the equipment used to make the submission batch, or other existing equipment, but not more than 10 times the size of the submission batch in dosage units. After ANDA approval, the firm can purchase and qualify larger equipment and use SUPAC to implement the production of larger batch sizes.

The FDA investigators will spend a lot of time during the PAI comparing the analytical data in the ANDA with that in the laboratory notebooks or other records. They often focus on any data that were rejected. Because the analytical methods used to test ANDA batches are generally new to the firm, unexpected method problems or chemist errors are not uncommon. The FDA is concerned that firms will reject valid data. Doing so may give an unrealistically favorable profile of the product. (The dilemma of when to properly reject laboratory data was one of the basic issues addressed in the "Barr Decision" [9].) Laboratory controls have become a very key element of PAIs. Much focus is placed on the handling of out-of-specification (OOS) test results. It is imperative that firms have written procedures in place regarding the investigation and ultimate disposition of OOS and other anomalous data. Often, a "decision tree" approach is used as the process can become complicated and the outcome can be dependent on a number of prerequisite steps including, but not limited to, sample reinjection, re-prepping and repeat testing, or, in extreme cases, batch resampling (Figure 7.1). Error simulation may be used as a means of confirming the cause of a suspect result and can add substantial weight to the overall quality of the investigation.

The ultimate disposition of a suspect result must be approved by the firm's QA unit after reviewing the associated investigation report. Thus, the investigating parties must ensure that the rationale for the proposed action is well documented and follows a logical sequence and that the data supporting the conclusions are referenced in the appropriate sections of the report.

On occasion, the FDA investigators have taken the position that the ANDA submission should contain reference to the existence of rejected data. Opinions among investigators vary on whether this is required for the submission to be complete or just something that makes the PAI easier. A firm should feel confident defending the exclusion of such references in its ANDA submission as long as the rationale for rejecting data is well justified, in compliance with its SOPs and has obtained QA approval. With this approach, the appropriateness of the firm's action becomes an issue for review during the PAI and does not unnecessarily complicate the application review process.

QA INVOLVEMENT IN R&D

Several generic drug manufacturers have found it useful to create a separate QA group for R&D. Members of this group receive special training so that they have a better understanding of the product development process. They are also free to concentrate on R&D without distraction or competition from the need to release other products for distribution. This practice can create efficiencies that have the effect of expediting the overall development, submission, and approval process. However, firms must be cautious in taking this approach. First, it is imperative to structure the reporting relationship such that a conflict of interest situation does not exist (i.e., this