by the toxicity of the compound in question. Because both equipment qualification and contamination control requirements for pilot biostudy batches approach those of submission and commercial batches, these types of batches are usually manufactured in production equipment. Larger firms may have a GMP R&D manufacturing facility for making these batches.

For experimental batches, cross-contamination must be low enough so that it does not alter the results of any measurements or tests performed on the batch. Because this level is usually many times higher than the threshold for batches administered to humans, equipment for experimental batches does not require isolation or stringent dust control. Many firms have a separate area for making such batches. This "pilot laboratory" has small versions of production equipment, usually contained within a single room. It is necessary to keep records of the cleaning of such equipment; however, QA sign off is not required.

DOCUMENTATION

Product development groups are strongly encouraged to have standard operating procedures (SOPs) that define how all activities are documented. Some firms use abbreviated batch records for experimental batches. These records may be completely or partially handwritten. They do not require QA or regulatory approval. Other firms prefer to document the preparation of an experimental batch in a laboratory notebook.

No matter which type of documentation the firm chooses, the records must clearly reflect what was done to produce the batch, all observations and test results, and a conclusion drawn from the results. The last item has, at times, been neglected by R&D departments. However, it is essential for reconstructing product development during an FDA PAI.

Pilot biostudy and submission batches must be manufactured under production conditions and cGMPs, with complete documentation. Complete documentation includes inventory records, batch records documenting every step in batch production, packaging records, analytical laboratory records (including retention of all raw data), and a certificate of analysis or analytical report. QA review and sign off are required. Firms should develop procedures that define prerequisite steps and requirements for release of such batches for biostudy testing.

OPTIMIZATION OF PROCESS PARAMETERS AND JUSTIFICATION OF IN-PROCESS SPECIFICATIONS

Since 1989, FDA investigators and reviewers have become more interested in optimization of process parameters and justification of in-process specifications. It is strongly advised that such activities be completed before ANDA submission batch manufacture. If the process is optimized at a later time, it will be necessary to amend master batch documentation to encompass the associated adjustments. This often leads to additional ANDA review cycles, which delay approval.