PREDICTING A SCRAMBLE TO IVDR READINESS

UK Medical Diagnostic (IVD) Sector

Abstract

A report describing the progress by UK Medical Diagnostic Manufacturers towards compliance to the new EU IVDR (In Vitro Diagnostic Device Regulations) for which transition ends in May 2022 after a 5-year journey. The report is an aggregation of an IVDR readiness survey conducted across the sector

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Executive Summary

This report was commissioned by Innovate UK to provide evidence of the readiness of the UK IVD sector for the new EU IVDR by the 26th May 2022. The intent by Innovate UK is to raise awareness of the issues, challenges and needs of the UK IVD sector and to engage critical stakeholders to formulate action plans to help mitigate a crisis both within the sector and more importantly across the UK healthcare sector.

The UK IVD sector are largely SMEs and Micro businesses, anecdotal evidence suggested that many were unprepared for IVDR with transition progress being further exacerbated by the challenges of dealing with the COVID global pandemic response and BREXIT transition preparations.

Certification under IVDR, a harmonised regulatory framework will be applicable for market access to EU27 markets to ensure the safety and performance of devices, requires extensive changes from the current IVDD from 26th May 2022. The new regulations places greater responsibility on manufacturers for enhanced transparency, increased oversight and stricter requirements around analytical performance and scientific validity. The IVDR requirements impact the full lifecycle from development through clinical and safety investigations, regulatory approvals and commercialisation of products.

Also, under the new regulations IVD manufacturers will be required to undertake conformity assessments and certification by a designated notified body (NB), for an extended scope of products classified under a new classification system (Classes A to D, e.g. high-risk blood screening/tissue typing devices, at class D level) according to their benefit-risk profile.

Ultimately, IVDR certification requires changes encompassing everything from technical documentation and labelling, conformity assessments, quality management and post-market surveillance, placing a significant financial cost and resource effort on businesses. And, disproportionally so on SMEs and micro businesses.

The readiness assessment was conducted using a survey which was sent to 400+ UK businesses from which 72 responses were received. The respondents, 92% identified as SME/Micro, we believe were representative of the UK IVD sector.

Amongst the key findings were the following. A significant proportion of the £2.9bn revenues are at risk if IVDR transition is not achieved as a significant proportion of products are sold into CE regulated markets with 52% stating that greater than 30% of revenue was in CE regulated product sales.

UK IVD sector at a glance[1,2]….

- UK IVD (diagnostic and analytical equipment) circa 460 businesses
- 97% of UK IVD are classified as SME /Micro businesses
- circa £2.9bn in annual turnover
- 15,200 employment which spans engineering, technicians, R&D, sales & marketing, regulatory affairs and quality assurances roles etc.
- UK IVD manufactures are a driver of regional growth attracting investments and adding jobs in the community
  - 87 % based in England (53 % regional locations outside London & South East)
  - 5.4 % based in Scotland
  - 5.0 % based in Wales
  - 2.6 % based in NIRL

…. and what failure to be ready for IVDR might impact

Product withdrawals will be inevitable as 26% of businesses indicated that rationalization of their portfolio was taking place as a result of the prohibitive cost of compliance of legacy devices under IVDR.

Access to product innovations are likely to see delays as 90% of businesses planning a product/variant launch in the next 3 years

anticipate significant interruptions. Specifically, if Notified Body (NB) availability to conduct the necessary audits and certifications manifests into the problem current data is predicting. With upwards of 85% of all IVDs currently on the market requiring NB certification[3] and as of September 2020, only 4 NBs being designated (21 NBs are designated under IVDD and only 11 of these have sent completed applications to the European Commission) surely, a predictable and challenging bottleneck. Of particular concern is for the 22% of the respondents classified as Pre-market of which 90% plan to launch in the next 3 years, delays as a consequence of regulatory disruptions, will likely require an increase in investment funding, placing concerns over their future viability.

In relation to where businesses have progressed to in their IVDR transition, the weighted average score on our IVDR readiness framework confirmed a level 3, indicating on-going gap assessments being conducted. With 18 months to go in a 5-year transition timeframe, a level 4 would have been anticipated indicating gap remediation work on-going across all of the elements of change.

Where the sector sees the biggest challenges impeding progress, survey respondents identified 3 critical areas. Access to information in the form of timely guidance from such bodies as the Commission, MHRA and Trade Bodies in relation to the regulation. Access to expertise to supplement internal resources in response to increased workloads. And access to funding, as the cost to transition has been estimated to be between 5-12% of CE revenues, as reported by MedTech Europe[4].

Throughout the 5-transition period the sector has had BREXIT to contend with and a fundamental question as to whether IVDR would be adopted in the UK under a mutual recognition agreement. Only in the recent September 2020 communications from the MHRA has it learnt that IVDD certified products will be valid until June 2023, that a new UKCA regulatory framework will come into place and that IVDR will not automatically apply post transition.

With 91% of respondents stating that they intend to continue to do business in the UK what this means is the complexity of having to transition to 2 different regulatory frameworks. UK IVD will be required to operate under the IVDR as a third country manufacturer and under a 'yet to be defined' UKCA framework on the 1st Jan 2021, to maintain current CE revenue levels.

Undoubtedly for those who had delayed transitioning in the hope of greater clarification from the BREXIT negotiations, their situation is further exacerbated by the disruption dealt by the COVID pandemic. With many businesses negatively impacted financially and having to furlough resources, business interruption has impaired transition progress.

…failure in EU IVDR transition by the UK IVD sector is NOT an option…

…to maintain this critical driver of economic growth and job creation…

Hence, the conclusion of the survey was that a large proportion of UK IVD businesses are not sufficiently progressed and are likely to be scrambling to be ready. With 86 % of businesses intending to continue to sell into the EU under IVDR getting over the line, is not an option

And of consideration is that the unintended consequence for UK healthcare systems is that failure to do so will result in supply interruption within the system having an impact on patients and health outcomes.

In-vitro diagnostics explained

In Vitro Diagnostic (IVD) medical device' means a medical device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. IVD medical devices include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles and are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status.

In vitro diagnostics are intended to be used by:

- Health professionals in the laboratory
- Health professionals at the point of care (near-care)
- Lay-person (self-testing)

And do not include research use only (RUO) devices.

Significant potential for hazards is inherent when using a device and must be proven safe and effective with reasonable assurances before regulating governments permit the marketing of the devices in their country.

As a general rule, as the associated risk of the device increases, the amount of testing required to establish safety and performance also increases. The classification of IVDs is introduced in the new IVDR regulations and has 4 classes, ranging from Class D (highest risk) to Class A (lowest risk).

The authorisation of IVDs is guaranteed by a declaration of conformity, issued by the manufacturer, however under IVDR it must be verified by a certificate of conformity issued by a notified body (NB).

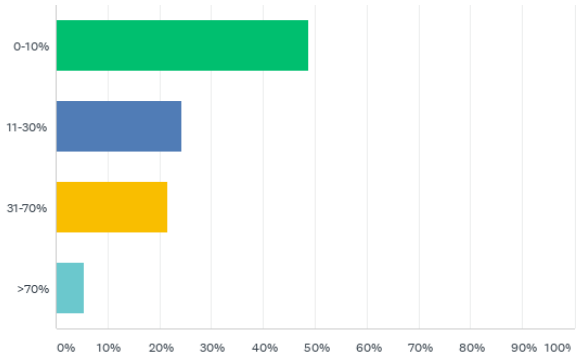
Class	Risk Level	Examples
A	Low Individual Risk and Low Public Health Risk	Clinical Chemistry Analyser, prepared selective culture media
B	Moderate Individual Risk and/or Low Public Health Risk	Vitamin B12, Pregnancy self-testing Anti-Nuclear Antibody, Urine test strips
C	High Individual Risk and/or Moderate Public Health Risk	Blood glucose self-testing, HLA typing, PSA screening, Rubella
D	High Individual Risk and High Public Health Risk	HIV Blood donor screening, HIV Blood diagnostic

Classification system for IVD devices.

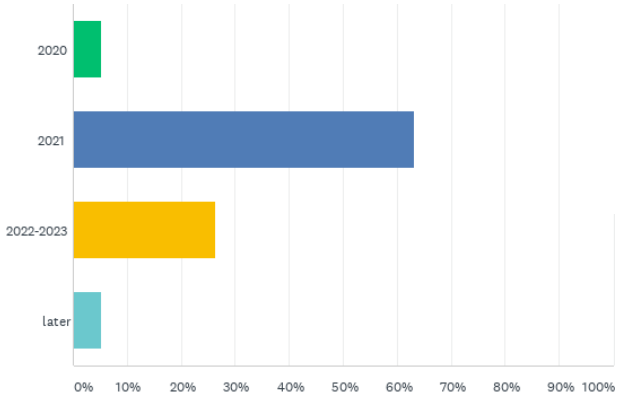
An overview of the IVDR transition journey facing UK IVD

UK IVD generates £2.9bn in annual turnover of which a significant proportion is sold into CE regulated markets

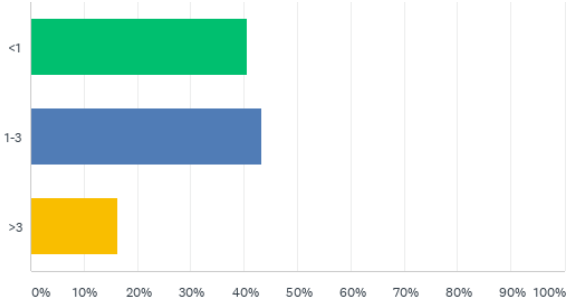
1. **EU27 dependency; 52% of respondents are highly dependent on CE products for >10% revenues**



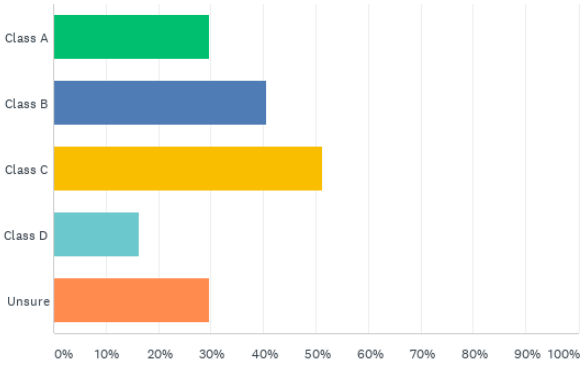
2. **Launch challenges; 63% are planning a product launch in 2021; 90% are planning to do so in the next 3 years**



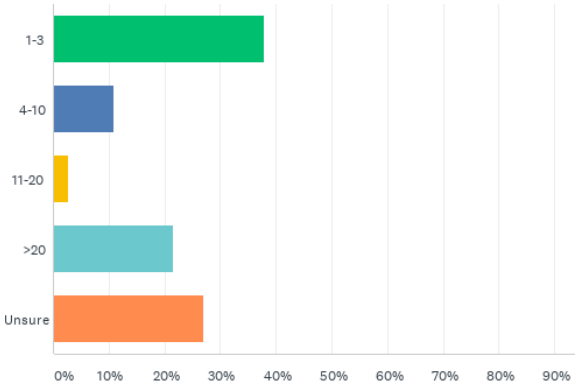
3. **Resource challenge; IVDR is a complex change program; 40% of respondents have <1 regulatory FTE available in the business**



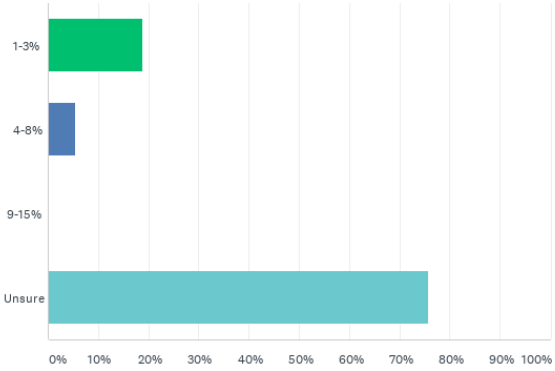
4. **Portfolio complexity; 8% of respondents contained 4 product classes and 24% had 3 classes**



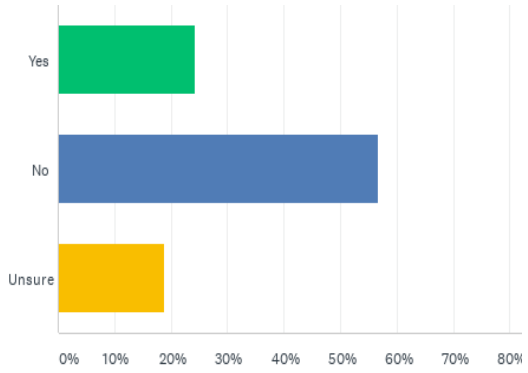
5. **NB capacity concerns; 28% of respondents will be submitting >20TFs for certification; 6% between 11-20 TFs**



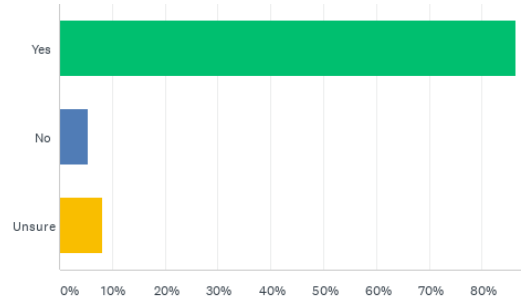
6. **Cost challenge; 32% of respondents who have a budget only 21% had provisioned sufficiently**



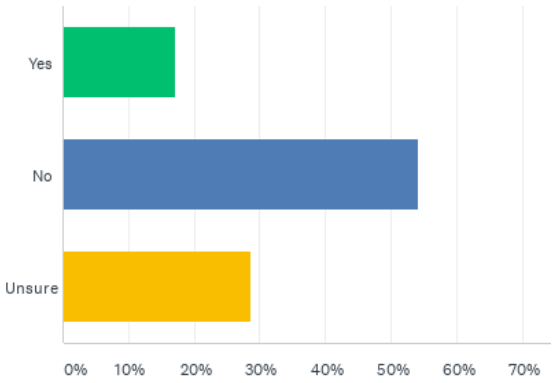
7. **Product challenge: Prohibitive compliance costs means 27% of respondents will rationalise their portfolio**



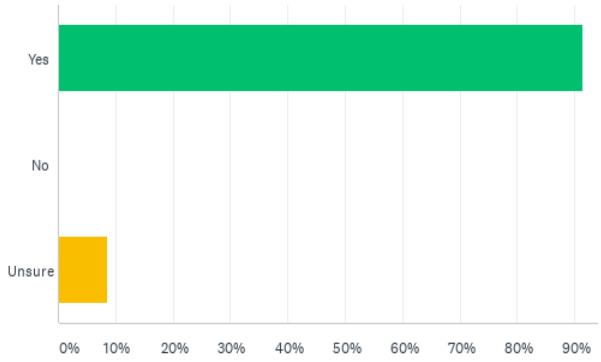
8. **Business viability: 83% confirmed that they would continue to do business in the EU27**



9. **BREXIT unknowns: 18% of respondents stated that alterations were made to their IVDR transition plans**



10. **Attractiveness of UK market post Brexit; 91% stated that they would continue to operate in the UK**



The insights from the participant data concluded that the viability of UK IVD is heavily dependent on successfully executing a challenging program of changes to IVDR by 26th May 2022 based on the need to maintain EU27 revenues levels.

What was also made clear was that over the next 18 months NBs would be required to certify a significant number of IVDs. We foresee a pending 'cliff edge' as a result of the limited progress in NB authorisations under IVDR.

Coupled with this is the added complexity to prepare for a UKCA regulatory framework which will necessitate changes to be implemented by the 1st Jan 2021 diverting already scare resources away from IVDR transition efforts.

Of concern in the data is the limited funding provisioned by businesses for transition. Despite published benchmarks from MedTech Europe[3] 8% of respondents do not have sufficiently funded programs.

Transition progress across UK

Utilising a competency framework, the IVDR readiness survey sought to establish progress in the remediation of products and the various operating model changes required to meet IVDR compliance.

As IVDR programs impact most elements of the business the survey also examined 4 critical paraments under **Business Readiness** seeking to establish the level of leadership alignment, regulatory control, funding and of importance NB engagement with the program.

a) What we expected to see.
With 18 months to run expectations of level 4 attainment across all parameters would have indicated that progress was where it needed to be.

b) What we saw in the data.
The weighted average score indicated level 3 progression across all parameters. What this illustrated was that leaders were still refining go/no go decisions on how to proceed. Regulatory was coordinating gap impact assessments and funding in budget planning phase. Critically, NB engagement was not progressed perhaps as a result of a lack of NB authorisations.

c) Considerations to accelerate transition.
IVDR programs need to be owned at business leadership level. Whilst facilitated by regulatory they required cross functional collaboration and coordination. Leadership needs to be visible as assigning and prioritising resources to meet the deadlines will need arbitration.

The role of regulatory is to facilitate the program, IVDR is extensive and requires interpretation in its application specific to a business. 'One source of the truth' will be imperative for a consistent application across all functional teams.

IVDR budgeting based on well costed remediations to close compliance gaps are essential to ensuring that the big decisions such as product rationalisation and market viability are taken.

IVDR Readiness Matrix : Business Readiness

Key : IVDR Readiness Level Scores
- Red | least mature
- Amber | weighted average
- Green | most mature

Focus Area	Maturity Parameter	Level 1 Descriptor	0	1	2	3	4	5	Level 5 Descriptor
Business Readiness	Leadership/ Management Alignment on IVDR	• IVDR generally understood by the Leadership /Management teams.	X			X		X	• Leadership/Management are confident IVDR transitioning is on track
	Regulatory Compliance Status	• Business operating under IVDD compliance	X			X		X	• IVDR transition program underway with progress on long lead-time activities • Alignment with Commission timetable/NB readiness , Implementing Acts etc. being managed
	IVDR Financial Planning	• Finance /Commercial teams aware that their will be Revenue and Cost impacts to the Business under IVDR	X			X		X	• Financial management in place • Financial reporting to Leadership /Management teams in place
	Notified Body Engagement	• Position of current Notified Body IVDR authorisation timing is understood	X			X		X	• Notified Body engaged and aligned to product certification plan

It cannot be overstated that early engagement of a NB is essential to supporting transition plan timelines with potential certification timeframes, to providing confirmation of interpretation and application of the new regulations to support correct remediation proposals by businesses.

Transition progress with Portfolio/Product compliance

The survey examined progress on **6 Portfolio/Product parameters.** Under the IVDR is the introduction of a new classification structure. Imperative is the selection of the right classification which drives the safety and performance levels required to be demonstrated to support certification.

Additionally, we surveyed progress with the General Safety and Performance Requirements (GSPR), Performance Evaluations, Product Surveillance, Technical Documentation and Labelling changes.

a) What we expected to see.
As remediations of products to close the IVDR compliance gaps contain a number of long-lead items i.e. GSPR and PER/P, expectations that level 4/5 would be observed in the results.

b) What we saw in the data.
The weighted average score indicated levels 2/3 progression. What this indicated was that many businesses are still conducting gap assessment work and yet to confirm remediation plans and to start implementation.

c) Considerations to accelerate transition.
Confirmation of a products classification is critical, as it drives many of a products compliance needs and certification pathway. In a recent presentation by the MHRA, alignment on classification was stated to be contentious particularly for boarder-line products, with businesses inclined to assess products into lower classes.

IVDR Readiness Matrix : Product /Portfolio Readiness

Key : IVDR Readiness Level Scores
- Red | least mature
- Amber | weighted average
- Green | most mature

Focus Area	Maturity Parameter	Level 1 Descriptor	0	1	2	3	4	5	Level 5 Descriptor
Product/Portfolio Readiness – Part 1	**Product Classification & Certification**	• New device classification and definitions (Annex VIII) understood to include Companion Diagnostics, Self- and Near- patient test devices and societal information services e.g. web-sites	X			X		X	• Product certification scheduled with NB • Additional scrutiny requirements incorporated in plan for Class D devices
	General, Safety & Performance	• Products compliant with IVDD (Directive 98/79/EC)		X		X	X		• Compliant GSPR data set available and formatted for inclusion to the Technical File Document – Annex II
	Performance Evaluation/ Studies & Interventional Clinical Studies	• Products compliant with IVDD (Directive 98/79/EC)		X		X	X		• Revised PE Plans/Reports updated into the Technical Document • Revised Clinical Performance Reports updated into the Technical Document • Class D – Summary of Safety & Performance (SSP) available for upload to EUDAMED

IVDR Readiness Matrix : Product/Portfolio

Key : IVDR Readiness Level Scores
- Red | least mature
- Blue | weighted average
- Green | most mature

Focus Area	Maturity Parameter	Level 1 Descriptor	0	1	2	3	4	5	Level 5 Descriptor
Product/Portfolio Readiness – Part 2	**Post Market Surveillance**	• Products compliant with IVDD (Directive 98/79/EC)		X	XX				• Revised PMS Plan/ Reports available for inclusion within the updated Technical Document • Revised PSUR available for inclusion within the updated Technical Document and made available
	Technical Documentation	• Complete and updated IVDD compliant Technical Documentation (Directive 98/79/EC)		X		XX			• IVDR Technical Documentation available for re-certification submission
	Product Labelling (Label & IFU)	• Complete product labelling compliant to IVDD (Directive 98/79/EC)		X		X	X		• Product labelling updated to IVDR and available for insertion in the Technical Documentation for recertification • Packaging operations updated to accommodate UDI printing/pack and insertion changes etc.

GSPR and Performance Evaluation studies tend to be long-lead and expensive remediations efforts and prioritised first. Awareness that access to Reference Labs will be a scare resource. GSPR, PER/P and PMSP/R remediations need to precede label and TF updates in the plan, to eliminate 'double handling'.

Both the CA and NBs are seeking greater levels of standardisation in Technical Documentation and EUDAMED submissions e.g. Periodic Safety Update Reports (PSURs) etc.

Many standardised templates are readily available to be leveraged across the sector.

Label translations, updates and potentially consequential packaging changes as a result of format changes are proving to be both expensive and extensive under IVDR.

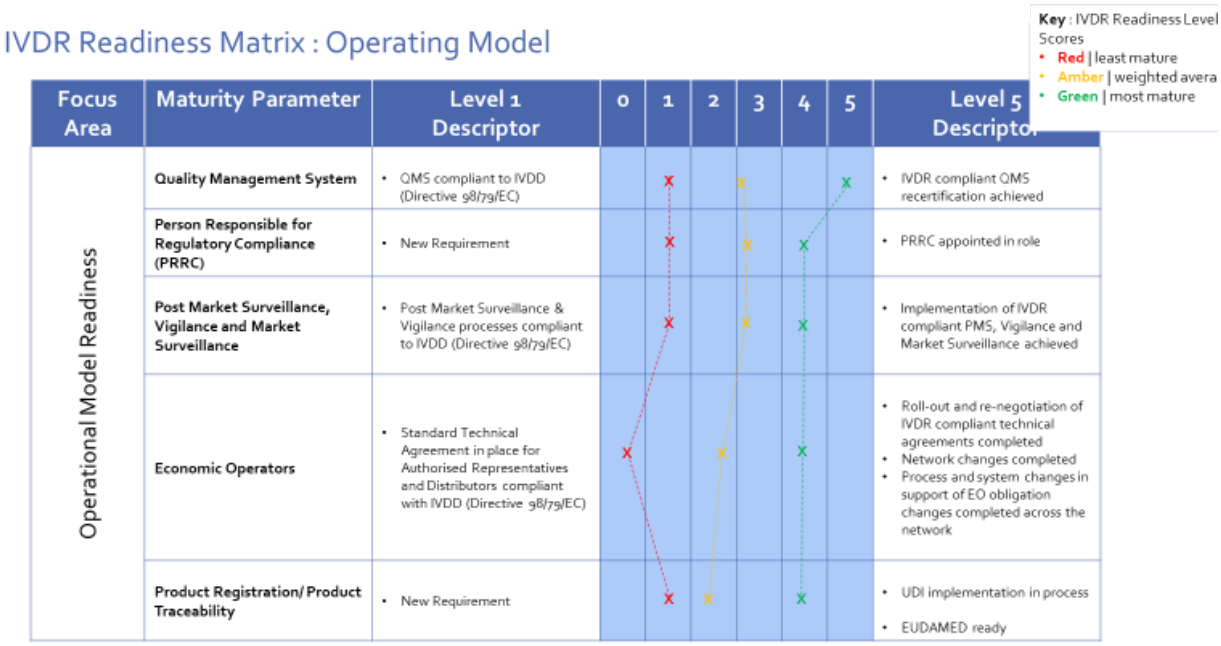
Transition progress with Operating Model changes

The third dimension to the IVDR readiness competency model sought to review **5** critical **Operating Model** paraments. Significantly and of priority the QMS and additionally progress was reviewed with the changes in relation to PRRC, Market Surveillance, Economic Operators and Product Registrations/Traceability.

a) What we expected to see.
Certainly, a QMS at levels 4/5 to support the remediation efforts. The remaining Operating Model parameters, all of which involve a process, organisational and/or IT change, expected at level 4.

b) What we saw in the data.
The weighted average score indicated a level 2/3 progression. What this illustrated was that businesses have focussed on the product related changes at the expense of progressing the more operational changes required under IVDR.

c) Considerations to accelerate transition
QMS changes and more importantly additions are not insignificant in level or effort. QMS changes are required in advance to support implementation and hence a priority component in transitioning.



Under IVDR there will be a significant increase in the level of reporting and accessible information to the Competent Authorities, HCP and Public.

Consequently, there will be significant data management and maintenance which will require uploading to EUDAMED supported by UDI introduction. A businesses IT team needs to be an integral part of the transition effort.

Also, not to be underestimated product traceability across the full product supply network will be a prerequisite for IVDR compliance. For Manufacturers placing purchased finished goods (PFG) onto the market will have significance, as will the role of Agents and Distributors, involved in the first placing of products from a third country onto the market with newly defined Importer roles and responsibilities. Identification of all economic operators and renewal of technical agreements will be necessary and may require renegotiation and/or reconfiguring of the network.

IVDR Transition Challenges

In the final part of the survey participants were required to rank a series of 12 potential key challenges and the opportunity to add their own. We also asked them to identify their top 3 challenges from the list.

a) What we expected to see.

In anticipation that implementation was underway access to expertise, funding and NB were expected to feature highly.

b) What we saw in the data.

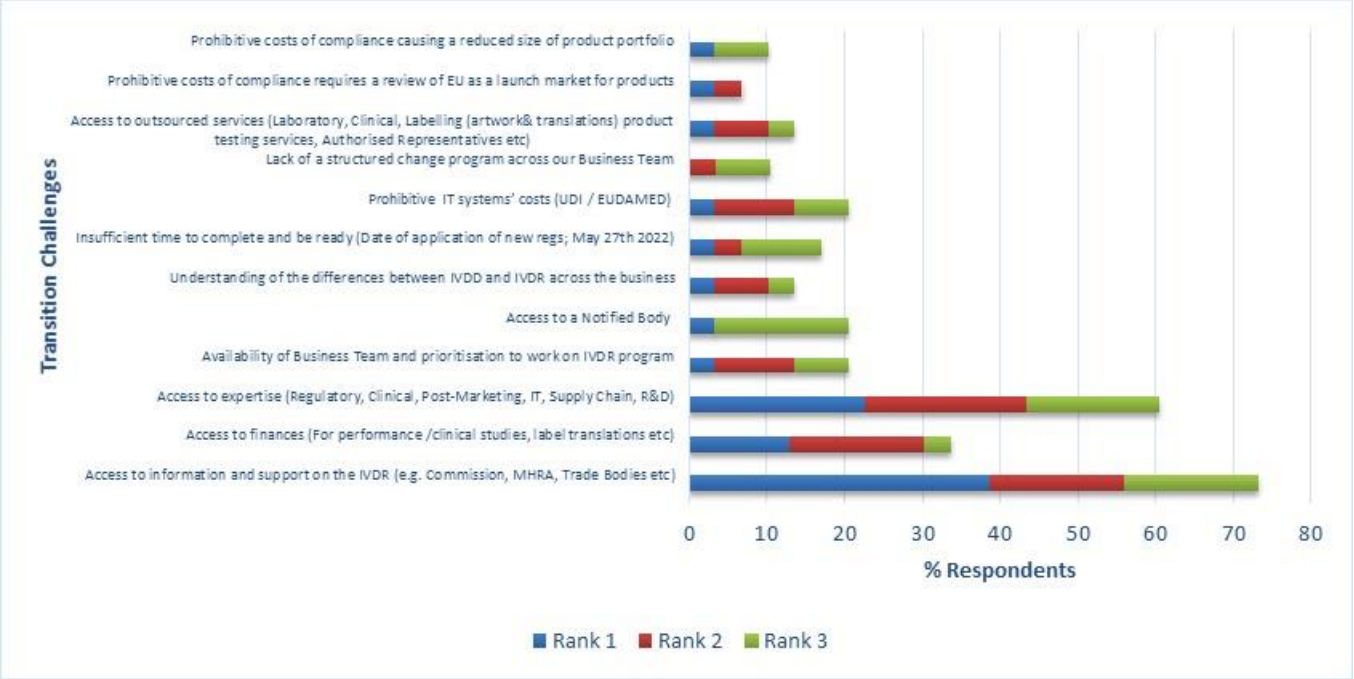
Access to expertise and funding featured in the top 3, however access to information from sources such as the Commission, MHRA and Trade Bodies not only featured higher than anticipated but

was most prominent with all participants as the top ranked challenge. What was surprising was that access to NB did not feature higher, in the top 3.

c) Considerations to accelerate transition

The sector has identified how it needs to be supported by the major stakeholders. Of interest is their top priority requesting greater access to information from the Commission, MHRA and Trade Bodies points towards support with details with interpretation of the regulations to specific implementation details e.g. Classification of devices, EUDAMED access, workings of the MDCG panel etc.

IVDR Transition Challenges : Ranking 1-3 of Challenges



Key Conclusions

Successful transitioning to IVDR of CE marked products supporting trade with the EU27 is critical to the UK IVD sectors viability and future growth aspirations.

Consequently, IVDR transition is not an option. Understandably businesses are currently dealing with both COVID-19 and BREXIT responses, however we conclude that IVDR transitioning requires acceleration.

And whilst the sector is pushing for an extension to the May 2022 deadline timescales are not yet critical, however if businesses fail to accelerate progress out of gap assessments and into implementation, realistically in the next 3-6months, this will not continue to be the case.

It is evident that picking up the pace of transition by UK IVD is being negatively impacted by the uncertainty with the UK-EU trade deal and awaiting details of the UKCA framework from the MHRA.

To keep transition on track the known concerns with NB capacity and availability cannot be ignored. The rate of progress in NB authorisations has to be addressed by the Commission and Competent Authorities together. The challenges to NBs to increase resources and expertise against enhanced roles and responsibilities under IVDR and its impact on designation rates cannot be ignored.

Key support requests by the sector are for:

1. Access to information and support on the IVDR (Commission, MHRA and Trade Bodies etc)
2. Access to expertise (CRO, Quality, Regulatory, Legal etc)
3. Access to funding

Key Recommendations

What has emerged from the COVID pandemic experience for the diagnostic sector is that much can be achieved if the ecosystem 'act together'.

In response to the needs placed on the UK IVD sector, government and regulators, has emerged the unprecedented demonstration by all parties to operate in such a way as to get things done. What has emerged is closer cooperation across business silos, changes to working practices between businesses, accelerated business actions for results.

In relation to IVDR transitioning, the UK IVD sector, policy makers and regulators, NBs and government agencies need to similarly 'act together'. Alignment to get things done across the ecosystem to successfully transition to IVDR is the need. The 'as-is' needs to be overhauled to include changes to the CA-NB-Manufacturer ways of working e.g. virtual audits, NB authorisations against specific product classifications, interim submissions for evaluation and feedback of complex IVDs prior to final certifications etc.

Finally, any coordinated support needs to reflect that ~95% of UK IVD are SME and Micro businesses. For Trade Associations specifically, the 'voice of their SME/Micro customers' in any response needs to be loud and clear. This subsector needs greater access to information beyond the mass generalised communications and documentations being released. Design of any SME/Micro support has to account for the limited capabilities specifically in funds, availability and expertise which can be allocated to IVDR transition versus 'keeping the lights on'.

Survey Details

The proprietary ISO Life Sciences EU IVDR Readiness survey was distributed to the UK IVD sector via various channels including ABHI, BIVDA and via Innovate UK to BIONOW, OneNucleus, BIA, Medicines Discovery Catapult, OBN, Medilink/SEHTA, MediWales and MedCity.

The report is an analysis of the 72 respondents from UK IVD organisations, approximately 17% of the UK IVD sector. The breakdown in IVD organisations represented were 8% >250 employee businesses; 54% SMEs and 38% Micro businesses.

The respondent roles within their organisations represented 15% CEO/MD; 7% CSO/Technical Director; 40% VP Global/Head of QA&RA; 27% Director/Mgr QA&RA.

The survey was open for a period of 4 weeks and close on Nov 6th 2020.

References

1. **ABHI** Diagnostics: A future Roadmap (August 2020)
2. **MedTech Europe** The European Medical Technology Industry in figures 2020
3. **Schlemmer, F**. Survey on NBs applications against IVD Regulations (Team NB 2019)
4. **MedTech Europe** Winding down to the EU IVD and Medical Devices Regulations Deadlines: The Finish Lines in Sight? (2019)

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