Horizon 2020 SME-Instrument topic: clinical research for the validation of biomarkers and/or diagnostic medical devices

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The European Commission released €130 million over 2014, 2015 and 2017 under the EU Framework Program for Research and Innovation, Horizon 2020, to support innovative small and medium-sized enterprises in the diagnostic area. The call topic focused on 'Clinical research for the validation of biomarkers and/or diagnostic medical devices'. It attracted 1194 applicants from all over Europe. The quality of the proposals was high and a large proportion of them were eligible for funding. In the majority, proposals were about *in vitro* diagnostics and tackled both clinical validation of new biomarkers and device optimization. The proposals dealt with various advanced technologies. One third of the proposers gave priority to the new and promising field of personalized medicine.

First draft submitted: 4 January 2018; Accepted for publication: 21 February 2018; Published online: 21 June 2018

Keywords: biomarker validation • diagnostic market • diagnostics • diagnostic technologies • EU • European SMEs • Horizon 2020 • medical device validation • personalized medicine • SME Instrument

On 5 April 2017, two new regulations on medical devices were adopted (Regulation [EU] 2017/745 and Regulation [EU] 2017/746) [1]. The novel legislation of the European Union (EU) will be applied in 2020 for the Regulation on medical devices and in 2022 for the Regulation on *in vitro* diagnostic medical devices. It is meant to improve the level of protection of public health and to allow manufacturers to reduce costs thanks to a unique regulatory framework. An important element of the new regulation is the requirement of proper clinical evaluation of diagnostics devices. This means that market authorization for diagnostics devices in the EU (CE marking) will require manufacturers to demonstrate both clinical and analytical performance of their products. Although market authorization follows different procedures in the USA and in the EU, the new European Regulations bring the two economic zones closer with respect to clinical validation legal requirements. Biomarker validation will become a major challenge for diagnostics companies in the EU, especially small- and medium-sized enterprises (SMEs) [2] which make up almost 95% of the medical technology industry [3]. Thousands of biomarkers are identified each year but only a few of them are translated into clinical practice [4]. Beyond common scientific reasons for failure, the cost of clinical studies is an issue. Investors are discouraged by the risk of clinical validation and the poor valorization of diagnostics (medical technologies represent around 7% of total healthcare expenditure and much less for the *in vitro* diagnostics [IVD]) [3]. In order to address this market failure and to support innovative SMEs, the European Commission released €111.2 million over 2014 and 2015 (H2020-SMEINST-2014–2015 [Topic PHC-12]) plus €18.6 million with an additional deadline in 2017 (SMEInst-05–2016–2017) under the EU Framework Program for Research and Innovation, Horizon 2020 [5]. The scope of the dedicated topic was: 'Clinical research for the validation of biomarkers and/or diagnostic medical devices' [6]. The concept of biomarker was understood in the broad sense given by the NIH Biomarkers Definitions Working Group [7]. The SME Instrument [8] was used and support was provided from the budget of Societal Challenge 1 'Health, Demographic Change and Wellbeing' of Horizon 2020. This article reports on the outcome of the call topic. In addition to evaluation statistics, a descriptive statistical analysis was performed on the proposals that passed the evaluation thresholds.

Table 1. Outcome of the call for the Health PHC-12 topic.

Phase	Number of eligible proposals	Proposals above evaluation thresholds (%)	Proposals funded (%)
Phase I	1206	198 (16%)	165 (14%)
Phase II	953	482 (50.5%)	37 (3.9%)
Both phases	2159	680 (31.5%)	202 (9.4%)

The SME Instrument of Horizon 2020

Innovation is a crucial element in industrial competitiveness and drives economic growth. The SMEs, which provide a major contribution to the economy, are no exception to the rule. The EU addresses their research and innovation needs with a SME tailored funding instrument in Horizon 2020, which shows similarities with the USA Small Business Innovation Research program. However, the two programs are not in competition because of their respective eligibility criteria. The dedicated SME Instrument supports activities for SMEs, with clear commercial objectives, that are established in the EU or a country associated to Horizon 2020. The SME Instrument consists of three separate phases:

- Feasibility assessment (Phase I). This phase is optional. Funding is available for: technical feasibility and commercial potential exploration and assessment. A lump sum of €50,000 is provided per project for durations of around 6 months with a view to applying to Phase II at a later date.
- Innovation (Phase II). Funding is available for activities aimed at bringing innovation to market (performance verification, demonstration, validation, etc.). Proposers can apply after a Phase I or directly to a Phase II. Considering the specificities of clinical validation, health projects of call H2020-SMEINST-2014–2015 (Topic PHC-12) could receive between €1 and 5 million for up to 5 years in innovation activities.
- Commercialization (Phase III). Networking and assistance are proposed in Phase III in order to facilitate commercial exploitation. Phase III is not for funding activities and is not considered in this article.

The SME Instrument is run as an open call with cut-off dates for evaluations. The projects selected can be implemented by a single SME and subcontracting is not excluded.

An Executive Agency for SMEs (EASME) has been set-up by the European Commission to manage the implementation of the SME Instrument. The proposals were evaluated remotely by four independent experts against three main criteria: impact, excellence and quality and efficiency of implementation. The profile of the valuation groups represented a mixt in innovation, business and finance experts. So the proposals had to be robust scientifically and convincing in terms of market opportunities and business model.

A huge interest from diagnostics SMEs

During the total period the topic was open for submission of proposals, the PHC-12 topic attracted 1194 applicants all over Europe (Figure 1). Since resubmissions were allowed, the number of applicants seems more pertinent than the number of proposals. The proposals were of very high quality. However, not all that were above the evaluation thresholds could be supported from the available budget (Table 1). Eventually the success rate depends on the funds available and the financial contribution requested per project. The average of the Phase II grants was €3.3 million, due to the necessity of expensive clinical studies. Therefore, despite the €120.7 million dedicated to Phase II projects, the ultimate success rate for this phase was low. This success rate, defined as the proportion of eligible proposals (953) actually funded (37), was only 3.9%. It should be noted, however, that according to the EASME report of the first two years of implementation of the SME Instrument, the success rates of the SME Instrument is still comparable to the selection rates of private investment funds and acceleration programs [9].

The outcome of this SME Instrument topic is a good indicator of the number, quality and maturity of innovative SMEs in the diagnostics area in Europe. This is also reflected by the ability of the PHC-12 topic companies to receive venture capital funding. EASME has analyzed data provided by Venture Radar [10]. They show that companies from the Health topic were the most successful in gathering private investments. Although health projects represent only 11% of all Phase II SME Instrument projects (PHC-12 was 1 of 13 thematic topics), their beneficiaries received 39% (€271 million) of the private equity funding gathered by SME Instrument beneficiaries [9]. This demonstrates a financial leverage effect of the SME Instrument for successful companies in the Health topic with a ratio of 2.27. Altogether it supports the rationale for a dedicated topic to the clinical validation of biomarkers and diagnostic

Figure 1. Geographical distribution of applicants.

devices, and it confirms the scarcity of funds for this developmental activity. It also seems that another objective of the call, which was to accompany the transition to a new regulatory framework, has been achieved. Based on an analysis of the proposals, it appears that one aim of the applicants was clearly to comply with the new regulation, either to obtain or to renew market authorization within the novel EU legislation.

At the forefront of the trends of the diagnostic sector

The NACE (statistical classification of economic activities in the European community) taxonomy is an EU classification of economic activities. It has been used to identify the sectors in which the SMEs supported are involved. It appears that ‘human health activities’ and ‘scientific research and development’ are predominant for the health topic and they represent respectively 47 and 31% of the SMEs funded [9]. It reflects the focus of the topic and the flow of innovation, which characterizes the sector of medical technology. In 2015, more than 12,400 patent applications were filed with the European Patent Office, more than in any other sector in Europe [3]. This trend is confirmed by the scope of the applications. An analysis of the Phase II proposals covering 2014, 2015 and 2017 deadlines that passed the evaluation thresholds gives a good indication of the activity sectors and the market targets of the relevant SMEs (replicates were removed from the pool analyzed). The majority of them (64.8%) aimed at implementing a project in the field of *in vitro* diagnostics. A minority of proposals focused on medical imaging (13.1%). Other areas included *in vivo* approaches such as electrophysiology and mobile monitoring. This

Table 2. Place of use for the diagnostic devices of the proposals.

Place of use for the diagnostic devices	Proportion of the analyzed proposals	Proportion of the funded proposals
Clinical laboratory	41.8%	32.4%
Medical premises	22.8%	32.4%
m-Health	8.4%	5.5%
Point-of-care	27%	29.7%

difference observed between IVD and imaging may result from the characteristics of the topic and the emphasis put on biomarkers. However, it is also worth mentioning that worldwide market growth perspectives (2015–2022) seem higher for IVD [3]. Among the proposals above the evaluation thresholds that addressed IVD, only 24.7% focused exclusively on the validation of an instrument (i.e., when the instrument measures already established biomarkers).

For 41.8% of the proposals considered in this analysis, the devices were designed for use in clinical laboratories (Table 2).

Point-of-care (POC) devices represent 27% of the total of the proposals analyzed (including self-test devices). This distribution may reflect changes in the IVD market where the share of POC devices has increased steadily during the last decades [11]. An increasing scientific interest in POC confirms this trend with a dramatic progression of the number of citations in the last 15 years [12]. This trend, which is enabled by technology progress in areas such as biosensors, meets the request of a more local and patient-centered approach to healthcare. In addition, it converges with the development of information and communication technologies (ICT) that become increasingly important in health [13].

The rise of ICT in healthcare impacts the medical diagnostics sector. So, unsurprisingly a number of proposals above evaluation thresholds (11.4%) aimed at developing ICT tools for diagnosis and patient monitoring (including e-health and mobile-health). This percentage is rather significant if we consider that the topic of the call gave importance to biomarkers. Indeed, many proposals combined ICT with biosensors, cameras or detectors for self-monitoring and medical imaging. However, if ICT transform medical diagnostics through digital solutions, they also generate innovative concepts. Some original proposals refer to new ‘computer type’ biomarkers. For example, the PReDicT project builds on emotional tests, based on facial expression, to improve the treatment and the management of depression in clinical practice.

The growing importance of personalized medicine

Personalized medicine is a new model in medicine. In this article, we apply a definition adopted in the EU ‘Council conclusions on Personalized medicine for patients’ of 7 December 2015 (2015/C 421/03): ‘*Personalized medicine refers to a medical model using characterization of individuals’ phenotypes and genotypes (e.g., molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention. Personalized medicine relates to the broader concept of patient-centred care, which takes into account that, in general, healthcare systems need to better respond to patient needs.*’ Biomarkers and medical devices are essential components of the deployment of personalized medicine prevention and therapeutic schemes. Applicants of the call showed interest in this innovative concept that holds promise for safer and more effective healthcare. Personalized medicine objectives were predominant in 35% of the proposals analyzed. It illustrates the growing importance of personalized medicine for diagnostics companies. The projects funded cover a wide range of approaches such as:

- Prognostic assay for early stage diagnosis (e.g., the OncoMasTR project for the prognosis of early stage breast cancer to help clinical decision);
- Screening programs for population groups at risk (e.g., the IMMPACT project on the early diagnosis of pancreatic cancer);
- Predictive monitoring (e.g., the MammaPrint project on the identification of the risk of cancer recurrence after surgical treatment. or the RADiCAL project for rapid imaging assessment of chronic liver disease);
- Efficacy prediction for identified classes of drugs (e.g., the BIOVALID project on the detection of thymidine kinase activity, a predictive and efficacy biomarker for cell cycle regulating drugs).

Table 3. Grouping of the proposals according to WHO classification.

ICD nomenclature	Proportion of the analyzed proposals (%)
Neoplasms	32.5
Certain infectious and parasitic diseases	13.5
Diseases of the circulatory system	12.7
Endocrine, nutritional and metabolic diseases	5.1
Diseases of the digestive system	4.6
Diseases of the genitourinary system	4.6
Diseases of the nervous system	4.6
Diseases of the respiratory system	3.8
Diseases of the musculoskeletal system and connective tissue	3.4
Mental and behavioral disorders	3.4
Pregnancy, childbirth and the puerperium	3.4
Diseases of the eye and adnexa	2.1
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1.7
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	0.8
Diseases of the skin and subcutaneous tissue	0.8
Injury, poisoning and certain other consequences of external causes	0.8
Certain conditions originating in the perinatal period	0.4
Cervical, endometrial and ovarian cancers. Test for HPV and gene methylation	0.4
Others	1.3

These are based on a conception of companion diagnostics that goes beyond what is usually understood as a match between a pharmaceutical and a specific diagnostic assay. For example, the definition given in the Regulation on IVD devices excludes devices that are used with a view to prevent disease or monitor treatment. The focus of the proposals may be seen as an attempt to overcome the uncertainties of the companion diagnostics business model and to avoid the alignment issue between drugs and diagnostic tests developments. European SMEs may be finding their way toward the comprehensive companion diagnostics market, which is expected to grow at a much higher rate than the IVD market globally. According to the business intelligence provider, Visiongain, the worldwide companion diagnostics market could reach \$10.5 bn in 2020 [14].

Advanced technologies for major diseases in the world

Molecular biomarkers are still predominant in clinical medicine and not surprisingly proteins and nucleic acids come first among the compounds analyzed in the proposals above thresholds (19.4 and 18.6%, respectively, of the total). However, many other types of biomarkers, such as images, score-based biomarkers, and so forth, are considered among the proposals. This diversity is reflected in a large number of advanced technological approaches among which immunoassays, molecular biology techniques, biosensors, ICT tools and multiple platforms can be found. A grouping of the proposals per disease was made according to the WHO international classification of diseases (Table 3) [15].

Although most major diseases in Europe were addressed, three categories clearly dominate in the proposals: malignant neoplasms (32.5%), infectious diseases (13.5%) and cardiovascular diseases (12.7%). This reflects only partially the statistics of the major groups that account for the total burden of diseases in Europe [16]. Disease burden, as measured in DALYs, is an interesting indicator since the scope of the proposals is not limited to diagnostics and encompasses screening, monitoring and prediction dimensions. In the European region, cardiovascular diseases, neuropsychiatric conditions and malignant neoplasms are the biggest contributors to disease burden. In the proposals analyzed, mental and behavioral disorders appear underrepresented (3.4% of the proposals), despite the need for new diagnostic tools in a domain where diagnosis relies predominantly on clinical examination. On the other hand infectious diseases may be overrepresented if we consider that, although important, they are not among the top five conditions that account for the total disease burden in Europe. So, the focus of the proposals appears to be more driven by global market perspectives and innovation opportunities than by health statistics in Europe. This fits the logic and the open business oriented approach of the SME Instrument. From this point of view, it should

be recalled that infectious conditions are the highest disease burden outside Europe and represent a big market for European diagnostics companies. In addition, important technology developments are being made in this area with POC testing. Another example of the limited correlation with disease burden in Europe is the proportion of proposals addressing cardiovascular diseases. It is relatively low in comparison to malignant neoplasms. This difference can be explained by the rising interest of diagnostics SMEs in the promising and growing market of personalized medicine. Noteworthy, half of the proposals oriented toward applications in personalized medicine had a focus on cancer, and this field is closely linked to the development of personalized medicine.

Conclusion

SMEs operating in the diagnostics area answered massively to the Health topic of the SME Instrument call. This reflects the need for financial support for the clinical validation of biomarkers and medical devices. The quality of the proposals was high and a broad variety of projects have been funded, as illustrated in Table 2. The applicants were innovative research-driven SMEs that make use of advanced technologies, tackle emerging market opportunities and are engaged in the evolutions of the diagnostics sector: POC devices, e-health, personalized medicine, etc.

Future perspective

Diagnostics is a fast moving sector boosted by innovation and demographic evolutions that has to confront changes in the healthcare and business landscapes. The sector is challenged by the apparition of disruptive technologies and the evolution of healthcare practice toward a patient-centered vision. Although the input to the H2020 SME Instrument call for the validation of biomarkers and diagnostic devices does not provide a random unbiased sample for analysis, it provides insight into the adaptive answers and the perspectives of European SMEs. We can identify the following tendencies:

- A broader conception of diagnostics tools including prognostics and prevention;
- A growing integration of multiples technologies, such as biosensors, microfluidics or ICTs, in order to address the demand for POC and connected devices;
- A clear value in clinically validated biomarkers; molecular and other types of biomarkers
- A move toward personalized medicine, including companion diagnostics and close to patient solutions.

Considering the cost and the failure risks of clinical validation studies, financial support from investors may remain a challenge for innovative SMEs in the diagnostics area. However, the diagnostics area is changing and is very promising. SMEs in this area can rely on the growth of the market that promises an increase in revenues and should attract investors.

Disclaimer

This article was written by J-L Sanne, Senior Expert at the Health Directorate, Directorate-General for Research and Innovation, European Commission. The views expressed in this article are those of the author and do not necessarily reflect the official position of the European Commission.

Acknowledgements

The author thanks F Vanstichel for her help with statistics and the preparation of Map 1, as well as A Crisafulli for providing data. He also thanks I Norstedt, E Nimmesgern, M Coyle and H Collier for careful reading of the manuscript.

Financial & competing interests disclosure

J-L Sanne is Senior Expert at the Health Directorate, Directorate-General for Research and Innovation, European Commission. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

No writing assistance was utilized in the production of this manuscript.

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Executive summary

- Diagnostics is a fast moving sector boosted by innovation and demographic evolutions that has to confront changes in the healthcare and business landscapes.
- Financial support is needed by European diagnostic small- and medium-sized enterprises**
- The European Commission has allocated €130 million over 2014, 2015 and 2017 under Horizon 2020 to support innovative small- and medium-sized enterprises in the diagnostic area.
 - The call attracted 1194 applicants from all over Europe.
 - On average, €3.3 million were requested for the validation of biomarkers and/or diagnostic devices.
- Advanced technologies & approaches**
- The majority of the proposals concerned *in vitro* diagnostics, and were mostly for use in clinical laboratories.
 - A growing interest in point-of-care devices was observed.
 - The proposals reflected the increasing importance in health of information and communication technologies.
- Interest in personalized medicine**
- About a third of the proposals eligible for funding were oriented toward personalized medicine applications.
 - The proposals addressing personalized medicine covered a wide range of approaches: prognostics, screening, monitoring, efficacy prediction.
 - The relevant proposals were based on a conception of companion diagnostics that goes beyond the match between a pharmaceutical and a specific diagnostic assay.
- Priority to major diseases**
- Most major diseases in Europe were addressed by the applicants.
 - Three categories were predominant in the proposals: malignant neoplasms, cardiovascular diseases and infectious diseases.
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