at the same time, maintaining these logs is an ideal task for Project Managers separate from those individuals who make or test experimental or submission batches. Investment of a few minutes each day to make sure that the logs are complete and up-to-date will reap substantial benefits during the PAI.

PREAPPROVAL INSPECTIONS

According to the FDA's PAI Compliance Guide, the FDA will always conduct a PAI for the first ANDA (or NDA) submitted by a firm. The compliance program also requires an inspection for the first submission of a given product and for all submissions whose reference listed drug is one of the top 200 sellers in the United States. Whereas the firm's FDA District will almost always choose to do an inspection in the former case, it is somewhat less likely to do so in the latter. This may be because the Compliance Program does not specify which top 200 list to use or because the lists change from year to year [6]. For submissions that do not meet any of these criteria, the FDA District may choose not to inspect, if the firm has had an acceptable cGMP inspection in the last 2 years, and has demonstrated successful PAI history over the same time period. The District will simply tell the FDA Center for Drug Evaluation and Research, Office of Compliance that it has no objection to the approval.

What will the FDA look for during a PAI? The FDA investigators will verify the accuracy and completeness of key information in an ANDA submission during the inspection. They will examine bulk active ingredient purchase orders, invoices, and packing slips to ensure that the material was actually available to make the batch on the dates recorded in the batch record. If any of the inactive ingredients were not previously used by the firm, receiving records may be checked as well. The FDA investigators will compare the batch records in the submission to the use and cleaning logs for the equipment used to determine if the dates (and times, if recorded) match. Both of these activities are intended to rule out the possibility of falsified batch records.

The FDA investigators will also determine whether the firm has the equipment designated in the master batch records for commercial-size batches intended for manufacture after approval. This provision of the PAI program has historically generated the greatest number of recommendations to withhold ANDA approval among the various categories of required inspectional elements. In FDA summaries of reasons for a District not recommending ANDA or NDA approval, this deficiency is included in the failure category "plant not ready."

What is causing this problem? In many cases, a firm does not wish to purchase any equipment that will be unique to the commercial process of a submitted product until it is needed to start commercial production. The PAI generally occurs months or, in some cases, years before the ANDA is approved.

Fortunately for industry, FDA now has Scale-Up, Postapproval Changes (SUPAC) Guidances for various types of dosage forms [7] and a general guidance to changes permitted under the FDA Modernization Act of 1997 [8]. Firms may use these guidances to scale up a process without prior approval from the FDA. When a firm is introducing a new type of equipment in a submission, it is recommended that the scale-up information in the ANDA reflect the largest size batch that can be made on