that provides for the following simpler submission requirements is applicable to generic drugs that are marketed after 20 or more years following initial marketing of the corresponding branded drugs.

For Level 3 site transfer of generic IR drugs, 3 months' accelerated stability data from one batch should be included in the CBE supplement and long-term stability data from the first production batch should be included in ARs.

For MR products, the Level 3 change requires a PAS. For site transfer of generic MR drugs, 3 months' accelerated stability data on one batch should be included in the PAS and long-term stability data of the first three production batches should be included in ARs.

COMPLIANCE ISSUES

Regulatory implications governing stability testing need to be clearly understood and communicated throughout an organization to assure compliance with regulations and guidances. It should not be forgotten that contract testing laboratories and drug substance manufacturers constitute an extension of the organization with respect to the need for prompt communication and compliance with regulations.

Drug Substance (API) Stability

Stability testing of the generic drug substance (API) is conducted by the API manufacturer following a protocol included in a DMF submission. Usually, the DMF is referenced in the ANDA application submitted by drug product manufacturers and its review is triggered by the submission of the ANDA. The DMF needs to be updated with new annual stability data as they become available. If accelerated stability testing was conducted to justify process change(s), such information should be provided via amendment of the DMF in a timely manner. Failure to update the DMF may adversely affect the compliance status of the drug substance as well as the corresponding drug product especially in the event of unreported significant process changes and unavailability of stability data. Significant changes in the manufacturing process and/or equipment and/or site of manufacture for a drug substance may require separate stability evaluation and supplemental submissions to the FDA in ARs, CBEs, or PASs. Therefore, it is imperative that the drug substance manufacturers keep the drug product manufacturers in the loop to ensure timely supplemental submissions on drug products. Theoretically, in the absence of timely submissions on significant process changes, the drug substances and drug products may both be considered to be out of compliance with the FDA regulations.

Drug Product Stability

Stability testing of the generic drug substance (API) is conducted by the API manufacturer following a protocol included in an approved ANDA application. The protocol specifies time points for "pulling" stability samples for analysis. A log of "pull" dates for all stability samples should be maintained. It may be advantageous to