IVDR article 58.1(a) should not be applicable to performance studies involving routine blood draws

Proposal for discussion

Actors conducting performance studies in the European Union are required to adhere to clear ethical principles and regulations. The In Vitro Diagnostic Medical Devices Regulation 2017/746 ("IVDR") outlines requirements for performance studies in articles 66-76. Additionally, sponsors of these studies are expected to comply with the ISO EN 20916 standard for clinical studies and uphold strong ethical principles. These measures ensure that the rights, safety, and well-being of study participants are protected at all times, regardless of the study's type or level of risk.

The risk to participants in studies in the vast majority of cases is extremely low. However, when a performance study involves a sample obtained through a surgically invasive sample-taking procedure, such as the removal of breast tissue to test for cancer, additional requirements must be met, as mandated by IVDR article 58. These include authorisation by the Member State from where the samples were collected and drawing up the considerable documentation in Annex XIV, among other things. Such studies are subject to greater scrutiny because of the risks associated with the invasive procedure and consequently require much more time and evidence to be approved.

MedTech Europe argues that the same requirements should not be applied to studies involving a non-surgical and low-risk procedure, such as blood or plasma drawings from a general population (non-vulnerable individuals); they should not fall under the scope of article 58.1 (a) and should not have the same documentation and approval track as do high-risk, invasive, performance studies. The medical technology industry, EFLM and BioMed Alliance believe that this differentiation guarantees a more efficient use of resources and supports the availability of new and improved medical tests, to the benefit of healthcare systems and society.

This means that low-risk studies will undergo Ethics Committee but will not need lengthy paperwork mandated by Annex XIV. The Ethics Committee is always involved in the evaluation of safety and risk aspects for the subject during the study approval process. This is mandated by the clinical study standard 20916 and applies to all IVDR studies regardless of type and risk. Therefore, in case of an overlap, the authorisation for the study from the Competent Authority shall prevail overthe Ethics Committee's.

Impact

Performance studies where venous and capillary blood is drawn in low-risk subjects pose a significant burden to the system when included in the scope of art 58.1 (a) due to:

- Delay in getting new IVDs and novel therapies to European laboratories and patients.
- Delay and reduction of treatment options for European citizens in clinical trials.
- Manufacturer's financial and administrative resources to pursue regulatory authorisations could be used for other areas, e.g., Research and Innovation. This is especially true for small and medium enterprises.
- Diverging resources of Competent Authorities.
- Adverse impact on other initiatives.

Objective of this document

To date, the IVD working group of the Medical Devices Coordination Group has indicated a preference for blood draws taken for the purpose of the performance study to fall under Article 58.1. This approach does not differentiate between routine venous and capillary blood draws versus other types of surgically invasive procedures, including those performed in high-risk patients. **MedTech Europe, the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) and Biomedical Alliance highlight an important number of implications to be urgently considered. These stakeholders ask for blood draws in the general population performed for the purpose of the study to be considered as not surgically invasive and thereby out of the scope of Article 58.1.**

Stakeholders highlight the significant and urgent challenges of including routine blood draws in Article 58.1:

- up to 4 months (details in the footnote[1]) are required to gain study approval for Art 58.1 studies.
- 1 month is needed to develop Art 58.1 performance study documentation including the application form and the other paperwork which is only required for such studies prior to submitting the application. A different set of documents is required for each country until EUDAMED is operational. Therefore, this timeline might be significantly increased by the number of countries where samples for the performance study are coming from.

  - 1-6 months and more are needed to run the study6-12 months are needed for the manufacturer to finalise their technical documentation
  - 13-18 months is the average time taken for almost 70% of IVDs to be certified
  - 3-6 months are needed for the Notified Body to issue the certificate
  - ~6 months are needed to label, manufacture and supply the device to laboratories and patients (longer time is needed for international markets)

[1] Around 4 months may be required to obtain MS authorization for the Performance Study, from IVDR the sequence is:
-Sponsor submit application to IVDR. Within 10 days after submission, the MS notifies the sponsor as to whether PS falls or not within the scope of IVDR or if application is incomplete.
-If the application is incomplete: 10-20 days are given to the sponsor to complete the application.
-MS will notify sponsor about completion of the application within 5-10 days.
-MS shall notify the sponsor of the authorization within 45-65 days.
To sum up 10+20+10+65=105 (work) days which means that the process can take between 3 and 4 months.

This means that it will take many months/years before the IVD will reach the market and benefit patients. Moreover, if timelines are burdensome, the application will be difficult or even impossible for some stakeholders. In the long term, patients will suffer from a lack of IVD if not developed on time due to onerous requirements. Essential tests could not be available to patients if initial feasibility studies are not performed timely.

Overall, a burdensome and long process could lead to:

- **Delay and reduction of treatment options for European citizens in performance studies.** The challenge, if left unaddressed, may lead to disruption of the supply of devices needed for health systems and patients accessing IVDs in the European market.
- **Innovation will be jeopardized or even halted** if clinical studies using routinary blood draw in low-risk patients are very challenging in time, resources and budget. A MedTech Europe survey[2] of the transition to the IVD Regulation (February 2023) found that IVDR is perceived as having a negative impact on innovation or changes/optimization activities of devices. Running performance studies in Europe was the third top[3] concern due to lack of predictable process, cost or time.
- **Additional cost and administrative burden.** Extra staff and financial resources will be required for Member State application compared to a regular International Ethics Committee submission, necessary for conformity with GSPR (Annex I), insurance, Investigator Brochure, GDPR and application itself.
- **Adverse impact on other initiatives.** Examples are Europe´s beating cancer plan and accelerating clinical trials in the EU.
- **Diverging resources of Competent Authorities.** Resources of Member States (Competent Authorities) could be used for other important tasks instead of reviewing studies in low-risk population which are evaluated (and approved) by Ethics Committee. Competent authorities should prioritize actions for interventional studies and those carried out with high-risk patients.

Moreover, currently, there is a lack of coordination between interfaces of Competent Authorities and Ethics Committees' submissions and approvals. Until EUDAMED is fully operational, there will be a need for the interoperability of Competent Authorities and Ethics Committees, and already stretched resources should not be duplicated for this particular type of studies.

It seems disproportionate to the actual risk involved in drawing blood to require that these be subject to such a stringent regulatory framework. Venous and capillary blood draws performed in low-risk patients represent the most common 'fresh' specimen collection procedure and differentiation should be made to arterial blood drawn, and to blood draws performed in at-risk subjects.

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[2] See: Transition to the IVD Regulation - MedTech Europe Survey Results for October 2022 - MedTech Europe

[3] The top three options selected in answer to the question, "What impact does the IVDR have on your innovation or changes/optimization activities?", were:

I. We expect a delay for the introduction of innovative medical products of our company in Europe
II. We are no longer making any changes/optimizations to our existing IVDs CE-marked under the IVD Directive

Running performance studies in Europe has become less predictable, costly or takes too much time.

MedTech Europe, EFLM, and BioMed Alliance, ask the legislators to reconsider the pathway for performance studies using venous and capillary blood drawn in low-risk subjects as not applicable to Article 58 and Annex XIV considering:

- Venous and capillary blood draw can be considered invasive procedures but not surgically invasive; This procedure is generally considered low or not at clinical risk for subjects.
- FDA considers normal/routine blood sample collection as exempt from invasive procedures.
- Ethics Committee is always involved in the evaluation of safety and risk aspects for the subject during the study approval process. Therefore, there is an overlap, the authorisation for the study from the Competent Authority will come on top of the one from the Ethics Committee.
- ISO 20916:2019 does not include venous or capillary blood drawn in the high-risk subpopulation as compared to lumbar puncture, tissue biopsy, neonatal or critically ill patients.

Prospective venous and capillary blood draws sampling is the most common sample type taken for performance studies in not low-risk subjects.

Recommendations

Blood draws are routinely done worldwide by health care professionals (doctors, nurses or pharmacists) according to recognized and accepted guidelines, standards and regulations that govern their practice for patient safety.

This type of blood sampling performed in low-risk subjects is generally accepted and considered not to pose a significant clinical risk for study subjects. Therefore, **MedTech Europe, EFLM, and BioMed Alliance, recommend reconsidering - through a study risk assessment (see example Flowchart below), whether Article 58 applies to IVDR performance studies. MedTech Europe is not asking for a whole exemption from Article 58 but only in cases of venous and capillary blood draws performed in low-risk subjects.**

It is undeniable that samples in vulnerable populations, including, among others, new-borns, infants, pregnant and breastfeeding women, patients with haemophilia and thalassemia, individuals taking anti-coagulant treatment, as well as instances when a high volume of blood is taken from a subject should fall under Article 58.

Based on the foregoing and considering the urgency and impact on European patients, MedTech Europe proposes that routine venous and capillary blood draws in low-risk study populations are exempt from Article 58 (1a) and Annex XIV. Similarly, the FDA considers normal/routine blood sample collection exempt from invasive procedures (although venipuncture follows the definition of invasive sample-taking procedure). ISO 20916:2019 does not include this procedure within the high-risk subpopulation category.

Furthermore, referring to the German national law under the IVDD (German MPKPV, Article 7 (1) 4 and MPG, Article 24), those studies that pose minor risk to patients can be conducted under simplified measures, including the involvement of the Ethics Committee. Prospective, routine blood draws in a low-risk population generally fall into this category.

There is no legal requirement arising from the IVDR, to categorise blood draws as being 'surgically invasive'. While there is a definition of 'surgically invasive' under the Medical Devices Regulation (EU) 2017/745, this definition refers to the device not to the procedure; also the IVDR falls out of scope of the Medical Devices Regulation, meaning that it is possible to make a truly IVD-appropriate interpretation of Article 58.

Important to note that in the case of Article 58 would not be applicable for performance studies performed when venous and capillary blood draw were performed in low-risk subject, still the Ethics Committee will review the scientific value of the performance study as well as the risk for the patient involved in the study.

Therefore, it is recommended to restrict the review and approval of specimen collection, associated risk and the maximum prospectively collected blood volumes to the Ethics Committee.

As already mentioned above, it is important to note that Annex XIV was originally foreseen for studies posing risk to patients, e.g., studies involving surgically invasive sample-taking, such as biopsy or cerebrospinal fluid aspiration or studies following interventional study design.

Conclusion

Based on the given arguments, MedTech Europe, EFLM, and BioMed Alliance, ask the regulators to find an appropriate solution for studies requiring venous and capillary blood draws in low-risk populations for which Article 58 (1a) and Annex XIV should not be applicable. To help with the solutions, we present a flowchart that would serve as an aid to determine whether Art.58 applies to performance studies using capillary and blood draws in low-risk patients. See Flowchart and additional arguments for this position in Annex II.

Excluding performance studies using blood draws in low-risk subjects is a reasonable solution to enable manufacturers and other stakeholders to meet their obligations while minimising any potential burden on healthcare systems and patients, ensuring a high level of safety and performance. The proposed solution in this paper does not affect the general requirements for interventional studies or those posing any risk to the patient.

Annex I – background

Depending on the specimen collection procedure and/or interventional study design, different requirements and obligations apply to performance studies under the IVD Regulation 2017/746 ("IVDR"). In particular, Article 58 (1) defines certain performance studies involving risks for the subjects as:

a) In which surgically invasive sample-taking is done only for the purpose of the performance study;

b) That is an interventional clinical performance study as defines in point (46) of Article 2; or
c) Where the conduct of the study involves additional invasive procedures or other risks for the subjects of the studies.

In general, these studies rely on taking 'fresh', or 'prospective' samples from subjects. They are subject to more stringent procedures and shall be notified, approved and conducted in accordance with Articles 59-77 and Annex XIV.

It is undisputed that interventional studies or studies requiring prospective sample-taking which pose particular risks to the study subject need to follow Annex XIV (Article 58 (1)). Examples, where sample-taking would pose risks, may include arterial blood draws, tissue biopsies, collection of cerebral spinal fluid, etc as well as blood draws performed in risk populations, i.e., new-borns, infants, minor, pregnant and breastfeeding women, patients with hemophilia and thalassemia, taking anti-coagulant treatment or when high volume of blood is taken (according to the WHO blood draws with >1% total volume at single time or >3% total volume draw during 4 weeks period). Venous and capillary blood draws are an invasive procedure but not surgically invasive. Moreover, most prospective sample-taking is done to draw venous and/or capillary blood specimens are performed in healthy and low-risk subjects.
The IVDR does not differentiate invasive (not surgical) versus surgically invasive and within the former group low risk versus at risk subjects. This clarification should be made in order to distinguish that performance studies are done in low risk patients and therefore for these Article 58 should not be applicable.

Arguments to consider venous and capillary blood draws in low-risk subjects not applicable to Article 58

There are several arguments for considering that Article 58 should not be applicable for venous and capillary blood draws performed in low risk subjects:

- **Venous and capillary blood draws should not be considered "surgical procedure" nor "surgically invasive".**

  A blood draw can be seen as an invasive procedure but not as surgically invasive. Generally, a surgical procedure includes broad destruction of skin (and tissue) and refers to a deeper penetration compared to a needle used in venipuncture. Generally, a surgically invasive procedure requires anesthetic.

- **Venous and capillary blood draws in healthy volunteers is generally considered low or not clinical risk for subjects of the study** and always performed by medical professionals. Medical professionals work under accepted and recognized guidelines, standards and regulations that govern their practice for patient safety. Safety, dignity, and well-being of the subjects is safeguarded.

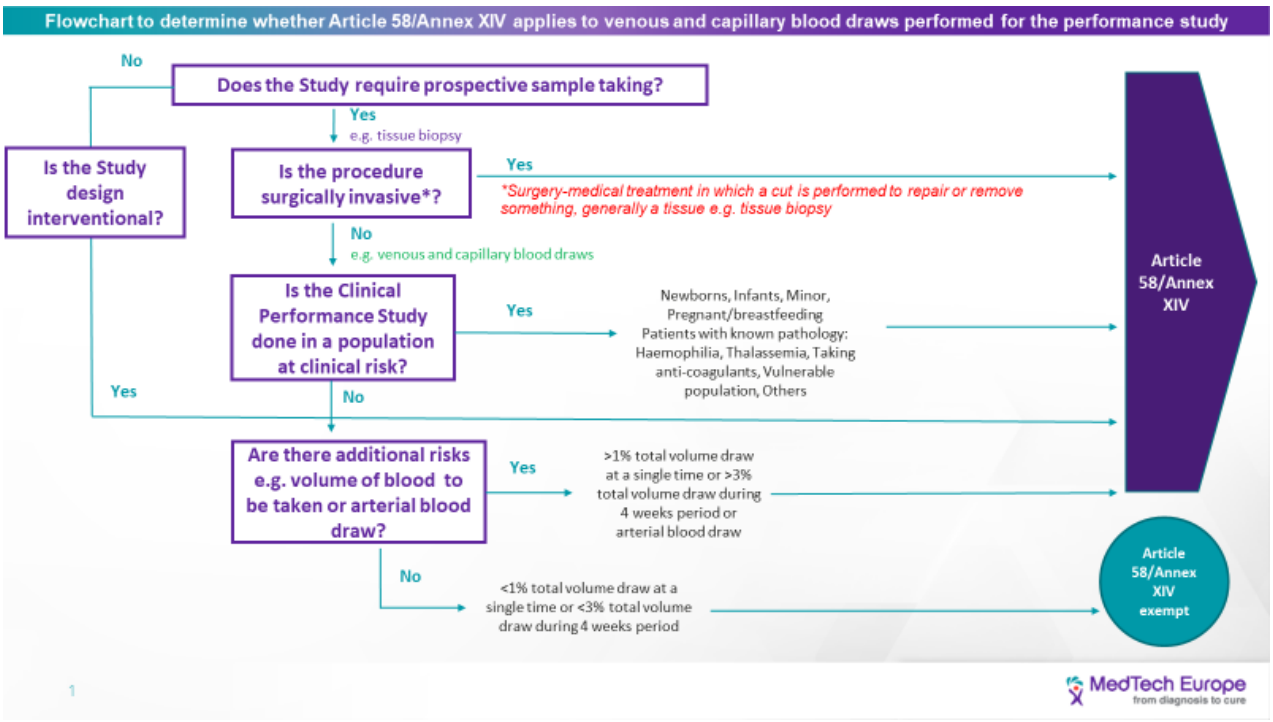
At risk (vulnerable) population includes new-borns, infants, minor, pregnant and breastfeeding woman, patients with hemophilia and thalassemia, taking anti-coagulant treatment. According to the WHO blood draws with >1% total volume at single time or >3% total volume draw during 4 weeks period is considered high risk [2]. For this high-risk population, notification and authorization from the Member State will be required. Additionally, the IVDR lays down specific requirements for certain populations (Article 60-64), including incapacitated subjects, minors, pregnant and breastfeeding women and subjects who are unable to give consent due to an emergency situation.

- **Needles and syringes are Medical Devices class IIa and as such regulated by MDR.**

- **Ethics Committee approval is always required.** Before commencing a clinical performance study, the sponsor will submit the study for Ethics Committee approval. Ethics Committee as independent body whose responsibility it is to review clinical investigations in order to protect the rights, safety and well-being of human subjects participating in a clinical investigation, will assess the risk associated with the participation in and/or conduct of the study. The sponsor will provide Ethics Committee related communication to MS in case a high risk is determined or if negative opinion issued.

- **FDA considers normal/routine blood sample collection, as exempt from invasive procedures:** "blood sampling that involves simple venepuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non investigational purposes is also considered noninvasive" [3].

- **ISO 20916:2019 [4] defines specifically a high risk subpopulation as lumbar puncture, tissue biopsy, neonatal or critically ill patients.** A single blood draw from healthy volunteer does not fall into this high risk category considering additional requirements.



Flowchart serves as an aid to determine whether Art.58 applies to performance studies using capillary and blood draws in low-risk patients.

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.

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4. ISO 20916:2019 standard *In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice*

5. Appendix 8 – Diagnostic venepunture: systematic review of adverse events. Non-invasive diagnosis assessment tolls for the detection of liver fibrosis in patients with suspected alcohol-related liver disease: a systematic reviw and economic evaluation. Halth Technology Assessment, No. 16.4 Stevenson M et al. Southampton (UK) 2012.