Letter addressed to: MDCG IVD Group, DG Sante - Unit B6, EMA

26 May 2021

Joint Stakeholder letter

Call to action to the European Commission to postpone and facilitate a phased implementation of the *in vitro* diagnostic Regulation

Representing cancer patients, diagnostic and laboratory industry experts and the pharmaceutical industry, we write to you with serious concerns related to the unaddressed implementation challenges faced by the healthcare sector across Europe ahead of the date of application of the *In Vitro* Diagnostic Regulation (IVDR). While we agree that well-regulated diagnostics are critical for patient access to high quality testing, various stakeholders within healthcare are concerned that the infrastructure supporting the transition toward a new regulatory system for diagnostics under the IVDR is not ready. Furthermore, it will not be ready on time to ensure the continued availability of tests required for patients whose conditions rely on the delivery of appropriate *in vitro* diagnostics.

With this letter, we would like to highlight gathered data that will provide insights into the issues faced by cancer patients where testing is vital to continued access to life-saving innovative precision medicines. While companion diagnostics represent one aspect of IVD utility within Europe it is, in fact, a very critical use as it determines patient access to potentially life-saving medicines.

With a year to go before the date of application of the IVDR (26 May 2022), the infrastructure necessary for its implementation is lacking. This includes EUDAMED, Reference Laboratories and Notified Body (NB) capacity[1]. A major concern is that while there were 22 NBs under the IVD Directive (IVDD), there are currently only 4 NBs designated under the IVDR. Further, under the new regulation 80% – 90% of IVDs will require conformity assessment by a NB, which is a 600-700% increase in the NB workload, while previously under the IVDD only 10 – 20% of products required certification. Additionally, current device certification capacity is so limited that product files are taking on average 9 – 12 months[2] to review regardless of the device classification. Clinical practice across the EU relies heavily on the use of tests developed by laboratories in-house or within a single hospital or institution. To continue using these tests, laboratories will need to meet the exemptions listed in the new requirements highlighted in the IVDR. This will impact patient testing.

These challenges are compounded by the restriction of on-site audits due to the COVID-19 pandemic. Moreover, 70% of small and medium IVD manufacturers don't have a NB under the IVDR[3]. **Even if the infrastructure required to support the transition toward the IVDR were put in place and fully functioning within this year, NBs could not possibly take on and manage this immense workload in such a short period of time to avoid market disruption.**

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[1] Panel for the Future of Science and Technology - The need for better EU policies for health - Multimedia Centre (europa.eu)

[2] AdvaMed/MedTech Europe Joint Webinar, 22 March 2021

[3] https://medtech.pharmaintelligence.informa.com/MT143858/EU-Must-Have-Courage-To-Take-The-Sensible-Decision-On-IVDR-Deadline-Says-German-Industry

A severe consequence of this will be that from 26 May 2022, most diagnostics currently on the EU market will not be authorised for use in the healthcare systems of EU Member States, causing a detrimental impact on the management of cancer patients across the EU. In a case study prepared by Diaceutics[4], 110,575 metastatic non-small cell lung cancer (NSCLC) and ovarian cancer patients will require testing for actionable biomarkers to have access to approved innovative and life-saving precision medicines in Europe in the year following IVDR implementation. **We estimate that the reduction in biomarker testing due to the implementation of the IVDR will impact the lives of as many as 65,000 NSCLC and ovarian cancer patients per year who will miss out on identifying the right treatment for the right patient.** This number will be greater if we consider all cancer types which require a biomarker test for access to a precision medicine.

It is sobering to note that the above case study considers only oncology biomarker tests which make up a small fraction of the diagnostic tests currently in use in Europe. **As diagnostic results are required for ~70% of clinical decisions[5], this is likely to adversely impact clinical management of millions of EU patients. It will also hinder Europe's Beating Cancer Plan** which is striving to build on the promise of personalised medicine for cancer prevention, diagnosis and treatment through new technologies, research and innovation.

Given the potential dire impact of this situation with only a year before the IVDR comes into full force, we appeal to you to consider these urgent measures:

- an initial one-year postponement of the IVDR date of application with immediate effect;
- following this postponement, a phased IVDR rollout which prioritises NBs' assessment of high-risk impact diagnostic tests (i.e. starting with class D devices);
- accelerated designation of sufficient NBs, prompt release of key guidance documents and full functionality enabled in Eudamed to ensure that the critical regulatory infrastructure required is in place on the new Date of Application.

As Vice President Schinas of the European Commission said[6], "Cancer care is no longer the responsibility of the health sector alone. The success of Europe's Beating Cancer Plan requires engagement and buy-in from a wide range of sectors and stakeholders, a whole-of-society effort."

We would therefore urge you to take action now to safeguard the continued and comprehensive access of patients and the healthcare system to life-saving and innovative diagnostic tests across the EU, and to ensure that the implementation of the IVDR does not have a detrimental impact on the care and lives of thousands of cancer patients.

Yours sincerely,

Ken Mastris, ECPC President

Nathalie Moll, EFPIA Director General

Peter Keeling, CEO Diaceutics

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[4] Diaceutics data and case study presented in the Appendix

[5] BIVDA (2019), The Value of IVDs. Available online at https://www.bivda.org.uk/The-IVD-Industry/The-Value-of-IVDs

[6] Remarks by Vice-President Schinas at the press conference on Europe's Beating Cancer Plan: https://ec.europa.eu/commission/presscorner/detail/en/SPEECH_21_410

Appendix

Diaceutics Case Study Methodology

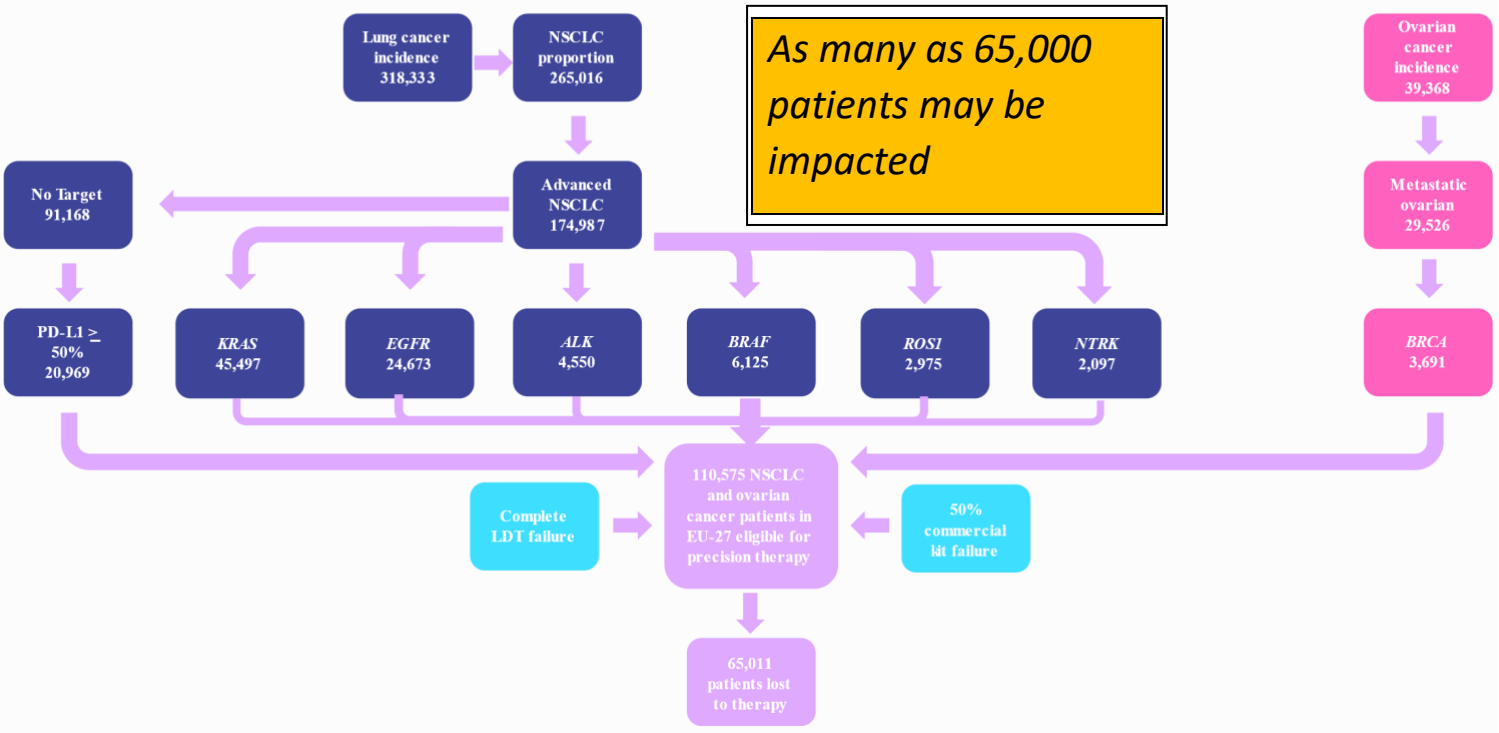
In order to produce a real-world analysis of this critical issue, Diaceutics has analysed insights from the world's richest source of diagnostic testing data enabled by its DXRX platform to model the potential patient impact.(1,2) The following is a summary of the methodology used.

Lung cancer incidence rates were sourced from the International Agency for Research on Cancer (IARC) database for the EU-27 Member States.[1] To these patient numbers the NSCLC fraction was applied and then the metastatic NSCLC rate.[2] To the metastatic NSCLC patient cohort in each Member State proportions of the following actionable mutation were utilized; *KRAS*, *EGFR*, *ALK*, *BRAF*, *ROS1*, and *NTRK*. [3–8] PD-L1 expression rates (cut-off at ≥ 50%) were determined from the remaining cohort with no druggable mutation.[9] Employing *EGFR* tests as a proxy for next-generation sequencing (NGS), laboratory developed tests (LDTs) to commercial kit ratios were determined from Diaceutics DXRX database, and PD-L1 LDT to commercial kit ratios were also calculated.

Ovarian cancer incidence rates were also sourced from IARC for the EU-27, the metastatic rate applied, and *BRCA* mutation proportion employed.[1,10,11] *BRCA* LDT to commercial kit ratios were ascertained from the DXRX database.

A scenario of complete non-availability of LDT and 50% non-availability of commercial kits was assumed under the application of the IVDR and these proportions implemented to calculate the number of patients who will potentially be lost to precision therapy.

Figure 1. Lung and ovarian cancer patients eligible for precision therapy in EU -27 and affect of IVDR



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EFPIA - **The European Federation of Pharmaceutical Industries and Associations** - represents the biopharmaceutical industry operating in Europe. Through its direct membership of 36 national associations, 39 leading pharmaceutical companies and a growing number of small and medium-sized enterprises (SMEs), EFPIA's mission is to create a collaborative environment that enables our members to innovate, discover, develop and deliver new therapies and vaccines for people across Europe, as well as contribute to the European economy.

European Cancer Patient Coalition (ECPC) is the voice of cancer patients in Europe. With over 450 members, ECPC is Europe's largest umbrella cancer patients' association, covering all 27 EU member states and many other European and non-European countries. ECPC represents patients affected by all types of cancers, from the rarest to the most common.

Diaceutics

At Diaceutics we believe that every patient should get the precision medicine they deserve**.** We are a data analytics and end-to-end solutions provider enabled by DXRX – our proprietary Network solution for the development and commercialization of precision medicine diagnostics. Diaceutics has worked on every precision medicine brought to market and provides services to 39 of the world's leading pharmaceutical companies.

In addition to the company's real-world EU datasets, Diaceutics' proprietary data repository digitally integrates multiple pipelines of claims, lab result and diagnostic profiling meta data from a global network of academic, community and reference laboratories and is enriched through real-time engagement by DXRX partners collaborating on the platform. Through the application of machine learning and standardization of aggregated data on DXRX, Diaceutics can identify the best possible testing journey or "Deductive Diagnostic Pathway (DDP®)" for patients at disease level for over 365 million patients and has today mapped 49 proprietary DDPs.