IDE & LDT – another set of hurdles?

Robert Nelson, on behalf of the EBF

06-07 June 2024 – Malaga, Spain

Investigational Device Exemption (IDE)

Investigational Device Exemption (IDE)

- An Investigational Device Exemption (IDE) is an application that must be submitted to FDA to **use a novel medical device in a clinical study**
  - This enables the collection of safety and efficacy data to take the necessary steps toward full market approval of the device

- An IDE application is required to obtain the FDA's approval of clinical study protocol prior to executing a clinical study
  - A clinical study is required for Class III and some Class II medical devices to **determine whether or not a medical device is safe and effective** for broad human use

What is considered to be a Medical Device?

- Per Section 201(h)(1) of the Food, Drug, and Cosmetic Act, a device is:
  - An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

  A. recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,

  B. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

  C. intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o).

- Medical devices include **in vitro diagnostic (IVD) products, such as reagents and test kits**

https://www.fda.gov/medical-devices/classify-your-medical-device/how-determine-if-your-product-medical-device

Level of risk of the device

- Investigational devices are covered under IDE regulations based on the level of device risk:
  - Significant Risk (SR)
    - Any device regarded as a significant risk (SR) must meet the IDE regulations, as well as having an IDE application approved by the FDA and Investigational Review Board (IRB) approvals before conducting any study.
  - Non-Significant Risk (NSR)
    - Devices regarded as non-significant risk (NSR) are only required to meet the amended IDE regulations, and only IRB approval is required before conducting any study
  - Exemption from IDE
    - Some devices may be exempt from IDE regulations
    - Generally, a device is considered exempt if it is non-invasive and not used to perform invasive sampling procedures

Bioanalytical assays in scope of IDE?

- A number of Sponsor companies have received regulatory feedback that diagnostic assays used to include patients in a gene therapy trials (e.g., pre-existing antibody TAb or NAb) are in scope
  - Feedback received during clinical trial application that the device (assay) is considered significant risk
  - Delays in trials whilst IDE application is prepared and submitted for review and approval

- Expectation of assay validation to align with CLSI guidelines (in addition to immunogenicity guidelines)

Differences/similarities in assay validation

		GCP/GCLP	IDE
Guidances		**Immunogenicity (FDA CBER/CDER, EMA)**	**CLSI (Clinical Laboratory Standards Institute) – FDA CDRH**
Parameters/ Performance	**Inter- and Intra-assay Precision**	20% CV (higher for cell-based) Controls tuned to cut point Low positive control near cut point	**15% CV** **Controls tuned to clinical cut-off** **Controls ~25% above and ~25% below clinical cut-off**
	Sensitivity	Needs mass/volume concentration	**Mass/volume concentration not needed**
	Stability	Samples only Freeze-thaw, short-term Two time/treatment points sufficient	**Samples and critical reagents** Freeze-thaw, short-term, **long-term, in-use, transportation** **Sufficient time/treatment points to allow detection of drift**
	Interfering Substances	Hemolysis and lipemia	**Panels of endogenous interferents plus OTC and concomitant medications**
Components	**Matrix**	Matrix as close as possible to samples	Matrix as close as possible to samples
	Positive Control	Defined concentration Can be (and usually is) animal-derived	**Defined concentration not required** **Must only be human-derived**
	Critical Reagents	One lot is sufficient No requirements for regulated manufacturing	**Multiple lots required** **Possibly GMP**

Lab Developed Test (LDT)

Laboratory Developed Tests (LDTs)

- LDTs are in vitro diagnostic products (IVDs) that are intended for clinical use
  - Designed, manufactured, and used within a single laboratory
  - Laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA)

- In September 2023, the FDA unveiled a plan to regulate LDTs across the United States

Evolution of LDTs

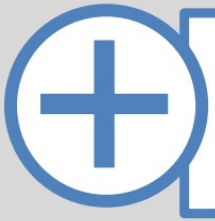
LDTs of 1976	LDTs of Today
Mostly manufactured in small volumes by laboratories that served their local communities	Often run in high volumes for large and diverse populations
Tended to employ manual techniques (and did not use automation)	Increasingly rely on high-tech or complex instrumentation and software to generate results and clinical interpretations
Tended to be performed by laboratory personnel with specialized expertise, and to be used and interpreted by physicians or pathologists in a single institution responsible for the patient	Many LDTs are manufactured by laboratory corporations that market the IVDs nationwide, as they accept specimens from patients across the country and run their LDTs in very large volumes in a single laboratory outside the patient's healthcare setting
Manufactured using components legally marketed for clinical use	More commonly manufactured with instruments or other components not legally marketed for clinical use
Typically intended for use in diagnosing rare diseases or for other uses to meet the needs of a local patient population or were generally similar to well-characterized, standard IVDs	More often used to inform or direct critical treatment decisions, to widely screen for common diseases, to predict personal risk of developing certain diseases, and to diagnose serious medical conditions

The risks associated with most LDTs today are therefore much greater than they were at the time FDA began implementing the MDA

Source: https://www.fda.gov/medical-devices/medical-devices-news-and-events/webinar-final-rule-medical-devices-laboratory-developed-tests-05142024

Changes to FDA regulation of LDTs

Substance of Rulemaking



Amends FDA's regulations to make explicit that IVDs are devices under the FD&C Act including if the manufacturer is a laboratory

Phases out FDA's general enforcement discretion approach for LDTs so IVDs manufactured by laboratories will generally fall under the same enforcement approach as other IVDs

Phase out policy

Beginning May 6, 2025
- Medical Device Reporting
- Correction and Removal Reporting
- Quality System Requirements re: Complaint Files

Beginning May 6, 2026
- Requirements not covered in other stages including:
- Establishment Registration & Device Listing
- Labeling Requirements
- Investigational Requirements

Beginning May 6, 2027
- Quality System Requirements*

Beginning November 6, 2027
- Premarket Review for High Risk IVDs

Beginning May 6, 2028
- Premarket Review for Moderate and Low** Risk IVDs

*For LDTs, FDA will expect compliance with:
- design controls under § 820.30;
- purchasing controls (including supplier controls) under § 820.50;
- acceptance activities (receiving, in-process, and finished device acceptance) under §§ 820.80 and 820.86;
- CAPA under § 820.100; and
- records requirements under part 820, subpart M

**Most Low Risk IVDs are exempt from premarket review

9

Summary

- Clinical trial assays that fall in scope of the EU IVDR are likely to fall in scope of the US IDE requirements
  - Many similarities in the documentation and assay validation expectations

- Assays currently being run as LDTs will be considered as IVD devices under the new FDA rules

Acknowledgements

- EBF member companies and AAPS collaborators who provided input to this presentation

Contact Information

Questions: info@e-b-f.eu

European Bioanalysis Forum vzw

www.e-b-f.eu