in vitro diagnostics test is submitted to the FDA by way of a submission known as the premarket approval (PMA) submission (218).

Validation tests that are typically included in a PMA submission are outlined below. Following this, is an account of the FDA's regulatory process for medical devices, such as medical devices that are in vitro diagnostic tests for biomarkers. The account of FDA's regulatory process for medical devices is not the same as that for FDA's regulatory process for a new drug (NDA; BLA). However, because FDA's approval for an in vitro diagnostic test may require a clinical trial for human subjects, it is the case that an account of medical device regulations fits into the scope of this textbook, and provides an interesting counterpoint for this textbook's account of FDA's drug-approval process.

VIII. BIOMARKER VALIDATION FROM FDA SUBMISSIONS FOR IN VITRO DIAGNOSTICS TESTS

a. Introduction

FDA's guidance for the validation of biomarkers that are to be used in clinical trials that are used in an NDA or BLA is somewhat sparse, as is evident in the cited Guidance for Industry documents (219,220). For this reason, detailed information on validation, as acquired from 501(k) submissions and PMA submissions is revealed below.

Validation tests for in vitro diagnostics, are available from various FDA submissions. The examples are from *510(k) submissions* and from *PMA submissions*. The differences between 510(k) submissions and PMA submissions are outlined a later in this chapter. Information from these FDA submissions, as available on the FDA's website, provide guidance for validating many types of biomarkers that are to be used in a clinical trial. Information from the 510(k) submissions and PMA submissions is valuable for this purpose, in the situation where the Sponsor only intends to gain FDA approval of the drug, and also in the situation where the Sponsor wants FDA approval of the biomarker test.

b. Validation of Genomic DNA Diagnostic Reagent in a 510(k) Submission

This example is from FDA's approval of a medical device that takes the form of purified human DNA with a preservative (221). The DNA is genomic DNA isolated from B lymphocytes of human donors. Each human donor possesses genomic DNA with 1 of 10 different variations of the cytochrome P450 (2D6) gene. The purpose of this purified human DNA is for use as a control during routine tests of DNA from human patients, where the goal is to detect or identify 1 of the 10 variations.

[218]Derion T. Considerations for the planning and conduct of reproducibility studies of in vitro diagnostic tests for infective agents. Biotechnol. Annu. Rev. 2003;9:249–58.

[219]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. E16 biomarkers related to drug or biotechnology product development: context, structure, and format of qualification submissions; 2011 (12 pp.).

[220]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Bioanalytical method validation; 2013 (28 pp.).

[221]510(k) Substantial Equivalence Determination Decision Summary for 510(k) no. K063224. Approval letter of Dec. 23, 2006. Approved by Jean M. Cooper, Office of In Vitro Diagnostic Device Evaluation and Safety, FDA. Documents accessed from FDA website on Mar. 1, 2015.