"browse" the USP where a large number of monographs, both for APIs and for dosage forms, contain cautionary statements. The need for cautionary statements really falls into three sectors at the dosage form development site:

1. Laboratory and quality assurance personnel who handle the compound for "testing"
2. Drug product development personnel
3. Finished dosage from manufacturing/packaging, quality control, and stability testing personnel

Finally, there are consulting services that can provide counsel on environmental handling issues for the API and the drug product incorporating the API related to Occupational Safety and Health Administration, Environmental Protection Agency, and cleaning validation.

REGULATORY OVERSIGHT OF API MANUFACTURERS

For a new manufacturer or a new API manufactured at an established site previously registered in filed DMFs, the FDA normally requires that a successful preapproval inspection occurs before the agency would grant approval to the filed ANDA, which incorporated the particular API. Typically, such inspections tend to be vigorous and cover both current good manufacturing practices as well as scientific, technological, and related matters such as environmental, Occupational Safety and Health Administration, compliance with Department of Transportation, and the like. A very detailed FDA guidance has been issued regarding "Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (Q7A, August 2001)." This guidance covers every aspect of the API manufacturing operation, from start to finish, including documentation at all stages as well as distribution and recalls.

BULK ACTIVE CHEMICAL, POST-APPROVAL CHANGES (BACPAC)

- BACPAC I: Intermediates in Drug Substance Synthesis Formal Guidance. Current update is February 2001.
- BACPAC II: Final Intermediate to Drug Substance. PQRI final draft, representing consensual industry input, will be provided to the FDA for crafting a "Draft Guidance."

The BACPAC guidances govern postapproval changes to the manufacture of active pharmaceutical ingredients [6]. BACPAC I covers the control of intermediates in drug substance synthesis and is a formal guidance. The current update is February 2001. BACPAC II covers changes in the final intermediate to finished drug substance. This is still not a formal guidance but is a final draft, representing consensual industry input. The information pools in the guidance cover all aspects of the API process ranging from manufacturing, ingredient sourcing, site changes, specifications, and test methods. In reviewing the guidance content, the two focal points that emerge are what impact does the change or changes have on the impurity profile and physical