NETWORKPARTNERS

THE IVDR TOP 8

A Roadmap For Transitioning To The European *in vitro* Diagnostic Medical Devices Regulation (IVDR)

NUMBER ONE

THE TIME FOR ACTION IS NOW

The impact of the EU IVD Regulation (IVDR) is much bigger than the impact of EU Medical Devices Regulation (MDR), which is a bold statement to make, considering the significant industry-wide impact of MDR. Notified Body (NB) representatives have been quoted calling EU IVDR the "big bomb" and are advising the IVDR industry that if they haven't started already, they may already be too late to meet the deadline for EU IVDR implementation on May 26, 2022. IVDR results in more products requiring review and far fewer NBs to perform these reviews.

Under the new regulation:

- No grandfathering of IVD products currently on the market
- No grace period for self-certified products under the prior IVD Directive

As a result, there will be about 70% more products under NB review for the **first time.**

Depending on the state of a company's technical documentation, it is estimated that IVD organizations will need 12 months to two or more years to set up their systems and processes and have completed technical files for NB review.

The IVDR will be fully enforceable on May 26, 2022. If this date seems far into the future, consider that we are already more than two years into the transitional period.

NUMBER TWO

CLASSIFICATION

The IVDR replaces the list-based classification with a risk-based classification. Due to this change, Notified Bodies expect more than 85% of IVDs will now require Notified Body review compared to roughly 15% of IVDs currently requiring review.[1]

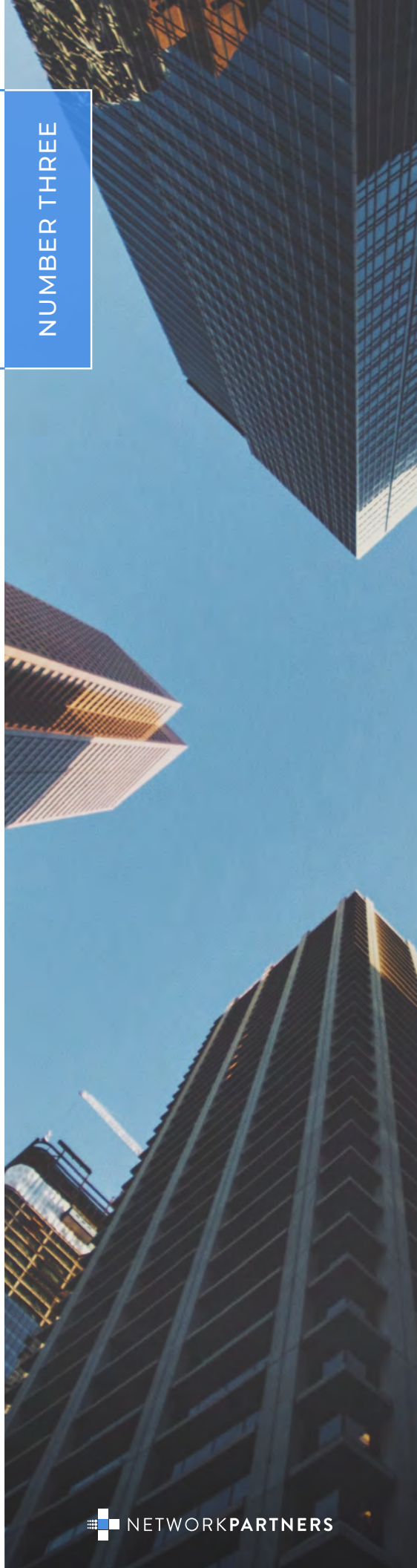
The new classification structure is similar to the class and rule system authored by Study Group 1 of the Global Harmonization Task Force in 2008.[2] While the IVDR aligns Europe with the rest of the world on IVD classification, the IVD manufacturer marketing in Europe will now — more likely than not — have a new risk-based up-classified IVD product. For example, devices not covered by other rules in the IVD Regulation and non-quantitative or non-qualitative controls are now classified as Class B. Under the IVD Directive, these devices were considered low risk and not subject to Notified Body assessments. Products classified as Class B, C or D, according to the IVDR, require the involvement of a Notified Body.

Start with the IVD's intended purpose and classify according to Annex 8. The intended purpose comprises several areas:

Intended Purpose	Examples
Role of the IVD	Diagnosis, screening, management, monitoring
User environment	Physician's office, home use, laboratory, mobile point of-care (POC)
User	Physician, technician, nurse, patient
User Population	Adult, pediatric, patients with heart disease
Additional Population Considerations	Cancer, diabetes, HIV
How disease concerned is being tested	Blood, tissue, breath, urine
Type of Test	Molecular, immunologic, microbiologic
Data	Qualitative, quantitative, semi-quantitative

NOTIFIED BODY DESIGNATION

NUMBER THREE



HAS YOUR CURRENT NOTIFIED BODY APPLIED FOR DESIGNATION?

The current expectation is five to seven NBs will be designated under IVDR. Competent Authorities and EMA are stating they may need to step in to perform audits/reviews.[3]

If you believe your NB will be designated, check with them to understand their timelines and capacity. If your Notified Body has not applied or if you believe they may not be designated, check with other Notified Bodies on their application status, as well as timelines and capacity.

NUMBER FOUR

INCREASED REQUIREMENTS FOR CLINICAL EVIDENCE & PERFORMANCE STUDIES

Analytical and clinical performance requirements are greatly expanded in the IVDR. Clinical performance was only mandatory for high risk IVDs according to the IVDD. Clinical performance studies must now be conducted "unless it is duly justified to rely on other sources of clinical performance data."

Per Annex VII, the Notified Body is required to assess performance evaluations and "critically examine" any justifications or deviations provided by the manufacturer. Thus, not only will several more studies be required, the Notified Body will review these studies with increased scrutiny.

Analytical performance includes new requirements for trueness and precision, thus expanding requirements for accuracy (true and precise).

IVDD and IVDR share the Clinical Performance requirements for diagnostic sensitivity and diagnostic specificity. However, the IVDR adds:

- **Positive Predictive Value**
- **Negative Predictive Value**
- **Likelihood Ratio**
- **Expected Values in normal and affected populations**

It is recommended to start planning and performing the additional testing described in Annex XIII now if you have not already started. Annex XIII is separated into two parts:

Part A: Performance Evaluation & Performance Studies

Performance Evaluation

- Performance Evaluation Plan
- Scientific Validity, analytical performance, and clinical performance
  - Key evidence for the Performance Evaluation Report (PER)
- Clinical Evidence and PER

Clinical Performance Studies:

- Purpose of clinical performance studies
- Ethical considerations for clinical performance studies
- Methods for clinical performance studies (design, plan, report)

Part B: Post-Market Performance Follow-Up (PMPF)

PMPF is a continuous process to update the performance evaluation and addresses the post market surveillance plan.

Newly published ISO 20916:2019 is the accepted international standard for clinical performance studies concerning IVD devices. An important change, IVDR 2017/246 Corrigendum, amends IVDR Recital (66) and changes ISO 14155 to ISO 20916:

> "The rules on performance studies should be in line with well-established international guidance in this field, such as the international standard ISO 20916 on clinical performance studies using specimens from human subjects, currently under development, so as to make it easier for the results of performance studies ...".

NUMBER FIVE

SOFTWARE

As with the new Medical Device Regulation, there is a heightened focus on software in the IVD Regulation. In the IVDD, the term "software" appeared only four times whereas it is mentioned more than 50 times in the IVDR. Software, *whether used alone or in combination, with the intention to be used in vitro for the examination of specimens* in accordance with the purposes outlined in the IVDR, is now part of the definition of an in vitro diagnostic device.

The classification and requirements for software should be carefully considered. Per recital (17):

> "It is necessary to clarify that software in its own right, when specifically intended by the manufacturer to be used for one or more of the medical purposes set out in the definition of an in vitro diagnostic medical device, qualifies as an in vitro diagnostic medical device, while software for general purposes, even when used in a healthcare setting, or software intended for well-being purposes is not an in vitro diagnostic medical device. The qualification of software, either as a device or an accessory, is independent of the software's location or the type of interconnection between the software and a device."

Moreover, with advances in software and cybertechnology, interconnected devices, new performance data requirements and the implementation of the Global Data Protection Regulation (GDPR) in May 2018, it is not surprising that the IVDR will hold the industry accountable for protecting patient data and addressing the industry risks. Annex I includes language around reducing (or removing) risks as far as possible that are associated with the negative interaction between IT networks characteristics and IT security measures. It is also required to provide the user with adequate information in the labeling concerning IT networks characteristics and IT security measures, including protection against unauthorized access.

NUMBER SIX

LABELING AND UNIQUE DEVICE IDENTIFICATION SYSTEM (UDI)

Section 20 in Annex I, General Safety and Performance Requirements, introduces more than 40 new requirements and more than 20 revised requirements for labeling.

Every label will change. New requirements include information on sterile packaging, when it is acceptable to provide electronic instructions for use versus paper format, more detailed information concerning the intended purpose of the IVD and specific information around particular warnings and hazards.

The UDI carrier must appear on the label. Other required information includes the date until the product can be safely used or date of manufacture, net quantity of contents and whether the device is single use only. Identical to the MDR (Annex I, section 23.3(a)), Annex I, section 20.3(a) in the IVDR requires the labeling to include "an indication permitting the sterile packaging to be recognised as such."

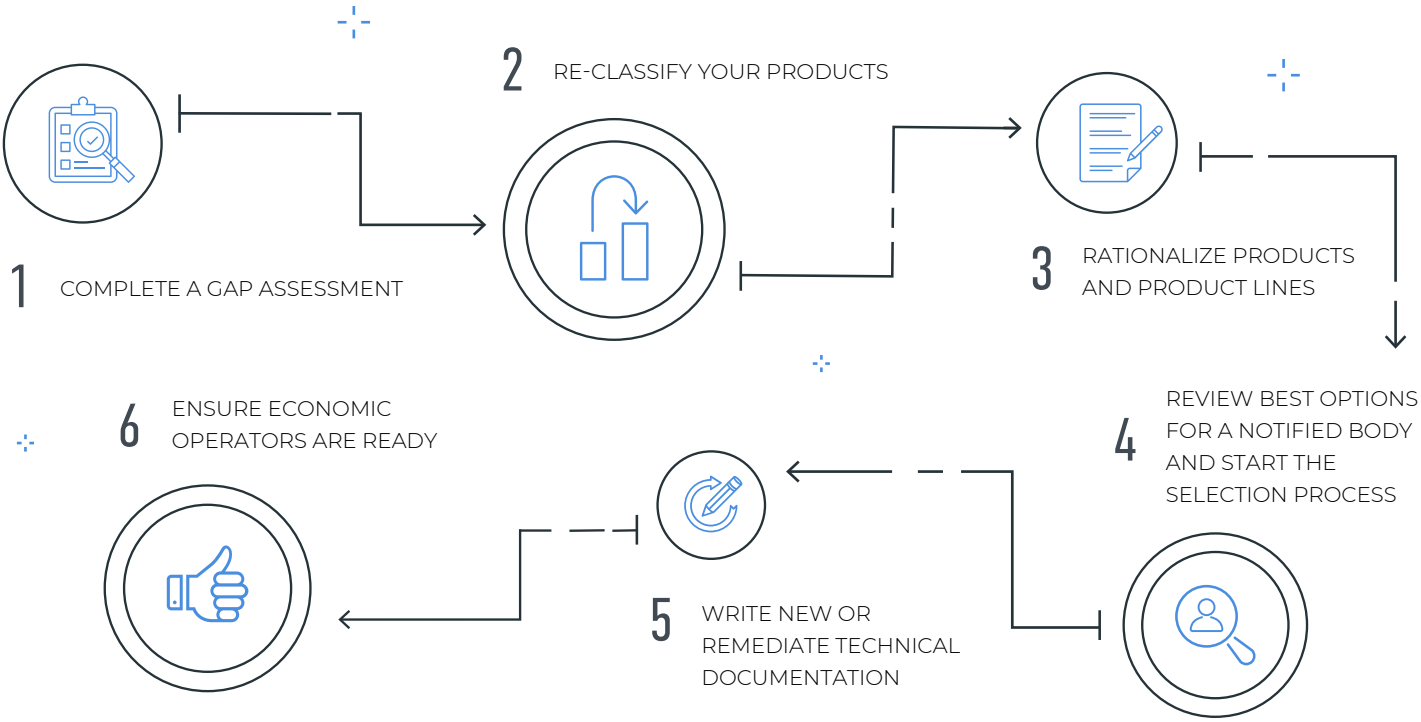
As reported in *Network Partners' EU MDR 10 Things Packaging Engineers Should Know,* the Sterile Barrier Association – the European trade association for companies who produce Sterile Barrier Systems (SBS) and associated equipment and accessories for the healthcare industry – proposed symbols to help healthcare professionals understand which parts of a package are sterile. The association has gathered industry feedback and is currently working with standardization bodies to consider the proposed symbols.[4]

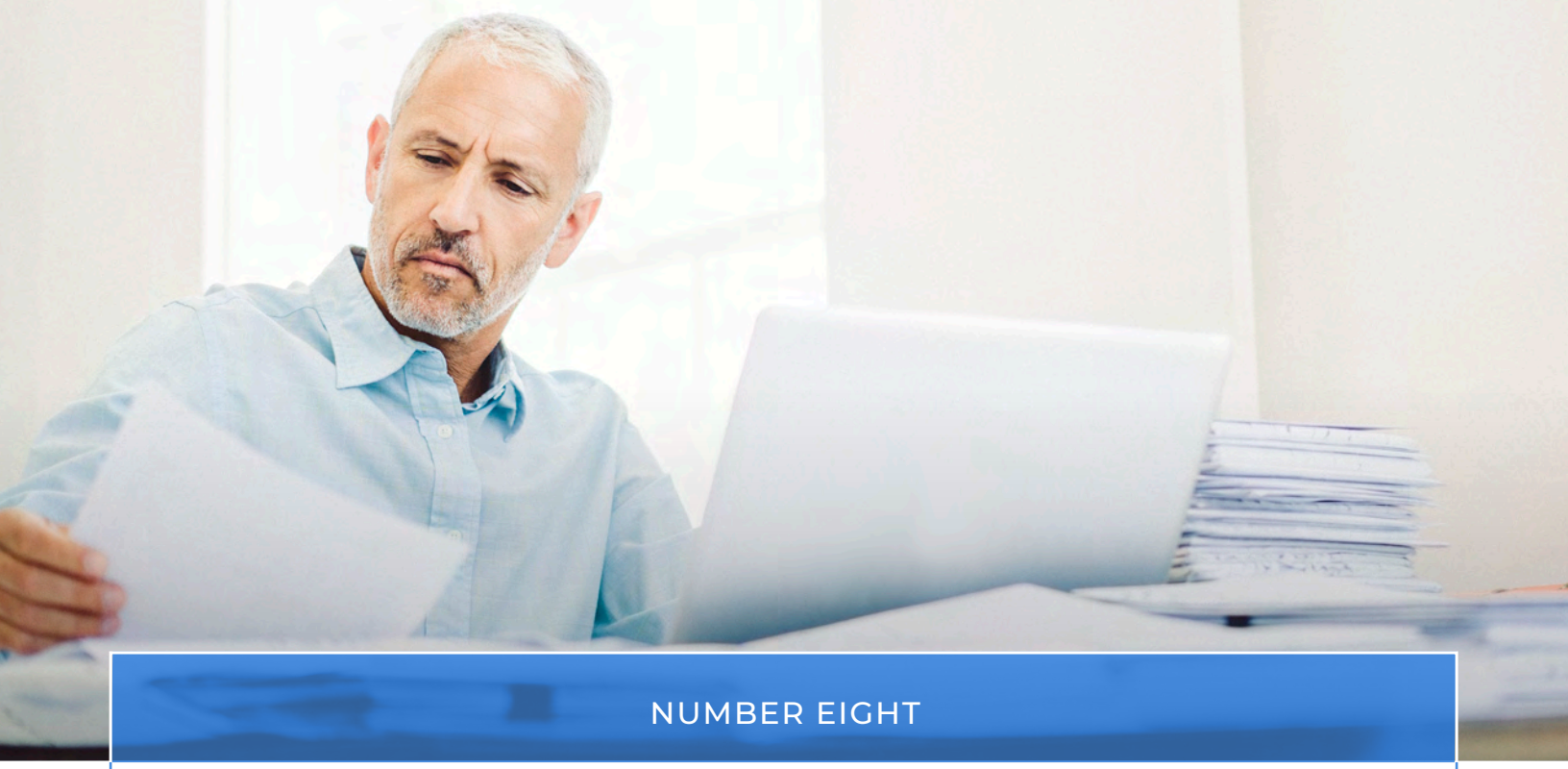
NUMBER SEVEN

NO GRANDFATHERING

All IVD products must have the appropriate clinical evidence to support the intended purpose of the IVD by May 26, 2022, or the products must be removed from the market. This includes lab developed tests (LDT), which are currently excluded from the Directive. Not only are LDT's subject to IVDR, the developers of LDTs must justify that in-house development tests are better than equivalent CE marked tests.

A SOLID STRATEGY IS KEY





NUMBER EIGHT

APPOINTMENT OF A PERSON RESPONSIBLE FOR REGULATORY COMPLIANCE

According to Article 15, certain Manufacturers and Authorized Representatives will be required to assign at least one person within the organization as responsible for regulatory compliance. While small (fewer than 50 employees/10 mil€) and micro (fewer than 10 persons/2 mil€) enterprises are not required to staff this role within the organization, they must have an individual within the EU available to fill this role **"permanently and continuously at their disposal."**

This individual (or individuals) must meet specific conditions of expertise to qualify as the person responsible for regulatory compliance activities. Responsibilities include but are not limited to — supervision and control of the manufacture of devices in accordance with the quality management system, post-market surveillance and associated vigilance activities.

Those familiar with 13485:2016 requirements for a management representative will notice similarities between these roles. Both the management representation and person responsible for regulatory compliance will typically participate in management review meetings, oversee the effectiveness of the quality management system, interact with regulatory authorities and Notified Bodies, and ensure non-compliant products do not enter the market.

ABOUT

NETWORK PARTNERS

Network Partners is a professional services firm that helps clients complete the work necessary to provide their products to patients. We serve the medical device, pharmaceutical and biopharmaceutical industries with core competencies in Regulatory Affairs, CER, Packaging Engineering, Labeling, Quality and Project Management.

Our business model allows team leaders to turn under-resourced teams into productive groups that are better for the company and morale. This approach delivers right-sized pricing as well as quantifiable ROI on stalled projects, cost-savings initiatives and much more. We consistently deliver on time and on budget, helping clients get work done and avoid project delays.

Visit us at **networkpartners.com** to learn more.

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2. Schmitt, S. M. Notified Body Q&A: 3NBs Talk EU MDR Enforcement, The IVDR 'Big Bomb,' 'Tough' Regulators – And More Insights. June 7, 2019: https://medtech.pharmaintelligence.informa.com/MT125215/Notified-Body-QA-3-NBs-Talk-EU-MDR-Enforcement-The-IVDR-Big-Bomb-Tough-Regulators--And-More-Insights

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