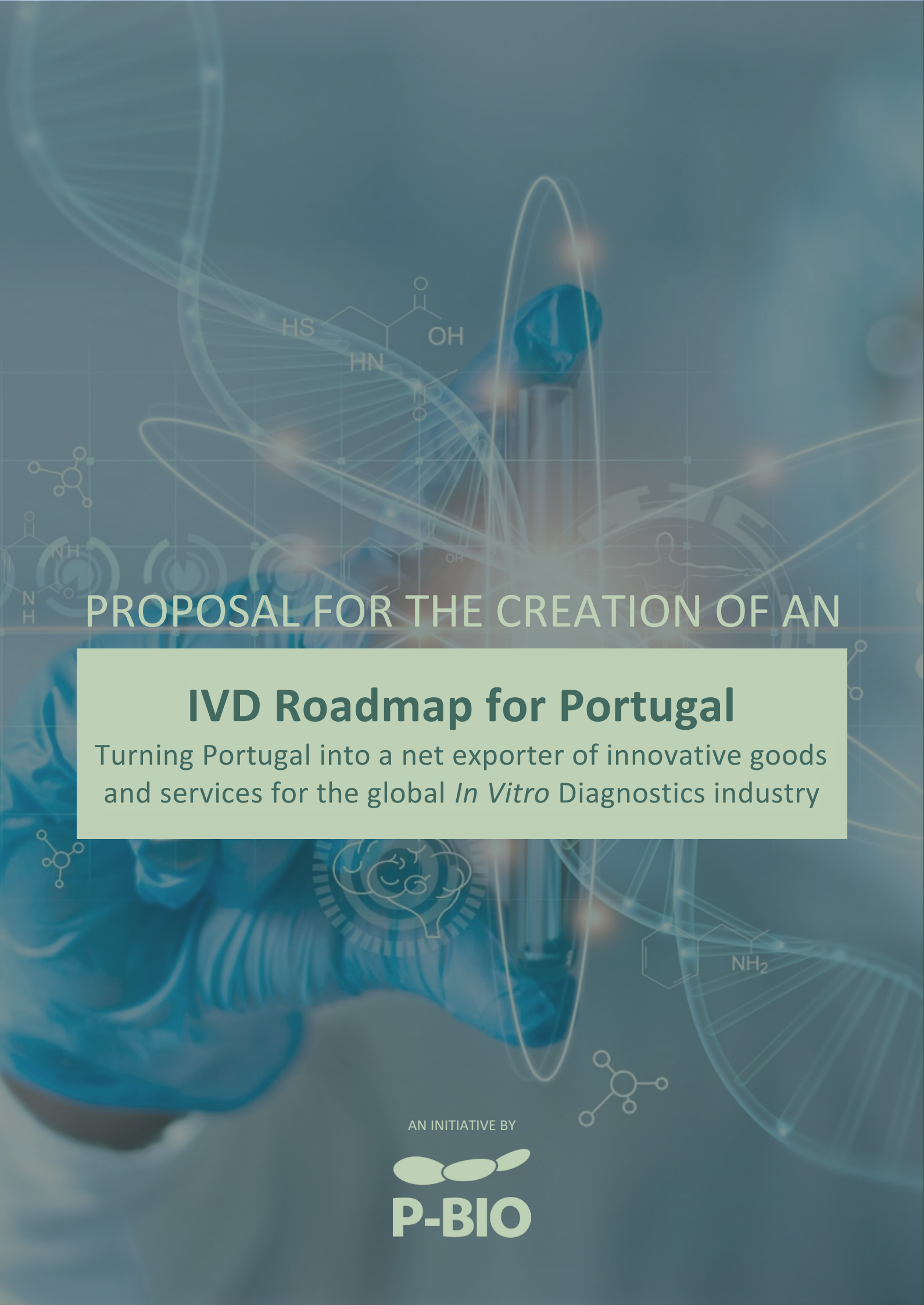

PROPOSAL FOR THE CREATION OF AN

IVD Roadmap for Portugal

Turning Portugal into a net exporter of innovative goods and services for the global *In Vitro* Diagnostics industry

AN INITIATIVE BY

P-BIO

PROPOSAL COORDINATION
José Pereira-Leal | jleal@p-bio.org

P-BIO - Portugal's Biotechnology Industry Organization brings together companies linked to the Biotechnology and Life Sciences sector in Portugal. Since it was founded in 1999, it has been the cornerstone for development and support of Biotechnology in Portugal. P-BIO seeks to develop an environment that is favorable to the creation and growth of start-ups, promoting their corporate development, nationally and internationally. As a member of EuropaBio, the Organization is key to linking companies and their relevant partners in government, investors, regulating agencies and other institutions linked to the industry.

MORE INFORMATION
https://p-bio.org/en/groups/diagnostics-precision-medicine-group/

IVD Roadmap for Portugal

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Executive Summary

The *in vitro* diagnostics industry is a vibrant industrial sector within medical technology wider domain, naturally driven by innovation in which SMEs play a major role, and create added-value specialized jobs. Like any other medical technology, it is a highly regulated sector, but where development cycles and investment needs are orders of magnitude smaller than, for example, in the pharmaceutical industry. Portugal, while having competitive research in life sciences, has failed to build an innovative industrial ecosystem. Here we propose a roadmap for its establishment, focusing on building an industrial sector based on innovation. The present roadmap is a detailed implementation for a specific sector of the vision proposed by P-BIO on the "Bio-Saúde 2030" roadmap (2020).

Context

Today, **70% of the medical decisions are based on *in vitro* diagnostics (IVD) tests**. We are familiar with them: from the regular blood checks we perform yearly, to advanced precision medicine tools that are used to tailor cancer patient's therapy.

The COVID-19 pandemic highlighted the importance of *in vitro* diagnostics in healthcare, powering a significant and sudden expansion of molecular and serological tests that contributed to control the pandemic and were essential components of our strategy to return to normality. However, this crisis only made more obvious the importance of IVDs that were already experiencing a **clear trend of technological development and rapid market growth associated with emerging models of precision medicine**, heavily relying on characterizing the patient to tailor therapy, and on persistent testing to enable early disease diagnosis.

Opportunity

The *In Vitro* Diagnostics (IVD) market is currently close to 90B$, representing ~14% of the worldwide market for medical technology with a forecasted Compound Annual Growth Rate (CAGR) of 8.16% by 2023. This is a mature market: molecular, biochemical, serological tests are the staple of modern medicine. It is a market in which products have reduced life cycles, prompting a **continuous need for innovation and new products**. These inherent innovative character drives the key players to be constantly trying to introduce innovative IVD devices on the market.

Such innovation needs to go hand by hand with highly specialized manufacture for chemicals, enzymes, antibodies, etc. It further requires regulatory approval for global market access. The recent COVID-19 crisis also revealed how limited was the manufacture and regulatory capabilities in this domain in Europe, and particularly in Portugal, and how reliant we were on production from other geographies.

In contrast to other health technology areas, and specifically to the discovery and development of new pharmaceutical products, the market for each *in vitro* diagnostics medical device is smaller while **the investment required and the time-to-market are also much shorter** than for pharmaceuticals: time from idea to market is less than 5 years in many cases.

Finally, the regulatory landscape in the EU is changing, creating an opportunity. Most *in vitro* diagnostic products require the involvement of a **Notified Body**, the official term for accredited test laboratory based in the EU responsible for assessing IVDs both pre- and post-market. Only Notified Bodies in the European Union can do the final assessment of conformity certification in accordance with EU directive(s). The coming into force of a new regulatory framework for IVD (Regulation 2017/746/EU, applied from May 26th 2022 onwards), requiring direct approval of almost all classes of *in vitro* diagnostics by Notified Bodies, **represents a major limitation to the growth of this market**: preciously few entities are certified by EU to grant CE Marks under the new regulation.

The steps to develop a new diagnostic test

The life cycle of a new *in vitro* diagnostics test can be outlined as follows. A medical need, typically associated with a medical decision, is identified by **clinicians**; fundamental biomedical and technological knowledge is harnessed by **life science researchers**, typically within **research institutions**, that demonstrate or discover a testing principle. **Proof of principle experiments** are necessary, in which the results obtained on cell cultures or animal models are shown to be reproducible on **human samples,** and at some point, **IP protection is sought**. Technology transfer offices/rules are critical in **licensing** this knowledge to existing companies or enabling scientists to become **entrepreneurs**; in all cases, **risk investment** and **public incentives to innovation** play a major role. Typically, the development of a new idea into a product, in its early steps, will happen in small companies, archetypal **start-ups**, that seek to **industrialize** the product, where the main hurdles are to produce **extensive clinical validation**, **manufacture** the final product, and obtain **regulatory approval** for market entry. Finally, the company attempts to **market its new product,** becoming a **scale-up** company, and/or is **acquired by a larger company**, de-risking the idea.

Portugal, Europe & the World

The *in vitro* diagnostics market is dominated by companies in a restricted number of geographies. North America is responsible for 45% of the exports, Europe 23% and Asia accounts for the remaining market share.

Europe has a trade surplus in the medical devices general area of roughly 11.7B€ in 2018, of which about half comes from the IVD class. In Europe, the *in vitro* diagnostics market of **Germany alone** accounted for a turnover of **more than 3.7B€ i**n 2016, and is estimated to reach >5B€ in 2023, growing at a CAGR of 5.5% from 2017 to 2023. In contrast, **Portugal has a trade imbalance of -674M€** in the general area of medical devices.

Most of the sector in Europe is comprised of small and medium sized enterprises (SMEs), with few giants like Siemens Healthineers (DE) and BioMerieux (FR). Jobs created in this industry are highly specialized and, hence, highly productive, as the added value per employee is estimated to reach €160,000.

Portugal has excellent Biomedical research and clinical centers operating at the cutting edge of medicine. It also has a large number of PhDs in multiple life sciences and engineering fields that are relevant to the IVD sector. However, this excellence has seldom translated into new services and products: in the specific area of IVD devices, the country lacks know-how, professionals and professionalized infrastructures, biobanks, and suitable investors. Portugal have also been unable to attract manufacture or R&D investment from companies in this sector.

Vision & Expectations

P-BIO proposes a vision to **establish in Portugal, an ecosystem for IVD production that can target this global market**. In this proposal, we tackle many of the steps and players involved in the development of new diagnostic tests to create a complete path from idea to market, creating additional exportable products and services in the process.

We envision the creation of:

- a new industrial ecosystem fully integrated in the European value chains for medical devices;
- significant export capability of manufactured IVD goods and services;
- significant export capability of regulatory services;
- global attraction of large- and small-scale companies to develop their products in this globally competitive ecosystem.

In 5 years, such ecosystem would be able to:

- develop >100 new diagnostic products to the market, tackling a combined market of >2B€;
- create >200 direct jobs, most of them highly specialized;
- balance the negative medical device trade imbalance of Portugal, creating a trade surplus;
- attract at least 10 small- and mid-sized companies to Portugal;
- attract at least 100M€ in direct foreign venture capital investment.

Proposal and major axis of intervention

The creation of this IVD ecosystem would be supported by the following major axis of intervention, indicating in blue the resources we believe would be required; in red we indicate impact in terms of export:

Axis 1 - CO-CREATION— linking clinicians, researchers and companies to promote innovation

The first axis aims to create an environment for co-creation program that joins scientists, clinicians, entrepreneurs and industry experts to promote the development and foster the translation of innovative ideas into new *in vitro* diagnostic solutions. It would encompass:

- A **Collaborative hub** that organizes seminars, workshops, match-making events and hackathons to bring people together and make the research, innovation and health related ecosystem more dynamic. A small central team would be able to identify and involve relevant players at the regional and national level and organize events that bring them together. These activities would increase the attractiveness of Portugal for R&D units of larger industries, or as a hotbed of new companies for international innovators, due to the simplified access to the relevant stakeholders in the IVD innovation process.
- A suite of professionalized **technical platforms** equipped and organized to provide access to equipment and technological expertise existing in our academia that can assist budding ideas and establishment of companies, as well as provide services to existing companies that allow risk-free exploration of new ideas. A central team would work with the National Scientific System institutions and the Research Infrastructures to ensure that relevant services and technologies are available with clear engagement formats and terms of service, visible in a dedicated web portal. This would support the individual institutions in making use of equipment partly unused, and to promote a contract research agenda.
- (At least) One **Clinical Research Organization(s)** (CRO) with a focus or expertise on IVD, product registration, consultation and services, clinical trial consultation and services, health economics study capabilities, etc. Funding for training of current teams and/or recruiting dedicated staff supported by incentives from structural funds would help to build these capacities in our research and innovation system as self-sustainable services, for example within the context of existing CoLabs. CRO services, particularly services specialized within specific fields, will compete for international clients.
- **Biobanks** of biological tissues of multiple disease conditions, with clear and wide-ranging informed consent and complying with European Best Practices, specifically designed to enable validation and exploratory work for IVD needs, a field that has sample requirements different from those met by actual Biobanks in Portugal and many in Europe; Biobanks with a clear business model that enables biobanks sustainability based on the service they provide to the R&D companies. Funding, through competitive incentives, for new or existing biobanks to become dedicated sample repositories for diagnostics research would enable the deployment of a clear business model aiming for global markets – the lack of IVD-relevant samples is not just a Portuguese problem.

Axis 2 - INNOVATION - translating knowledge into new diagnostics solutions

- A **Proof of Concept and Technology Transfer program,** where scientists, innovators and medical doctors can apply to get funding, and infrastructure if required, at existing academic institutions or established companies to test ideas for new services and products, facilitates and stimulates technology transfer and product and service generation from Portuguese and global R&D centers, inspired by the proof-of-principle programs of the European Research Council or the recently announced proof-of-principle program of the Municipality of Oeiras. Dedicated funding via ANI (the Portuguese Innovation Agency) and/or FCT (the Portuguese Foundation for Science and Technology) with shorter evaluation times and dedicated supervision/mentorship from industry experts would make this possible. This program would allow the validation and maturation of potential IVD solutions prior to their market entry, contributing to increase their success rate.
- One **Acceleration program for IVD medical devices** aimed at recruiting the best ideas and teams from Portugal and globally, to rapidly accelerate the transition from abstract idea into a business case with a completed Target Product Profile, elaborated together with final users and reimbursement organizations, a clear regulatory roadmap, and a budgeted plan for proof of principle implementation. This program would be established and executed by a core team, but aiming at involving the full scientific and clinical system in Portugal. External funding from international investors and large companies that aim at identifying early-stage ideas would support this program; partnerships with international universities or regions interested in running this acceleration program locally can further support the sustainability of this activity.
- Support for the creation of **several specialized investment funds in the life sciences/IVD domain**, involving private investment, national and international, leveraged on public funds and catering to investment **from pre-seed to Series A**. This plugs into well-established mechanisms of supporting the establishment of venture capital in Portugal and must be subjected to the best practices of investment due diligence and business case; the challenge is to attract experienced investors that can support smart money investment. Local co-investment will greatly facilitate the attraction of international investment by the largest boutique investment companies.
- Collaborate with **business incubator(s) for the support of new IVD medical device companies**, operating in physical proximity with established start-up and scale-up companies, allowing rapid prototyping with low capital investment, and therefore de-risking of early business-ideas and facilitating the investment-case. The IVD domain demands specialised infrastructure and equipment so we envisage a challenge to existing incubators and technology schools to the establishment of these incubators/incubation programs, leveraged on dedicated funding for its adaptation. Successful incubators become self-sustainable through spaces and services provided to IVD companies. Incubators with a strong emphasis on IVDs and their integration into a wider IVD and innovation ecosystem are rare worldwide and will attract international start-ups and scale-ups to Portugal.

Axis 3 - TRAINING - adapting and preparing life scientists and MDs for the IVD industry

- A **Post-graduation/MSc program for *in vitro* diagnostic development** for scientists and clinicians interested in transitioning into *in vitro* diagnostic development, creating both future entrepreneurs, key-staff members for companies, as well as regulatory and medical affairs experts. A central team would liaise with Portuguese and international industrial players to tailor a dedicated program, and work close to business and technology schools in establishing them. There is preciously little offer in terms of specific training for the IVD business environment, and this would represent an opportunity to attract international fee-paying students to our academic institutions. In addition, trained technical and support staff would further support the attractiveness of Portugal for international companies.
- A **regular program of short training courses** aimed at the global medical devices' companies, focusing on regulatory affairs in aspects and formats pertinent to the development and commercialization of *in vitro* diagnostics medical devices. A central team would support existing companies and academic centers offering relevant trainings to integrate a centralized platform of short training courses, and liaise with industry to help them in the identification of specific training needs. The current common use of online training platforms makes these courses easily exportable services.

Axis 4 - MANUFACTURE - organizing the value chains

- Identify and leverage existing manufacture capabilities in Portugal for production (plastics, glass, packaging), services (consultancy, IP, etc), go-to-market and distribution of products in this sector, **establishing a fully integrated value chain and logistic hub**. This work would be managed by a central team. It will support existing companies to plug into the IVD international value chain, facilitating the export of goods and services.
- **Promote the creation of OEM (original equipment manufacture) businesses**, university spin-offs or existing companies with relevant technological know-how, aimed at producing full diagnostic solutions and/or components for the global IVD industry, serving local and global IVD companies. This work would be managed by a central team in liaison with the National Authorities (E.g.,: ANI). These business units would be mostly focused on targeting the international value chain, becoming exporters of goods and services.

Axis 5 - Market access - enabling products and services to access the global market

- The establishment of a **Notified Body** with a code for IVD, targeted at the global medical devices industry, that can become one of the reference regulatory bodies in Europe. The coming into force of the new regulatory environment for medical devices creates challenges and opportunities for this industry. A notified body is by necessity an independent, for-profit project but one that requires support from local authorities. We propose that the national health/economy/science authorities work closely with entrepreneurs in Portugal wishing to invest in the creation of these business(es) and ensure that the required political and institutional support is granted. Notified bodies export regulatory services, such as the CE ICD marking and ISO13485 certification services.

- A **Global Distribution Platform**, including a logistics hub and partnership of distributors operating according to the *Good Distribution Practices*, and final clients, that enables rapid market prototyping and access to global distribution. A central team would manage the identification and maintenance of up-to-date lists of service providers and also know-how for distribution of IVD devices; close collaboration with AICEP (the Portuguese Trade & Investment Agency) would be beneficial.
- A **Business development and Marketing platform** that promotes the ecosystem and its individual players aiming to obtain research contracts, promoting the IVD Hub to attract international companies, involving international venture capital firms, organizing joint participation in trade shows and creating a national **Medical Device branding**. This would be managed by a central team in close collaboration with AICEP and other relevant governmental agencies.

Axis 6 - HEALTH CAMPUS (Campi)

Support the establishment and visibility of **iconic *campi*** at the heart of major cities where significant Health-related research activity is already present, to attract the best people from all over the world, where research, innovation, regulatory bodies, and companies work side by side, in proximity to major private and public health institutions. This would be a mixture of for-profit, real-estate operation and engagement of existing stakeholders, such as research and clinical centers; relevant players would be sought and brought to the table through the actions of a central team.

Who can achieve this?

The development of this roadmap would require initial focused strategic investment, followed by targeted utilization of existing mechanisms of incentives for innovation and production, and the participation of private investment. It would further require:

- A Central Team, which we envision to be established through the collaboration of existing industrial associations and funded through **strategic governmental support**. P-BIO is willing and motivated to participate in this development and in involving other relevant industrial associations;
- Closer collaboration with National Authorities: INSA, INFARMED, Foreign Office, Health Ministry and Science Ministry, must be involved for the relevant areas;
- City Councils: of regions for which life sciences and IVDs are strategic and where a IVD cluster can be built;
- Direct involvement of Universities and Research centers;
- Clinical centers with interest and dimension in supporting clinical research and clinical trials;
- Portuguese private investors already interested in this domain.

Why Portugal should, WHY PORTUGAL MUST!

P-BIO presented here a proposal to create a new industrial ecosystem that builds resilience for the Portuguese Healthcare sector, integrates Portugal in the medical devices global value chains, and contributes to strengthen our economy, balancing our trade-deficit and turning Portugal into a net exporter of medical technology and services, with concomitant creation of high value jobs. We propose an ecosystem that has the potential to become self-sustaining in a short period of time.

The funding and political support needed from the Portuguese government aims to change Portugal into a key industrial player in one of the most dynamic areas of economic and technological development - healthcare - a priority in the next cycles of EU funding and the UN development goals.

A detailed business model and funding needs and formats will be simple to propose if required. This public and private investment, together with the know-how potential that our country already holds in this area, represents an opportunity that we can chose to seize now, or remain in the sidelines as other nations build their high tech industrial capacity.

LIST OF ACRONIMS

AICEP – Portuguese Agency for Investment and Foreign Trade

ANI – Portuguese Innovation Agency

CAGR – Compound Annual Growth Rate

CE – marking that certifies that products sold in the European Economic Area have been assessed to meet high safety, health, and environmental protection requirements.

COVID-19- Disease caused by coronavirus SARS-CoV-2

CRO – Clinical Research Organization

DE – Germany

EU – European Union

FR – France

FCT – Portuguese Foundation for Science and Technology

ICD – Intelligence Community Directive

INSA – Portuguese Institute for Public Health

INFARMED – Portuguese Authority of Medicines and Health Products

IP – Intellectual Property

ISO – International Organization for Standardization

IVD – *In Vitro* Diagnostics

MDs – Medical Doctors

OEM – Original equipment manufacture

P-BIO – Portugal's Biotechnology Industry Organization

R&D – Research & Development

SME – Small and Medium Enterprises

UN – United Nations

P-BIO

P-BIO - Associação Portuguesa de BioIndústria
Biocant Park- Parque Tecnológico de Cantanhede, Núcleo 04, Lote 02
3060-197 Cantanhede

www.p-bio.org