ESTHER

Proposal for an Industry Driven Initiative on Emerging and Strategic Technologies for healthcare

Outline

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1 Executive summary

The healthcare system is currently undergoing a major transition towards precision medicine and smart connected medical devices. Along with these new medical trends, the healthcare industries, namely the Pharmaceutical, Medical Technology ('Medtech'), Diagnostics, Biotechnology and Digital Medicine[1] sectors are undergoing **a profound transition** towards a more collaborative approach. This development is driven by the convergence **of Key Enabling Technologies (KETs)** with **IT and digital technologies.** The marriage of multi-KETs smart medical devices with the Digital Single Market will create **new industrial platforms for healthcare,** to improve healthcare efficiency while reducing the financial burden on the healthcare systems.

To establish such new platforms it is necessary to **interface so far largely disconnected multibillion euros industries** with different innovation processes and time frames to work and share technologies together. To achieve this, scientific progress on emerging technologies will need to be matched in an **Open Science** approach with industrial strategies addressing societal and patient needs.

The Medtech industry has a central role to play since it will develop the smart connected devices for more personalised approaches in Pharma (e. g. Companion products) and Digital Medicine. In addition, with a total market of roughly € 100 billion[2], Medtech represents a substantial contribution to Europe's healthcare economy by providing more than 575,000 high-quality jobs across 25,000 Medtech companies in Europe. To leverage the innovation potential of these SMEs as main drivers of smart connected technologies, and to counteract their limited investment capacity, an **Open Innovation** approach with new formats of collaboration with multinational companies as well as publicly and privately co-financed infrastructures need to be established.

To further enlarge the investment in R&D and manufacturing, Europe needs to optimise the complex regulation and reimbursement systems in Europe (28 non-harmonised national markets) which often hamper access of new products to the market. A joint initiative of industry and public authorities in Europe is needed to help especially SMEs to adapt to these systems and to discuss how to streamline the approval systems towards a "fast but safe track" to innovation to keep Europe **Open to the World** for foreign healthcare players and investments.

To address these issues the Medtech industry has reached a consensus among MNCs and SMEs to join forces with public authorities and other healthcare stakeholders in an **Industry Driven Initiative on Emerging and Strategic Technology for Healthcare (ESTHER) to make Europe the leading place to invent, develop, manufacture and implement smart and cost effective healthcare solutions.**

ESTHER is an **open and flexible association acting as a platform** to align the efforts and interests of all stakeholders to achieve a synchronised and balanced implementation of all activities. It takes into account the current challenges slowing down innovation and market access and **proposes 20 structuring actions** to support to R&D and disruptive innovation in smart connected devices and improvement of the framework conditions to enable innovations to faster reach the patient.

ESTHER will **leverage private R&D investments with public funding sources** based on Industrial Decision Points and **Key Performance Indicators** to improve the success rate of R&D&I funding. The **impact** of the proposed actions will be evaluated in terms of economic growth of the healthcare industry, number of innovations within sustainable healthcare systems and attractiveness of Europe as the leading region for healthcare technologies.

[1] Also called e-medicine, e-health, tele-medicine, connected medicine

2 Background for EU healthcare transition

The demographic changes in Europe will challenge the healthcare system(s) of the EU at an unprecedented level in terms of quality of service and cost. A **paradigm shift** currently taking place in healthcare from symptomatic treatment of (acute) diseases by blockbusters towards Predictive, Preventive, Personalized, Participatory and Precision medicine will offer new opportunities to address this challenge.

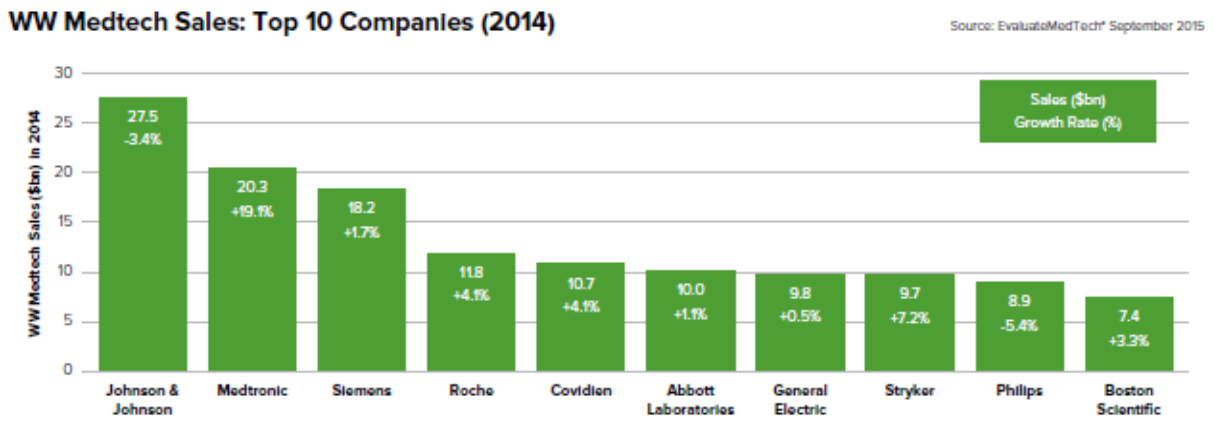
Along with these new medical trends, the healthcare industries, namely Pharma, Medtech, IVD, Biotech and Digital Medicine, will undergo **a profound transition** in the coming years towards a more collaborative approach. For example, Biotech will deliver better characterized and validated biomarkers, which will be utilized by Medtech/IVD to develop new smart diagnostic devices and companion tests used to guide targeted therapeutics produced by Pharma. This development is driven by the convergence **of Key Enabling Technologies (KETs)** namely nanotechnologies, advanced materials, micro/nano electronics, photonics, biotechnologies, and advanced manufacturing. In addition, **IT and digital technologies** will increasingly connect all healthcare sectors and technologies. The Big Data approach to merge for example IVD and imaging data of patients with their personal daily body sensor data (e. g. fitness or Quantified-Self trackers) transmitted via internet will revolutionize personalized diagnosis and therapy monitoring. **The marriage of multi-KETs smart medical devices with the Digital Single Market will create new industrial platforms for healthcare.**

To establish such new platforms it is necessary to provide an interface between largely disconnected **multibillion euros industries** that have very different innovation processes and time frames to work and share technologies together. For example, Medtech is very different from Pharma by the much shorter life cycle of its products, of about 2-3 years vs 10-12 years in Pharma. These differences not only create big challenges for the involved industries but also for the related scientific R&D communities, especially SMEs, which will mainly provide the multi-KETs innovations for the connected smart medical solutions. To achieve this scientific progress emerging technologies need to be matched in an **Open Science** approach with industrial strategies addressing societal and patient needs.

The **Medtech industry** has a central role in setting up the new healthcare platforms, since it will not only develop the smart connected devices for more personalised diagnostics but also the delivery systems for the targeted therapeutic approaches developed by the Pharma industry (e. g. Companion products). In addition, it develops the devices and IVD systems ready for integration of digital and IT features of smart and connected medical systems. This role and the economic weight of the Medtech Industry are often underestimated although central for European economy. With a total market of roughly € 100 billion[3], equivalent to around one third of the global medical technology market, this industry provides a substantial contribution to Europe's healthcare economy. It provides more than 575,000 high-quality jobs, across almost 25,000 medical technology companies in Europe. It is driven by world leading multinational companies (MNCs) such as Johnson & Johnson, Boston Scientific, Medtronic, Siemens, Roche, bioMérieux, Fresenius and Stryker investing in Europe in manufacturing and R&D. Europe is highly attractive for Medtech[4].

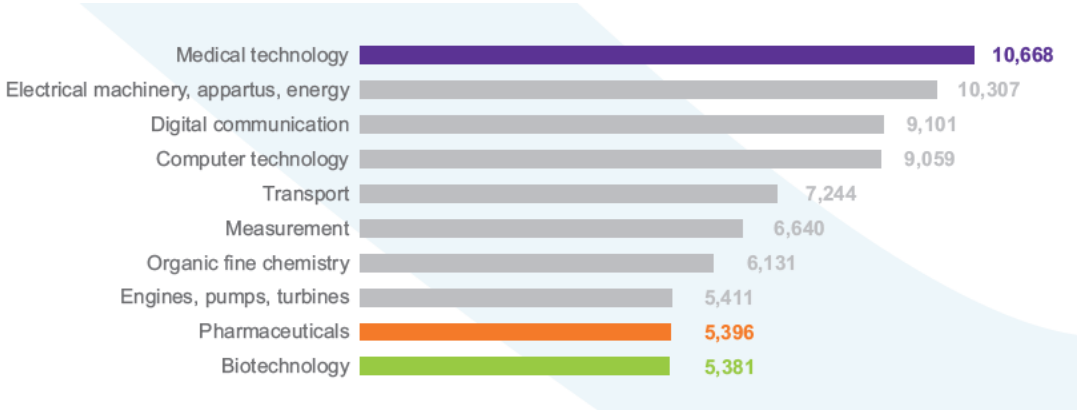
[3] Note: *different figures exist, depending on included countries, e.g. from Global Data 2013 sales are €72 billion, 25% of worldwide market (Medtech Europe seems to be optimistic)*

[4] http://www.qmed.com/mpmn/medtechpulse/us-or-europe-true-king-medtech



Exporting countries are Germany, Ireland, Switzerland, Netherlands, Belgium, Denmark and Finland, which contribute significantly to a positive trade balance in Europe (+ € 15bn). The Medtech sector has a continuous growth rate of 4 to 5% in the past (after 2008 crisis), and growth is forecasted by several analysts[5] to continue at the same level

Besides its significant effect on the European economy in terms of employment, wealth, positive impact on productive and healthy citizens, the Medtech industry is a real **engine of innovation**. The number of patents filed in Europe compared to other industries is extremely high, underlining significant invention/innovation/IP generation capability. Whether medical devices are simple (like a tooth brush) or complex (like a pacemaker) they all constitute **knowledge-based products** since they have been submitted to high constraints in terms of safety, non-toxicity and manufacturing traceability.



Source Medtech Europe from EPO 2013

Medtech will show an even stronger innovative potential in the future. **The R&D intensity (R&D spent related to turnover) is on average 4 to 15 % depending on company size and activity**[6].

Analysts from Evaluate[7] provide interesting figures about R&D spend of Medtech companies.

[5] Average growth is estimated at 5,9% worldwide between 2013 and 2020 and 4,9% in Europe (Global Data 2015). BMI's estimates is 2,7% between 2014 and 2019 given the low trend for economic growth in Europe. These figures depend a lot on segments considered (the Esther task force can provide details).

[6] To be compared to pharmaceutical industry 14% and biotechnology about 20%

[7] Evaluate Medtech World Preview 2015, october 2015

WW Medtech R&D Spend (2007-20)

Source: EvaluateMedTech® September 2015

Year	WW Sales ($bn) 2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Medtech R&D Spend	18.1	19.9	19.6	20.7	22.6	23.2	23.9	24.0	23.9	24.9	26.0	27.2	28.3	29.5
R&D Spend Growth %		+9.8%	-1.5%	+5.3%	+9.6%	+2.5%	+2.9%	+0.6%	-0.4%	+4.0%	+4.4%	+4.5%	+4.2%	+4.2%
WW Medtech Sales	274.2	302.6	306.3	323.8	349.9	359.0	366.3	375.2	368.7	387.8	409.1	431.5	454.0	477.5
R&D as % of Medtech Sales	+6.6%	+6.6%	+6.4%	+6.4%	+6.5%	+6.5%	+6.5%	+6.4%	+6.5%	+6.4%	+6.4%	+6.3%	+6.2%	+6.2%
R&D as % of Medtech Sales (Top 20 in 2020)								7.9%						7.7%

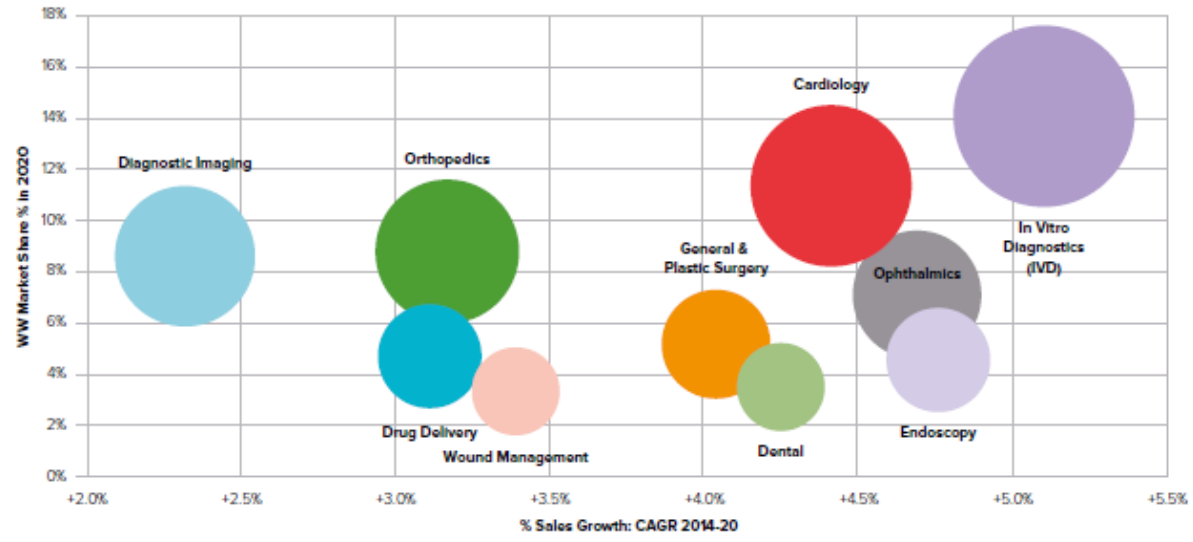
With the following assumptions:

- R&D spend above corresponds to 75% of activity (Top 20 companies only)
- European sales represent roughly a third of global sales
- Investment in R&D shows its impact 4 to 5 years later in sales (product life cycle)

A kind of "**amplifier effect**" between R&D spend over 4 years and sales over the next period of 4 years[8] can be calculated. Accordingly, the forecasted annual R&D spend in Europe for 2020 (from Evaluate Medtech) is equivalent to €11.5 billion[9][10]. With an **additional contribution of €150 million of public funding** for R&D projects annually (similar to IMI II) the expected impact, to be measurable 4 to 5 years later, would be around **€10 billion of additional sales** over a 4 years period.

Analysis on Top 10 Device Areas in 2020, Market Share & Sales Growth (2014-20)

Source: EvaluateMedTech® September 2015



Note: Size of Bubble = WW Sales in 2020

[11]

Among Medtech segments, In vitro diagnostics is the most dynamic in terms of innovation and growth. The global in vitro diagnostics market is expected to reach $74 billion in 2020, with an average annual growth rate of 5.3 % from 2014 to 2020[12]. R&D intensity is high for IVD: bioMerieux dedicates 12 %[13]

[8] A factor of 17 is applied. contact ESTHER task force for calculation details

[9] It can be calculated as follows (29,5/075)x0,33 = 13 billion$ which is equivalent to 11.5 billion€

[10] Consistent with figures given by EFPIA for pharma 30 billion€ in 2013, for a larger sector, more R&D intensive.

[11] Source Evaluate Medtech World Preview 2015, october 2015

[12] Global In vitro Diagnostics, 2013-2020, Allied Market Research

[13] Source bioMerieux

of its turnover to R&D. Technology is one of the main driver of IVD and convergence of technologies a major opportunity.

For example, photonics is a Key Enabling Technology for Medtech. In 2012, medical optical in vitro diagnostics, endoscopy and medical lasers represented a global market of €37 billion. This market is expected to reach €64 billion in 2020[14].

Digital health will also deeply impact Medtech products and services. The 4 main segments (telehealth, mobile health, Electronic Health Record and wireless health) represented in 2013 $61 billion and will see a tremendous growth to $233 billion in 2020[15]. Established **digital industries are looking to expand into new areas and digital health** (Apple, Google, Verizon, IBM, SAP…). This convergence will create new opportunities for Medtech.

Besides market dynamics and technology drivers, the **sector is consolidating, with a lot of Mergers and Acquisitions** (211 M&A in 2014) like Medtronic which bought Covidien for $50 billion (mega deal closed in 2015). This demonstrates that funding is available to finance M&A in medtech. On the contrary, **venture financing felt by 14%**. Importantly, all of the top 10 financing rounds in 2015 were done by US-based companies.

European companies, mostly SMEs, are almost absent from this M&A activity consolidation process because they **have limited financial capacities and no or limited manufacturing and sales operations**, in great contrast with the great innovation capacity. To more efficiently foster the translation of their technological solutions to smart medical systems an **Open Innovation** approach with new formats of collaboration as well as publicly and privately co-financed infrastructures needs to be established. This will create an efficient multi-KET supply chain for healthcare products based on innovative SMEs. It will also be used by large MNCs, which can successfully bring new products to the patient but don't have any longer the resources and know-how to develop in-house multi-KET smart products.

To sustain or even enlarge the investment of MNCs in the new value chains, Europe needs **to optimise the ecosystem for translation of emerging technologies into healthcare products**. One important target for **improvement is the complex regulation and reimbursement systems** in Europe (28 non-harmonised national markets) which often hamper access of new products to the market. These systems also face the challenge to adapt to the speed of the development of smart and connected healthcare products. US-FDA has already started to adapt by providing the necessary fast tracks for innovative medical technology approval. In addition, US-FDA works closely with SMEs to further facilitate market access for innovative products in the US. In contrast the new European Medical Device Directives, for example, coming into force in 2016 will significantly increase the standards for CE approval for Medtech products. The proposed joint initiative of industry and public authorities in Europe will especially help SMEs to adapt to these new conditions and to discuss how to streamline the approval systems towards a "fast but safe track" to innovation.

Once in place, these actions will keep Europe **Open to the World** and maintain investments of global Medtech players in European R&D and manufacturing. This will not only increase the diagnostic and therapeutic arsenal for healthcare, but also boost the European industrial competitiveness, number of jobs and economic growth in the global competition with the US and Asia.

[14] Market study conducted by AT Kearney for BMBF (German Ministry of Research), article in Optik & Photonik Volume 9, Issue 2, may 2014 http://onlinelibrary.wiley.com/doi/10.1002/opph.201400051/pdf

[15] On the road to digital health, European Biotechnology, Autumn edition, vol 14, 2015, market figures from AD Little, GSMA, Allied Market Research, Accenture, HIS, Marketsandmarkets

To achieve this the Medtech industry represented by their trade associations Medtech Europe, Eucomed, and EDMA has recognized the need to accompany the major transition of European Healthcare and therefore proposes an **Industry Driven Initiative on Emerging and Strategic Technology for Healthcare (ESTHER)** supported by the Pharma industry represented by EFPIA, several European Technology Platforms (Nanomedicine, Biomaterials, Smart Systems) and several Directorates General of the Commission

3 Initiative to drive EU healthcare transition

A truly multi-dimensional and coordinated European effort of all public and private stakeholders is necessary to sustain the attractiveness of Europe as a leading global region for healthcare technologies. To reach this goal a better alignment of scientific and technological progress with industrial strategies and medical needs is required. If efficient structures are in place to leverage the innovation capacity of industry, of research & technology providers, and of the clinical ecosystem, **Europe could become an even more attractive and successful place in the global competition for ideation, translation, and validation of smart healthcare technologies**.

Driven by the Medtech industry, a consensus among multinational companies and SMEs was reached to join forces with public authorities and other healthcare stakeholders in an **Industry Driven Initiative on Emerging and Strategic Technologies for Healthcare (ESTHER)**. The mission is to

Make Europe the leading place to invent, develop, manufacture and implement smart and cost effective healthcare solutions

ESTHER is an open and flexible platform to align the efforts and interests of all stakeholders to achieve a synchronised and balanced implementation of all activities at all levels (EC, national and regional). This will **ensure the global competitiveness of the European healthcare industry** in the emerging sectors of precision medicine and smart connected systems.

ESTHER takes into account the current limitations which are slowing down or even blocking innovation and market access and proposes structuring actions in two directions: a) **support to R&D** and disruptive innovation in healthcare and b) **improvement of framework conditions** to enable innovations to faster market access (shortening of development lifecycle).

ESTHER will **leverage private R&D investments with public funding sources** coming from Horizon 2020, the European Investment Bank, the European Regional Development Fund, and the European Fund for Strategic Investments (EFSI), along with national and regional funding programs of individual Member and Associated States.

The monitoring is based on Industrial Decision Points and Key Performance Indicators necessary to improve and evaluate the success rate of R&D&I funding. The impact of the proposed actions is evaluated in terms of economic growth of the Medtech industry, number of innovations within sustainable healthcare systems and attractiveness of Europe as the leading region for healthcare technologies.

4 Objectives and Actions of ESTHER

ESTHER will act as a promoter and manager of collective actions to reach 3 main objectives. These correspond to the 3 priorities "Open Science", "Open Innovation" and "Open to the world" set by Commissioner MOEDAS.

1. **Foster research, development and innovation towards smart and connected medical devices** by aligning scientific progress and emerging technologies with industrial strategies addressing societal and medical needs. **(Open Science)**

2. **Accelerate the translation process of smart medical solutions on healthcare markets** by increasing economic and social outputs of public investment and R&D efforts on smart medical devices. **(Open Innovation)**

3. **Increase attractiveness of Europe for global healthcare industries** by keeping European skills and regions attractive for global talents and investments. **(Open to the world)**

To reach these objectives a coordinated program of all stakeholders is needed without generating a significant extra administrative burden. Some of the proposed actions will be performed by the ESTHER association, while others need to be implemented in collaboration with industry or public actors such as the EC, the Member States, regions or public bodies such as regulation agencies or even healthcare providers.

4.1 Open Science

Developing R&D&I excellence in science and technologies is a priority to realize a connected digital healthcare market by developing smart medical technologies. This R&D&I must be based on excellent basic interdisciplinary research aligned with R&D topics of industrial relevance. Therefore, the input of industry, both large and small companies, is a *sine qua non* condition for turning these topics into marketable innovations, taking into account the needs from end-users (patients, clinicians, healthcare systems).

The first targeted audience for developing this excellence are the technology providers (technical universities, RTOs, SMEs). It is estimated[16] **that 3000 - 4000 European SMEs have the capacity to perform R&D in smart medical devices**. Their innovations often come from the cooperation between clinicians knowing and expressing properly the clinical needs, and engineers of SMEs bringing their technological knowledge to develop a preclinical or early clinical proof of concept. Therefore ESTHER will serve as a platform where scientific research, industrial organisations and healthcare providers will meet regularly to **match scientific progress and new technological trends with industrial strategies**. Furthermore, representatives of the approval systems (Notified Bodies, Regulation Agencies) should be involved early on to take into account possible problems in the approval process of products based on multiple technologies. The result of these discussions will be a hierarchy of R&D topics for various public EC, national or regional funding agencies/programs. This integrated approach will significantly increase the chance of turning excellent science in to marketable products

Action #1: Prioritise and update of the Strategic Research and Innovation Agenda (SRIA) for smart connected Medtech

Action #2: Support multi-KETs collaborative project development until to de-risk the opportunity sufficiently to enable private investment

[16] Source : unpublished data from Medtech-Europe

Action #3: Support experts and S&T networks in smart Medtech

4.2 Open Innovation

Development of new Medtech products is highly challenging based on the duration of the required development cycle, and the many risk factors involved in the process. While most large Medtech companies in the past had fully integrated R&D facilities and expertise, within minimum requirement for outsourcing, the new generation of devices for Medtech will require expertise and infrastructure for integration of such diverse aspects as pharma / biopharma active ingredients, additive manufacturing, connectivity and cyber security, and power management. Therefore, vertical integration of the supply chain within the large companies is no longer possible, while SMEs will be greatly challenged to gain access to the relevant technical expertise and infrastructure to enable products development and manufacture. The additional challenges such as access finance for product development, the need to address regulatory hurdles for Class IIb and Class III devices, and navigation of the often ambiguous reimbursement requirements in different healthcare systems within and outside the EU, can be overwhelmed for SMEs. **ESTHER will streamline the processes for development and commercialisation of smart medical devices within the EU and act as a Translation Hub to accelerate the industrial deployment of KETs in smart Medtech** by improving the financial, regional and regulatory ecosystem for translation.

4.2.1 Access to public finance

Europe is in an intense global economic competition with the US and Asia about jobs and economic wealth. This is especially critical in situations where industries are going through a transition towards new value chains and markets. To foster the current transition of the healthcare industries, Europe has increased public funding of R&D activities in KETs for healthcare, which has led to technological breakthroughs and working prototypes at the laboratory level. Relevant research and development under FP7 had a volume of about €2.5 billion through EU funding provided by the NMP, ICT, HEALTH, Marie-Curie and ERC programs for around 1250 grants. In the calls for proposals from **H2020 Work Programme 2014,** in the order of **€500 million** has been committed so far for about 240 projects involving KETs relevant for healthcare. In addition, the EIT-Health Knowledge and Innovation Community of the European Institute of Technology (EIT), has been granted a budget of €250 million to promote entrepreneurship and innovation in active and healthy ageing.

ESTHER will **mobilise and ensure synergies between different public funding sources** coming from Horizon 2020, the European Investment Bank including the InnovFin SME Guarantee scheme, the European Regional Development Fund, the European Fund for Strategic Investments (EFSI), along with national and regional funding programs of individual Member and Associated States. The regional activities visible in many European regions already represents a huge financial commitment by public and private actors. These existing public and private commitments offer great synergy potential, which could be further enhanced if the interface across regions could be coordinated and the current subsidy restrictions are strategically revised to target novel healthcare solutions for EU citizens and the future competitiveness of the EU medtech industry.

The public funding provides excellent and attractive conditions for global companies, investors and researcher to come to Europe and support the transition of the healthcare sector.

ESTHER will initiate discussions on those topics with the relevant public and private stakeholders such as EC, regional governments or corporate investors of large companies to make them aware of the

potential of the different instruments with regard to speed of translation, impact on economic wealth and new cost effective medical treatment for patients.

Action #4: Analyse the financial tools provided by EIB for accelerating the development of Medtech SMEs; Prepare a business case for mobilization of the European Funds for Strategic investments

Action 5: Set-up the bases of the development of Important Projects of Common European Interest IPCEI in medical technologies

Action #6: Facilitate access of suppliers of smart Medtech to Public Procurement

4.2.2 Innovation in SMEs

i. Improving knowledge about **market access** conditions for SMEs

Implementation of multi-KETs in new smart medical devices will require new combinations of industrial sectors such as Pharma, Biotech, Imaging, ICT or electronics. The **new value chains need to be analysed and set-up** to enable the corresponding business opportunities. ESTHER will provide tools and platforms to enable exchange of information between different industries to interface and adapt their production capacities to the new technology requirements. It will especially enable SMEs to integrate their innovative technologies into the manufacturing lines of these value chains.

Interfacing between the different stakeholders will take place through

- **technology days, brokerage events** at large fairs or conferences such as Medica, BioEurope or NanoMed Europe
- **web based forums or market places** (like *ComeToWin*, *GateOne* or *SmarterSi*).
- **bi-annual showcases** of the most translatable products/technologies to MNCs back to back to annual meetings or conferences of industrial associations like EFPIA, Medtech-Europe or COCIR
- **exposure to VCs and investors** in parallel sessions at large European/international business conventions like Bio-Europe, European Medtech-Europe

Action #7: Implement a series of information, communication and training tools and events specifically dedicated and accessible to SMEs, on translation and market access

Action 8: Integration of ESTHER priorities into EIT Health

ii. Translation Advisory Board

An important instrument to enable SMEs and research groups to successfully use the above instruments is a **Translation Advisory Board (TAB)** [17]. The TAB will consist of high level industrial experts **with a recognized track record in technology translation and innovation** to make **promising projects grow faster** into innovative products for healthcare. ESTHER will continue the successful board set-up by ETPN and the H2020 project ENATRANS to shape interesting projects and increase their potential and chances to bring their product(s) to the market.

[17] on the model of the TAB - Translation Advisory Board – established in 2015 under the ENATRANS H2020 Coordination and Support Action

Action #9: Set-up and run a Translation Advisory Board composed of industrial experts with proven expertise which will guide, help and accompany SMEs at the successive steps of their translation pathway

4.2.3. Implementation in regional clusters

A very promising approach to effectively interface different KETs and integrate them into smart medical solutions, is the clustering of all stakeholders covering the whole value chain from TRL1 to TRL8 in close vicinity to each other. The proximity to each other facilitates personal interaction of researchers, engineers and clinicians with companies, investors and authorities. This creates a constructive seed-atmosphere building up mutual trust and understanding each other's language, expectations and business requirements. In addition, SMEs can join forces with other SMEs present in the region, to share costs of employing regulatory experts to enable regulatory approval of their products. Examples for such **smart specialization of regions** are the German BioRegion STERN, the French Rhone-Alps cluster and the Irish medical technology cluster. Close coordination with networks of Regions like in the Vanguard Initiative will be utilized.

With the help and support of ESTHER, regional clusters will

- initiate mapping and interfacing of regions with highest potential and organize exchange of good practice between them, building, for example, on initiatives such as the Vanguard Initiative[18]
- identify needs such as critical R&D infrastructures or competent clinical investigation centers for improving the performance of a region
- help to develop new concepts for R&D centers, which pick-up proof-of-concept results from basic research and transform them with their own technical personnel and business staff into industry-ready prototypes. Such infrastructures will improve the current low translation rate of IP at universities and other basic research institutes, will create many high value jobs at the interface between science and products not available right now, and will significantly de-risk R&D for companies.
- make proposals for financing such infrastructures based on existing Instruments such as ESFRI, ERDF, EIT, and EIB

The coordination and implementation of these actions are mandatory to establish and foster a SME based supply chain of key enabling technologies for the emerging new healthcare value chains.

Action #10: Implement a network of advanced smart Medtech regional clusters

Action #11: Establish support to infrastructures of European interest

Action #12: Regional support to clusters and infrastructures

Action 13: Launch a worldwide *start-ups Catapultor* (accelerator of start-ups development) in 4 regional clusters

[18] www.s3vanguardinitiative.eu

4.2.4 Development of regulatory sciences

The healthcare system is highly regulated involving many different authorities at EU, national and even regional level. To get market access a new product has to pass a complex and time consuming process of pre-clinical and clinical approval followed by pricing and reimbursement evaluation and negotiations. Starting in 2016, new EU Regulations on Medical Devices and In Vitro Diagnostic Devices will come into force, which will put an even higher burden on getting market approval. It is expected that many small and mid-sized companies will not have the financial and personnel resources to bring their products through the new regulation process. ESTHER will provide concrete support by:

- **Establishing information portals for SMEs** to inform about the main EC and national systems for market approval and reimbursement based on the H2020 project ENATRANS which has started to establish this service.
- **Linking with regulators, HTAs and healthcare payers** to initiate and maintain a dialog with European and national public authorities like EMA or EU HTA NET[19]. The goal is to inform public authorities about the latest trends and future developments in innovative Medtech and, vice versa, to update the community about changes in the approval requirements.
- **Training of specialised personnel** in SMEs by helping to transfer the few already existing training courses such as the one offered by DGRA[20] to other member states. In addition, ESTHER will engage with universities to set-up courses in basic regulatory requirements to establish a basic awareness and understanding of this important barrier to the market.
- **Definition of Topics for regulatory science projects** based on the requirements from industry and regulators for improvement of scientific knowledge as a basis for regulation, and for standardization of test methods.
- The multi-KETs nature of new products also requires the identification and **accreditation of clinical research centers** which will enable SMEs to quickly identify which facilities have the relevant expertise and capacity to evaluate/validate their cross KET prototype/product shortening the time to validation often not compatible with current durations for investment cycles.

Action #14: Establish a dialog with regulators, Health Technology Assessment agencies and payers

Action #15: Improve training of specialised personnel on regulatory science, accessible to SMEs

Action #16: Define of topics and business cases for regulatory science projects

Action #17: Facilitate access of SMEs to the regulatory system

4.3 Open to the World

Most emerging markets are investing heavily in their healthcare systems, and there is a growing middle-class population in the emerging markets which are demanding the high standard products that EU develops and manufactures. However, most products currently developed and manufactured within the EU were designed for western markets, and the business models were based on the richer healthcare systems and the often relatively low volumes of sales possible. Based on the expanding

[19] EU-HTA-NET is a network of European HTA agencies http://www.eunethta.eu/
[20] http://dgra.de/english/dgra/purpose_and_aims.php

opportunities in these new markets, different business models are possible without compromising on safety or margins. This will enable EU based SMEs to leverage from the quality reputation of European Medtech products, to access new and emerging markets for new smart diagnostic and therapeutic products. As for the telecoms industry, many of these markets don't have the established healthcare infrastructure like in EU and US, so there are great opportunities for ESTHER to enable EU SMEs to exploit the opportunity to deliver new affordable healthcare solutions to the global population. Therefore, a benchmark of the Medtech markets and regulations in the main regions of the world would be very helpful for SMEs willing to export and which have a limited capacity for a global survey of market access conditions. ESTHER will ensure that the high quality smart Medtech-based products and services developed and manufactured within the EU, will be the global benchmark in safety and affordability for the global population, thereby ensuring that emerging markets provide new opportunities for the EU smart Medtech industry.

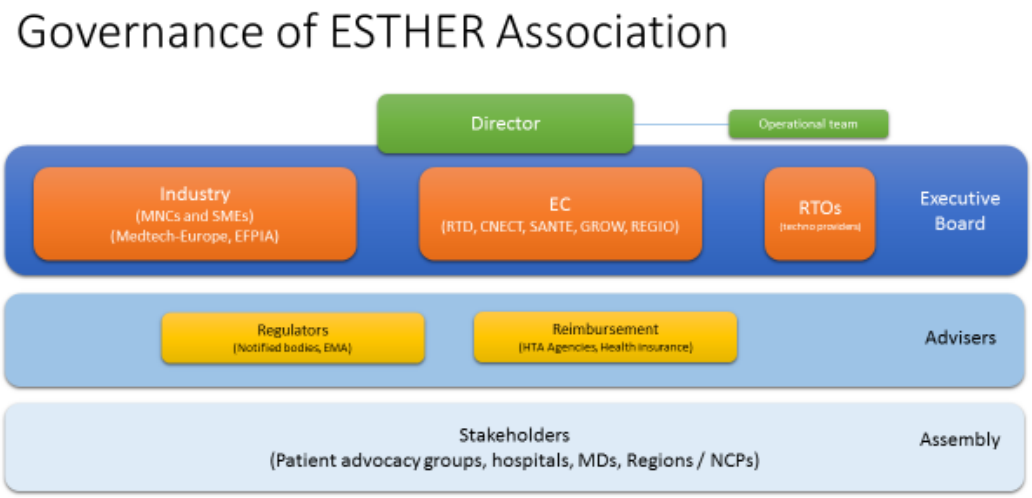
As a support for future exports, establishing exchanges of personnel between research organisations and industry would initiate R&D co-operations between these countries, which could lead to an economic cooperation in a few years.

Action#18: Benchmark and monitoring of US and Asian markets and regulations as a support to European exports

Action #19: Set-up training networks for exchange of personnel between Europe and Emerging Economies

5 Implementation and governance

Currently there is no unique trade association covering the entire panel of industries contributing to healthcare technologies. Therefore, Medtech-Europe, which represents by far the largest industrial community covering both MNCs and SMEs, is the best organisation to mutually drive ESTHER together with other private stakeholders (industrial companies, industrial associations, research institutes, health insurance, patient advocacy groups), and in partnership with public organisations (European Commission, National and Regional governments, public health authorities, regulation bodies, public buyers).



ESTHER is organized as an **Association** open to stakeholders in the field of healthcare technologies and led by an Executive Board with representation of industry, the Commission, and RTOs in close collaboration with regulators and healthcare providers as advisers. Such association is a totally new concept which will significantly increase the visibility of the smart healthcare technologies industrial sector.

The ESTHER Association aims at signing an agreement for a multi-annual partnership with the EC to align, implement and drive the efforts of all stakeholders at all levels to achieve a synchronised support for implementation of all activities listed above. This will help to maintain the global competitiveness of the European healthcare industry in the context of the new medical trends precision medicine and smart systems.

Action#20: Implementation and operation of ESTHER Association, including the partnership with EC

6 Impact assessment and Key Performance Indicators

Performance measurement using key performance indicators (KPIs) is an integral part of ESTHER. This provides important feedback on the delivery and performance of services. It also promotes accountability by demonstrating to key stakeholders the achievement of targets and demonstration of results that the new measures are achieving.

Three main categories of Key Performance Indicator are proposed:

- Premarket business operations
- Financial performance
- Regulatory

6.1 Premarket business operations

Key Performance Indicators in this category should aim to demonstrate how the scientific and innovation development process is progressing along with key business and financial developments. Progress is preferably assessed on passing certain value-added milestones, like passing from pre-clinical development to obtaining approval for clinical testing, which will allow investors to assign value to the R&D achievements. The aim is to attain a Technology Readiness Level that is compatible with being ready to enter clinical testing in humans. These would comprise:

- The number of projects financed from the European Commission and national funding agencies
- The volume of financial investments going into these projects.
- The number of projects that attain Technology Readiness Level 6[21] (First testing in Human)

6.2 Financial Performance Indicators

- The number of Venture Capital and other Investments in Healthcare Companies and SMEs
- The number of SME and other company set-ups in the healthcare field
- The number of SME and other company mergers and acquisitions in the healthcare field
- The number of failures of SMEs and other companies in the healthcare field

[21] TRL6 :Technology Demonstration : Phase 1 clinical trials support proceeding to phase 2 clinical trials. Investigational New Drug (IND) application submitted to and reviewed by FDA (CBER) (source : Table 2 Technology Readiness Level Descriptions for A Pharmaceutical Product, US Army Medical department, Medical research and Material command)

- The annual turnover of the sector

6.3 Regulatory Key Performance Indicators

- Number of applications received by EMA or Notified Bodies for Scientific Advice.
- Number of applications received by EMA or Notified Bodies for Data Certification.
- Number of applications received for market authorization by EMA and Notified Bodies.
- Number of product approvals by EMA and Notified Bodies relevant to Key Enabling Technologies

Additional parameters to be considered might comprise:

- Processing times for applications for registration of KET-related products
- Number of marketing applications received for KET-related products
- Number of notifications of clinical trials received for KET- related products
- Number of inclusions on the EU Register of KET- related products.

It is of course possible that further Key Performance Indicators will need to be devised as time progresses.

7 Conclusions

ESTHER will deliver transformational benefits for Europe based on four key pillars.

1. **ESTHER will drive the convergence of technologies, business models and industries** that will ensure that the EU will be the choice location for invention, development and manufacture of the new generation of smart medical devices.

2. **ESTHER will facilitate the efficient translation of clinical needs into healthcare solutions based on smart medical devices**, by adopting a holistic approach to address challenges for SMEs related to R&D&I, clinical validation, finance, reimbursement, regulation, and other challenges as applicable.

3. **ESTHER will enable sustainable healthcare systems within the EU**, by ensuring the development of smart technologies which deliver cost-effective healthcare solutions, such as enabling early diagnosis, early discharge from hospital, independent living, telemedicine and ensuring clinical proficiency of healthcare workers.

4. **ESTHER will ensure that the high quality smart Medtech-based products and services developed and manufactured within the EU, will be the global benchmark in safety and affordability for the global population**, thereby ensuring that emerging markets provide new opportunities for the EU smart Medtech industry.

8 Annex 1: Cross-KETs solutions for healthcare

Among the many potential innovations in the health and healthcare domain, the integration between KETs is deemed to be of highest benefit to innovation fields in the following domains *(ref : European Commission Key Enabling technologies and Cross-cutting Key Enabling Technologies, RO-cKETs, Roadmap for cross-cutting KETs activities in Horizon 2020, November 2014.)*

Examples are:

Devices and systems for targeted diagnostics and personalised medicine	**More efficient and less invasive drugs and therapies**	**Smart systems and robots for healthcare services**
Portable point of care devices for instant diagnosis based on microfluidics and biosensors. Technologies to identify and validate biomarkers for predictive personalized medicine. Targeted molecular Imaging diagnostics and/or focused therapies Minimally / non-invasive devices for diagnostics and/or focused therapy or surgery Multiplexing devices for fast, accurate and easy in vitro diagnosis of liquid biopsies.	Implantable devices for controlled drug delivery (e.g. diabetes or pain therapy and management). Improved delivery systems, surface coatings and coating techniques for drugs Bioengineered tissues (including organs) for regenerative therapies	Connected systems for ambient assisted living Robots supporting professional care Robotized systems to assist patients mobility or other living functions

9 Annex 2: Examples of cross-KETs smart medical solutions

9.1 Additive manufacturing for personalized smart devices

Additive manufacturing is revolutionising the way some devices are made, moving from traditional precision engineering tools for grinding things down, into 3D printing in a wide range materials. These will enable personalised devices, reduce manufacture times and make it easier to provide bespoke personalised solutions for individual patients e.g. based on the patient's unique anatomy. However, transformation of traditional precision advanced manufacturing into products primarily based on additive manufacturing will require modification of the materials leveraging KETS in nanotechnology and advanced materials, modifying the material properties using the photonics KET, and in the case of combination products, this will also leverage the industrial biotechnology KET. Examples of products which include such multi-KET competences include prostheses, artificial tissues / organs, and smart implantable systems. To date, SMEs have primarily relied on Research Performing Organisations (RPOs) to provide the research infrastructure and capabilities that they lack for developing these multi-KET systems. However, an alternative model is that many large companies could open up their infrastructure and processes (i.e. like a foundry) to provide access to SMEs (and even RPOs) to very advanced capabilities around design and manufacturing such as additive manufacturing, electronics (e.g. Philips Innovation Services and Greenhouse pilot line within InForMed). This ecosystem could support a symbiotic relationship between SMEs, multinationals and RPOs which accelerates translation of medical devices by opening up manufacturing facilities of industry to non-competing SMEs (and RPOs) such as those working on different product ranges to that of the host. In this case, it can also resource the host company to grow and enhance its own capabilities based on the external revenue stream. ESTHER will also identify where applicable the needs for dedicated facilities and expertise to support this shared advanced manufacturing capabilities (in MNC, SME and RPO facilities), which might have been considered as incremental research previously, but which is evolving very rapidly with new materials, processes, and products, as well as the crossKET integration aspects.

9.2 Smart wearable and implantable systems

Smart wearable and implantable systems will be developed for enabling longitudinal monitoring with closed loop feedback for monitoring both the delivery of drugs or Advanced Therapy Medicinal Products, and the achievement of the desired therapeutic effect. This will ensure that the dosage and treatment is personalised and optimal for each patient. Such integrated closed loop systems are already in place for cardiac rhythm management, and are well advanced for emerging neuromodulation and electroceutical systems. Integrated solutions are needed, which can sense the therapeutic products themselves or reporter molecules integrated with the therapeutics, as well as various electrophysiological stimuli (e.g. EEG, ECG and EMG), biomarkers (e.g. glucose, lactate, corsisol, hormones, inflammatory markers, etc), and a range of analytes (e.g. CO2, O2, Ca+, Mg+, etc). Integrated signal processing will be needed to monitor and alert for significant physiological changes as a means of monitoring disease, as well as providing feedback on the efficacy of a treatment programme. These systems will communicate with relevant EMR (electronic medical record) systems and action healthcare professionals as applicable based on sophisticated algorithms designed to identify patterns or ranges of concern (i.e. informing unambiguous clinical decision protocols). These smart wearable and implantable systems will therefore require multi-KET capabilities, involving integration of micro- and nanoelectronics , photonics (components and subsystems), likely including integrated circuits and photonic integrated circuits for miniaturisation and power efficiency, energy harvesting and storage technology, advanced sensors, proprietary embedded software for signal processing, data encryption and communication to EMR system. They will also require biocompatible packaging (advanced materials) and need to combine precision engineering and electronic / photonic

assembly (advanced manufacturing in accordance with ISO13485). ESTHER will be key to enabling the development of these systems where cross-KET expertise and infrastructure needs to be combined into a complex supply chain, but one which will distinguish EU from other global sites for the development and manufacture of these technologies.

9.3 Smart surgical device for augmented reality during surgical procedures

Smart surgical device for augmented reality during surgical procedures. A new generation of surgical devices and instruments are being developed which will have advanced sensing and actuation capabilities, designed for realtime identification of target tissues (e.g. metastatic cancer tissue) while enabling tissue sparing of critical tissues such as nerves and blood vessels. These systems require advanced biophotonics, electrochemical and other sensing modalities to be integrated into ergonomic surgical tools, with realtime feedback on the tissue types at or near to the advancing surgical tool as applicable. The challenges of miniaturisation, realtime sensing and augmented reality visualisation require cross-KET approaches, with some robotic systems also integrating autonomous actuation based on complex sensing and image / sensor processing. ESTHER will help drive the development of solutions for such “augmented reality” during surgical procedures, involving sensing in the patient, on the surgical tool, on the clinical professionals and in the environment to facilitate precision medicine and minimise the risk of adverse events. In parallel, ESTHER will facilitate the development of new advanced simulators to enable training of clinicians based Proficiency Based Progression, to minimise the number of avoidable medical errors.

10 Annex 3: Tentative budget

A tentative budget over 8 years is proposed, to cover all actions listed in ESTHER proposal. These figures should be confirmed by the different funding sources mentioned. This table is just intended to give a scale of the ambition of ESTHER action plan.

Priorities	Sub-priorities	#	Actions	Funding source	DG	Instrument	2016	2017	2018	2019	2020	2021	2022	2023	Total
R&D&I (Open science) to realise a connected digital healthcare market by developing smart medical technologies	Prioritisation of R&D topics	1	Elaboration and update of SRIA	LEIT	CNECT, RTD	CSA	0,2		0,2		0,2		0,2		0,8
		2	Support to multi-KETs R&D collaborative projects	LEIT, SC1	CNECT, RTD	RIA, IA		150	200	200	200	300	300	300	1650
	Excellence in science	3	Support to individuals and networks in KETs applied to smart medtech	ERC, MSCA, FET	ERC			100	100	200	200	200	200	200	1200
Translation hub (Open innovation) to accelerate the industrial deployment ok key enabling technologies in smart medical systems	Access to risk finance	4	EIB : Loan, Equity, InnovFin, ESFI	EIB					100	100	200	300	400	400	1500
		5	et-up the bases of the development of Important Projects of Common European Interest IPCEI in medical technologies		GROW			0,2	0,2	0,2	0,2	0,2	0,2	0,2	1,4
		6	Access to Public Procurement		RTD	RIA, IA			20		20		20		60
	Innovation in SMEs	7	Improving knowledge about market access conditions for SMEs	ESTHER	RTD	CSA		0,5	0,5	0,5	0,5	0,5	0,5	0,5	3,5
		8	Integration of ESTHER priorities into EIT Health	EIT	EAC			10	10	10	10	10	10	10	70
		9	Set-up and run a Translation Advisory Board	ESTHER	RTD	CSA	0,5	1	1	1	1	1	1	1	7,5
	Regional clusters (implementation)	10	Network of smart medtech regional clusters (incl. Mapping and interfacing) ; Exchange of good practices among regional clusters	Spreading Excellence	REGIO	ESIF		0,3	0,3	0,3	0,3	0,3	0,3	0,3	2,1
		11	Support to infrastructures of European interest	INFRA	RTD	ESIF, INFRA		20		20		20		20	80
		12	Regional support to clusters/infrastructures	ESIF	REGIO		5	10	20	40	40	40	40	40	235
		13	Start-ups Catapultor	COSME	GROW			50	40	40	40	40	40	40	290
	Regulation of medtech	14	Linking with regulators, HTAs and payers	COSME	GROW	CSA			0,2	0,2	0,2	0,2	0,2	0,2	1,2
		15	Training of specialised personnel on regulation		EAC		0,1		0,1		0,1		0,1		0,4
		16	Definition of topics and support to regulatory science projects		GROW			0,2	5	5	5	5	5	5	30,2
		17	Easier access for SMEs to the regulatory system	COSME	GROW				10	10	10	10	10	10	60
Internationalisation (Open to the world) to make Europe a stronger global actor	Keep Europe attractive for smart medtech companies	18	Benchmark and monitoring of US and Asian regulations for EU exports	COSME	GROW	CSA	0,4		0,5	0,5	0,5	0,5	0,5	0,5	3,4
	Disseminate European excellence in smart medtech	19	Set-up training networks for exchange of personnel between Europe and Emerging Economies	Marie-Curie-Sklodovska Actions		MSCA		2	2	2	2	2	2	2	14
Operating ESTHER		20	Operating ESTHER Association and partnership with EC	Medtech-Eur			0,5	0,5	0,5	0,7	0,7	0,7	0,7	0,7	5
							6,2	344,2	510	629,7	730	929,7	1030	1029,7	5215