

applicants, the Office of Generic Drugs (OGD) of CDER stated that its accelerated stability condition, $40 \pm 2^\circ\text{C}$, $75 \pm 5\%$ RH, in support of controlled room temperature tentative expiration dating for ANDA products, was identical to the ICH conditions and would remain unchanged for ANDA submissions [20].

In 1995, the OGD issued a position paper on the conditions required for long-term stability testing of generic drugs, which was posted on the FDA website [20]. The long-term stability testing is required to validate the tentative expiration dating derived from accelerated stability studies. The OGD stated that the ICH recommendations of $25 \pm 2^\circ\text{C}$ and $60 \pm 5\%$ RH, would be acceptable for long-term stability testing for ANDA applications. Alternatively, the OGD would also continue to accept long-term stability data conducted at the previously allowable conditions of 25°C to 30°C and at ambient humidity. Although both sets of conditions have continued to be allowed by the OGD in ANDA submissions, the international generic community has clearly progressed toward harmonization with the ICH conditions.

STABILITY PROTOCOL

The stability protocol should be carefully developed by the quality-control unit responsible for conducting and monitoring stability studies. The protocol should consist of the stability study design factors, such as package sizes, sampling time points, strengths, bracketing, and matrixing. It should specify the environmental conditions for accelerated and long-term stability of packaged products and for bulk stability of unpackaged products. It should also include validated stability-indicating analytical procedures and stability specifications. The protocol must be included in an ANDA submission for approval by the OGD. Subsequently, if any changes are made to the protocol, the revised protocol must also be submitted for approval again by the OGD.

The following lists some key points of a stability protocol for a long-term stability testing program of a solid oral dosage form consisting of one strength and packaged in multiple sizes:

- The first three production lots will be packaged for stability testing.
- A bracketing design will be employed because the container/closure systems of the multiple sizes are chemically equivalent.
- The smallest and largest package sizes only will be stationed in the long-term stability chamber under the ICH storage conditions of $25 \pm 2^\circ\text{C}$ and $60 \pm 5\%$ RH.
- At least one production batch will be packaged in the smallest and largest package sizes and added annually to the long-term stability testing program.
- Testing will be conducted at 0, 3, 6, 9, 12, 18, and 24 months and annually after 24 months until the expiration date has been reached or longer to evaluate the possibility of extending the current expiration period.
- Stability testing criteria will include appearance, assay, loss on drying, known and unknown degradation products, and dissolution.
- Stability data will be evaluated to justify expiration dating and statistical analysis may be employed if required.