



Regulating IVDMIAs

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Definition of *medical device*

The term “device” means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

- (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
- (2) 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
- (3) 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.

Federal Food, Drug, and Cosmetic Act regulates the following with regard to devices:

- Research
- Design
- Testing
- Manufacture
- Safety
- Labeling
- Storage
- Record keeping
- Advertising
- Distribution
- Production

Classification of medical devices:

Class I

Class II

Class III

Class I devices

Least risky, least complicated

Examples: dental floss, tongue depressor, manual surgical instrument

Subject to general controls:

- Facility registration

- Product listing

- Record keeping

- Filing reports re marketing experience

- Quality System Regulation (GMPs)

Exempt from further regulation by FDA

Class II devices

Subject to general controls and special controls

Special controls might include performance standards, post-market surveillance, patient registries, FDA guidelines

Examples: x-ray machines, oxygen masks, and dialysis systems

Generally subject to 510(k) premarket notification

510(k) premarket notification

Requires a showing of “substantial equivalence” to a legally marketed Class II device (called a “predicate device”)

Elements of a 510(k) submission:

- Description of the device

- Its intended use

- Draft labeling

- Support for claim of substantial equivalence to a marketed device

FDA may request preclinical, bench testing, clinical data to support substantial equivalence determination

FDA review time: 4-12 months

Leads to FDA “clearance”

Class III devices

Require premarket approval (PMA) by FDA to ensure their safety and effectiveness

They are life supporting, life sustaining, implantable, or new devices that have not been found to be substantially equivalent to legally marketed devices

Examples: heart valves, breast implants, drug eluting stents, bone growth stimulators

Elements of a PMA submission (designed to show device's safety and effectiveness):

- Preclinical and clinical data

- Reasonable assurance from valid scientific evidence that probable benefits of using device for its intended uses with adequate directions and warnings outweigh probable risks

Leads to FDA approval

In vitro diagnostic products (IVDs)

In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in the Federal Food, Drug, and Cosmetic Act, and may also be biological products subject to the Public Health Service Act.

In vitro diagnostic products (IVDs)

Like other devices, IVDs are:

- subject to premarket and postmarket controls
- classified Class I, II or III

IVDs are also subject to Clinical Laboratory Improvement Amendments of 1988 (CLIA)

General purpose reagents (GPRs)

21 CFR 864.4010 General purpose reagent.

(a) A general purpose reagent is a chemical reagent that has general laboratory application, that is used to collect, prepare, and examine specimens from the human body for diagnostic purposes, and that is not labeled or otherwise intended for a specific diagnostic application. It may be either an individual substance, or multiple substances reformulated, which, when combined with or used in conjunction with an appropriate analyte specific reagent (ASR) and other general purpose reagents, is part of a diagnostic test procedure or system constituting a finished in vitro diagnostic (IVD) test.

(b) Classification. Class I (general controls). The device is exempt from the premarket notification procedures in this chapter.

Analyte specific reagents (ASRs)

Analyte specific reagents (ASR's) are antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens.

Classification. Class I (general controls).

When to use ASRs:

In conjunction with GPRs and general purpose instruments by a laboratory to set up:

In-house (“home brew”) test or

Laboratory testing services

Not used outside the single lab that sets up the service

ASRs are the active ingredients of an in-house test but are provided without instructions for use or performance characteristics

It is the responsibility of the lab using the ASR to develop the test and to establish and maintain the test’s performance

Sale of ASRs restricted to “high complexity” labs under CLIA

In vitro diagnostic multivariate index assays (IVDMIAs)

An IVDMIA device is a device that:

Combines the values of multiple variables using an interpretation function to yield a single, patient-specific result (e.g., a “classification,” “score,” “index,” etc.), that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, and

Provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user.

Examples of IVDMIAs

Gene expression profiling assay for breast cancer prognosis

Device that integrates quantitative results from multiple immunoassays to obtain a qualitative “score” that predicts a person’s risk of developing a disease or condition

Device that integrates a patient’s age, sex, and genotype of multiple genes to predict risk or diagnose a disease or condition

Regulation of IVDMIAs

510(k) or PMA

Investigational use of IVDMIAs

Postmarketing requirements