commercial needs of the sponsor, the goal of the clinical trial that uses in vitro biomarker tests may, or may not, be to gain FDA-approval for that particular test.

Medical devices, such as tongue depressors, in vitro biomarker tests, and X-ray machines, can be classified as either class I, class II, or class III. Class I medical devices pose a risk that is low to moderate, and are subjected to FDA regulations called "general controls." Class II medical devices pose a risk that is moderate to high, and are also subjected to general controls. Class I and class II medical devices require a submission called, "510(k)." The 510(k) is also known as *premarket notification* submission. Class III medical devices pose a high risk and require a *PMA* submission to FDA (231).

Class I and class II medical devices are usually evaluated on whether they are equivalent to devices that are already marketed, and it is only occasionally that these devices require data from clinical trials (232). Only a small percentage of 510(k) submissions require clinical data to support the application (233).

To provide an example of the decision-tree that determines whether 510(k) or PMA is to be used, an in vitro biomarker diagnostic test can be evaluated by the 510(k) regulatory path if it is equivalent to an existing marketed test. But if the in vitro biomarker diagnostic test is not equivalent to an existing test, and if it is used to make a critical medical decision on diagnosis or treatment, then PMA is the appropriate regulatory pathway (234). In other words, the 510(k) is a submission to FDA that demonstrates that the Sponsor's medical devices are at least as safe and effective as an existing legally marketed device that was not subjected to PMA (see, 21 CFR §807.92(a)(3)).

Also, if FDA has determined that general controls are not sufficient to evaluate safety and efficacy of class III medical devices these devices require a PMA application to obtain clearance for marketing (235). As is the case with clinical trials in support of drug approval, where a Sponsor submits a PMA application, the Sponsor must submit information on all applicable clinical trials to the ClinicalTrials.gov registry (236).

Classification as class I, II, or III, can depend on the *intended use* and on the *indications* for use. For an in vitro biomarker test, *intended use* can be the detection of a genetic mutation, while the *indication* describes why a patient would be tested for this mutation. In an *in vitro* biomarker test for measuring a new type of analyte, or for a new intended use of an existing analyte that has not yet been subjected to FDA review, the test (device) may automatically be placed in class III, and thus require a PMA application (237).

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