ACRO Innovate Advocate Collaborate

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Isabelle Clamou, Policy Officer, European Commission
Louise Schluter, Policy and Legal Officer, European Commission
Olga Tkachenko, Policy Officer, European Commission

RE: Follow up to our 28 June virtual meeting – ACRO Request for Clarification of 'Health Institution' Definition in Regulation (EU) 2017/746 on In Vitro Diagnostic Medical Devices

Dear Ms. Clamou, Ms. Schluter, and Ms. Tkachenko

Thank you for meeting with ACRO (virtually) on 28 June 2023 and also for your invitation to ACRO to put our concerns in writing so that you can share them with the Member States during the next MDCG meeting. As discussed during our virtual meeting, ACRO is concerned about the lack of clarity regarding the definition of 'health institution' under Regulation (EU) 2017/746 on in vitro diagnostic medical devices ("IVDR"). This uncertainty poses a potential barrier to the participation of EU citizens in clinical trials for therapies that utilize novel diagnostic assays for which no commercial options are available.

This document summarizes ACRO's concerns and ACRO's arguments in support of enabling central laboratories to fall within the scope of the health institution definition.

In brief, we ask the Commission and the Member States to undertake a revision of Question-and-Answer guidance documents MDCG 2022-10[1] and MDCG 2023-1[2] to clarify that the definition of a 'health institution,' as defined in the IVDR, covers central laboratories.

ACRO's concerns

The IVDR introduces important requirements for in vitro diagnostics to ensure patient health and safety. There is a narrow exemption from some of its requirements for in vitro diagnostics that are manufactured and used within the same health institution, so-called in-house devices. This exemption is granted to ensure that health institutions can address the specific needs of target patient groups, by allowing health institutions to manufacture and use in-house devices.

Currently, there is uncertainty about whether central laboratories, which operate outside of hospitals, are considered health institutions within the meaning of the IVDR. Central laboratories play a vital role in providing diagnostic data for clinical management of clinical trial subjects in the EU. More specifically, central laboratories provide globally combinable testing options to EU patients and investigator sites which are themselves EU health institutions. Today, over 50% of all in vitro diagnostics used in clinical trials in the EU are

[1] MDCG 2022-10, entitled '*Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR)*'.
[2] MDCG 2023-1, entitled '*Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746*'.

developed by laboratories because commercial options are not available.[3] Central laboratories thereby function as an extension of hospitals and hospital laboratories to fulfil a testing need defined within an approved clinical trial protocol, or for a special diagnostic treatment. In recent years, ACRO members have seen a sharp increase in demands for developing in-house devices to service patients with novel treatments as commercial alternatives are not available. Of these in-house devices, more than a third are dedicated to oncology clinical trials.

The lack of clarity on whether testing of clinical trial subject samples performed by central laboratories, which operate outside of hospitals, are considered health institutions within the meaning of the IVDR presents several concerns. Already today, this uncertainty is resulting in three main challenges:

- **The EU is becoming less competitive for clinical trials:** With the implementation of the IVDR, there is already a decrease in the perceived viability of conducting clinical trials in the EU. Ultimately, this perception negatively impacts access to innovative treatments for EU citizens, which runs counter to the intent of the Accelerating Clinical Trials in the EU ("**ACT EU**") initiative, which aims to further develop the EU as a competitive centre for innovative clinical research.

- **More time will be needed at the onset to start a clinical trial in the EU:** Even if the EU is still considered for a clinical trial, there will likely be delays at the onset of the trial. These delays are due to the potential unavailability of CE marked diagnostic assay alternatives to fulfil testing needs currently available only via in-house devices developed by a central laboratory. The option to conduct performance studies for some non-CE marked IVDs is impacted by the lack of harmonization within the Member States on the interpretation of the IVDR and the absence of a functioning EUDAMED to provide a harmonized platform to perform submissions under the IVDR.

- **All data generated through use of in-house devices in central laboratories intended to inform treatment decisions in a clinical trial are impacted by the IVDR:** All clinical trials in the EU rely on data from study participants to inform decisions regarding the safety and efficacy of a potential new treatment. Sponsors and investigator sites rely on the data from central laboratory testing on patient samples to bring clear insights to guide decisions on clinical trial and patient management. Today, the uncertainty regarding whether central laboratories are within the scope of the 'health institution' definition of the IVDR impacts the application of these data.

[3] For some in-house devices, a commercial alternative may be available, but it does not completely fulfil the testing needs of the clinical trial, making it an unsuitable replacement. Reasons for this include: (a) the assay includes more or different markers, variants, etc.; (b) the assay has better sensitivity and precision; (c) the commercial kit is not available globally and as a result our members would not be able to ensure clinical trial combinability across a global study; (d) the bio analysis assays are specific to the drugs from clinical trial sponsors as well as the clinical indications, and thus no commercial alternatives are available.

It should be noted that these concerns are shared by other relevant industry associations and patient organisations (e.g., BiomedAlliance,[4] EFPIA[5] and Lungevity[6]).

ACRO's arguments

To tackle these challenges, we urge the Commission and EU Member States to revise MDCG 2022-10 and MDCG 2023-1 to clarify that the definition of a 'health institution' as defined in the IVDR covers central laboratories.

- **Amending the 'health institution' definition does not require a legislative change:** In our view, the current definition of 'health institution' in Article 2(29) of the IVDR covers central laboratories. ACRO, therefore, does not believe that a legislative change is necessary. Rather, MDCG 2022-10 and MDCG 2023-1 should be updated by a decision of the MDCG to clearly reflect this and ensure a uniform interpretation by industry and Member States.

- **Central laboratories are able to meet Article 5(5) requirements:** Clinical Research Organisations ("**CROs**") that offer central laboratory services operate in a highly regulated environment, with frequent inspections and audits. Some laboratories are already ISO-15189 certified and would make modifications, as needed, to meet the IVDR requirements of a health institution in all laboratories that perform testing on EU subject samples.

  The quality requirements outlined in Article 5(5) of the IVDR will ensure the safety and efficacy of in-house devices in central laboratories in the same way as they do for hospital laboratories. Specifically, to ensure data consistency, central laboratories use validated machinery, standardized methods and reference ranges, and trial-specific testing kits. Globally standardized materials and processes as well as efficient logistics (sample stability) are of crucial importance. As a result, only few central laboratories operate around the globe, with only two ACRO members together serving approximately 80% of the market.

  Just like hospital laboratories which are covered under the health institution definition in the IVDR, in-house diagnostic assays developed by central laboratories are developed under the highest quality standards to ensure patient safety. Additionally, central laboratories are fully vetted and capable of complying with all requirements applicable to health institutions under the IVDR. Finally, just like hospital laboratories, central laboratories are subject to inspections by the national competent authorities.

[4] *See* "Main findings IVDR Questionnaire BioMed Alliance," December 2021, available here: https://www.biomedeurope.org/images/news/2021/BioMed_Alliance_IVDR_statement_final.pdf.
[5] *See* "EFPIA statement on the concerning impact of the In Vitro Diagnostic Regulation," 3 June 2022, available here: https://www.efpia.eu/news-events/the-efpia-view/statements-press-releases/new-european-legislation-designed-to-protect-patients-is-delaying-clinical-trials-for-thousands-of-people-with-cancer-and-rare-diseases/#:~:text=EFPIA%20is%20urging%20all%20partners,taken%20from%20the%20human%20body.
[6] *See* "Multi-stakeholder open letter expressing concerns regarding the impact of IVDR implementation on patient access to clinical trials," including signed by Lungevity, 17 March 2023, available here: https://www.lungevity.org/sites/default/files/public-policy/031723_Multi-Stakeholder%20Concerns%20regarding%20IVDR%20and%20Patient%20Access%20to%20Clinical%20Trials.pdf.

- **Central laboratories are key for the functioning of EU clinical trials:** Central laboratories develop in-house devices where no commercial alternatives are available, or where a CE marked alternative does not completely fulfil the testing needs of the clinical trial. Therefore, it is critical that the IVDR enables central laboratories to develop these in-house devices for clinical trials, without going through a multi-year review process with Notified Bodies.

Currently, some central laboratories take the view that they meet the 'health institution' definition, while others are awaiting clearer legal guidelines. While the former benefit from their own interpretation, the latter are concerned that the Member States' competent authorities may take different views based on today's available guidelines and, therefore, take a more cautious approach. Such an unlevel playing field contradicts the intentions of the IVDR and the core principles of the EU's internal market.

In conclusion, we ask the Commission and the Member States to discuss and undertake a revision of MDCG 2022-10 and MDCG 2023-1 to clarify that the definition of a 'health institution' as defined in the IVDR covers central laboratories. We believe that this clarification would help create a level playing field between central laboratories.

We thank you for your consideration and support.

Yours sincerely,

Karen Noonan
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