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Laboratory Developed Tests (LDTs): a comparison between EU IVDR and new FDA rule to end general enforcement discretion of LDTs

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Laboratory Developed Tests (LDTs) or "in-house IVD" (IH-IVD) are in vitro diagnostic testing methods that are performed by using in vitro diagnostic medical devices (IVD) not available on an industrial scale. LDTs are developed, manufactured, and used within a single health institution and its corresponding laboratory to diagnose and monitor patients in a wide range of emerging and/or rare diseases[1]. LDTs can play an important role in healthcare and in the global field of medical laboratory testing. Their significant medical relevance has also been proven, more recently, by their considerable contribution during the COVID-19 pandemia. LDTs performance, safety and quality requirements within an appropriate regulatory environment is relevant since it has high impact on individual patient care and on public safety and health[1]. In EU, LDTs (called IH-IVD) were exempted from all the requirements under the previous 98/79/EC but with the new Regulation 2017/746[2] ("EU IVDR") healthcare institutions must ensure that the developed in-house manufactured devices comply with the relevant performance and general safety requirements set out in Annex I. It is essential that health institutions document and regularly update the compliance proof of their IH-IVD with Annex I[3]. The documentation will then be used by competent authorities to assess compliance with Article 5(5) of the EU IVDR. Additionally, critical changes made to IH-IVD should be evaluated and documented. With the exception of what is described in Annex I, the requirements of EU IVDR shall not apply to IH-IVDs provided the health institution adheres to the conditions laid out in Article 5(5) of the relevant Regulation[3]. The Medical Device Coordination Group (MDCG) assists the stakeholders in applying the EU 2017/746 IVDR providing clear and practical guidance on the requirement of the LDTs (MDCG 2023-1[3]). In USA, from 1976, FDA assured an interstate oversight on all medical devices including also LDTs. At the beginning LDTs were simple tests and FDA didn't enforce any specific regulatory requirements, but the risks associated with the modern LDTs are much greater compared to those used decades ago. However, since LDTs are developed and intended for use in a single laboratory, it could be argued that they do not enter interstate commerce and are not regulated by FDA. Consequently, LDTs are mainly covered by the Center for Medicare & Medicaid Services (CMS) which regulates all laboratory testing (except research) performed on humans in the USA through the Clinical Laboratory Improvement Amendments (CLIA). Under CLIA, clinical laboratories must determine the analytical validity of the test, but don't need to determine its clinical validity which falls under FDA authority in the FD&C Act during the premarket review. Indeed, LDTs are not required to comply with it thank to the enforcement discretion even if this doesn't equal exemption. Thus allows the FDA to choose to enforce full regulatory compliance of an LDT "when appropriate, such as when it is appropriate to address significant public health concerns[4]". The FDA is aware of the high number of potentially unsafe, ineffective, inaccurate, or poor quality IVDs offered as LDTs that caused or may have caused patient harm. For these reasons, on April 29th 2024[5], the FDA announced a final rule which amends the FDA's regulations to clarify that IVDs are devices under the FD&C Act also when the IVD manufacturer is a laboratory. In this way FDA wants to finalize a policy under which it will provide greater oversight of LDTs through an enforcement discretion approach phaseout over the course of four years, as well as targeted enforcement discretion policies for certain categories of IVDs manufactured by laboratories. Starting from these considerations, the present work aims to provide an overview of LDTs regulatory requirements by comparing EU and USA guidelines with a focus on the new FDA rule.

1. Spitzenberger et al. *Therapeutic Innovation & Regulatory Science* (2022) 56:47-64
2. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices (IVDR), *Official Journal of the European Union*, 2017
3. MDCG 2023-1, Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746, January 2023
4. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/inova-genomics-laboratory-577422-04042019
5. U.S. Food & Drug Administration, FDA Takes Action Aimed at Helping to Ensure the Safety and Effectiveness of Laboratory Developed Tests, 29 April 2024

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