the above tables. The greater the number of factors and greater the number of levels in each factor, the greater is the extent of reduction in the number of samples to be tested. Any reduced design is justifiable only if it has the ability to accurately predict shelf-life.

An intended matrixing design should be included in the stability testing protocol of the ANDA application. Because of the potential complexity of matrixing designs, it is advisable to discuss a design in advance with the OGD before its implementation in the stability program. If the ANDA application does not contain the matrixing design, a supplemental application and approval will be required before implementation of the design.

Controlled Room Temperature

Generally, drug product labeling specifies storage temperature and, in some cases, humidity requirements to maintain product stability. The General Notices section in the USP defines various storage conditions and should be used as a guide to ensure appropriate storage conditions consistent with the product's labeling requirement. The majority of drug products require controlled room temperature storage.

In the USP, the controlled room temperature is defined as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20°C to 25°C (68°F–77°F), which results in a mean kinetic temperature (MKT) calculated to be not more than 25°C, and that allows for excursions between 15°C and 30°C (59°F and 86°F) that are experienced in warehouses, pharmacies, and hospitals. Provided that the MKT remains in the allowed range, transient spikes up to 40°C are permitted as long as they do not exceed 24 hours. Spikes above 40°C may be permitted if the manufacturer provides data on effects of storage temperature variations. The MKT is a calculated value that may be used as an isothermal storage temperature to simulate the nonisothermal effects of storage temperature variations. The procedure for calculation of the MKT is included in the USP, General Chapter <1151>.

Stability of Products Containing Iron

In 1997, the FDA published the iron regulations requiring label warnings and unit-dose packaging for solid oral drug products that contain 30 mg or more of iron per dosage [23]. The regulations were issued to reduce the likelihood of accidental overdose and serious injury to young children through the use of unit-dose packaging. Such packaging was considered to limit the number of doses a child may ingest if the child gained access to the product.

Appropriate expiration dates for drug products in unit-dose packages were required to meet the iron regulations. Accelerated stability testing was not considered to be applicable to drug products containing iron, especially multivitamin products, because they were known not to perform well under the unrealistic stressed accelerated conditions. Therefore, long-term stability testing was the only method to determine the expiration date. After publication of the iron regulations, which became