Evaluating the impact of the entry of IVD-R in the biopharmaceutical industry, with a focus on evidence requirements and time to launch

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KEY TAKEAWAYS

1. IVD-R is here to stay, and it will affect both the development of new CDx and IVD due to increasing regulatory burden on product development and evidence generation
2. As a result of increased evidence requirements and review by NBs, IVD-R is expected to change level of investment and timeframe (>90 days)
3. Uncertainties remain around the long-term impact of IVD-R implementation, even among individuals whose role/functions will be affected by IVD-R

INTRODUCTION & OBJECTIVE

- The EMA will transition from the In Vitro Diagnostic Directive (IVDD) (in place since 2003) to the new in-vitro diagnostic regulation (IVD-R) over the next 5 years[1]
- IVD-R implementation will consolidate the Europe IVD regulatory framework IVDs, and standardize commercialization requirements[2]
- Under IVD-R, manufacturers will have to demonstrate IVD safety, scientific validity, analytical performance, and clinical performance[1,3]
- Notified Bodies (NBs) will be responsible for independent review, long-term monitoring, and compliance for a larger proportion of IVDs. Post transition, it is estimated that the number of IVDs that would require NB approval would increase from 3,300 IVDs to 24,000 IVDs (an increase from 8% to 80% of submitted reviews)[4,5]
- The newly implemented IVD-R also requires eligible IVDs that are currently approved under IVDD to be recertified
- IVD-R has recognized a broad definition to include a wide range of products that require inspection including any medical device, reagent, apparatus, instrument, pieces of equipment, or software used for in-vitro sample examination[6]
- IVD-R also now includes companion diagnostics (CDx) (i.e., in-vitro diagnostics that provide essential information related to the safety and effectiveness of a corresponding drug that is under administration) under class C risk and will have to go through NB approvals and will need to meet stricter performance requirements, including clinical evidence[7,8]

OBJECTIVE

This research aims to understand and provide insight into the impact that the new EU IVD-R will have on the biopharmaceutical industry, the ongoing preparation by the industry for the upcoming IVD-R, the impact it has had, and the impact it will have on research and development and evidence needed to support regulatory evaluation and product launch.

METHODS

Secondary Research

- The study utilized secondary research to understand how pharmaceutical and diagnostic industries are approaching the development of IVDs, collaborations, and the approach to evidence generation
- The team identified key topics of interest from an academic and industry perspective by utilizing PubMed and Google databases and carried out targeted hand searches to gather industry-developed resources that covered the implementation of IVD-R by biopharmaceutical and IVD companies
- To determine if IVD focused publications in Europe have changed over time, a search strategy was developed in PubMed (**Table 1**) to evaluate the extent to which the number of publications have changed on IVDs over time

Table 1. PubMed Search Strategy

Category	Search Terms
IVD Terms	"in vitro diagnostic"[Text Word] OR "in vitro diagnostics"[Text Word] OR "in vitro diagnostic"[Text Word] OR "in vitro diagnostics"[Text Word] OR ("in vitro"[Text Word] AND "Diagnostic Equipment"[MeSH Terms])
Temporal Limits	2012-2022

Primary Research: Quantitative Survey

- The quantitative survey was a 10-min questionnaire filled out by industry professionals quantifying the impact of IVD-R on various factors in the pharmaceutical and diagnostic industry like time taken to launch, evidence generation plans, and level of investment required for evidence generation among other factors
- Open-ended questions were also included in the survey about the change organizations were going through in terms of planning needs, change in launch strategy, evidence generation, impact on overall budget, and organization structure to prepare for IVD-R.

CONCLUSIONS

This research reviews the impact of IVD-R on launch planning, evidence generation, and time to launch in the EU market and improves the overall understanding of how the pharmaceutical and diagnostic industry are preparing to address the changes introduced by IVD-R. While most pharmaceutical and IVD manufacturers have initiated preparation for IVD-R, uncertainties remain around the long-term impact it will have on pharmaceutical and IVD manufacturer collaborations, CDx use, access to targeted therapies and diagnostics.

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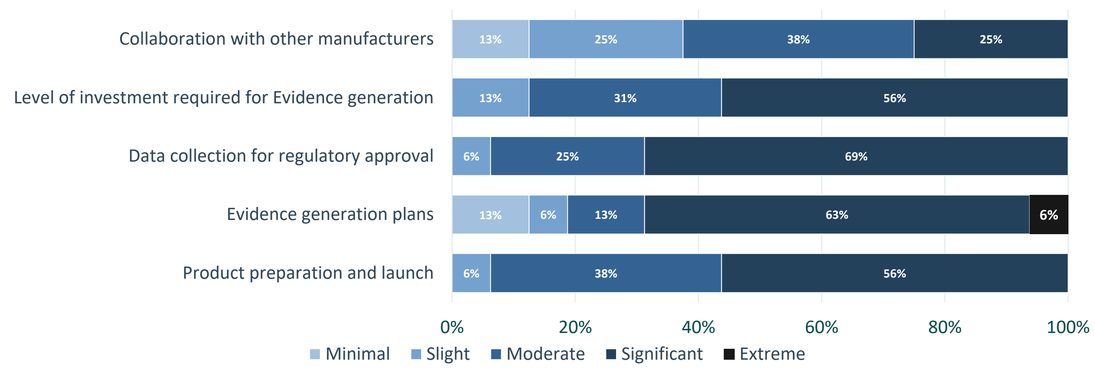
RESULTS

Primary Research with Industry Experts

Figure 1. Impact of IVD-R on product launch (N=16)

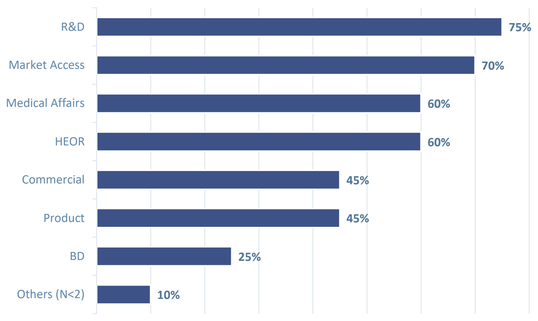


Respondents indicted that IVD-R will have a moderate to significant impact across many aspects of launch readiness. This includes both increased investment in evidence generation and closer collaboration between biopharmaceutical and IVD manufacturers (Figure 1 – Impact of IVD-R on product launch).

> *"From the perspective of a company that invests a great deal in the clinical evidence of our testing services, we sincerely hope IVDR will provide more transparency to HCPs and patients who have no hope of navigating the complex competitive landscape for high-risk genomic profiling. We don't allow just anyone to sell drugs made in their basement, we should also have a higher standard for high-risk diagnostics."*

> *"The co-development of a CDx which can cause significant delays in approval and other undesirable consequences, especially if the competition comes in before the new regulations and do not have a CDx specified in their label."*

Figure 2. Departments impacted by IVD-R (by number of times selected)



Respondents indicated that the Medical Affairs, R&D, Market Access, and HEOR functions were the most likely to be impacted by the transition to IVD-R (Refer to Figure 2 – Departments impacted by IVD-R). These departments will be responsible for alleviating the pressures that IVD-R will have on product planning requirements, evidence development and implications for market-entry. Sensitivity and specificity, product tracking capabilities and scientific validity of the tests were highlighted as the most important tracking items for approval through the new IVD-R process.

> *"We had to engage in conversation with the regulatory bodies, to confirm alignment between our understanding of the new guidelines and actual requirements."*
> *"IVD-R has impacted the initiation of clinical performance studies and the requirements for having clinical evidence for all IVD devices."*

Additionally, respondents raised concerns around additional changes coming into play in the next few years, given the updates they have seen over the last 20.

> *"We expect the process to be a lot more dynamic as it will now require buy in from the authorities and seeking their position on proposed strategies."*

Beyond evidence generation requirements and financial burden, IVD-R will also impact timeframes for evidence generation and product launch. Most of the respondents believed that IVD-R will extend the data generation timeframe by at least 60 days, and the timeframe for review and launch by a minimum of 90 days. Respondents mention the limited number of certified Notified Bodies as the main bottleneck to the timely review of IVDs and expect for the EMA to certify additional companies to perform this function.

Table 2. Respondent Background

Pharmaceutical Manufacturer	IVD Developer / Manufacturer	Others
9/16	5/16	2/16

Secondary Research

Table 3. Secondary Research Themes and Findings

Themes	Findings
IVD-R Implementation Purpose	The transition from IVDD to IVD-R is due to technological advancements in healthcare along with tackling the increased safety concerns around medical and invitro diagnostic devices.[6,9]
Published Literature	Published literature focuses on the differences between IVD-R and IVDD and the important changes that are introduced in the new legislation. However, very little evidence has been found on what this change means for the diagnostic and pharmaceutical industries and the preparation both manufacturers would need to make in their working environment, department structures, and time required to launch.
Risk based classification	Risk-based classification of devices will be used for determination of diagnostic approvals. (Table 4) Evidence and documentation required for submission will differ based on risk classification of individual device[10,11]
Evaluation of Devices by NBs	All devices will be evaluated on scientific validity, analytical performance, and clinical performance by NBs. A sizable increase in the number of devices needing NB reviews has created increased demand for the services of designated NB bodies. Currently however, a total of only seven NBs are approved/designated for certification in the EU which will likely result in long wait times for product reviews from the NBs.[6,12,13]
Performance Evaluation Report	A performance evaluation report (PER), consisting of documentation for scientific validity, analytical performance, and clinical performance is not required under IVDD but is a mandatory document for IVDR compliance. Collection and retainment of post-market clinical data will be mandated for assessing potential safety risks. This will require all manufacturers to perform tests, collate data, analyze, and validate every device for its analytical and clinical performance prior to the NB review[3,5,13,14]
Impact on Legacy products	Existing products will also need to comply with IVD-R changes and undergo review if necessary. The anticipated challenge for companies with legacy devices would be the run the gap analysis between IVDD and IVD-R changes and submit appropriate documentation to ensure all new standards are met[15,16,17]

Table 4. Risk-based Classification of Devices

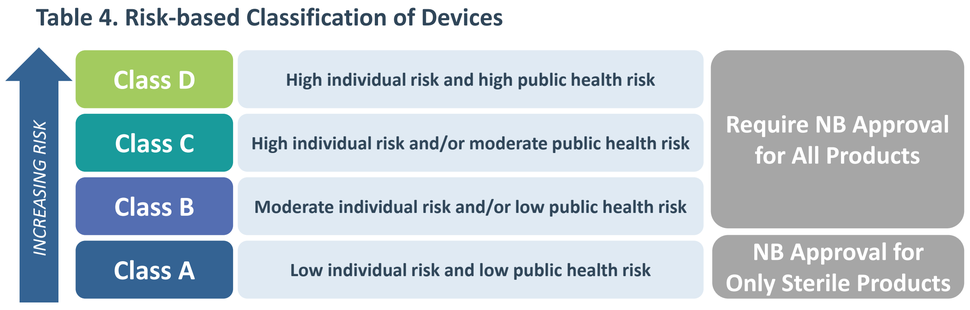


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Figure 3. Publications related to IVDs in the last 10 years

Distribution of types of Publications related to IVDs (2012-2022)

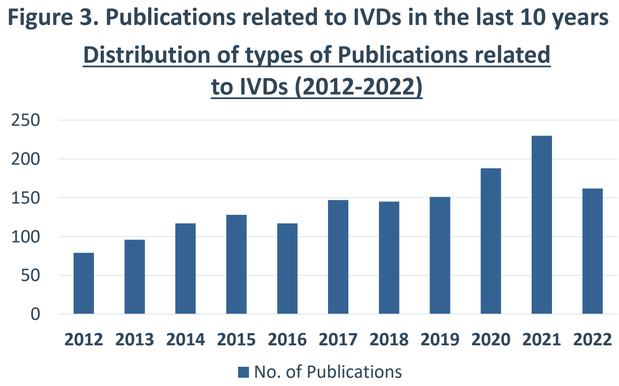
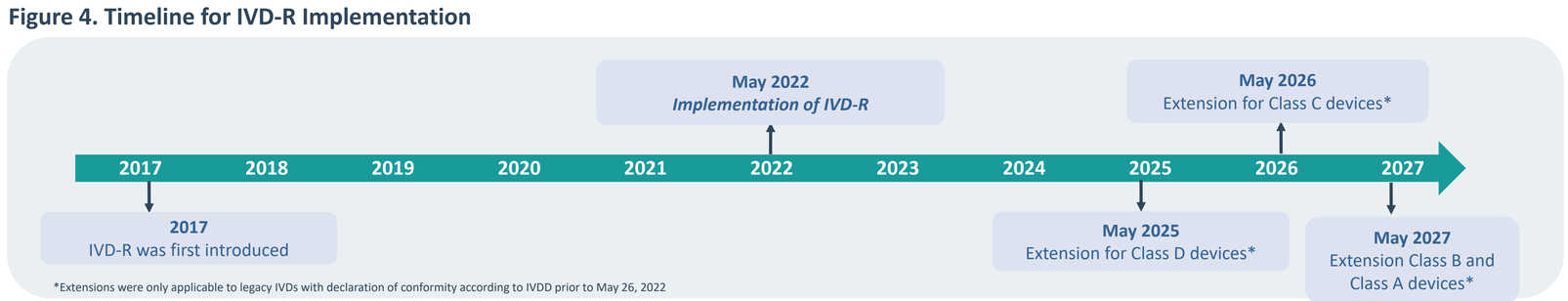


Figure 4. Timeline for IVD-R Implementation



*Extensions were only applicable to legacy IVDs with declaration of conformity according to IVDD prior to May 26, 2022

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