Ensuring a successful transition to the new IVD Regulation in light of COVID-19

09 July 2020

MedTech Europe
from diagnosis to cure

POSITION PAPER

Executive Summary

In vitro diagnostic tests (IVDs) are critical in the screening, diagnosis, prediction and monitoring of medical conditions in Europe, including infectious, rare or genetic diseases and physiological conditions. The role of diagnostics in the COVID-19 pandemic, where tests represent an indispensable part in managing the acute crisis and in supporting effective exit strategies, is a prime example of how critical these devices are.

Looking forward, Europe needs a well-functioning and predictable regulatory framework for diagnostics. This is why the medical technology industry welcomes the new EU IVD Regulation (IVDR) - due to enter into legal application by 26 May 2022 - and is fully committed to making it succeed in order to continue serving patients and healthcare systems with high-quality tests. For that to happen, the EU needs to rapidly complete its deployment of the new regulatory infrastructure well before the May 2022 'legal' deadline. Manufacturers depend on the early availability of this infrastructure in order to (re-)certify all tests on time in accordance with the new rules. It is of utmost importance that updated and reliable information is given by authorities about the implementation plan.

Unfortunately, the circumstances of the COVID-19 outbreak have put the IVDR implementation process de facto on hold, as the European Commission and Member States, as well as manufacturers, needed to redirect significant resources towards managing the COVID-19 crisis. This has essentially stalled the work required to move forward with IVDR implementation. Moreover, the recent postponement[1] of the Medical Devices Regulation ("MDR") to May 2021 means the MDR will now only enter into full application one year before the IVDR. The co-legislator intended for the IVDR to apply at least two years after the MDR, in light of the significant work needed to fully implement the new IVDR system in a timely fashion and to avoid an overlap between MDR and IVDR implementing measures and efforts.

The IVD industry, therefore, **urges the European Commission, Member States and the European Parliament to enact substantive solutions to make the IVDR workable, while ensuring that all relevant stakeholders maintain maximum focus on helping healthcare systems combat and recover from the impact of COVID-19**.

[1] See Regulation 2020/561/EU of 24 April 2020

Various solutions should be strongly considered, including but not limited to:

1. Communication of a clear, updated IVDR implementation plan from the Commission and Competent Authorities as soon as possible, enabling all stakeholders to plan in a predictable way.

   This should be based on:

2. Urgent and open discussion with affected stakeholders about contingency plans that may need to be proactively implemented to make IVDR work in light of the impact COVID-19 has had on the transition.

   For instance:

   - Enlargement of the IVDR "Grace Period" to additional categories of existing tests in a risk-based manner (as was done in the December 2019 MDR corrigendum)

   - Phased IVDR implementation combined with immediate strengthening of the existing IVD Directive (to start realising the IVDR's benefits even if the infrastructure needs more time to be built)

   - Postponement of the 26 May 2022 date of application (as was done in the April 2020 MDR amendment)

Introduction

The IVD industry welcomes the new *in vitro* Diagnostic Regulation (IVDR) and is fully committed to playing its part to transition to the new CE marking system.

The implementation and success of this significant system change require the deployment of necessary resources from all parties involved.

However, the COVID-19 outbreak has put the EU's IVDR implementation progress to a halt, in particular to the running operations of Notified Bodies, Member State authorities and manufacturers, critical elements of the new regulatory system that did not exist even before the beginning of the pandemic, making it challenging for all actors to transition to the new Regulation. This directly threatens the timely establishment of the new regulatory system and the issuing of CE-marking certificates under the IVDR.

In this paper, MedTech Europe outlines the concerns that the IVD industry identified in the implementation of the IVDR. Because of these concerns, MedTech Europe requests for urgent solutions from authorities to address these concerns in order to ensure that existing and new diagnostic tests will be available for patients and healthcare systems.

Key Challenges of Transitioning to the IVD Regulation

1) The COVID-19 pandemic has derailed ongoing IVDR implementation

COVID-19 has shifted the focus away from IVDR implementation because all efforts and available resources had to be redirected towards combating the worst pandemic Europe has lived since the Spanish flu. As COVID-19 is slowly being controlled and countries re-emerge from lockdowns, the IVDR implementation system needs to be addressed as soon as possible.

All stakeholders have been heavily impacted

COVID-19 has shifted the focus away from IVDR implementation. Member State authorities, laboratories, health institutions and the IVD manufacturers are dedicating significant resources to the fight against the pandemic. The lack of predictability of the short to medium term future makes it impossible to plan sufficiently ahead.

Member State authorities, including regulatory agencies, are managing the response to and exit from the pandemic. This includes sourcing and overseeing the quality of devices, including COVID-19 related diagnostic and antibody tests, personal protective equipment, emergency health and respiratory machines, software tracking systems, etc. Attention has shifted away from the giant task of coordinating and ensuring guidance for manufacturers, notified bodies, reference laboratories and health institutions to implement the IVDR.

Laboratories and health institutions have been re-dedicated to managing patients suffering from COVID-19, while also dealing with health conditions and physiological states not related to COVID-19. While laboratory study sites are focused on testing COVID-19 samples and health institutions on managing patients, they have little to no capacity to run performance studies to generate evidence for new and existing IVDs and to prepare for the new IVDR requirements on assays produced by health institutions. Long delays in running much needed studies are foreseen.

Manufacturers developing COVID-19 relevant tests have needed to redirect development, quality assurance, regulatory, clinical, production and supply team resources away from the IVDR preparation, in order to meaningfully respond to the demands of healthcare systems and society for increased COVID-19 testing capacity. Even manufacturers with tests other than COVID-19 assays have suffered significant worldwide impact from the pandemic: securing international supply chains and production against lockdowns and social-distancing measures; adjusting to significant decreases in demands for certain IVDs, adjusting to delay and disruption in performance evaluation studies, etc. This means that resources have been taken away from industry's efforts to certify against the IVDR.

The COVID-19 lockdowns around the world have likewise disrupted the ability of manufacturers to produce the needed evidence for IVDR submissions. See **Annexes I and II** for examples of essential activities that have been stopped or significantly delayed.

It must be considered that after this emergency, there will be less resources available to all parties than before the crisis. This will be a source of inequality for countries, institutions, and companies with smaller budgets. It will also be more difficult to restart key IVDR preparation activities such as clinical studies which have been put on hold – in fact, these may need to be re-launched altogether, leading to many delays.

2) The new IVD regulatory infrastructure needs to be ready in 2020 to allow a smooth transition

Most elements of the IVDR are new. In particular, the involvement and workload of notified bodies in certifying tests will increase significantly. MedTech Europe therefore believes that the majority of IVDs would need to file for certification latest at the end of 2020 / early 2021 to be on time before the deadline for application. This means that the practical deadline for the IVDR infrastructure to be fully established is not 2022, but 2020.

The COVID-19 pandemic has halted work in putting into place the EU's IVDR implementation infrastructure. However, this infrastructure is needed already today in order to meet the date of application of 26 May 2022.

The IVDR significantly transforms multiple regulatory requirements for IVDs, including:

- the classification system for IVDs, which changes completely
- the significant increase in clinical evidence requirements
- the systemic change away from self-certification towards notified body certification: notified bodies will need to oversee the CE marking of 85-90% of IVDs, for the very first time.

If certification of new and existing tests against the IVDR is not successfully completed in full by 26 May 2022,[2] Europe risks experiencing potentially catastrophic disruption to the availability of IVDs to healthcare systems.

Furthermore, the vast majority of IVDs must be certified against the IVD Regulation by the date of application. There is no so-called 'grace period' foreseen for the vast majority of IVDs. This means the amount of time available for certification versus the number of tests that need to go through the procedure is fixed, and the IVDR contains no built-in contingency plans if tests are not certified by 26 May 2022. To avoid creating a 'time crunch' in the final months of the transition period, the core IVDR infrastructure must be ready and have sufficient capacity to work, not two years from now but *today*.

3) Today there is a lack of essential 'regulatory infrastructure' to make the IVDR succeed

The regulatory infrastructure for IVDs needs to be established and overhauled based on the requirements of the new IVDR. Elements of this infrastructure include guidance documents, EU reference laboratories, and common specifications; besides, notified bodies, must be re-designated against considerably strengthened requirements. Without this infrastructure being made fully available, the certification of tests cannot be completed.

There are many important elements of the regulatory infrastructure which are essential to have in place before manufacturers can certify new and existing tests against the IVDR. Many of these milestones are delayed or missing:

- **Notified bodies** to certify manufacturers' IVDs and quality management systems. Today, there are only four (DEKRA Germany, BSI Netherlands, BSI UK, TUEV SUED) compared to over 20 that exist under the IVD Directive.

[2] A small number of IVDs have IVD Directive certificates and can stay on the market until latest 26 May 2024

- **EU reference laboratories** to conduct batch release for highest-risk tests, such as those for fighting COVID-19.

- **Common specifications (and, in their absence, expert panels)** to harmonise performance requirements of the highest-risk tests.

- **Implementation guidance** needed for smooth implementation by all actors, e.g., in the areas of risk classification, clinical evidence ('performance evaluation'), performance studies, class D devices and the roles/responsibilities between authorities and notified bodies for companion diagnostics.

All these elements were already missing before the COVID-19 outbreak, and the disruption of the pandemic has made this lack of IVDR infrastructure even more concerning.

4) The postponement of the MDR date of application directly impacts the IVDR implementation

As the MDR is postponed by one year, the same authorities must use most of the same resources to implement both regulations. This halves the time that key stakeholders can focus on the significant IVDR work, where a lot of procedures and evidence requirements are being changed and upgraded. The work on the IVDR needs full attention by all stakeholders involved.

These concerns have become aggravated, especially in light of the recent MDR postponement,[3] which means there is now only a 1-year 'gap' between MDR and IVDR's dates of application. Since most authorities and several notified bodies are shared between MDR and IVDR, the reduction of the timeframe between the implementation of MDR and IVDR amplifies the already existing bottleneck in resources. This could jeopardise critical IVD infrastructure being available early enough and thereby the supply of IVD tests to the European market to continue smoothly beyond 26 May 2022.

The combination of the above factors makes the timely implementation of the IVDR ahead of May 2022 highly doubtful.

[3] See Regulation 2020/561/EU of 24 April 2020

Call to action to address the transition challenges

The IVD industry continues to strongly support the goals of the IVDR and remains fully committed to doing its part to see the benefits of the Regulation properly implemented. At the same time, like all other actors, industry is committed to help Europe combat COVID-19 and recover from the crisis. However, the pandemic impact on the IVDR implementation has been considerable, and this must be neither underestimated nor ignored.

Urgent solutions are therefore needed to address the IVDR transition and make it manageable for all parties, thereby enabling them to focus on addressing the current public health challenge and to appropriately adjust IVDR activities.

Various solutions should be strongly considered, including but not limited to:

1. Communication of a clear, updated IVDR implementation plan from the Commission and Competent Authorities as soon as possible, enabling all stakeholders to plan in a predictable way.

   This should be based on:

2. Urgent and open discussion with affected stakeholders about contingency plans that may need to be proactively implemented to make IVDR work in light of the impact COVID-19 has had on the transition.

   For instance:
   - Enlargement of the IVDR "Grace Period" to additional categories of existing tests in a risk-based manner (as was done in the December 2019 MDR corrigendum)
   - Phased IVDR implementation combined with immediate strengthening of the existing IVD Directive (to start realising the IVDR's benefits even if the infrastructure needs more time to be built)
   - Postponement of the 26 May 2022 date of application (as was done in the April 2020 MDR amendment)

Time is needed to deploy all the necessary resources and to establish the new regulatory system as well as to generate the needed evidence, and thus guarantee the continued availability and quality of diagnostic tests on the European market.

The IVD industry, therefore, urges the European Commission, Member States and the European Parliament to find solutions to address the IVDR's transition challenges now, ensuring that all relevant stakeholders maintain maximum focus on helping healthcare systems to combat COVID-19, assist in the recovery of the economy and address the pandemic's impact on the whole healthcare ecosystem.

The IVD industry is fully ready to engage in further discussions to find workable solutions and make the implementation of the new framework successful.

About MedTech Europe

MedTech Europe is the European trade association for the medical technology industry including diagnostics, medical devices and digital health. Our members are national, European and multinational companies as well as a network of national medical technology associations who research, develop, manufacture, distribute and supply health-related technologies, services and solutions.

For more information, visit www.medtecheurope.org.

For more information, please contact:

Oliver Bisazza
Director Regulations and Industrial Policy
MedTech Europe
o.bisazza@medtecheurope.org

Giovanni Dalle Nogare
Officer Government Affairs and Public Policy
MedTech Europe
g.dallenogare@medtecheurope.org

-

ANNEX I:
IMPACT OF THE COVID-19 PANDEMIC IN TRANSITION PROCEDURES

Activity	Impact
To support the COVID-**19 demand, new test kits or adaption of existing test solution**s **are under development**	Less product development, clinical, quality assurance, regulatory, project management resources for necessary IVDR projects
Ability to continue and complete ongoing **clinical studies, whether with clinical research organisations or run in hospitals and in the field**	Delay (estimated as being as long as 9 months) in getting the study results completed – cannot develop needed evidence for use in IVDR submissions
Notified Bodies do not proceed with planned (on-site) audits needed to complete the conformity assessment process.	Delays in the issuance of IVDR certificates needed to CE mark tests to the new Regulation
Permanent new planning and production challenges to support the COVID-19 demand. Additional complexities in daily manufacturing. Also, site closures. Re- start of manufacturing of standard products to support the customer demand	Cannot manufacture as normal, resulting in delays, accumulation of work, managing social distancing, shift-based operations, diverting resources to management of situation and ensuring consistent supply of critical IVD tests. Strong need for more planning of resources and integration of new employees
Ability for teams to meet and prepare for the IVDR	Delay in completing regulatory submissions for IVDR
Additional **complexities in supply chain daily manufacturing**[4]	COVID-19 business impact extends throughout the supply chain, from raw materials production and procurement to distribution networks – diverting resources to management of the situation and ensuring consistent supply of critical IVD tests
The worldwide shortage of plastic materials Development & ordering of new plastic injection moulding tools and production machinery for production of e.g. plastic tips, specific plastics for IVD instruments	Technical designer, product development, quality assurance and project management must focus on organising the increased need for plastic materials. These resources are missing for necessary IVDR projects
To support the COVID-19 test demand, the consequences of vacation backlog and accumulation of overtime pose a major challenge for **2020/2021.**	Reduction of vacation backlog and overtime will furthermore reduce the availability of necessary resources for IVDR projects in the different areas.

[4] Materials related to COVID-19 assays are in strong demand / lacking. Some backlog materials are used in other devices too. For example, companies report a worldwide lack of pipette tips. Or take Guanidine, which is a basic material for sample preparation kits, specific PCR enzymes, dNPT´s. Such standard genetic biochemicals are used in all non-COVID-19 PCR devices too.

ANNEX II: IMPACT OF COVID-19 ON INDUSTRY'S IVDR TRANSITION

Operational disruption	• **Company-wide nature of IVDR preparation:** Regulatory -, production- and supply team resources have been re-directed - *away from IVDR preparation* - to support the production and supply of COVID-19 related tests. • One member company is in the process to ramp up the production to increase the production of COVID-19 products by a factor of 10. This is only possible with 100% focus on ramp up, which does not allow to focus on IVDR implementation as necessary, in a context where the transformation and effort for some IVD companies can be significant, as some of them only know the current self-declaration process.
Project disruption	• Resources have been withdrawn from certain IVD RECAST projects to support COVID-19 related projects/activities, resulting in a delay to have Technical Documentation ready for assessment by the notified body. This may impact the planned execution of the project milestones • Impact on Notified Bodies and other stakeholders, such as Reference Laboratories and EMA is currently unclear. This may originate a post-pandemic 'traffic jam', which will constrain their operation. • In order to cope with the demand spike manufacturers have been forced to start immediately significant capital investment projects to upgrade manufacturing capabilities and to prioritise process developments of COVID 19 related products and assays, which has led to a redirection of project management resources to focus entirely on capital investment projects instead of Recast projects

Clinical studies	**General**	• The IVDR has inserted several new performance-related terms and requirements. The planned MDCG Guidance on IVD Performance Evaluation is a key guidance document to design a valid IVDR clinical study concept and set expectations for the level of clinical evidence data which will be needed. Further delay in the publication is an additional risk on the study planning. Furthermore, our potential external laboratory study sides are focused on testing COVID-19 samples. Study capacities are reduced.
		• Additional details:
		  ○ Disruption of clinical routine leads to decreased capacities to perform clinical performance evaluations.
		  ○ Enrolment of subjects into clinical performance studies is negatively impacted due to delay in schedulable medical interventions.
		  ○ Qualification of sites (installation qualification, operational qualification, performance qualification) is negatively impacted.
		  ○ Product availability for studies might be impacted.
		▪ Social distance measures adopted onsite and availability of external SME consultants have resulted in delays to validation of equipment required to conduct stability studies by a minimum of 1 to 2 quarters.

	Spillover effects	• This has a direct impact on manufacturers' ability to produce the needed evidence for IVDR submissions. External reasons for the delays are site closures, study site city/region under quarantines, site study staff being ill, study site capacities for study conduct/testing reduced and low or no enrollment due to the pandemic. Internal reasons are that required on-site visits by the staff are not possible due to travel and/or border restrictions, study supply delivery is delayed, clinical research organisations have pandemic-driven restrictions and finally, staff being ill. We are already doing a lot to mitigate these risks, e.g. (depending on study and phase) looking for other study sites and supporting and monitoring remotely. But there are limits to what we can do remotely. • Disruption of ability to carry out non-COVID-19 performance studies. Other industry sectors within the health area report similar difficulties: GlobalData found that the majority of clinical trials, at 69.9%, were disrupted due to the suspension of enrollment.[5] ○ One company example: 102 sponsored IVD studies carried out internally by the clinical operations committee. 39 of these are facing up to 3 months delay or more.

[5] See 'Update on clinical trials disrupted due to Covid-19' (14 May 2020) on https://www.clinicaltrialsarena.com/comment/disrupted-clinical-trials-covid-19/

	Preliminary impact assessment	• Our experts estimate that a 3-month delay in the start of a study may, however, correlate to as much as a 6-9 months (the study completion time of 6-9 months is so long due to the **expected enrolment challenges** post pandemic) delay in getting the study results completed and thus able to use in regulatory submissions. Even post-pandemic, we expect enrollments will be slow and exhausted hospital staff will need some time off, so efficiencies at multiple operators may be lost due to lack of personnel. The 6-9-month regulatory impact is a rough and preliminary projection.
	Specific product example	**On-going clinical studies of innovative point-of-care tests are already facing several months delay due to the COVID-19 crisis** • These types of products support e.g. the diagnosis (or ruling out) of heart attacks. They are already part of the standard of care in hospital laboratories and would be beneficial in more ambulatory settings. Several of the clinical studies aim to support regulatory submissions under IVDR. We are very concerned about the impact of the delays on our general planning for IVDR compliance. Our plans are carefully tailored to meet specific milestones not only for study finalisation but also for Notified Body involvement which is a must for these types of tests.

Notified Bodies	**Designation**	**Notified Body (NB) IVDR designation expected in Q2/ Q3 2020 under risk?** • Since QM-System certification is a mandatory requirement for IVDR compliance, any delay of the NB designation will stress the already limited capacity of the NB later when it comes closer to 26 May 2022. • In addition, assessment of the Technical Documentation of Class B, C, and D IVD Medical Devices as required per the Conformity Assessment Scheme might be impacted as well.
		NB IVDR designation in Q3 /Q4 2020 under risk? • During the exit from the pandemic COVID-19 outbreak, the NBs expect a delay in their designation, which could be delayed into 2021. Seeing the Medical Device Regulation designation has not yet been granted, designation under the IVDR could potentially drift further into Q1/2 2021. One company reports: “We would then need to make an application to them for a Technical Documentation assessment for our Class B and C devices. They have previously communicated that the TD assessment time frames would be 6 months as a best case scenario, this would then take us into Q3/4 2021 for TD assessment completion, after which they would need to undertake a QMS assessment, which only leaves late 2021 into early 2022, this all assumes they are ready to start their process as soon as they get designated. These timelines leave no room for delays / resources constraints, etc.” Other companies report that their notified body will need 6-8 months to evaluate their class C devices if they start in 2020, but ‘up to 12 months’ (twice as long!) if they start in 2021. These timelines are best case

		scenarios and give great cause for concern.
	Audit constraints	• Currently NBs do not perform planned on-site audits. Companies try cover as much as possible on a remote basis. Nevertheless, on-site audits are required for new certificates, recertification or in case of significant change or incidents. • Already companies report that their auditors for ISO 13485/MDSAP are having difficulties in keeping their commitments for conducting audits.
		• Example from one member company: "The EC Quality System certificates are linked with the member's ISO 13485 certification process. The current certificates expire on the 3 November 2020. We are being told by NB that they will do a remote desk top audit for some aspects of the quality management system and will issue some form of bridging document until they can undertake a production system site audit before they will issue a 3-year extension to our ISO 13485 certificate and potentially to our EC Quality System certificates.

Legacy products	• Development resources (i.e. staff, as well as technical equipment and reagents and other materials) are heavily blocked by development of COVID-19 assays. That means that fewer resources are available to work on legacy products to fulfil new IVDR-specific requirements. • If the IVDR date of application remains unchanged, compliance will come at the cost of niche legacy products that become forced out of the market • Required distance working has restricted access to the (hard-copy only) data files of some legacy products

Supply chain under pressure	For example: forced changes to material or component suppliers − needing to be immediately addressed, e.g., via updates to IVDs with CE marking under the IVD Directive, which have the following consequences: • Manufacturers' capacity is temporarily redirected away from IVDR implementation • Global suppliers of chemical reagents and instruments have similar challenges. The availability for such necessary components needs to be organized daily and requires more internal resources. • With regards to the urgently required ramp up of production for SARS nCoV2 test related material there is indeed a global shortage of many key components just to mention a few of them Guanidine, Poly A / G, dNTP, plastics components, various enzymes and therefore the focus within the manufacturers organisations has been distracted from IVDR implementation to supply chain planning and short term product changes to address and circumvent the raw material shortages

Reduced ability to work on IVDR implementation due to social distancing	• **Limited external interaction, i.e. with consultants and other partners.** Telephone and/or video conferences are not always of the same efficacy as face-to-face meetings. • Difficulty in hiring and training new resources to be devoted to IVDR implementation by all stakeholders due to Covid-19 social distancing measures.

Unforeseeable impact on workforce in 2020	• **Potential impact on the ability to implement IVDR.** Even with early implemented strict rules of conduct to respond to the COVID-19 situation, this cannot protect 100% against all potential threats, either foreseeable or unforeseeable.