provide to the drug product developer/manufacturer appropriate reference standards for the conduct of those tests requiring such standards.

## DRUG MASTER FILE

A Drug Master File (DMF) is a submission to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storage of one or more human drugs. See the FDA website (http://www.fda.gov/cder/guidance/dmf.htm) for full details. Upon submission of a complete DMF, the FDA assigns a number to the DMF. The number entry becomes part of the DMF database.

One can search the DMF database and obtain information such as the name of the article included in the DMF, the name and address of the sponsor or holder of the DMF, and the date of original submission. The filed DMF is typically used in the generic drug environment to support the filing of an ANDA. A DMF holder provides letters of authorization to the FDA and the ANDA sponsor indicating that the FDA can refer to information in the DMF to support the filed ANDA, which utilizes the API for the drug product, which is the subject of the filed ANDA. There are five types of DMFs. The Type II DMF is limited to the drug substance or drug substance intermediate and the materials used in their preparation. A drug product can also be the subject of a Type II DMF. The FDA does not approve DMFs but can question the content and hold up a filed ANDA, which employs the particular API that is the subject of the DMF, until satisfactory responses are received. The DMF sponsor is required to update the filed DMF annually with information concerning any changes that were made in the manufacturing or controls employed for the production of the API, including specifications and test methods. As part of the procedure and practice of making any changes to a filed DMF for an API, the DMF holder is requested to notify all "customers" who purchase that API, and who have referenced the particular DMF in their ANDA, of such changes. The ANDA holder then is obligated to incorporate the information into its filed ANDA. Such incorporation may range from including the information in the Annual Report for the ANDA, file a Supplementary Changes Being Effected Supplement (CBE) to the filed ANDA, or file a Prior Approval Supplement (PAS) with the FDA for the filed ANDA.

An important aspect of developing APIs is to have a complete understanding of the chemical class of the drug substance being produced and identifying at an early stage what special handling issues may be needed for the particular API at issue. These include APIs in the category of controlled substances (follow mandates and dictates of the Drug Enforcement Agency for control and containment). Additional categories requiring special considerations are certain types of hormonal products and cytotoxic compounds. These handling precautions normally would get entered into batch manufacturing records, Material Safety Data Sheets, and on Analytical Test Methods. The required handling precautions should follow the trail of movement of the API all the way to the final user. There are a number of websites, including the USP, where MSDSs can be reviewed for the terminology and handling precautions cited for compounds in all risk categories. An interesting approach is to