NoBoCap

PULSE REPORT

MILESTONE MS15- First Annual MD/IVD Industry pulse report

AUTHOR : STAMATIKI KRITAS, YVES VERBOVEN

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VERSIONS TABLE

Issue	Date	Description	Author(s)
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FOREWORD

On the efficiency and competitiveness of a changing MDR/IVDR regulatory environment and the enabling initiatives to unlock the innovation ecosystem in Europe to support the preparedness and strive for a timely predictable and seamless pathways for the accessibility of innovation in health systems across Europe.

INTRODUCTION

As a first milestone of this deliverable to be finalized by the end of this project, which also contains a 1st year input, a first step is the creation of an outline describing a changing environment, the impact with a specific focus on start-ups and scale-ups (SME Innovation), and the supportive initiatives taken at all levels — from EU policies (implementation of regulation, guidance) and EU-driven surveys, to national and regional government initiatives, as well as local actions by Innovation Hubs/Clusters and knowledge and know-how partners — supported by surveys indicating the state of play.

THE ENVIRONMENT AND POLICY LEVEL

The European environmental policy is based on the principles of precaution, prevention, and rectifying pollution at source, and on the 'polluter pays' principle. The EU faces complex environmental issues, ranging from climate change and biodiversity loss to resource depletion and pollution. Environment policy has recently been moved to centre stage in EU policymaking, with the Commission launching the European Green Deal (2019) as the main driver of its economic growth strategy.

The European Parliament plays a major role in shaping EU environmental law. During its eighth term (2014–2019), it dealt with legislation deriving from the Circular Economy Action Plan (on waste, batteries, end-of-life vehicles, landfilling, etc.), climate change issues (ratification of the Paris Agreement, effort sharing, accounting for land use, land-use change and forestry in the EU's climate change commitments, Emissions Trading System reform, etc.) and more.

EU AND GOVT. LEVEL REPORTS ON IMPACT REGULATION GENERAL/ ON INNOVATION

- Multi-faceted, ambiguous and complex relationship between (EU) regulation and innovation in the economy.
- Discusses the innovation enhancing potential of certain regulatory approaches as well as factors that often reduce incentives to innovate.
- The relationship between European level regulation and innovation emerges both when looking non-parametrically at patent density around the threshold and in a parametric exercise where we examine the heterogeneous response of firms to exogenous market size shocks (from export markets).
- On average, firms innovate more when they experience a positive shock, but this relationship significantly weakens when a firm is just below the regulatory threshold.
- Data and literature are used to calibrate the structural parameters in the model.
- For example, using estimates of the R&D cost function, the magnitude of the regulatory tax from the ratio between the slopes of the innovation-size relationship for large firms compared to small firms.
- Our baseline estimates imply an aggregate innovation (and therefore growth) loss of about 5.4% and a lower bound on the loss of welfare of about 2.2%.

EPSCO

The EPSCO Council

- works to **increase employment levels** and

- improve living and working conditions, ensuring a high level of human health and consumer protection in the EU.
- brings together ministers responsible for employment, social affairs, health and consumer policy from all EU member states.

NETHERLANDS Govt. Call Action

- The government-wide programme for a Circular Dutch Economy by 2050 outlines how we can transform our economy into a sustainable, fully circular economy by 2050. The programme describes what we will need to do to ensure we use raw materials, products and services in a smarter and more efficient way.
- The National Circular Economy Programme 2023-2030 (NPCE) elaborates the ambitious circular economy goal, which is simultaneously a climate goal. After all, by steering and facilitating national and international sustainable, circular systems, circular economy policy also promotes climate targets.
- The Netherlands has one of the most advanced economies in the world. But it is also facing some challenges. It is still overcoming a protracted recession. Ongoing demographic change requires that economic growth increasingly depends on productivity gains.
- Dutch exporters have benefited less than some other EU countries from the expansion into emerging markets. Innovation is a key to future growth and competitiveness, and is also needed to address societal and environmental challenges, including energy supply and climate change.
- Dutch policies in the area of innovation recognize these challenges and reflect high aspirations, aiming to place the Netherlands among the top five knowledge economies globally. Considering the high quality of its human resources and excellent universities, the Netherlands is in a good position to fulfil this ambition. Further improvements in innovation policies and performance can help.
- The new top sectors approach based on public-private partnerships is well suited to achieve alignment of strategies and pooling of resources. It has the potential to bring about closer cooperation between business and knowledge institutes, such as universities, and to raise the scope and ambition of business innovation (including in performing more R&D).
- Dutch enterprises are among the world's leading innovators, with strong technological capabilities and performance. However, the business sector as a whole invests less in R&D and in knowledge-based capital than is the case in other advanced innovation systems. It would be important to broaden the base for innovation and engage more firms in innovation activities, especially in sectors that, relative to other advanced systems, collaborate little with knowledge institutes and conduct little R&D.

EU LEVEL SURVEY OUTCOME ON STATUS REGULATION IMPACT INNOVATION

EU survey

Case Study: EU biotech regulation as a penalty on innovation

- Two of the core principles of 'better regulation' are that regulation should be science- and evidence-based, and that risks – not hazard properties – of a substance or good should be the focus of health, safety and environmental benefits for society. Hazard-based approaches therefore lead to overregulation, possibly heavily so. In turn, risks should be established by globally respected, rigorous science- and evidence-based risk assessment methods. Since 'better regulation' principles are increasingly accepted as rational and least-cost in the EU by all stakeholders, those advancing political conjectures or echoing consumer aversion have embraced the 'precautionary principle' as the respectable route to restricting or prohibiting new products or initiatives, even when little or no hard scientific evidence is available.
- This is the predicament of two submarkets of biotechnology in Europe, namely for genetically modified organisms (GMOs) and for crop protection. GMOs have significant and proven societal benefits. Worldwide, many millions of farmers experience greater certainty and less poverty due to GMOs' capacity to protect their harvests. This is certainly true in large quantities for developing countries' farmers growing cotton (80%) and soybeans (70%). Given the reality of reduced land, water and fertilizer resources, it is essential that more food be produced sustainably worldwide. In EU regulation as well as in debates in the two bodies colegislating the rules, these formidable benefits seem to play no role. The upshot in the EU is that only two new GMO products have been allowed to be cultivated: NK603 GM maize and the Amflora potato. In 2012, after having waited for more than 13 years, BASF gave up on
- Amflora and transferred that activity to the US. The maize is cultivated practically only in Spain; no other EU country accepts it and NGOs discredit the cultivation or the company behind it. As a result, the EU has hardly been able to innovate in this area, a growth sector in the rest of the world. From a regulatory point of view, the restrictiveness of GMO regulation brings no benefit to European society whilst damaging the biotech industry, even though there is no scientific empirical evidence of any risk. The state of denial is so bad in the EU that no fewer than 23 national academies of science in the EU felt compelled to write a report ("Planting the future") in June 2013, stressing that there is nothing in the scholarly literature to justify suspicions that GMOs thus far allowed in non-EU OECD countries are a risk to society. The EU biotech industry is not dead, far from it; it is doing well to avoid specialization in GMO or other crop-protection products. But even that is not without dangers. Recently, a very controversial decision to temporarily ban a (much used) neonicotinoids pesticide because of a suspected connection to the decline of Europe's bee population – again, under the precautionary principle – although several other reasons are at least as likely to have caused this decline, show that science-based risk assessment was bypassed, damaging the prospects for a relatively new and successful product, and perhaps discouraging the industry from pursuing others.

KEY ACTORS CALLS FOR ACTION

- The Innovative Health Initiative Joint Undertaking (IHI JU) is a public-private partnership between the European Union, represented by the European Commission, and several health industries from the biopharmaceutical, biotechnology and medical technology sectors.

Figure 1 A snapshot of MedTech Europe market
Source: MedTech Europe

These industries are represented by:

- COCIR (medical imaging, radiotherapy, health ICT and electromedical industries)
- EFPIA, including Vaccines Europe (pharmaceutical industry and vaccine industry)
- Europa Bio (biotechnology industry)
- MedTech Europe (medical technology industry)
    - MedTech Europe's purpose is to make innovative medical technology available to more people, while helping healthcare systems move towards a more sustainable path.

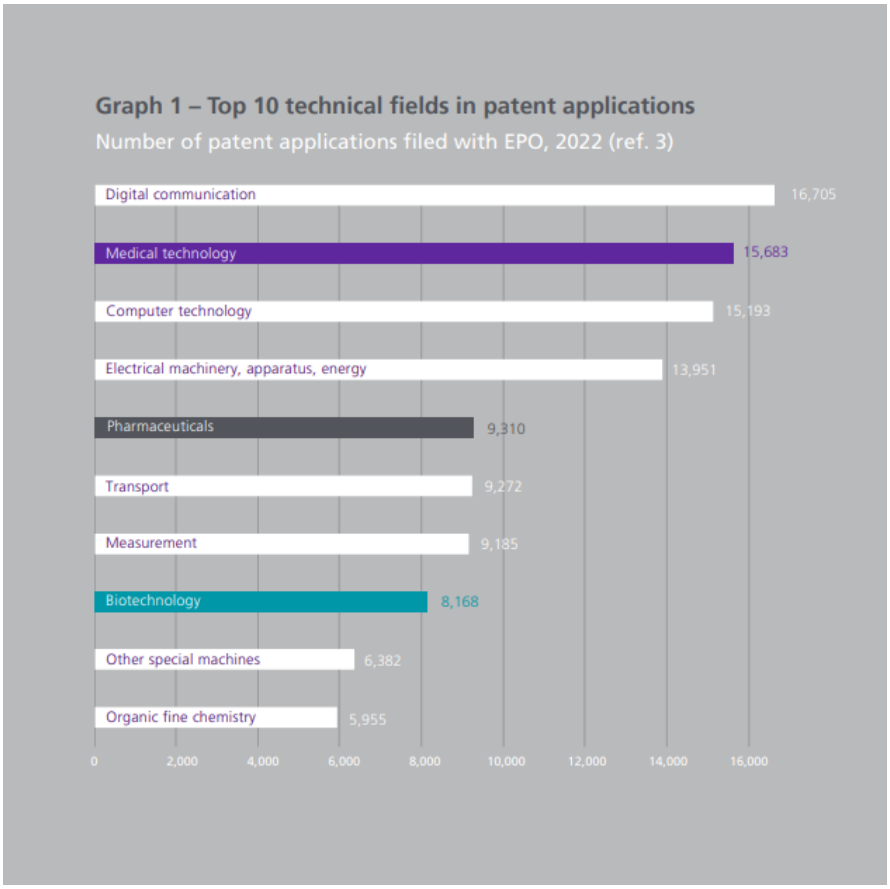

Figure 2 Top 10 technical fields in patent applications
Source: MedTech Europe

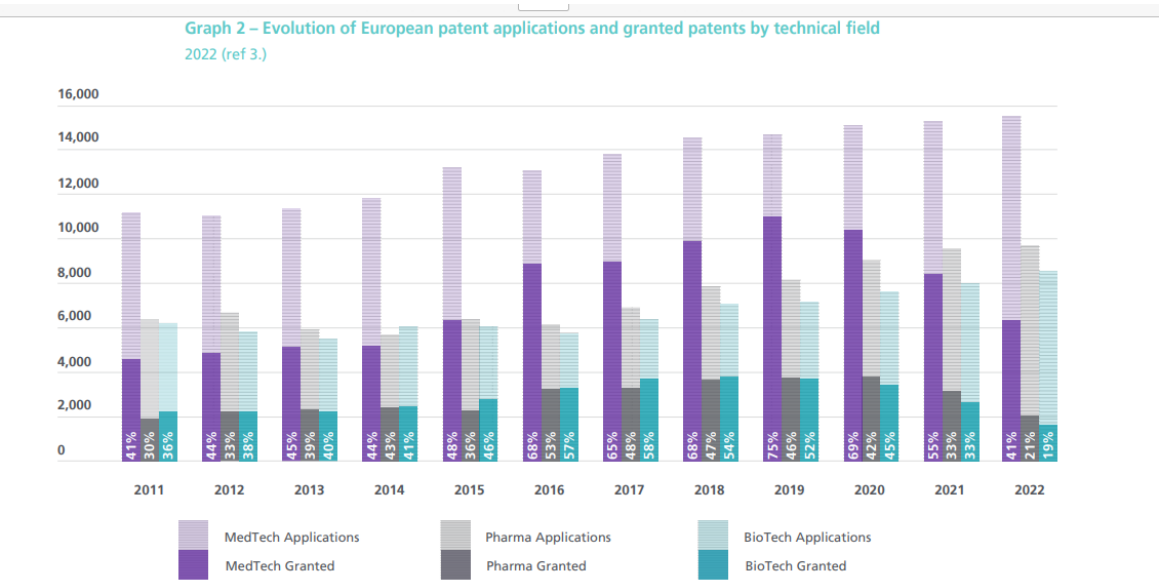

Figure 3 Evolution of European patent applications and granted patents by technical field
Source: MedTech Europe

PROFESSIONAL ASSOCATIONS (EUROPEAN PEDIATRIC professional associations. ANECDOTICAL CASES

- The European Academy of Paediatrics (EAP) ...
- The European Society of Paediatric and Neonatal Intensive Care (ESPNIC) ...
- The European Society for Paediatric Research (ESPR)

A FURTHER CHANGING ENVIRONMENT – NEW REGULATION TO IMPACT INNOVATION ACCESS

The Data Act, proposed by the Commission on 23 February 2022, agreed by the co-legislators in June 2023 and in force since 11 January 2024, introduces harmonized rules on fair access to and use of data . It is the second key pillar of the European strategy for data, making an important contribution to the digital transformation objectives of the Digital Decade Policy Programme 2030.

The Data Act is a comprehensive effort to address the challenges and opportunities presented by data in the European Union, emphasizing data protection, fair access and user rights.

VIEW BY INVESTOR COMMUNITY

The Invest EU Guarantee Agreement signed by the European Commission and the EIB Group in March 2022 paves the way to implement the Invest EU financial products under the Research, Innovation and Digitization window through which the EIB Group will deploy EUR 5.5 billion to support breakthrough innovations up to 202739. Building on a successful pilot, the European Scale-Up Action for Risk Capital (ESCALAR) mechanism will be expanded under Invest EU. The expansion will attract more and new private funds and institutional investors in particular, by complementing VC equity with quasi-equity having a reduced risk profile. This has the potential to double a given VC fund's investment capacity without distorting the character of the European VC landscape by attracting additional private investment based on a non pari-passu approach. In support of this, the Commission will convene leaders of large institutional investors (pension, insurance and sovereign wealth funds) to explore opportunities and requirements for increasing investments into VC funds. Efforts to help financial institutions and their investment experts better assess, value and valorize intangible assets to facilitate the use of IP as collateral by SMEs will also be explored under Invest EU. Further, together with Member States and the EIB, the Commission will assess the complementarities between existing EU funding instruments and recent initiatives such as the European Tech Champions Initiative (ETCI, to which the EIB Group will initially commit up to EUR 500 million), with a view to addressing the scale-up gap for European deep-tech companies.

(**References**: **1**. https://www.eif.org/what_we_do/equity/escalar/index.htm, **2.** Investments benefitting from certain additional protections that reduce investment risk compared to other share classes or similar. In recognition of the lower risk, the investment will not benefit from

the same return entitlements as other investors subscribing other share classes or similar with higher risk. **3.** https://www.eif.org/what_we_do/equity/news/2022/eib-supports-the-pan-european-scale-up-initiative-to-promote-techchampions.htm)

OPERATIONAL – APPLICATION TO FOSTER EFFICIENT EU ACCESS

NOTIFIED BODIES CAPACITY: FACT AND FIGURES/ STATUS

Notified Bodies (NBs) – A Key Pillar of the Medical Technology Regulatory System

Notified Bodies are the only recognized third party carrying out the assessment of the performance of construction products. Notified Bodies are designated by EU countries. The European Commission ensures cooperation between Notified Bodies.

The tasks of Notified Bodies include:

- assessment of the performance of a construction product
- certification of constancy of performance
- factory production control certification

Notified Bodies are responsible for assessing and (re-)certifying most MDs and IVDs, allowing products to be placed on the market. Both new regulations introduce new obligations for Notified Bodies and will require the assessment of more products than ever before. For example, 35,000 IVDs will be covered by Notified Bodies for the first time.

In the European Union, medical technologies are tightly regulated by laws that govern the safety and performance of devices across their lifetime, before and after they are placed on the market. The European medical technology sector is currently transitioning from being regulated under the EU medical devices and IVD directives to two new regulations.

With the adoption of the Regulation (EU) 2017/745 (MDR), the regulatory framework for medical devices has changed significantly. The main objectives of this Regulation are to “establish a robust, transparent, predictable and sustainable regulatory framework for medical devices which ensures a high level of safety and health whilst supporting innovation”. However, despite the significant effort from the European Commission and the Medical Devices Coordination Group (MDCG), there is a growing concern for the readiness of the sector on 26 May 2024, when the transitional provisions allowing medical devices certified under the Active Implantable Medical Devices Directive 90/385/EEC (AIMDD) and the Medical Device Directive 93/42/EEC (MDD) to be placed on the market will expire.

Classification of ***In Vitro*** **Diagnostic Medical Devices**

The In Vitro Diagnostic (IVD) sector is regulated by the **Regulation 2017/746/EU**.

Classification of IVDs is important as it determines the level of involvement by a third party (the “notified body”) in assessing IVDs both pre- and post-market. This level of control generally reflects the risk of an incorrect result from the test.

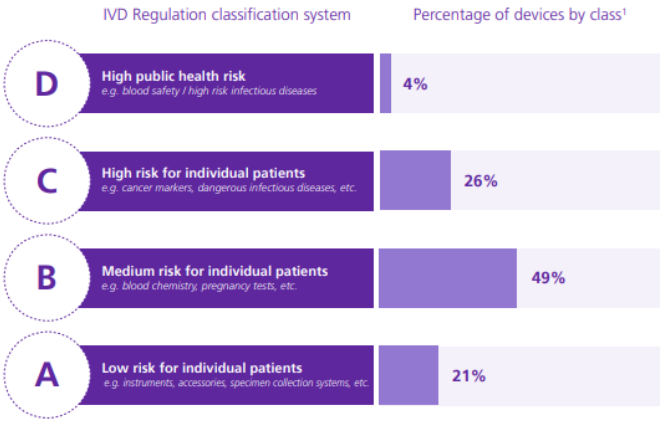

Figure 4 IVD Regulation classification system
Source: MedTech Europe

Classification of **Medical Devices Since 26 May 2021**, the medical device (MD) sector has been covered by **Regulation (EU) 2017/745**, the so-called ‘Medical Devices Regulation’ (MDR), which has come into full application.

Classification of medical devices drives many pre- and post-market requirements. Due to the large variety of products, the level of control made by a third-party (the “notified body”) before placing them on the market depends on the level of impact on the human body that their use might imply. The same notified body is involved post-market to ensure the continued safety and performance of medical devices.

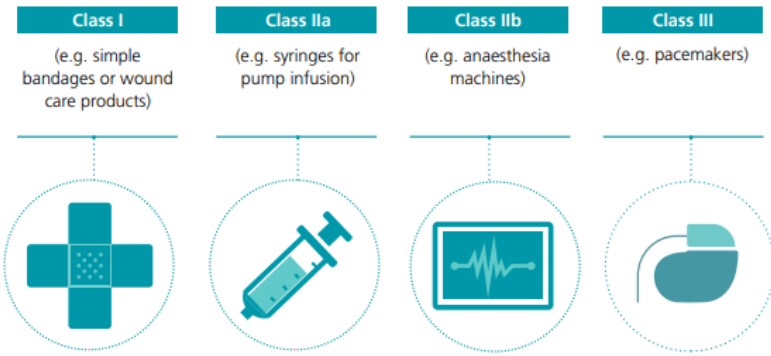

Figure 5 Classification of Medical Devices
Source: MedTech Europe

NOTIFIED BODIES CAPACITY

European Regulators Move to Increase Notified Body Capacity

The European Commission (EC) has taken new measures to relieve some of the pressure on Notified Bodies and free up capacity to perform medical device and in vitro diagnostic (IVD) conformity assessments. Notified Bodies are assessed and monitored by Competent Authorities and the EC according to Articles 35-50 of the Medical Devices Regulation (MDR), and Articles 31-46 of the In Vitro Diagnostic Medical Devices Regulation (IVDR). Every three years a complete re-assessment of the Notified Body is required, taking a significant amount of time for all parties involved.

ACCESSIBIILTY TO NB – WAITING TIME

In December 2022, two Commission Delegated Regulations were adopted, amending the MDR and IVDR requirements regarding the frequency of complete re-assessments of Notified Bodies. These amendments are intended to change the timing of the first complete re-assessment of a Notified Body after notification from **three** to **five years**, and to establish the frequency of subsequent complete re-assessments for every **five years**.

With their publication in the *Official Journal of the European Union* (OJEU), these delegated acts haven taken into effect as of March 8, 2023:

- Commission Delegated Regulation (EU) 2023/502 of 1 December 2022 amending Regulation (EU) 2017/745 of the European Parliament and of the Council as regards the frequency of complete re-assessments of Notified Bodies
- Commission Delegated Regulation (EU) 2023/503 of 1 December 2022 amending Regulation (EU) 2017/746 of the European Parliament and of the Council as regards the frequency of complete re-assessments of Notified Bodies

According to the EC, *"This will allow the Member States' Designating Authorities to focus on the assessment of new applications for designation as notified body, and notified bodies to process a high number of certifications during the transitional periods, in line with the efforts we are making to improve the effective implementation of the Regulations."*

- **Timeline challenges**

The timeline for implementing the strict IVDR rules depends on the respective class of IVD devices. Manufacturers and marketers of such devices should start the transition periods as early as possible and meet the relevant deadlines for their products to comply with the IVDR. The capacity of Notified Bodies is limited, putting significant pressure on the industry.

How long does it take to obtain a certificate from a Notified Body?

The time it takes to get a certificate of compliance from a Notified Body varies depending on the complexity of the product, the type of assessment required, and the quality system the manufacturer uses. In general, shorter tests can be completed in 6-12 months, whereas more sophisticated reviews can take up to 18-24 months. They do have an extension in place for

the MDR conformity, but most medical device manufacturers will not take any risk and book their notified body as soon as possible.

EFFICIENCY – IN GENERAL AND SPECIFIC NOTIFIED BODIES

While there are some requirements specific to device risk classes, often the regulatory framework takes a 'one size fits all' approach to the extremely diverse array of medical technology products without clear, predictable, dedicated and efficient pathways for regulatory clearance and oversight over the certificate lifetime. These inefficiencies in the short-term create a gap between medical technologies and the patients and medical professionals who need them, while in the long-term undermine trust in the regulatory framework and its long-term viability. Europe needs a more efficient and fit-for-purpose CE marking system, which guarantees access to devices and innovations which live up to their safety and performance claims. A regulatory framework that is modern, sustainable, agile and functions seamlessly is envisioned to ensure medical technology rapidly reaches patients, healthcare professionals and health systems by taking the best of the current process and building in greater efficiency, predictability and convergence.

PREPAREDNESS – (QUALITY DOSSIER)

There are two main types of evaluations: the first one that leads to CE marking and the annual one that checks for continuous conformity.

The Notified Bodies audit's scope has to be obtained before the beginning of their preparation. **Technical, quality, and clinical documentation, as well as the Quality Management System and MDR compliance as a whole, will be audited independently**. They will try to find any inconsistencies and suggest immediate measures to fix them throughout this evaluation. The Notified Body will grant CE marking only once all of these requirements have been met.

The Notified Body will inspect the product and manufacturing procedure thoroughly. All aspects of the Quality Management System (QMS), including relevant standards, labeling mandates, and risk management documents, must be thoroughly reviewed to ensure regulatory compliance. During the on-site audit, the Notified Body may also conduct interviews with employees and witness testing or production processes.

How to make the auditing approval processes easier?

Preparation is essential for making the process easier and should begin well before the application deadline. Here are some pointers to think about:

- Engage with the Notified Body early on to understand their expectations.
- Prepare and review the technical documentation with a third party to guarantee MDR compliance.
- Create a robust Quality Management System and put it in place well before the audit.
- Ensure the clinical data is appropriately organized, acquired using the appropriate technique, and accurately documented.

- Work with a professional regulatory affairs specialist who can guide through the MDR application procedure.

INITIATIVE IN SUPPORT OF SME

Notified bodies are often criticized for prioritizing larger clients over small or medium-sized enterprises (SMEs). However, the TEAM-NB survey from 2022 demonstrates that notified bodies already allocate 74 % of their time to SMEs (TEAM-NB 2023, p.4). Moreover, notified bodies offer trainings for manufacturers, ensuring that SMEs are able to participate at discounted rates.

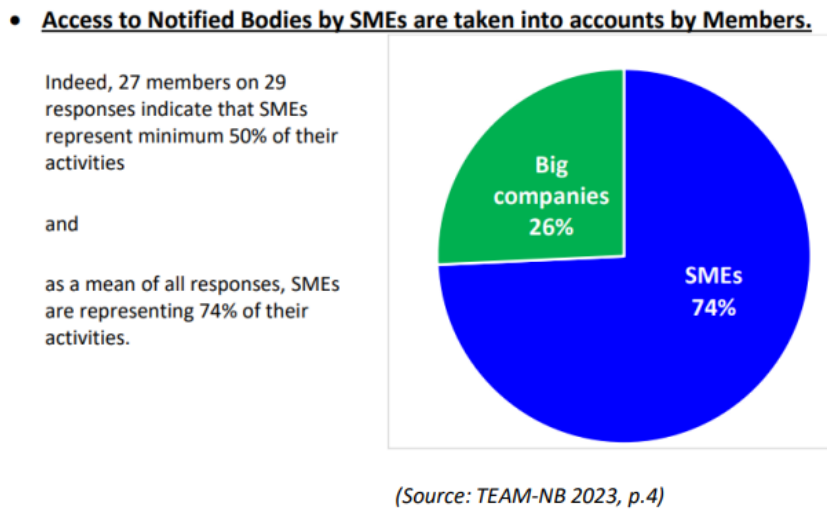

Figure 6 Capacities for SMEs
Source: TEAM-NB 2023

SUPPORTIVE GOVERNMENT INITIATIVES

The Single Market Programme aims to improve SMEs' access to finance and markets. The programme is managed by the European Innovation Council and SMEs Executive Agency (EISMEA).

SMEs are also eligible for funding under the Connecting Europe Facility (CEF) programme, which finances projects related to energy, transport and ICT. The CEF strands are managed by the European Climate, Infrastructure and Environment Executive Agency (CINEA) and the European Health and Digital Executive Agency (HaDEA).

The EU's principal funding programme for research is Horizon Europe, the successor of Horizon 2020. It supports research projects in numerous fields, carried out by organizations or individuals.

SUPPORTIVE NOBOCAP INITIATIVES

(e-guided tool, Matchmaking platform, Training,

- A Voice for start-ups and SMEs in the regulatory ecosystem.
- A Backbone service platform to unlock EU regulation for all.
- A Source of expertise and personas for the regulatory ecosystem.

INNOVATION HUBS – BEST PRACTICES

European Digital Innovation Hubs (EDIHs) are strategic partners in a company's journey to tackle digital challenges and become more competitive. While EDIHs have a regional presence, they also benefit from being part of a pan-European network. These one-stop shops are designed to offer region-specific support while also being part of a broader European network. Their localized knowledge ensures services tailored to the specific needs and innovation ecosystem. The EDIH network's European coverage fosters the sharing of best practices and specialized services across different regions and countries.

PARTNERS

Networks for SMEs

- The Your Europe Business Portal is a practical guide to doing business in Europe. It provides entrepreneurs with information and interactive services that help them expand their business abroad.
- The Enterprise Europe Network helps SMEs and entrepreneurs access market information, overcome legal obstacles, and find potential business partners across Europe.
- The SME Internationalisation support page provides information on foreign markets and helps European business internationalize their activities.
- The single portal on Access to Finance helps SMEs find finance supported by the EU.
- The European Cluster Collaboration Platform offers dynamic mapping of over 1000 profiled cluster organizations worldwide or supports the emergence of new value chains through cross-sectorial cooperation.
- Erasmus for Young Entrepreneurs is a cross-border exchange programme that gives new or aspiring entrepreneurs the chance to learn from experienced entrepreneurs running small businesses in other participating countries.
- COSME, the EU Programme for the Competitiveness of Enterprises and SMEs, supports SMEs in accessing finance, markets and creates a business-friendly environment.
- The SME Assembly, the most significant event for SMEs in Europe, presents different approaches to promoting SME entrepreneurship.

EU INITIATIVES ON REGULATORY SCIENCE

Gaps exist in regulatory science that need to be addressed to improve medicine development and evaluation, ultimately to enable access to innovative medicines that address patients' needs. The European Medicines Agency (EMA) identified around one hundred topics, published as the 'Regulatory science research needs' list. By publishing this list, the Agency hopes to stimulate researchers and funding organizations to consider addressing these needs in their work and programs. The list will be updated periodically with new topics and references to related research.

Examples:

1. Establish the best practices and standards for validation of surrogate endpoints and biomarkers for both regulators and HTA/Payers.
2. Conduct comprehensive review to identify strong candidates among clinically validated biomarkers for regulatory qualification.
3. Map the scientific and technical bottlenecks for the alignment of regulatory authorities for multisite manufacturing of ATMPs, including decentralized manufacturing.
4. Explore the organizational and infrastructural needs to improve the translation of ATMPs from clinical development to clinical use (including bed-side manufacturing) in close collaboration with HTAs.