manufacturer must comply with the Code of Federal Regulations, specifically 21 CFR Part 820 which mandates design control and use of a quality management system (QMS) for tracking. Of importance, the time it takes to develop a companion diagnostic can vary depending on the biomarker assay and technology being used. Typically, development times range from 12 to 15 months so planning is quite important when incorporating a CDx into a pivotal clinical trial.

There are various stages of the development of a CDx. As mentioned previously, the LDT or prototype assay can be used early on to support drug trials. This type of assay will be labeled as a research use only (RUO) assay preventing any results to be used in treatment decisions. An investigational use only (IUO) assay is the next phase of the CDx development and builds upon the RUO assay: Using the RUO assay, this assay will be further tested, the reagents will be checked for stability issues, and the conditions to achieve the maximum sensitivity and specificity will be identified. Once all of the various components and conditions of the assay have been tested and identified, the assay is considered locked and at this point the IUO assay cannot be further changed or optimized. The additional testing of the RUO to the IUO is all documented in the QMS and a design history file is created. Over the course of time, if one reagent changes, this change will be documented in the design history file and shows why and when this change occurs. The IUO is the assay that will be used in most pivotal phase III trials.

5.3 Regulatory Authorities

In addition to the design control element of the CDx, there is also a regulatory component of the assay. In order to use the RUO/IUO assay to test human samples that are prospectively collected specifically for testing purpose, an Investigational Device Exemption application must be submitted to the Center for Device and Radiological Health (CDRH) at the FDA. This application consists of manufacturing information, the analytical study design and data (validation), and the clinical trial plan including statistical analysis and cutoff values. Once received at CDRH, there is a 30-day waiting period, and if CDRH has no comments or concerns and the 30 days has passed, the test can be used. If there are concerns surrounding the test or the clinical program, a presubmission packet can be assembled collaboratively between the diagnostic and pharmaceutical companies and sent to CDRH for comments as well requesting a meeting. This packet allows for the diagnostic and pharmaceutical companies to align on expectations and assure that the assay and clinical approach/suggestive cutoff is acceptable to the FDA. The last two additional regulatory elements that are needed are the completion of the premarket approval application which contains all of the diagnostic data collected during the pivotal trial. This data should be filed to CDRH at the same time the drug data is submitted to CDER/CBER which is a very crucial part of the process. The last remaining regulatory element is the postmarket surveillance that occurs after the CDx and drug have been granted approval. This monitoring accesses the safety, effectiveness, and performance of the diagnostic and drug.