 2016).

The breast cancer clinical pathway in UK is in Figure 7.

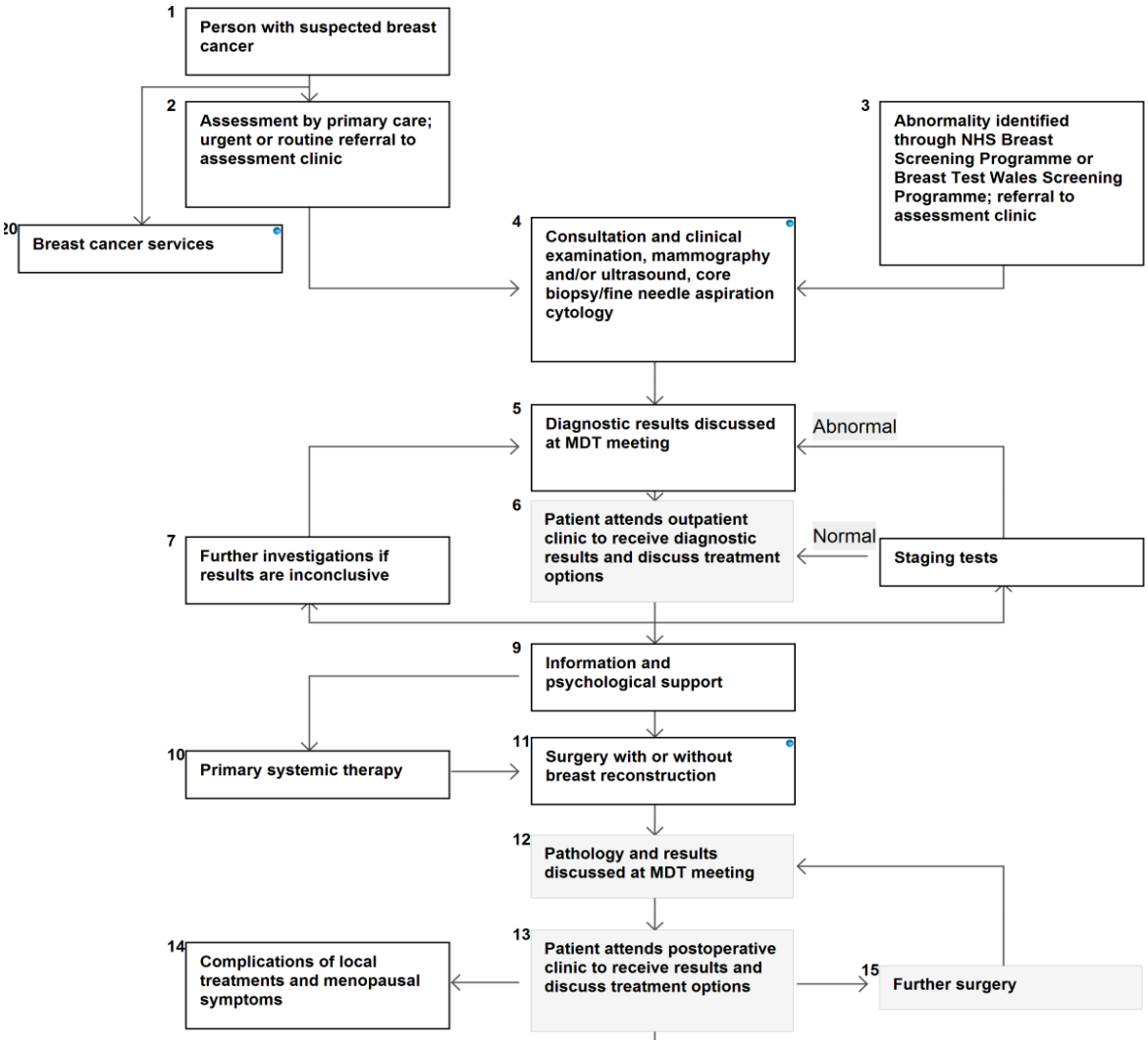

Figure 7: Breast cancer clinical pathway.

Source: Adapted from NICE, accessed on 16 August, 2016.

In the 4th and 12th steps of the BC clinical pathway, diagnostic tests are performed, to inform further management strategies. Outcomes for those treatment decisions should be the endpoints to evaluate the efficiency and benefit from corresponding diagnostic tests.

5.3 Breast Cancer subtyping

The molecular characterization of BC subtypes is the foundation for the PM approach to BC treatment. By predicting response to treatment and risk of recurrence, molecular subtypes merit inclusion in international guidelines for breast cancer treatment. Although various subtype

classifiers have been developed (Sorlie, 2001; Perou, 2000), the different classifiers generally agree on a taxonomy of breast cancer, reinforcing its robustness, and typically dividing invasive BC in four subtypes: Luminal A, Luminal B, HER2-enriched, Triple negative or Basal-like (Bianchini, 2016).

For logistic and financial reasons, a genomic analysis is not offered in the clinical practice and surrogate approaches have been developed using more simple and cheaper IVD tests, such as IHC and ISH. Influential clinical practice guidelines (promulgated by the National Cancer Center Network (NCCN), the American Society of Clinical Oncologists (ASCO) and St. Gallen International Expert Consensus) support that these subtypes are defined by the detection of expression of certain proteins that are considered "drivers" or biomarkers of the disease and that can predict response to therapy (Senkus, 2015). BC subtyping is based on biomarkers presented on Table 5.

A cancer biomarker is any molecule such as DNA, RNA, or proteins that is present in tumor tissue or blood (Biomarkers Definitions Working Group, 2001). Biomarkers can be classified according to their usefulness (Ziegler, 2011):

- **Prognostic biomarker** is a biomarker that predicts the likely course of disease in a defined clinical population under standard treatment conditions.
- **Predictive biomarker** is a biomarker that forecasts the likely response to treatment. Treatment response may be measured either as efficacy or as safety.

Breast cancer biomarkers are both predictive and prognostic, as shown in Table 5.

Table 5: Biomarkers in use for breast cancer subtype.

Biomarker	Biomarker purpose	Information provided
Estrogen receptor (ER)	Predictive Prognostic	Tumor responsiveness to endocrine therapy
Progesterone Receptor (PR)	Predictive Prognostic	Tumor responsiveness to endocrine therapy
HER2	Predictive Prognostic	Response to treatment with anti-HER2 agents
Ki67	Prognostic (ratio)	Chemotherapy if high ratio

Source: Adapted from St. Gallen Consensus Paper (2015).

Currently, the BC subtypes Luminal A, Luminal B, HER2 positive and TNBC are defined by the combined result of IHC tests for each biomarker, complemented with ISH tests when necessary, as shown on Table 6 (Senkus, 2015).

Table 6: Breast cancer subtypes based on biomarkers.

BC subtypes	**Biomarker profile (IHC test)**	**Treatment**
Luminal A	ER and PR positive	Hormone therapy (targeted therapy)
Luminal B	ER positive; Ki67 high ER and HER2 positive	Hormone therapy (targeted therapy) + CHT Hormone therapy + anti-HER2 (targeted therapy)
HER2	HER2 positive (ER and PR negative)	Anti-HER2 agents (targeted therapy) + CHT
TNBC*	ER, PR and HER2 negative	CHT (lack of targeted therapy)
CHT – Chemotherapy.		

Source: Adapted from St. Gallen Consensus Paper (2015).

Current techniques employed in clinical laboratories as companion diagnostics are the following:

- **Immunohistochemistry (IHC):** Uses antibodies to detect proteins in tissues. Has the advantage to combine morphologic and protein expression directly in cancer cells, and allows for semi-quantitative analysis. Partially automated technique, validated *in-house* and sensitive to multiples critical factors along the sampling to report pathway (De Matos, 2010);
- ***In situ* hybridization (ISH):** this technique unfolds DNA strands and uses a probe labeled (with fluorescent or silver) DNA strand that hybridizes with the target, complementary sequence and thereby identifies and quantifies the target sequence in the cell nuclei of interest in the tumor sample.
- **Microarrays and sequencing**: these technologies simultaneously measure RNA, cDNA, or DNA SNP (single nucleotide polymorphisms), or genome regions.

In BC clinical practice IHC and ISH are the current leading techniques. Their main advantages are the low price per test and the availability of required resources in the large majority of

hospital laboratories. These techniques have several recognized limitations described in Table 7.

Table 7: Limitations of current IVD CDx.

Immunohistochemistry	**In situ hybridization**
Factors affecting analytical validity: – Pre-laboratorial variable conditions – Intra-laboratorial techniques and consumables – Multiple suppliers – Only partial automation – Different cut-off values used Formalin fixation can affect IHC	**Factors affecting analytical validity:** – Pre-laboratorial variable conditions – Only partial automation – Different cut-off values used – Requires skilled and trained technicians Requires specific equipment only available in reference centers
Factors affecting clinical validity: – Subjective interpretation criteria – Interobserver variability Reporting accuracy	**Factors affecting clinical validity:** – Subjective interpretation criteria – Interobserver variability Reporting accuracy

Source: Wolf (2014); Gheybi (2016); De Matos (2010); Edith (2014).

HTP technologies (NGS and GEP) have been claimed to meet the requirements gap of the current tests, but regulations and affordability are still important barriers. Several adoption factors for IVDs based on HTP technologies were identified by Pant (2014): higher data quality; shorter turn-around-time (TAT); lower cost per sample (multiplexing reduces costs with reagents and consumables); lower operator dependency; sample multiplexing capability; small sample required; targeted panel (possibility to create a customable or patient-tailored panel).

5.2.1 BC subtyping turn-around-time (TAT)

Currently, the TAT for BC diagnosis and subtyping requires a minimum of 4 to 5 days (shown on Figure 8). The pathologic assessment (microscopic examination) is performed before the IVD ordering, and guides IHC and ISH tests ordering. IHC test requires at least one working day to be available for interpretation. Most of the IHC are performed in semi-automated platforms, in overnight runs. When IHC results are imprecise for HER2 status, ISH tests are ordered, adding additional days to the TAT.

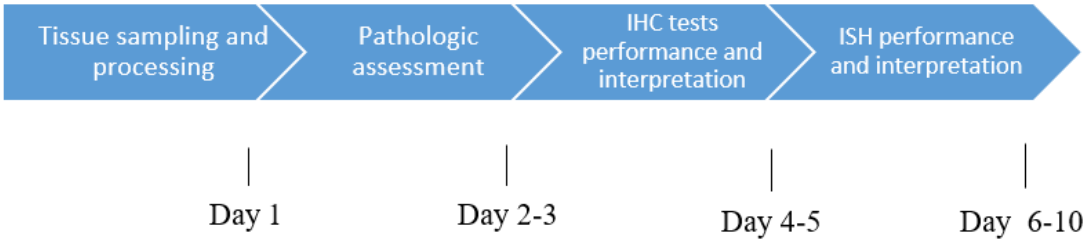

Figure 8: Current TAT in BC diagnosis and subtyping.

5.2.2 IHC and ISH testing costs

Both IHC and ISH costs are highly variable across European countries. ISH costs, including reagents and personnel, vary from 220€ in NHS (UK) to 495€ in Netherlands, and can vary significantly in the same country (e.g in Germany it costs 257€, in public health institutions and 398€, by private health insurance) (Vogler, 2013). The cost of IHC test, including IVD reagents and personnel costs, by 2006, varied from 103€, in UK, to 190€ in Ireland and between public and private settings (Enzing, 2006).

5.2.3 IVDMIA tests for breast cancer

Several IVDMIA tests were recently made available to be used as prognostic and/or predictive tests to complement the subtyping assessment, and to predict the benefit of adjuvant chemotherapy, namely: OncotypeDx (Genomic Health); Prosigna (Nanostring); Mammaprint and Blueprint (Agendia); Mammastrat (Clarient Diagnostic Services) and Endopredict (Syvidion).

These tests are approved for patients with early-stage BC and only for those that are ER-positive. Is it estimated that 15% of these patients have no benefit from chemotherapy. The main aim of those tests is to identify those 15% of patients that have no benefit and to avoid their exposure to the potentially life-threatening chemotherapy associated. Until recently, the IHC test for the Ki-67 biomarker, was used to decide whether a patient should or not receive additional chemotherapy, but the analytical validity of Ki-67 has been proven to be significantly lower than molecular testing (Prat, 2013; Nielsen, 2010). None of those tests are CDx, since any is able predict response to any particular drug, instead, their results can support clinical decisions on treatment course (Myers, 2016).

5.4 Triple negative breast cancer (TNBC) subtyping

TNBC comprehends 15 to 20% of all invasive BC and encompasses a heterogeneous group of aggressive and poor prognosis BC cases (Yasdav, 2015; Le Du, 2015; Lehmann, 2015). This group is labelled as "triple-negative" because their tumors have no expression of ER, PR nor HER2 amplification, as assessed by IHC and ISH, and consequently do not respond to any targeted therapy clinically approved so far (Lehmann, 2015). TNBC primary treatment is still based on traditional chemotherapy, followed by surgery if indicated. Patients with TNBC who achieve complete pathologic response[1] after neoadjuvant chemotherapy (pre-operatory chemotherapy) have significantly better overall survival (Ring, 2016; Le Du and Ueno, 2015; Lehmann, 2015). However, between 60 to 70% of TNBC patients do not respond completely to chemotherapy regimens (Bianchini, 2016), and consequently have high risk of relapse and shorter overall survival (Crown, 2012). TNBC patients have a 5-year recurrence rate of 30% (Ring, 2016). The rate of recurrence and metastasis is higher in the first 3 years after diagnosis (Liedtke, 2008).

Due to its worse prognosis and lack of targeted therapy, an accurate diagnosis is of utmost importance and depends on the exclusion of the expression of ER, PR and HER2 amplification by IHC and ISH. Those techniques are known to be subject to significant pre-analytical, analytical and post-analytical variability, and despite the criteria standardization efforts (Wolf, 2013; Hammond, 2010) discrepancy of the results between laboratories persist (Bianchini, 2016).

To employ a personalized therapeutic approach, a characterization of specific biomarkers for this TNBC subtype are needed. Such biomarkers will allow novel targeted therapies to be used on specific TNBC patient subpopulations to ensure the greatest therapeutic benefit along with reduced side effects (Crown, 2012; Lehamnn, 2015; Bianchini,2016). Currently, there is no clinically approved molecular characterization tool for TNBC (Ring, 2016).

Due to high molecular diversity TNBC subtyping is necessary to better identify molecular-based therapies and several classifications have been already proposed (Bianchini, 2016). A research team from Vanderbilt University pooled gene expression data from 21 breast cancer data sets and 587 TNBC cases were selected by filtering estrogen receptor (ER), progesterone

[1] Pathologic complete response: means absence of viable cancer cells detectable by pathologic assessment of the specimen obtained by surgery, after chemotherapy. The specimen is the part or total breast tissue and might include axillary lymph nodes.

receptor (PR), and HER2 based on mRNA expression. Using hierarchical clustering, six TNBC molecular subtypes were identified, including two basal-like (BL-1 and BL-2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem-like (MSL), and luminal androgen receptor (LAR) subtype. The TNBC subtyping gene signature is now licensed by Insight Genetics, a company that intends to starting sales of the tests, as an LDT, by the end of 2016. Clinical trials are now ongoing to further assess specific therapeutics within these distinct TNBC subtypes (Lehman et al, 2011).

Drug developers have already recognized that TNBC represents a major unmet need. There are several new drugs in the late-stage pipeline that are expected to have high efficacy in specific subsets of TNBC patients who carry BRCA mutations or BRCAness mutational phenotype (Syed, 2014). This also underlines the clinical need for tests able to select the right patients for clinical trials and in clinical practice. In November 2015, there were 170 active pharmaceuticalcologic interventional clinical trials in TNBC, see Figure 9 (Bianchini, 2016).

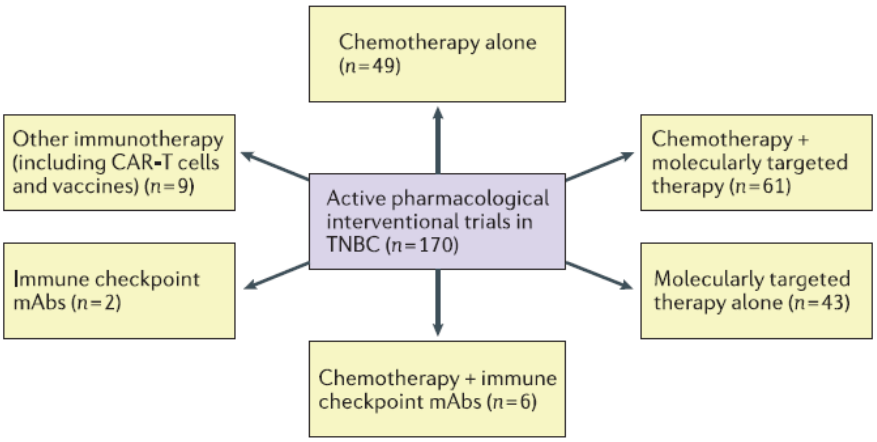

Figure 9: TNBC pharmacologic trials running in 2015.

Up to 90% of TNBC that persist after chemotherapy contain genetic alterations in molecular pathways that can be targeted with therapeutic agents already in clinical investigation (Bianchini, 2016).

6. MACROENVIRONMENTAL ANALYSIS

6.1 PEST analysis - Germany

"Scanning the Business Environment", a book of Francis Aguilar, dates back from 1967 and is the first reference to the usefulness of environment screening as a technique for strategic business planning (Costa, 1995). The author proposed that four environment factors should provide information to analyze the long-term prospects of a firm: Economic, Technical, Political, and Social, giving rise to the ETPS acronym (Aguilar, 1967). Subsequently, other authors reinforced the importance of the macro-environment analysis for business planning, (Fahey and King, 1977; Kefalas and Schoderbeck, 1973; Thomas, 1974; Fahey and Wokutch, 1983; Hambrick, 1981, Stubbart, 1982, Fahey and Narayanan 1986) and expanded the initial taxonomy to add other factors such as demographic, legal, and ecologic that resulted in the current use of different acronyms: PEST, STEP or PESTLE (Morrison, Renfro, and Boucher, 1984).

The purpose of the PEST analysis was summarized by Costa (1995):

- Awareness and understanding of events and trends in the external environment;
- Establishing relationships between them;
- Extract the main implications for decision making and strategy development.

Despite the globalization trend, firm's competitiveness is known to be modulated by their location country. Moreover, nation competitiveness helps to predict where potential competitors are and will appear, and supports decisions on where to locate company's activities (Serra, 2012).

The following PEST analysis explores how the location in Munich, Germany, and particularly in the Munich biotechnology cluster will influence DEOXY Technologies development.

Information was collected from Official German governmental websites (Germany Trade and Invest (GTAI)), OECD, non-governmental Medical technology industry associations and Cancer non-profit and research organizations. Economic data was also collected from World Bank and complemented with international journal articles and published CEO interviews from life science's industry.

6.1.1 Political and legal factors

Comeback time (2015) considered Germany as one of the most attractive countries for business locations in the world. Worldwide renowned by its stable economic, legal and political frameworks, Germany provides the necessary security for business investments, even in nowadays economically challenging times (GTAI, Medical Technology Industry, 2015).

The World Bank Group report: Doing business 2016: Measuring Regulatory Quality and Efficiency, ranked Germany as the 15th easiest economy to do business by benchmarking the scores of 189 economies.

In an attempt to reinforce the competitive economic position through technological innovation, in 2006, the German government launched the High-Tech Strategy program, an initiative that as the purpose of advancing new technologies and bring them to the market in shorter time. Around 4 billion € have been invested each year, in the development of new technologies through financial support to R&D projects in the form of grants. The Leading-Edge Cluster Competition, was launched in 2007, as part of the High-Tech strategy and each winner receives up to 40 million € in funding, over a period of 5 years. The initiative contributed to launch 40 business startups (GTAI, R&D grants, 2015).

The "Gründungsoffensive Biotechnologie" (GO-Bio), launched in 2005 by the German government, is a grant to stimulate start-up activities in biotechnology. The GO-Bio funding is intended to support validation (proof-of-concept) research of early marketable ideas that do not fulfill the high standards of technological validation required by venture capitalists. Startup teams from the life sciences intending to found a company are potential candidates for GO-Bio funding, which covers a maximum of two to three-year periods. Applying inventors are encouraged to think how they want to market their ideas. The 39 funded projects are mainly focused on development of new drugs or services for pharmaceutical industry (Bundesministerium für Bildung und Forschung, 2016).

The "INVEST Zuschuss für WagnisKapital" is an assistance measure created on 15th May, 2013, by the "Bundesamt für Wirtschaft und Ausfuhrkontrolle" (BAFA) an authority subordinated to the German Federal Ministry for Economic Affairs and Energy to provide young, innovative companies with more sustainable access to capital. This initiate makes the entrepreneurs grant application available for business angels to offer 20% of the value of the new company investment by up to 25 % of its shares (GmbH - limited liability company or AG - stock corporation). Grants may also be provided for investments for new companies pending startup (BAFA, 2016).

In 2007, the German Federal Ministry for Economic Affairs and Energy launched an R&D project funding initiative for SMEs the "KMU-innovativ". The program aims to promote technology-related research in the fields of biotechnology, medical equipment, information and communications technologies, nanotechnology, among others, by offering 60 to 70% of the R&D associated costs. The "KMU-innovativ" includes financial support and liaison service that aids with the grant application. The basic requisite for funding is that the firm is already operationally active and able to afford its obligatory share of the financing without jeopardizing the operating business (BMBF, 2010; Förderung kleiner und mittelständischer Unternehmen in der Biotechnologie).

The BMWi created the program EXIST for Startups, which intends to support universities, young researchers and students to develop knowledge-based startups projects. The EXIST includes 3 lines of funding: for universities; seed grants for innovative startups and translational research (idea viability) for startups

Other awards available in the BioM4 Cluster are the BioM4 award of 500 000 € for promising biotechnology startup projects and the Medical Valley award of up to 1 500 000 €. The Bonn biotechnology cluster also has a project incubator: Life sciences incubator – Bonn, that offers laboratory place and funding for company shares (Medical Valley, accessed on 4 September, 2016).

The Bundesministerium für Bildung und Forschung (German ministry for education and science) created the Validierungsföerderung grants up to 300 000 € for validation studies of potential new products (Bundesministerium für Bildung und Forschung, accessed on 16 September, 2016).

For companies located in Bayer, the Bayern Kapital GmbH, a subsidiary of the LfA Foerderbank Bayern (Bavaria development bank), makes financing available for R&D, product market launch, diversification and expansion of the market share.

The High-Tech Gründerfonds (HTGF) is another German seed stage investor. The HTGF finance technology-driven companies active in the fields of robotics, drugs, chemical processes or new software, by offering grants of 500 000€ for 15% of the company shares (high-tech-gruenderfonds, accessed on 13 September, 2016).

Germany shares the legal framework of the European Economic Area (EEA), this means that the European Directives regarding the manufacturing of IVD medical devices are applicable: 3TG, RoSH II, REACH, WEEEII, and packaging directive, which are detailed in the next chapter.

6.1.2 Economic factors

The German tax burden for corporations is around 30%, varying up to 8% according to municipalities, which makes the overall tax rate on average 22,83%. German tax system is considered competitive among high industrialized countries (GTAI, Medical Technology Industry, 2015; Deloite, Highlights of Germany, 2016).

The German inflation rate has been decreasing from 2,1% in 2012 to 0,8% in 2014 (Ellermann, 2015). The refugee migration is a new challenge for economic policy. Germany is projecting to spend an additional 0.5% of GDP per annum in 2016 and 2017 to meet initial needs of the immigrants and to integrate them in the labor market (OECD, Migration Policy Debates, 2015).

Beyond the governmental sources of investors, there is global increasing presence of strategic investors in small medical technology companies, namely large medical technology companies such as: Medtronic, Abbot, Johnson & Johnson and large pharmaceutical companies: Roche Venture Fund, Novartis Venture Fund, Merck Global Health Innovation, Pfizer Ventures, GlaxoSmithKline's SR. In Europe and USA, a record number of medical technology companies went on IPO's between June 2014 and June 2015 (Ernst & Young, Beyond Borders, 2015).

6.1.3 Geographical and logistic factors

Germany has strategic central location in Europe, which enables the country to be an ideal distributor of services and products (GTAI, Medical technology Industry, 2015; GTAI, Economic Overview Germany, 2015). The nation is recognized as a "logistic hub", as demonstrated by the annual revenues of nearly 230€ billion, more than France and UK, the second and third European largest logistics revenues, combined (GTAI, Economic overview Germany, 2015). The German manufacturers have the benefits of a multimodality transportation infrastructure that was on the 1st position by World Bank Logistics Performance Index (2014). The infrastructure includes a dense highway system; a high-speed railway network, sea and inland waterways with some large ports as Hamburg and Bremerhaven, a relevant network of airports with 21 international airports (GTAI, Economic Overview Germany, 2015). Trade between Germany and UK is facilitated by short distances and multimodal transportation available: less than 2 hours by flight, 6 hours by train, less than 12 hours by truck and the possibility to use seaports as trading conduit (GTAI, Economic Overview Germany, 2015).

6.1.4 Social factors

Germany has the lowest European rate of labor cost growth and the unit labor costs decreased by a yearly average of 0.3%, between 2004 and 2013 (GTAI, Medical Technology Industry, 2015). The country also has a pool of highly qualified human resources with 33% of the university students in the sciences, mathematics, computer sciences and engineering. A ratio of 328:1 000 000 PhD graduates in the population and the fact that 21% of the European researchers are living in Germany ensures the availability of highly specialized workers (GTAI, Medical technology, 2015).

6.1.5 Technologic factors (and related supporting industries)

The German industry of around 3.7 million companies is 99.6% composed of SMEs and the German Medical Technology industry is no exception. According to the German Medical Technology Association (BVMED), in 2015, 95% of the 11.000 medical technology firms were SMEs with less than 250 employees each, mainly focused on niche markets. The Medical Technology industry employs around 195,000 people in over 12,000 companies in Germany. Export markets represent around two thirds of the German company's sales and grew nearly 7% in 2012 to more than 15€ billion. Europe is the destiny of the largest share of German medical technology exported products, accounting for 37% (BVMED, 2016; GTAI Medical Technology Industry, 2015).

Medical technology "made in Germany" is highly valued around the world and is seen as seal of quality (Ernst & Young, 2015; BVMED, Annual Report, 2015). The German disciplined management system was recognized by Porter (1990) for its successful application in technical and engineering-oriented industries that require the precision manufacturing and careful product development of complex products.

The total R&D expenditure in Germany was of almost 90 billion €, in 2013, making Germany the Europe's biggest research investor (Laskaw, 2015).

Porter (1990) considers that "home-based related and supporting industries provide innovation and upgrading, an advantage based on close working relationships". Most German Medical biotechnology is belongs to the industry segment that develops drugs and diagnostic tests, and so are complementary and potential alliance partners to medical technology firms focused on molecular diagnosis. There are 385 medical biotechnology companies in Germany, being a very dynamic and growing industry sector alongside with the general biotechnology segment (GTAI, Medical Technology, 2014)

Industry Clusters

The success of biotechnology and medical technology industry in Germany is based on strong and efficient cooperation between industry, universities, research institutions, policy makers (e.g., national and local authorities), clinical networks and investors, which make up the entire value chain from research to market. This regional concentration of players defines the known German bioregions, the biotechnology clusters. In Germany, there is a national network of more than 30 clusters focusing on medical technology. Each bioregion specializes in a particular area. Bioregions also include bioparks with laboratory space and rooms for startups and early established companies (GTAI, Medical technology clusters in Germany, 2015; Segers, 2016).

A longitudinal study based on 977 German biotechnology firms, between 1996 and 2012 corroborated the hypothesis that industry clusters support the new entrants in the internationalization process, through formal network relations and imitation processes between peers (Oehme and Bort, 2015).

Bavaria is home of a leading biotechnology cluster in Germany – Cluster Biotechnology Bavaria. In the Greater Munich, the biotechnology industry is concentrated in the Munich Biotech Cluster M^4 which rents the IZB laboratorial spaces in Martinsried, Munich and integrates The Medical valley, a leader cluster in medical technology. Two thirds of the companies are SMEs, most of them spin-offs from academic institutions such as Ludwig Maximilians-Universität (LMU), Technisches Universität München (TUM) and the Max Planck Institutes (MPI) also located inside the cluster (Biotech Bavaria, 2016; Bio^{M4}, 2016). Bio^{M4} is a non-profit organization, funded by the Bavarian State Ministry of Economic Affair and is focused on Personalized Medicine and Targeted Therapies. The Bio^{M4} Biotech Cluster Development - GmbH is responsible for the management of the Bavarian Biotechnology Cluster.

The results from PEST analysis are summarized in Table 8.

Table 8: PEST analysis systematization - Germany.

PEST identified factors		**Relevance**	**Impact**
Political	Multiple public grant programs High business attractiveness Applies European regulations	High Moderate Moderate	Positive
Economic	Stable and growing economy Available investors and Bank financing for R&D dependent companies	Moderate High	Positive
Social and Demographic	Available specialized workers High quality logistic infrastructure	High High	Positive
Technological	Network of biotechnology clusters Supporting industries are highly active	High High	Positive

6.2 PEST analysis - United Kingdom

This business plan explores UK, starting by England as the first targeted market for DEOXY Technologies molecular diagnostic products.

To perform the PEST analysis, information collection was based on Official governmental websites from United Kingdom, non-governmental medical technology industry associations and cancer non-profit and research focused organizations. Economic data was mainly collected from World Bank and complementary information was collected in international journal articles.

6.2.1 Politico-Legal factors

UK is one of the most successful nations in terms of the application of law, control of corruption, government effectiveness, and regulatory quality (Index of Economic Freedom, 2016). The World Bank report, Doing Business indicators for 2015, ranked UK as one of the highest levels of GDP per capita in terms of purchasing power parity and is the 6th best country in the world in terms of doing business (World Bank, 2015).

UK and Germany are both members of the European Economic Area and the trading between them benefits from the freedom of movement according to the EEA agreement (EFTA, 2016). Euro-skepticism have been on rise in UK, on past 23th June, 2016, the UK government referendum on EU membership result was in favor of leaving European Union. Currently, there are no new established trade agreements between Europe and UK. UK is a relevant economic partner for Germany, as shown by the 2015 Ranking of Germany's trading partners in Foreign Trade: UK ranked 3th on export destinations of German product and 2nd in total trade balance between the 2 countries with a positive result of 50 958 619.000€ favoring Germany (Statistisches Bundesamt/Federal Statistical Office, 2016).

In UK, there is a national publicly-funded healthcare system - the National Health Service (NHS). The NHS is primarily funded through the taxation system and is under supervision by the UK Department of Health. Every legal UK resident has access to NHS services, and most of the services are provided for free, being considered as merit goods.

The share of healthcare expenditure of the public sector in UK, in 2013, was of 83,3%, higher than most other member states of the OECD, which spent on average 71,8% of their public funding in healthcare services (Office for National Statistics, 2015). Since the largest majority of healthcare services and products in UK are provided by the NHS, the UK Government (represented by the Department of Health) is the practically the “only buyer” of healthcare

products. Economically this situation in defined as a market monopsony. In monopsony markets, buyers exert strong pressure on price control.

The NHS has a unique supply chain organization whose major objective is to benefit of NHS trusts, hospitals and other healthcare organizations. The NHS Supply Chain organization negotiates national contracts for products and services that are strategically critical to the NHS and simultaneously, ensures implementation of the NHS plan, for the implementation of the New Opportunities Fund (allocation of £93 million to cancer prevention, detection, treatment and care). NHS articulates with NICE to ensure that the purchasing and supply contracts are according to any guidance issued to the health service (Government Opportunities, 2016).

Regulations in UK (and Europe)

In UK, medical devices are regulated by the following EU Directives (European Commission):

- European Council Directive 93/42/EEC - covers most of the medical devices;
- European Council Directive 90/385/EEC on active implantable medical devices:
- European Council Directive 98/79/EC on *in vitro* diagnostic medical devices.

Other European Directives applicable to medical devices, including IVDs are:

- **WEEE II (for Waste Electrical and Electronic Equipment II)** is the European Directive (2012/19/EC). This directive intends to increase recycling of and reduce waste from electrical and electronic equipment. Under WEEE II, EU Member States must achieve collection rates of 45% beginning in 2016 and collection rates of 65% by 2019. All categories of electrical and electronic equipment, including medical devices and *in vitro* medical devices, are subject to WEEE II recovery targets, since 2012.
- **RoHS for Restricted Hazardous Substances in Medical Devices**, is the Directive 2011/65/EU as of 8 June 2011, also known as RoHS II. IVD medical devices are required to comply with hazardous substances restrictions, since 22 July 2016. This directive restricted the use of the six chemicals lead, cadmium, mercury, and hexavalent chromium, as well as flame retardants poly-brominated biphenyls (PBBs) and poly-brominated diphenyl ethers (PBDEs). The RoHS Directive forces manufacturers to replace these chemicals in their products by less hazardous substances.
- **REACH for Registration, Evaluation, Authorization and Restriction of Chemicals**, is the European Regulation 1907/2006/EC. Applied since 1 June, 2007. REACH applies to substances manufactured or imported into the Europe area in quantities above or equal to 1 ton per year

- Packaging and Packaging Waste Directive, 94/62/EC, applies to all packaging used to bring medical and IVD medical devices to market, including all the retail pack and transit packaging. The directive restricts the use of heavy metals such as cadmium, lead, mercury, and hexavalent chromium and any combination of these heavy metals must not exceed 100ppm or 0.01% by weight of the packaging item.

Patent protection in UK has been a result of the fully implementation and harmonization of the European Directive on the Legal Protection of Biotechnological Inventions 98/44/EC.

These and other European directives are currently transposed to each national law of the European countries. However, negotiations between UK and Europe, following the "Brexit" referendum can potentially change the regulatory landscape.

The CE Marking system

The letters "CE" derived from the French *Conformité Européene* which means "European Conformity". CE mark was officially stablished in the Directive 93/68/EEC in 1993. "CE Marking" is now used in all EU official documents (European Commission, accessed on 13 August, 2016). Any medical device intended for sale in EU/EFTA, including Turkey must bear a CE marking before it can be sold or put into service. The CE marking is affixed to indicate conformity with the essential health and safety requirements set out in the respective European Directives (European Commission, accessed on 13 August, 2016).

The regulatory responsibility is assigned to three organizations: competent authorities (CA), manufacturers, and notified bodies (NB), which are third party certification organizations (European Commission, accessed on 13 August, 2016).

After being contacted by the manufacturer or distributor, the CA reports to the Minister of Health in the member state. The CA ensures that the requirements of the Medical Device Directives are applied according to each member state National Law. CAs are also responsible for the surveillance of medical devices on sale, in their member state, and the evaluation of adverse events (European Commission, accessed on 13 August, 2016).

The New Approach Notified and Designated Organizations (NANDO), a web site from the European Commission contains the list of Notified bodies, and defines notification as the "act whereby a Member State informs the Commission and the other Member States that a body, which fulfils the relevant requirements, has been designated to carry out conformity assessment according to a directive" (European Commission, accessed on 13 August, 2016).

In order to promote global harmonization of regulations on medical devices, a Global Harmonization Task Force (GHTF) drafted several new guidance documents updating definitions and directives for medical devices (International Medical Device Regulators Forum (IMDRF), 2016). The IMDRF, created on 2011, is reviewing and publishing the GHTF documents (available at www.imdrf.org).

A new European regulation for medical devices has been under discussion and its formal publication is expected to occur by the end of 2016. The formal translation of the consolidated text for EU member states and the application are expected to occur by late 2021 or early 2022 (Emergo Group).

The proposed IVD classification is based on the perceived risk for the patient and the public heath according to the intended use stablished by the manufacturer. This new regulation is expected to have a high impact in IVD devices manufacturers deriving from the additional requirements such as clinical evidence proportional to the assigned risk class. Premarket applications for medium-to-high-risk (Class C) and high-risk (Class D) IVDs will require a summary of safety and clinical performance studies which can increase the time to market and upfront costs (MedTech Europe, 2015).

The proposed classification of IVD Medical Devices

The new risk based IVD classification is more sensitive and adequate to the current technological landscape. IVD devices are classified from class A through D following an increasing of risk for individual and public heath, summarized at Table 9.

Table 9: Risk-based classification of in vitro medical devices.

CLASS	RISK LEVEL	EXAMPLES
A	Low Individual Risk and Low Public Health Risk	Clinical Chemistry Analyzer, prepared selective culture media
B	Moderate Individual Risk and/or Low Public Health Risk	Vitamin B12, Pregnancy self-testing, Anti-Nuclear Antibody, Urine test strips
C	High Individual Risk and/or Moderate Public Health Risk	Blood glucose self-testing, HLA typing, PSA screening, Rubella; companion diagnostics.
D	High Individual Risk and High Public Health Risk	HIV Blood donor screening, HIV Blood diagnostic

Source: Adapted from Principles of IVD Medical Devices Classification "Final Document of GHTF/SG1/N045 (2008).

IVDs intended to be used as tests for "screening for selection of patients for selective therapy and management, or for or for disease staging, or in the diagnosis of cancer. Example: personalized medicine, should be classified as Class C", according to the proposal of European Council (European Commission). However, a guidance specifically addressing companion diagnostics is not drafted. Manufacturer responsibilities for Class C devices registration are presented in Annex II.

CA registration

In the Article 10 of Directive IVDD 98/79/EC registration with one CA is required for every IVD medical device manufacturer intending to place a product on the marker under their own trading name.

In England, UK, the national law is Medical Device Regulations 2002: Regulations 19 and 44 registration of persons placing general medical devices and/or IVD medical devices on the market, and the CA is the MHRA (available at www.MHRA.com).

The MHRA is an executive agency of the Department of Health whose primary objective is to protect public health and to promote uptake of innovative medical technologies. MHRA certifies the analytical validity and safety of new drugs and medical devices and delivers regulatory approval through CE marking.

MHRA will proceed to the following regulatory steps:

- Classify the medical device and specify the code for the IVD;
- Select and follow the most appropriate conformity assessment procedure;
- Apply for certification by a Notified Body;
- Ensure that the medical device complies with essential requirements;
- Establish technical documentation;
- Issue a declaration of conformity and affix CE Marking.

In the UK, there are other institutions responsible for regulating and assessing drugs and medical devices are the following;

- the National Institute for Health and Clinical Excellence (NICE) in England and Wales;
- the Scottish Medicines Consortium;
- the All Wales Medicines Strategy Group (AWMSG).

Manufacturers of new or innovative medical technologies, including diagnostic devices, can apply to NICE's medical technologies evaluation program (MTEP). MTEP selects and evaluates devices based on advantages their offer over current practice. The program intends to increase NHS adoption of cost effective medical technologies. The selection for evaluation depends on clear and high-quality scientific evidence supporting these advantages (NICE, accessed on 13 August, 2016).

European quality requirements

Standardization systems - The use of standard systems is a key to develop medical devices able to go over EU and USA regulations. There are two standard systems for medical devices: International Organization for Standardization (ISO) and Association for the Advancement of Medical Instrumentation (AAMI).

The ISO system

International Organization for Standardization (ISO) is a non-governmental, independent international organization with 161 nation members. Through its voluntary international boards of experts, ISO develops the international standards that intend to provide global solutions.

ISO provides specifications for products, services and systems, to ensure quality, safety and efficiency. They are key quality elements when the goal is to develop products for international trade**.**

It is optional to use any international standard. Since these standards have been harmonized to the medical device directives, compliance with them ensures conformity with the relevant parts of the European IVD directive. ISO is also close to the FDA GMPs requirements. The ISO standards applicable to IDV medical device manufacturers were updated on 13th May, 2016 (European commission, 2016):

- **EN ISO 13485:2016** specifies requirements for a quality management system to IVD medical devices and excludes need for ISO 9001.
- **EN ISO 15223-1:2012 -** Identifies requirements for symbols used in medical device labelling that convey information on the safe and effective use of medical devices. It also lists symbols that satisfy the requirements of ISO 15223-1:2012.
- **EN ISO 14971:2012 -** Application of risk management to medical devices.
- **EN ISO 18113-2:2009 -** *In vitro* diagnostic medical: specifies requirements for information supplied by the manufacturer of *in vitro* diagnostic (IVD) reagents for professional use 18113-2:2009 also applies to information supplied by the manufacturer with calibrators and control materials intended for use with IVD medical devices for professional use; can also be applied to accessories and to the labels for outer and immediate containers and to the instructions for use.
- **ISO 23640:2011 -** Is applicable to the stability evaluation of in vitro diagnostic medical devices, including reagents, calibrators, control materials, diluents, buffers and reagent kits; can also be applied to specimen collection devices that contain substances used to preserve samples or to initiate reactions for further processing of the sample in the collection device.
- **ISO 15198:2004** describes a process for manufacturers of *in vitro* diagnostic medical devices to validate quality control procedures they recommend to their users. ISO 15198:2004 applies to all *in vitro* diagnostic medical devices.
- **ISO/TR 16142:2006** considers and identifies certain significant standards and guides that can be useful in the assessment of conformity of medical devices with recognized essential principles of safety and performance.
- **ISO/TR 16142:2006** is intended for use by manufacturers, standardization bodies, regulatory bodies, and for conformity assessment purposes.

- **ISO 15378** Quality management system for medicinal packaging materials suppliers to meet quality objectives for your primary packaging materials for medicinal products.

Suppliers should be selected according to their demonstration of compliance with expected quality levels by integrating quality management systems (QMS), such as ISO or good laboratory and manufacturing practices (GLPs and GMPs) in their manufacturing and distribution processes**.**

Reimbursement of medical devices in UK

Reimbursement and coverage are commonly used interchangeably, however, while coverage refers to the range of services a payer will pay and under what circumstances, reimbursement refers to the level of payment (Deverka and Dreyfus, 2014). Herein, both concepts will be used to refer to simultaneous coverage and reimbursement. The coverage and reimbursement processes are organized differently in Europe and USA. In USA coverage and reimbursement decisions are made by private health insurers while in Europe, reimbursement decisions are a nationwide strategy to maintain affordability and sustainability of national health systems (Schreyögg, J., 2009; Kruger, 2014). In Europe, contrary to regulations, decisions regarding reimbursement and pricing are made at the member state level (Schreyögg, J., 2009; Kruger, 2014).

Ultimately, reimbursement decisions depend on the relationship between clinical outcomes and associated costs. Different payers may use different metrics, different treatment options available, as well as variable financial constraints, to decide upon what should be considered optimal health outcomes (Frueh, 2013).

Reimbursement is definitively a major barrier to market entrance for innovative oncologic tests. Early health technology assessment (HTA) should be set as high priority during development phase to fasten the market entrance and penetration (Joosten et al, 2016; Retèl, V. P., 2008). During test-drug development phases, communication of value to all stakeholders by means of HTA, health-economic studies and outcomes research may improve reimbursement success (Akhmetov, 2015b).

According to WHO, a HTA is "the systematic evaluation of properties, effects, and/or impacts of a health technology. HTA is a multidisciplinary approach to analyze the social, economic, organizational and ethical issues of a new health care service, product or technology. HTA main purpose is to inform a policy decision making" (WHO accessed on 14 June, 2016).

HTA main recognized limitations are that the studies assume a static situation "*ceteres paribus*", in respect to the competing therapies and prices (Smith, 2013). Market and technology

dynamics are claimed to be fundamental when assessing medical devices due to price erosion (Retèl, 2008; Smith, 2013).

In UK, NICE serves as a HTA agency by providing clinical and economic advisory. NICE uses cost-utility health-economic studies, measured by cost per QUALY to generate guideline documents of medical devices that should be available on NHS (Akhmetov, 2015b; Schreyögg, J., 2009).

In England and Wales, NHS is legally obliged to fund and resource drugs and devices that received NICE appraisal. NICE is internationally recognized for rigorousness processes used to produce recommendations and is a reference to other countries (NICE; Miller, 2011).

There is no regulation of prices of medical devices supplied by the NHS. Most of the devices are reimbursed at prices set by companies. A list of reimbursement prices is available on the website www.nhsbsa.nhs.uk.

To help manufacturers to deal with the complex regulations and standards the British National Innovation Centre of the NHS has an online available free-to-use tool to support new product development (National Innovation Center of NHS). www.nic.nhs.uk)

6.2.2 Economic factors

UK GDP was of 451,260£ Million, by 30 June 2016 and the annual growth rate, between 2013-2015, was of 2,5%, following a positive trend, registered since 1995 (Office for National statistics, OCDE). UK is classified as a high-income country by OECD.

Between 2001 and 2014, the GDP per hour worked evolved from 88.0 to 102.6 in OECD countries, while in UK it evolved from 88,8 to 100.4. Low productivity has been a source of concern in UK (Department for Business, Energy & Industrial Strategy (BEIS, 2012).

The 10-year evolution of the currency exchange rate GDP/EUR reveals that the GBP to Euro rate evolved favorably to GBP, but a depreciation trend has been registered since the “Brexit” voting. UK has been keeping a low inflation rate (Consumer prices index – CPI), that was of 0,5% on 19 July, 2016 (Office for National Statistics, 2016).

UK national debt has been increasing, since 2005, when it was less than £0,5 trillion and is expected to go over £1,5 trillion at the end of 2015/2016 fiscal year (Office for National statistics, 2016). The UK debt-to-GDP ratio more than doubled in the last 12 years has shown by an increase from 40,2% in 2004 to 89.20% in 2015 but a decrease was registered in the first quarter of 2016 (Eurostat, 2016).

Despite the public-sector reforms, the UK government strategy is "to invest 120£ billion a year by 2020-21 to protect the position of the NHS as a world class health system", in real terms, the NHS will be provided with more £10 billion per year compared to 2014-15 (UK government, spending review and autumn statement, 2015). In 2015, 9% of GDP was allocated to healthcare, comparable with 8,9%, average, in OECD nations (OECD Health Statistics, 2016). The annual growth in *per capita* healthcare spending, in real terms, according to OECD Health Statistics 2015, increased by 1% in 2014 (OECD, Health Statistics 2015). In per capita terms (using purchasing power parities), UK spent 4 015.2, in 2015 (OECD Health Statistics, 2016).

According to the EDMA (2014), UK spent 12,6€ in IVD tests, *per capita*, in 2014, when, in average, European countries spent 18,6€. UK is the only IVD market among the 5 largest European markets with overall growth, while Germany, France, Italy and Spain had a slight decrease ranging from 0,1% to 0,7%, between 2013 and 2014. The UK IVD expenditure increase of 7.6%, was due to immunohistochemistry and hematology (EDMA, 2014).

6.2.3 Social and demographic factors

Demographic trends affecting the medical technology sector are an aging population and western lifestyle associated diseases, which contribute to the growing demand for health care services (Deloitte, 2015, EvaluateMedtech, 2015).

Population studies have evidenced that the UK population is steadily aging with over 11.6 million (17.8% of the population) aged 65 and over and 1.5 million (2.3% of the population) aged 85 and over in mid-2015. Between 2005 and 2015, the UK population aged 65 and over has increased by 21%, and the population aged 85 and over has increased by 31% (Office for National Statistics, 2016).

UK population reached 65.1 million in mid-2015, with an increase of 0.8% in the last year, similarly to the growth rate of the last years. England increased by 0.86%, and reached 54,786,300, accounting for 84% of the UK' s population (Office for National Statistics, 2016).

The UK population is projected to grow over the next 10 years. The causes and numbers at the end of each 5-year period are shown at

Table 10 (Office of National Statistics, 2015).

Table 10: UK population projections 2014-2039.

(Millions)	2014-2019	2019-2024	2024-2029	2029-2034	2034-2039
Population at start	64,6	66,9	69,0	71,0	72,7
Births	3,9	4,0	4,0	4,0	4,1
Deaths	2,9	2,9	3,0	3,2	3,4
Natural change	1,1	1,2	1,0	0,8	0,6
Net migration	1,2	0,9	0,9	0,9	0,9
Total change	2,3	2,1	2,0	1,7	1,6
Population at end	66,9	69,0	71,0	72,7	74,3

Source: Office for National Statistics, National Population Projections: 2014-based Statistical Bulletin (2015).

Patient awareness follows the educational and its increasing level predicts that the expectations and litigation questions, related to health services, might rise in the future (Bowling, 2012).

Breast cancer in UK

The UK breast cancer incidence rate is the 5th highest in Europe (EUCAN, 2012). The age-standardized incidence rate for breast cancer has increased by 5.5% in 10 years, from 161.0 (2004) to 169.8 (2013) cases per 100,000 females (Office for National Statistics, 2015).

Breast cancer is the most common cancer in the UK, accounting for 16% of all cancer cases registered in 2012 (GLOBOCAN, 2012). In 2014, 46.417 new cases were registered in the National Cancer Registration Service (Office for National Statistics, 2015).

The age and gender distribution of all breast cancer cases in UK, highlights its female predominance, with 99% of cases being females, and 46% at the age 65 years-old and over (Cancer Registration Statistics, 2013). The NHS Breast Screening program offers a screening test (X-ray) to all woman aged between 50 and 70 years-old, every 3 years. Screening allows breast cancer patients to be diagnosed at an earlier stage, which are usually easier to treat and better prognosis (Cancer Research UK).

6.2.4 Technological factors

Innovation and breakthrough medical technologies are essential to find blue oceans in any industry (Kim and Maubourgne, 2005). Personalized medicine is a new paradigm, offering uncountable opportunities for all biotechnology industry. In medical technology industry, particularly in the molecular diagnostic segments, technologic innovation rate is fast, as it exploits advances in bioscience and widens technical possibilities for healthcare product development (Krishnamoorthy, 2015; Kolominsky-Rabas, 2015, Santos, 2102). Medical technology is characterized by a constant influx of technological advances and typically, products have a short life cycle of around 18-24 months, before an improved version becomes available (Vallejo-Torres, 2008).

In the near future, the technological innovation rate in the medical technology sector, is expected to keep on a fast pace based on the fact that, in 2014, more than 11,000 patent applications were filed with the European Patent Office (EPO). Around 7% of the total patent applications belong to the medical technology sector, more than any other sector in Europe (MedTech Europe).

Molecular testing is experiencing astonishing development, in terms of platform, technology, and supporting bioinformatics (Goodwin, 2016). Price, speed, and automation also have the potential to create advantages for service providers and reduce laboratory errors (Goodwin, 2016; Meldrum, 2011). The promise of molecular-based patient treatment will, however, face several operational, technical, regulatory, and strategic challenges (Pant, 2014).

Aware of the medical technology innovation contribution to efficiency and excellence care, NHS is actively pursuing an innovation strategy, NHS innovation program “Test Beds” (NHS England, 2016). The UK PEST analysis is systematized in Table 11.

Table 11: PEST analysis systematization - UK.

PEST identified factors		Relevance	Critical barriers/uncertainties
Political	Public sector reforms	Low to moderate	
	Regulations (MHRA/CE marking)	High	European Regulations are changing
	NICE HTA	High	Reimbursement dependent on NICE
	Market monopsony	Low to moderate	Product differentiation and price
	UK high purchasing power	Moderate	IP protection in UK after Brexit?
	IP protection laws	High	
Economic	High income and GDP	High	
	Brexit effect	High	Brexit impact
	Healthcare % GDP growth	High	IVD market evolution (healthcare spending)
	IVD market growth	High	
Social and Demographic	Growing population	High	
	Ageing population	High	
	Growing BC incidence	Moderate	Market size
	Public awareness of health issues	Moderate	
	Ethnic variability	Moderate	
Technological	Adoption of GEP-based tests	High	Product development strategy
	NHS innovation programs	High	Innovation capacity
	High rate of innovation, higher completion?	High	

7. MICROENVIRONMENTAL ANALYSIS

7.1 Porter's 5 forces

To develop a competitive strategy in any industry is essential to analyze how that industry is related with its own environment, so an accurate analysis of the industry structure and competitors is central to the strategic planning of a new firm. The long run profit potential of one industry depends on how the value created by the industry is divided among its players and how much each player can influence that industry (Porter, 1998).

7.1.1 Entrance barriers

There are several barriers to enter the medical devices market, and particularly for the molecular diagnostic market: the need for high specialized knowledge, large capital investments, legal and regulatory complex framework, and channels of distribution.

There are several companies with NGS and or GEP platforms already in the market, namely by global companies such as Nanostring, Illumina, Thermo Fisher Scientific, among others, with research use only (RUO) approval and others approved for clinical use (Nanostring). These companies have already established sales channels and benefit from economies of scale. Economies of scale mean that the cost per unit of a product declines as the number of product production increases per period. To overcome the stablished economies of scale of large companies, entrants must start their commercialization process with a cost disadvantage, or implement efforts to come in into market in large scale, which requires higher upfront investment along the value chain (Porter, 1980). Additional capital requirements might increase financial risk critically, in an industry inherently characterized by high financial demands.

Every new IVD test or new technique to perform a test, before be integrated in a diagnostic laboratory must be validated and compared to the previous gold standard technique, which disincentives laboratory managers from changing suppliers too often.

Technical requirements to perform IVD testing have been on a simplification and automatization trend, which reduces barriers on adoption of new kits with new tests/applications, by requiring significant less laboratory investment and service redesign. Currently, the capital required to acquire a molecular diagnostic platform, accounts for most of the switching costs due to the platforms high price (e.g. the nCounter

Analysis FLEX from NanoString costs more than 200.000,00€). Besides the switching costs, the new entrants offering substitutive tests also have to demonstrate significant technical advantages, such as speed, price, service and new capabilities.

Large upfront capital needs are one of the most important barriers to medical technology firms, particularly in the early company phases, whose value creation is dependent on the innovation capacity. To overcome difficulties in capital access many medical technology small firms frequently establish agreements and alliances with larger pharmaceutical companies. NGS platform developers have been largely acquired by leader biopharmaceutical companies: in 2014, an agreement between Roche and Genia Technologies, a California headquartered company that developed the NanoTag sequencing technology, in collaboration with Columbia and Harvard University. Genia shareholders received 125 million US$ in cash and may receive up to 225 million US$, in contingent payments, depending on the achievement of agreed milestones. Genia proprietary technology is expected to reduce the price of sequencing while increasing speed and sensitivity. Mergers and acquisitions (M&A) are a profitable and common exit strategy for small and early-stage medical technology firms.

European and FDA regulations on medical devices constitute a significant barrier to new entrants, and fail of getting CE mark or FDA clearance can impede the market entrance.

Market entrance and penetrance is also dependent on coverage by third payers and reimbursement decisions. Since reimbursement policies are based on evidence for additional benefit, new entrants must demonstrate additional advantages (higher safety, price, turn-around-time or other) to enter the market as innovative, substitute or complementing test sellers. In western countries, a recent model shift changed dramatically the criteria for new drugs and devices to be integrated in clinical practice. The Value-Based Healthcare Model, as Proposed by Michael Porter (Porter, 2006) is changing the reimbursement landscape throughout the world, and its effects are being felt particularly in Germany (AMNOG, accessed on 13 August, 2016).

Through IP protection laws and secrecy established firms can operate exclusively in one market for a determined period of time. Patents, brands and copyrights also include product design, services or processes that give advantages to encumber firms, independently of their size. Some companies rely on strong brands, such as Roche, Thermo Fisher Scientific and Illumina. Powerful brands are perceived as a warranty of quality, safety and innovation, that could result in high customer loyalty, although in the healthcare sector price and utility are becoming the stronger market drivers. Product

differentiation by offering solutions for unmet clinical needs are required to overcome incumbent firm's advantages.

The learning curve also work as an entry barrier particularly to small and unexperienced startup firms. Lack of experience pervades the whole value chain from development to market launch and sales.

7.1.2 Suppliers characterization

Medical technology suppliers are other highly specialized biotechnology companies and general laboratory equipment suppliers. Suppliers are numerous, the majority being large and international companies, many also based in Germany. Most of the supplied products, such as laboratory consumables and equipment, have low to moderate differentiation and there is high price competition among their sellers.

Laboratory supply companies have universities and government funded laboratories as their primary market, usually benefiting from brand loyalty and long term contracts. The medical technology companies benefit from negotiable discounts on consumables.

There are 6 main necessary suppliers identified, so far, discriminated in Table 12**Erro! A origem da referência não foi encontrada.**.

Table 12: Suppliers required by material/reagent.

Products	Suppliers	Bargaining power
Scaffold DNA	Tilibit nanosystems – Munich, Germany	Can be produced *in-house.*
Structural DNA for Nanoreporters	Euroffins – Ebersberg (Bavaria) has ISO, GLP, GCP, and cGMP certification. Many others: Integrated DNA technologies; Sigma Aldrich, Iba-life sciences, etc	Heavy price competition Goods that will be consumed in large quantities (probable benefit of scale discounts) Can be produced *in-house*, requires acquisition of an oligo-synthesizer.
Fluorescently modified DNA for Nanoreporters		
Microscopy chips	Ibidi - Munich, Germany Many others: Lab-Tek, Eppendorf, Thermo Fisher Scientific	Low product differentiation and high price competition.
General reagents	Many potential suppliers and several based in Germany: VWR, Sigma Aldrich, Carl Roth.	Low product differentiation and many suppliers available.

	All with ISO certification	

Vertical integration of the supply chain is also possible, by producing *in house* consumables, such as the "DNA scaffold", fluorescence modified DNA and structural DNA for the nanoreporters, requiring low additional investments. These suppliers have no technological capacity to downstream vertical integration, since it is dependent on protected intellectual property.

Suppliers must be selected according to stringent purchasing control regulations, as directed by FDA, ISO and European Union regulations to ensure that the final products will be approved for marked by the corresponding regulatory agencies.

Switching costs associated with new suppliers might be high, assuming products should be validated *in house* before integration in research and manufacturing activities.

The biotechnology instrumentation sector is a growing market and is expanding, driven by an increase in demand, all over the value chain, and in several fields, such as food, agriculture and medical technology. Many suppliers are German based companies, leading to low cost of shipping and potential benefits from closer relationships.

7.1.3 Buyers characterization

Buyers are highly concentrated, they are governmental purchasing entities, public and private hospitals and less commonly patients. There is also a growing pressure to keep health care services expenditure under tight control. Combined these factors increase the buyers bargaining power.

IVD tests are fundamental to ensure high quality healthcare services and to continual improvement in quality service, moreover, when clinical utility and validation are provided, manufacturers can set premium prices.

A growing number of molecular testing platforms for clinical application will increase price sensitivity, especially if several tests are developed for the same clinical need. However, IVD tests represent less than 2% of healthcare expenditure, such a small cost impact leads to an expected lower costumers price sensitivity.

Buyers have no capacity to vertical integration.

7.1.4 Potential Substitutes and Competitors

For cancer subtyping, there are 3 main groups of potential substitutes to be considered: companies focused on antibody development to be used as IHC and ISH based techniques; companies focused on GEP technology development; Other molecular technologies already used for molecular diagnostic tests, such as: NGS, PCR and Microarrays.

In Table 13, FDA-approved tests as CDx for breast cancer are identified, following a stratification by technique. Since new biomarkers, including those to guide therapeutic decisions, can potentially be detected by CDx tests using these techniques, the corresponding manufacturers are potential competitors, and the techniques potential substitutes. Ventana Medical Systems Inc., DAKO, Leica and Abbot Molecular Inc. are market leaders in tissue diagnostics (IHC and ISH). These companies benefit from a strong clinical evidence of cost-effectiveness, economies of scale and well established distribution and commercializing capabilities. However, technologically they have significant limitations when compared to GEP technologies.

Table 13: FDA-approved HER2 testing kits as CDx for HER2-targeted treatment.

Assay type	Trade name	Manufacturer	Date of FDA approval
IHC	PATHWAY ®	Ventana medical systems, Inc (Roche)	11/2000
Semi quantitative IHC	HercepTest™	DAKO	9/1998
IHC	InSite®	Biogenex Laboratories Inc	12/2004
Semi quantitative IHC	Bond Oracle™	Leica Biosystems	04/2012
FISH	PathVysion®	Abbot Molecular Inc	12/2001
FISH	PharmDx™ Kit	DAKO	05/2005
CISH	SPoT-Light®	Life Technologies Inc	07/2008
CISH	INFORM HER2 dual ISH DNA	Ventana Medical Systems Inc (Roche)	06/2011
CISH	PharmDx™	DAKO	11/2011

CISH – chromogenic in situ hybridization; HER2 – Human epidermal growth factor receptor.

Note: The table do not include HER2 tests using PCR. PCR-based tests for HER2 do not show superior performance to IHC and ISH.

Source: Adapted from Edith (2014).

Potential competitors with High-throughput (HTS) platforms

Currently, there are several HTS platforms available in the market. Considering their potential to be validated or be adapted to perform similar clinical applications they are potential substitutes.

NGS platforms can be divided in RNA sequencing (gene expression) and DNA sequencing (mutational analysis), by their capacity to read (long or short sequences) and by their error type. The leading NGS platforms are the MiSeq from Illumina, Inc. and the Personal Genome Machine (PGM) from Life Technologies, Inc., which together comprised more than 85% of NGS market, in the beginning of 2014 (Ernst & Young, 2015). Illumina technology products have been setting the pace of output capacity and reduction costs (Reuter, 2015) and most of NGS research is being conducted with Illumina's instruments (Goodwin, 2016).

Recently, Roche Molecular Diagnostics agreement with Pacific Biosciences (PacBio), and acquisition of GnuBIO by Bio-Rad heralds the entry of the two leader companies into the MDx market (Goodwin, 2016).

Other GEP technologies have the potential to for simultaneous reading of multiple biomarkers and are technically closer competitors. Examples of alternative technologies are the nCounter System Analysis FLEX (NanoString), the qPCR TaqMann and Microarrays techniques. GEP and NGS technologies are compared in Table 14: Technology comparison.

Table 14: Technology comparison.

Technology	**Brand**	**Multiplexing**	**Quantification**	**Process simplicity**	**Sensibility**	**Cost**
Microarrays		+ + + +	+	+ + +	+ +	+ + +
TaqMan (qPCR)	Thermo Fisher Scientific	+ +	+ +	+ + +	+ + +	+ + +
NCounter Analysis System (FLEX)	NanoString	+ + +	+ + + + +	+ +	+ + + + +	+ +
RNA sequencing (NGS)	Illumina	+ + + + +	+ +	+ +	+ +	+
Capability level: ++ Low; +++ Moderate; +++++ High						

Source: Goodwin (2016); Reuter (2015); Byron (2016); Luthra (2015); Loman (2012).

Competitors focused on breast cancer market

Breast cancer has been the target of several molecular diagnostic companies. Tests available in the market are based on different technologies and the majority are focused in two breast cancer clinical needs: subtyping in Luminal A, B, HER2 positive and Triple-negatives, which allows the identification of the type of treatment; and stratifying Luminal A and B type patients in low and high risk groups, to support the decision of adding traditional chemotherapy or not.

In the USA and European clinical market, there are 8 IVD tests based on multivariate index assays (IVDMIA), discriminated at Table 15, developed to address breast cancer clinical needs.

Table 15: IVDMIA tests for breast cancer subtyping.

MANUFACTURER	TEST Technique	BUSINESS MODEL	CLINICAL UTILITY	TAT	FDA/CE mark/ CLIA waved	MARKET DISTRIBUTION	TEST PRICE
nanoString technologies, Seattle, WA	Prosigna® nCounter FLEX	Kit	Subtyping and Risk stratification for Luminal BC (<5years)	1-2 days	510k Cleared CE-IVD	Germany (AGO guidelines) UK (NICE guidelines)	UK: £182,600 (nCounter) £1382 (including RNA extraction Kit)
Genomic Health Redwood City, USA	Oncotype DX ® PCR	Service (LDT)	Risk stratification for Luminal BC	14	CLIA lab CE-IVD	USA UK Germany (AGO guidelines)	(USA) $3,416 (UK) undisclosed (EUR)
Agendia, Amsterdam, the Netherlands	Mamaprint ® FFPE and FF Microarrays	Service (LDT)	Risk stratification for Luminal BC (<5years)	-	510k Cleared CE-IVD	USA, Europe	?
Myriad Genomics (Sividion)	Endopredict® PCR	Kit	Risk stratification for Luminal BC (>5years)	1-2 days	CE mark Applied to 510k Cleared	Germany, Austria, Switzerland, UK, Spain, Czech Republic, USA	€1800
Agendia, Amsterdam, the Netherlands	BluePrint ® Microarrays Microarrays	Service	Subtyping	-	CLIA	-	-
Agendia, Amsterdam, the Netherlands	TargetPrint ®	Service	Receptor status - endocrineTh	-	CLIA	-	-
BioNTech AG, Germany	MammaTyper® RT-qPCR	Kit	Subtyping	1-3 days	CE-IVD	Europe, China, Azerbaijan, Georgia	-
BioTheranostics, Inc, San Diego, USA	Breast Cancer Index	Service	Benefit of extended endocrine therapy (>5years)	7 days	CLIA	USA	$4950 $3450

Abbreviations: TAT – Turn-around-time. Mean time consumed to perform test and make report available for clinicians. **LDT** – Laboratory developed test. A test sold as a service by a company laboratory. Requires CLIA and CE-IVD mark. **Kit** – A test sold to service providers. Requires FDA and CE-IVD mark. **Subtyping** – Identification of molecular subtypes of cancer, according to their response to therapy. **Stratifying** - Identification of patients with high and low risk of disease progression, to avoid unnecessary chemotherapy in low risk patients. **PCR** – Polymerase chain reaction (molecular biology technique).

7.1.5 Rivalry between competitors

The MDx market and, particularly the HTP based diagnostic tests developed for oncology are expected to keep growing in the next years, driven by the fast-paced discovery of new biomarkers, target drugs, by the launch of successfully improved technologic versions of HTP platforms, and the increasing awareness of their potential benefits.

Rivalry is based on product differentiation, regulatory and clinical validation know-how, as well as, installed capacity to commercialize and distribute.

Product differention mainly determines the market scope, which offers unlimited opportunities in medical field (HTP platforms are heterogeneous regarding technologic limitations, sensitivity, type of detectable molecules; type of genetic alterations detected, cost, time to run a test, and usability). Product differentiation is dependent on the innovation capacity, which is mostly concentrated on research institutions and its spin-off biotechnology companies.

Larger biopharmaceutical companies, maintain their competitive advantage by acquiring small and innovative technology developers.

HTP platforms, software systems and sample preparation apparatus require significant capital investments, which is driving the emergence of more flexible business models, e. g., NanoString, offer the possibility of leasing the nCounter Analysis platform, to attract new customers.

7.1.6 Exit barriers

Highly specialized assets usually have high costs of transfer or conversion. The IVD medical technology companies' main barrier to exit is their highly-specialized IP and the large up-front investment on one product development for niche markets. M&A are a profitable exit for medical technology entrepreneurs (Agarwal, 2015). Exit strategies should be planned due to short life cycle of technology based products.

13. CONCLUSIONS

Molecular diagnostics market is growing mostly driven by the increasing adoption of precision medicine. Breast cancer is an example of successful application of precision medicine and is the second most frequent cancer worldwide.

An extensive literature review revealed that TNBC subtyping has been largely recognized as an emerging medical need and pharmacological industry is investing significantly in new drug validation for this group of patients, as shown by the registration of more than 179 clinical essays running only in 2015.

To avoid direct competition with the closest strategic and technologic competitor DEOXY Technologies should consider alliances with companies having complementary assets, such as Insight Genetics.

The roadmap to market includes strong focus on prototype development, to reduce technological immaturity and increase the success likelihood of fund raising in the next seed funding round, followed by a regulatory and reimbursement plan.

The financial viability of the project is shown to be highly dependent of the financing sources, where German government grants available are expected to have a positive impact, and also from an efficient market expansion plan to other European and non-European countries.

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ANNEX I

USA market regulations - Food and Drug Administration (FDA)

In USA the distribution and commerce of IVD devices is regulated by the Food and Drug Administration (FDA) under the Food, Drug, and Cosmetic Act (FD&C Act). IVD devices are controlled by the Office of in Vitro Diagnostic Device Evaluation and Safety (OIVD) which belong to the Center for Devices and Radiological Health (CDRH). The clearance of a new device depends substantially on a robust scientific rationale and public health safety. (FDA, 2005)

Any IVD device intended to be commercialized in USA should be submitted to FDA approval via **Premarket notification - 510(k) or Premarket approval (PMA).**

The decision to get test approval via the 510(k) or PMA process depends on largely upon the perceived risk for patient health associated with the test which also defines the class to each the device should be assigned:

The IVD devices classification assigns devices into 3 different classes depending on the intended use of the device and on indications for use, as presented on **Erro! A o rigem da referência não foi encontrada.**.

Table 1: Medical devices risk classification. FDA.

FDA class	**Risk level**	**Examples**	**Regulatory controls**
Class I	low to moderate	Immunohistochemistry	General controls
Class II	moderate to high	Detection on non-diagnostic markers	General controls and Special Controls
Class III	high	Detection of (pre)malignant or malignant cases	General controls and PMA

The general controls that typically apply to class I devices include prohibitions against adulteration and misbranding, requirements for establishing registration and device listing, adverse event reporting, and good manufacturing practices.

Special controls include performance standards, design controls, and post-market surveillance programs.

The 510(k) process

A 510(k) submission should be submitted 90 days before the device is put on sale and is required every time a manufacturer introduces modifications that can affect safety or new intended uses in an already approved device. The 510(k) process consists on comparison the submitted IVD device with a legally marketed substantially similar IVD device already approved. The new IVD is cleared by 510(k). If a new IVD device has no predicate example a *de novo* 510(k) pathway will be followed with reclassification of the IVD by FDA and control requirements according.

The 510(k) process is appropriate for NGS-based tests to be utilized for monitoring or other tests with lower perceived risk and categorized as Class II. In those cases, the new method is compared with the current to a gold standard method which for most of the DNA applications is the Sanger sequencing method.

According to an Emergo review of public data on medical devices cleared by FDA, more than 15.000 IVD devices were 510(k) cleared with a mean time of 151 days, between January 1, 2011 and December 31, 2015. In 2015, most of the 3015 devices got cleared after 9 months but usually IVD devices take longer review time. (www.emergogroup.com)

The PMA route

All IVDs with substantial importance for prevention of diseases, reasonable risk of causing injury by themselves or by influencing medical decision-making are considered class III devices. Oncology tests based on NGS are usually used to support medical decisions about treatment and so they are likely to be assigned as class III and to be required to follow a PMA route in order to demonstrate safety and efficacy, and also will be compared with the current gold standard method.

PMA submission for CDx NGS-based tests requires simultaneous review of the drug by the Center for Drug Evaluation and Research (CDER) and of the device by the CDRH.

A PMA application should include a complete record of all the studies to support safety and effectiveness and information on how the device is designed and manufactured.

A reasonable assurance of safety and effectiveness for the intended used is required for PMA approval. Contrary to the 510(k) comparison to other devices is not necessary or even sufficient. For the purpose of market approval, an IVD device must be considered a system including reagents, hardware, software, data analysis and the result reporting.

A PMA approved IVD should notify any modification to the test or device prior to approval. (Pant, 2014)

Informal interviews with consultants in the biotechnology industry, NGS-based CDx are advised to enter on negotiations with FDA CDHR and OIVD, early in the product development cycle.

Table 2: PMA validation levels.

Premarket application (PMA) validation data required	
Preclinical validation	**Analytical validation** - demonstrates that the device can accurately and reproducibly measure the analyte under controlled conditions.
Clinical trials	**Clinical validation** - a test system reproducibly identifies genetic abnormalities in patients with a clinically manifest hereditary disease, and does not report abnormalities in those who that do not have the disease. Clinical data from other countries can be used if similar clinical practice, protocols, ethical approval and there are sample availability limitations.

Investigational Device exemption (IDE)

When an IVD device requires extensive clinical studies for validation as those used to select certain patients with serious conditions for treatment, and exclude others, commonly in cancer and heritable diseases. The manufacturer may present the FDA with a proposal for evaluating the device. If the assumptions are that the risks are adequately disclosed to patients and that the potential benefits are sufficient to offset the risks of the study, an IDE is granted by FDA. FDA may inspect the studies compliance with specific

regulations (in 21 CFR parts 50 and 56; the studies may also be subject to 45 CFR part 46).

The FDA's IVDMIA draft guidance states that "Clinical investigations using human specimens conducted in support of premarket submissions for IVDMIAs are subject to the human subject investigations requirements of 21 CFR Part 50." This investigational phase should focus on safety and effectiveness of the product/the clinical performance characteristics and cut-off and range values are determined in the intended patient population. During this phase these products must be labeled, "For Investigational Use Only. "Depending on the nature of the study initiated, sponsors may require an approved investigational device exemption (IDE) (21 CFR Part 812), although many IVD studies, such as those using blinded or retrospective data, may be exempt from certain IDE requirements including prior FDA approval."

Pre-IDE FDA informal review of study plan (meeting)

The first and arguably most important step in the clinical validation process is the pre-IDE meeting, in which the company, often accompanied by the lead clinical investigator(s), meets with FDA/ CDRH to present data about the device, its clinical development program, and its intended use after approval. The FDA/CDRH staff reviews existing bench and animal data (as well as any outside-the-United States clinical data) and makes informal non-binding suggestions regarding the need (if any) for additional pre-clinical data (bench and animal), as well as the study design. The sponsor then submits an IDE application to FDA/CDRH for formal review. OIVD recommends the use of the pre-IDE process in order to facilitate the regulatory process. (FDA, 2007)

Other FDA guidance documents:

- 513(g) Request classification
- IDE (Devices or reporting IVD results)
- Pre-submission meeting:
- Quality System Regulations ("GMPs")

Quality management systems required by FDA

The quality systems required for FDA products applying for approval are known as Current Good Manufacturing Practices (CGMPs). For IVD devices the Quality System Regulations (QSR) - QSR CFR Part 820 – are based on ISO 13485.

The QSR inspections of 510(k) products by FDA occur after clearance and include:

- Manufacturing facilities
- Company quality system

For PMA candidates the FDA inspection will occur before approval and includes:

- Clinical studies locations
- Investigator files
- Manufacturing facilities
- Company Quality System

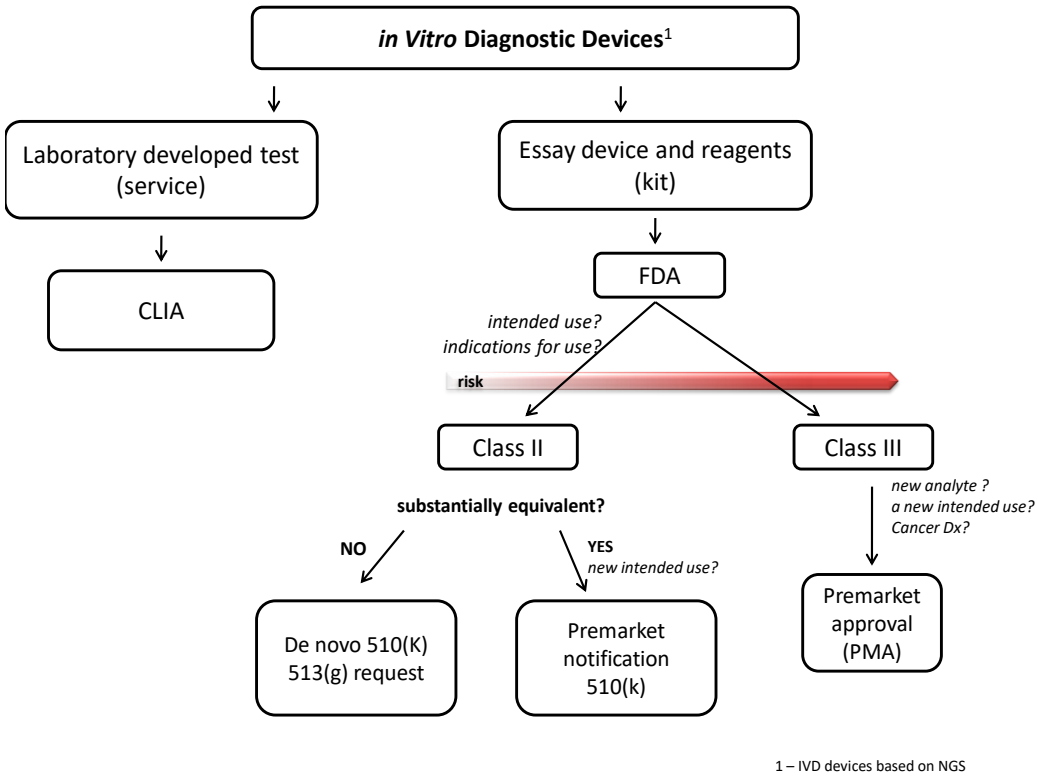


Figure 1: Regulatory requirements according to test type and risk, in USA.

ANNEX II

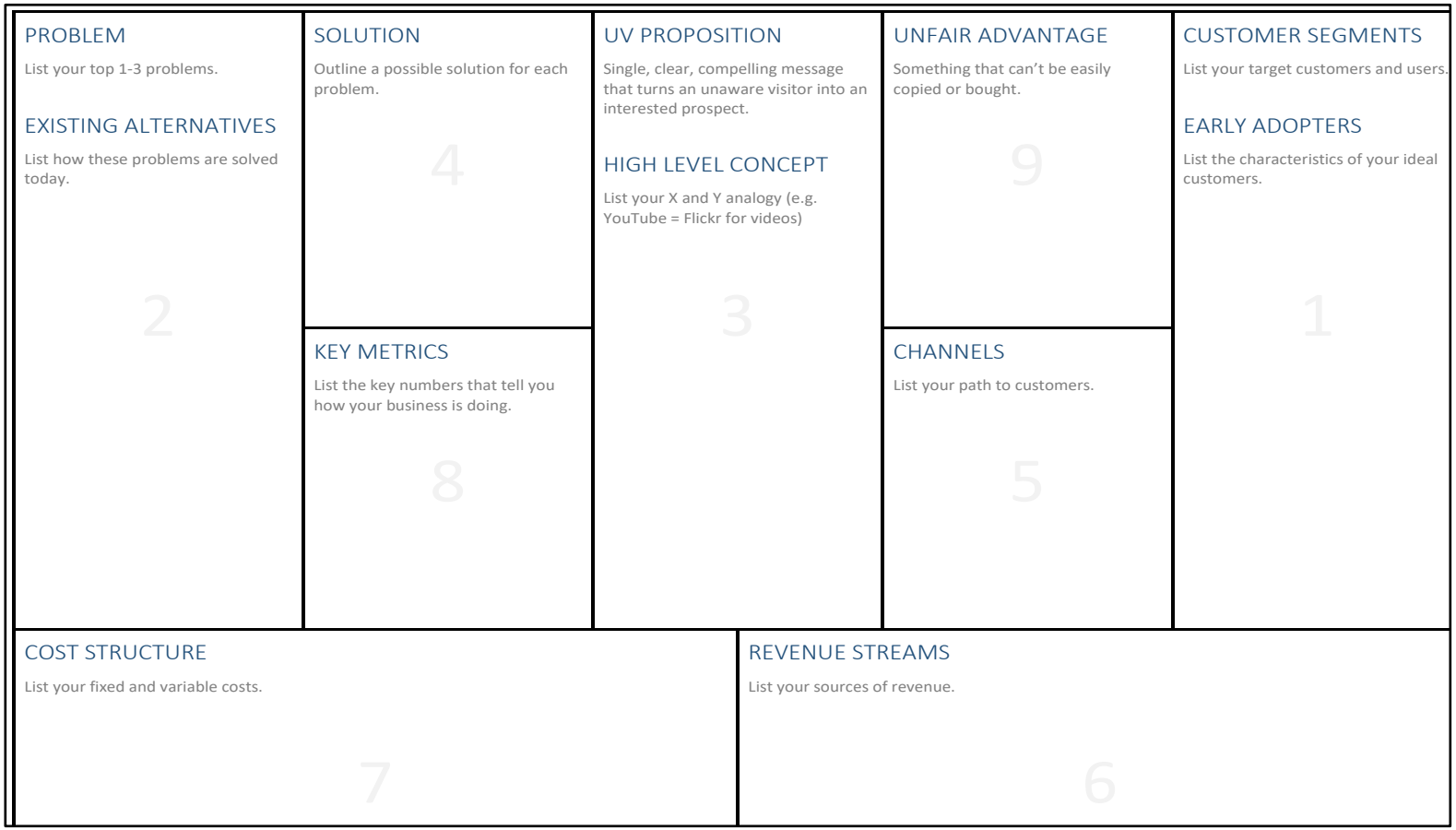
CLASS "C" DEVICE

Conformity Assessment Element	Manufacturer Responsibility	RA / CAB Responsibility	Section
Quality Management System (QMS)	Establish and maintain a full QMS.	Be satisfied that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to marketing authorization.	5.1
Post Market Surveillance	Establish and maintain an adverse event reporting procedure according to GHTF SG2 guidance.	Be satisfied that a current and appropriate adverse event reporting procedure is in place as part of the QMS.	5.2
Technical Documentation	Prepare and submit STED for review.	Receive and conduct a premarket review of the STED to determine conformity to Essential Principles.	5.3
Declaration of Conformity	Prepare, sign and submit.	Review and verify compliance with requirements.	5.4
Registration of manufacturers and their devices	Perform according to regulatory requirements.	Maintain and verify as appropriate.	5.5

Note: Although the RA/CAB responsibilities for Class C and Class D IVD medical devices are the same, it needs to be understood that the STED for a Class C IVD medical device will contain less elaborate information than the STED for a Class D device. The main difference for a Class D STED would be in the level of details in the clinical/performance data and details of the manufacturer's QC release program. The RA/CAB should in the review process not normally require more elaborate information for a Class C device however this does not preclude the RA/CAB from requesting such information in specific cases. (Study Group 1 is developing a STED guideline for IVD medical devices as a matter of priority.)

ANNEX III

Business model on Canvas.



ANNEX IV

INVESTMENT MAP	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	TOTAL
1 – CAPEX											
IT - Computers	7 500	1 250	10 000	2 500	0	0	10 000	0	0	0	31 250
Value per person	2 500	2 500	2 500	2 500	2 500	2 500	2 500	2 500	2 500	2 500	
Number of new employees	3	1	4	1	0	0	4	0	0	0	
Furniture	1 500	500	2 000	500	0	0	2 000	0	0	0	6 500
Value per person	500	500	500	500	500	500	500	500	500	500	
Number of new employees	3	1	4	1	0	0	4	0	0	0	
Equipment	0	0	250 000	0	0	0	350 000	0	0	0	600 000
Laboratory			150 000				150 000				
Manufacturing machines			100 000				200 000				
Communication (website, trademark rights)	0	0	80 000	0	60 000	120 000	0	0	0	0	260 000
Pre-market publicity			80 000								
Clinical market						60 000					
Key Opinion Leaders	0	0	0	0	60 000	60 000					
Machines for clinical trials	0	0	0	0	243 000	0	0	0	0	0	243 000
Quantity					6						
Unit price					40 500						
MHRA Submission							200 000				200 000
R&D expenditures	242 000	289 500	501 000	621 500	629 530	643 530	813 000	369 000	369 000	369 000	4 847 060
SUBTOTAL	**251 000**	**291 250**	**843 000**	**624 500**	**932 530**	**763 530**	**1 375 000**	**369 000**	**369 000**	**369 000**	**6 187 810**
2 - Substitution investment											
IT - Computers					7 500	1 250	10 000	10 000	1 250	10 000	12 500
TOTAL	**251 000**	**291 250**	**843 000**	**624 500**	**940 030**	**764 780**	**1 385 000**	**379 000**	**370 250**	**379 000**	**6 200 310**

Table 2 - Map of R&D investment.

R&D Items	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	TOTAL
R&D	242 000	289 500	501 000	621 500	643 930	657 930	813 000	369 000	369 000	369 000	4 875 860
Kits for clinical trials	0	0	0	0	20 000	20 000	0	0	0	0	40 000
Quantity					1 000	1 000					
Unit price					20,0	20,0					
Scientific publications	0	2 000	2 000	0	0	2 000	2 000	0	0	0	8 000
Quantity		1	1			1	1				
Publication fee		2 000	2 000			2 000	2 000				
Laboratory consumables	48 000	48 000	96 000	96 000	96 000	96 000	96 000	96 000	96 000	96 000	864 000
Number of employees	2	2	4	4	4	4	4	4	4	4	
Cost per researcher per month	2 000	2 000	2 000	2 000	2 000	2 000	2 000	2 000	2 000	2 000	
Salaries	182 000	227 500	331 500	442 000	442 000	442 000	715 000	273 000	273 000	273 000	3 601 000
Maintenance of equipment (1%)	0	0	2 500	2 500	4 930	4 930	0	0	0	0	14 860
Energy, water and electricity	0	0	3 000	3 000	3 000	3 000	0	0	0	0	12 000
Travel and accommodation	12 000	12 000	12 000	24 000	24 000	36 000	0	0	0	0	120 000
Laboratory rent (Munich)	0	0	45 000	45 000	45 000	45 000	0	0	0	0	180 000
Insurance	0	0	6 000	6 000	6 000	6 000	0	0	0	0	24 000
Cleanliness, hygiene and comfort	0	0	3 000	3 000	3 000	3 000	0	0	0	0	12 000

Table 3: Map of costs with human resources.

HUMAN RESOURCES	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
General administration										
CEO/CTO/COO	**182 000**	**182 000**	**182 000**	**182 000**	**182 000**	**182 000**	**182 000**	**182 000**	**182 000**	**182 000**
FTE	2	2	2	2	2	2	2	2	2	2
Annual salary	70 000	70 000	70 000	70 000	70 000	70 000	70 000	70 000	70 000	70 000
Chief Financial Officer	**0**	**0**	**0**	**0**	**0**	**0**	**91 000**	**91 000**	**91 000**	**91 000**
FTE	0	0	0	0	0	0	1	1	1	1
Annual salary	70 000	70 000	70 000	70 000	70 000	70 000	70 000	70 000	70 000	70 000
Office management	**0**	**0**	**39 000**	**39 000**	**39 000**	**39 000**	**78 000**	**78 000**	**78 000**	**78 000**
FTE	0	0	1	1	1	1	2	2	2	2
Annual salary	30 000	30 000	30 000	30 000	30 000	30 000	30 000	30 000	30 000	30 000
Manufacturing										
Technician	**0**	**0**	**0**	**0**	**0**	**0**	**78 000**	**78 000**	**78 000**	**78 000**
FTE	0	0	0	0	0	0	1	1	1	1
Annual salary	60 000	60 000	60 000	60 000	60 000	60 000	60 000	60 000	60 000	60 000
Sales										
Sales	**0**	**0**	**0**	**0**	**0**	**0**	**78 000**	**78 000**	**78 000**	**78 000**
FTE	0	0	0	0	0	0	1	1	1	1
Annual salary	60 000	60 000	60 000	60 000	60 000	60 000	60 000	60 000	60 000	60 000
R&D team										
Head of R&D	**91 000**	**91 000**	**273 000**	**273 000**	**273 000**	**273 000**	**273 000**	**273 000**	**273 000**	**273 000**
FTE	1	1	3	3	3	3	3	3	3	3
Annual salary	70 000	70 000	70 000	70 000	70 000	70 000	70 000	70 000	70 000	70 000
Technician	**0**	**0**	**65 000**	**130 000**	**130 000**	**130 000**	**195 000**	**195 000**	**195 000**	**195 000**
FTE	0	0	1	2	2	2	3	3	3	3
Annual salary	50 000	50 000	50 000	50 000	50 000	50 000	50 000	50 000	50 000	50 000
Pathologist	**0**	**45 500**	**45 500**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
FTE	0	0,5	0,5	0	0	0	0	0	0	0
Annual salary	70 000	70 000	70 000	70 000	70 000	70 000	70 000	70 000	70 000	70 000
Medical Scientific Liaison	**0**	**0**	**0**	**91 000**	**91 000**	**91 000**	**91 000**	**91 000**	**91 000**	**91 000**
FTE	0	0	0	1	1	1	1	1	1	1
Annual salary	70 000	70 000	70 000	70 000	70 000	70 000	70 000	70 000	70 000	70 000
TOTAL (gross salaries)	**182 000**	**227 500**	**331 500**	**442 000**	**442 000**	**442 000**	**715 000**	**715 000**	**715 000**	**715 000**