Implementing Successful Stability Testing Operations

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Stability studies are essential to every phase of a drug's life cycle. They not only document that a product will maintain its potency during its stated shelf life, but that it will do so under a variety of storage conditions as well.

Once a candidate drug reaches use in humans, all stability storage and testing must be conducted according to current good manufacturing practices (CGMPs). The regulatory mandate for stability testing in the United States is contained in 21 *CFR* Part 211 Section 166, which states that

> There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include….

Although 21 *CFR* addresses stability data treatment and reporting for expiration dating, it says almost nothing about how to ensure control within the stability storage operation or how to design stability protocols. There are many ways to run a stability operation in a GMP-compliant manner, but the bottom line is to have written procedures and protocols with documented evidence that they are followed.

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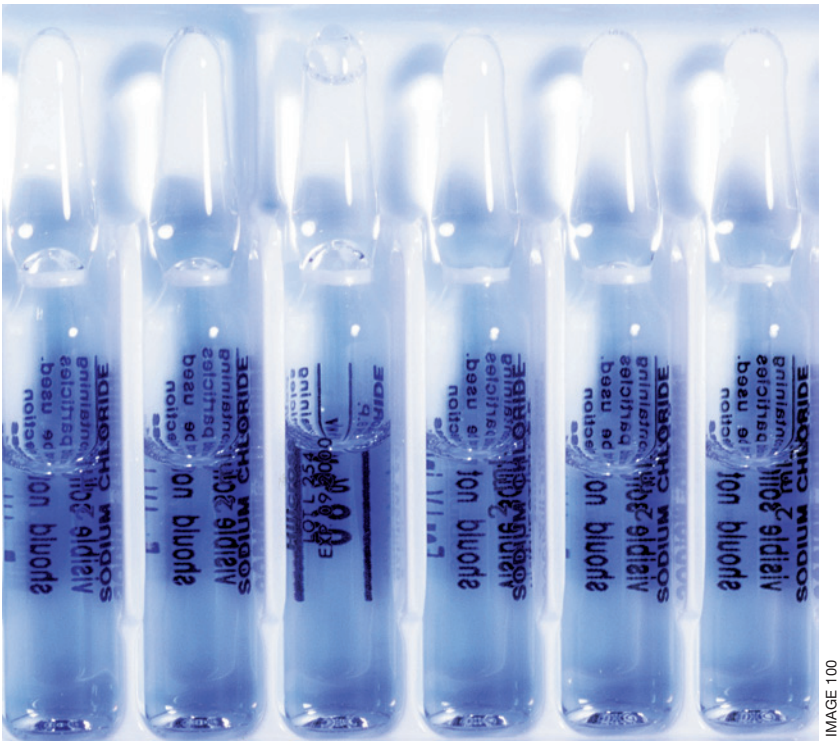

IMAGE 100

FDA soon will publish a final new guidance document, published in draft form since 1998, entitled "FDA Guidance for Industry: Stability Testing of Drug Substances and Drug Products." The document will replace the first guidance issued in February 1987. The new guidance incorporates the requirements for stability testing established by the International Conference on Harmonization (ICH)—a joint international effort initiated in 1990 to standardize requirements for the safety, efficacy, and quality of new drugs for registration in Western Europe, Japan, and the United States. ICH Q1A(R) "Stability Testing of New Drug Substances and Drug Products" has been adopted and published in each of the three regions.

Q1A(R) serves as the central ICH stability guidance. Other final guidances are Q1B "Photostability Testing," Q1C "Stability Testing for New Dosage Forms," and Q1D (at Step 4, this guidance can for all practical purposes be considered final) "Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products." Q1E "Evaluation of Stability Data" and Q1F "Stability Data Package for Registration in Climatic Zones III and IV" are likely to reach Step 4 during the February 2003 Expert Working Group meeting.

The FDA Stability Guidance covers several topics outside the scope

of ICH Stability Guidances (e.g., testing for INDs, testing for ANDAs, testing for postapproval changes, testing for specific dosage forms, sampling, and labeling storage statements). It also covers issues unique to the United States or not addressed in Q1A(R), including annual stability batches, site-specific stability data, thermal cycling, physician samples, container storage orientation, intermediate or bulk product storage, and reporting stability data.

A wealth of specific information is contained in the FDA Stability Guidance and ICH Stability Guidances identified as Q1A(R) through Q1F. These documents are required reading for all stability professionals and can be found on their respective Web sites www.fda.gov/cder/guidance and www.ich.org.

Stability protocols

Although all stability protocols contain a schedule for testing samples stored at one or more controlled storage conditions, the protocol specifics can differ significantly from one product to another.

If a drug product is to be marketed solely in one country, then it is possible to design a straightforward stability protocol on the basis of local regulations. However, international marketing complicates stability testing and requires significant planning and knowledge to anticipate all the regulatory requirements of the various countries.

The key parameters that make up a stability protocol include the following.

The sponsor must justify relevant label and packaging insert claims and meet any specific regulatory requirements.

Testing. This should include the (bio)-chemical, physical, or microbiological tests that measure the properties important to safety, quality, and efficacy that may change over time or when exposed to environmental conditions of temperature, humidity, and light. The sponsor must justify all relevant label and packaging insert claims, and any specific regulatory requirements of the various countries targeted for approval to market must be met.

The FDA guidance sets out recommendations regarding the specific tests that should be run on stability samples once they have been pulled. Generally speaking, these are a subset of the tests run for product release. For instance, in the case of a solid dose product, the stability tests will typically include

- potency assay: a stability-indicating assay that can differentiate between the active ingredient and degradation products, usually run on an HPLC instrument
- an impurities assay, which in many cases is incorporated into the potency assay
- dissolution test

Consult FDA and ICH guidances for information about what to do when significant changes occur at accelerated conditions.

- appearance
- hardness
- moisture content.

Tests of other physical or chemical properties are included as dictated by the specific characteristics of the particular drug product.

Storage conditions. Stability samples are stored in chambers in which temperature and humidity conditions are carefully controlled. Typically, samples are stored at label conditions (typically room temperature, refrigerated, or frozen) and at "accelerated stability" conditions that are meant to stress the product during a short period to approximate long-term stability. The standard accelerated conditions for solid dose products are 25 °C/60% RH, 30 °C/60% RH, and 40 °C/75% RH. The reader should reference the FDA and ICH guidances for standard storage conditions for biologics and other products as well as what to do when significant changes occur at accelerated conditions.

Various regulatory agencies and industry associations have generated a great deal of data, opinions, and debate about this topic during the years. However, a compromise has been reached to settle the discrepancy between the World Health Organization long-term stability condition of 30 °C/70% RH for Climatic Zones III and IV and the ICH intermediate storage condition of 30 °C/60% RH. ICH Q1F proposes that 30 °C/65% RH be used for long-term stability studies to support marketing in Zones III and IV. This appears to be well accepted by the ICH parties. Such changes, however, raise many questions about protocol design, converting existing product lines, changing packaging, adding new storage capacity, and possibly modifying outsourcing strategies.

Schedule. Samples are pulled from stability chambers for testing according to a predetermined schedule. Under most circumstances, the storage condition claimed on the product label is tested at 0, 3, 6, 9, 12, 18, and 24 months and annually thereafter. An accelerated storage condition for a new drug requires at least four time points, including time zero, the endpoint, and two time points in between. A typical program is to pull samples at months 0, 1, 3, and 6.

Complications arise when companies attempt to reduce testing through *bracketing* (i.e., only testing samples representative of parameter extremes; for example, largest and smallest package size) and *matrixing*, which is a study design typically used for stability studies in support of NDA filings that reduces the

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amount of testing required while maintaining the statistical power of the study.

ICH Q1D outlines acceptable approaches to these practices. When attempting bracketing or matrixing, sponsors should consult a statistician and, in most cases, submit the bracketing/matrixing proposals to the reviewing FDA chemist before initiating the studies. Although there is time and effort associated with this practice, it will help avoid problems and delays caused by nonacceptance of the proposed expiry period as a result of insufficient statistical power.

Storage operations

Sample traceability is a common theme behind the systems and procedures supporting a successful stability storage operation. This is true whether one is responsible for marketed products, R&D, or a contract facility or whether one handles innovator, generic, over the counter (OTC), active pharmaceutical ingredient (API), or veterinary products. Sample traceability can be used to challenge the design of all systems and procedures associated with a stability storage operation.

Although the bottom line is compliance, little FDA guidance exists specific to a stability storage operation or what the FDA looks for when inspecting a stability storage facility. The one certainty is that there must be written procedures as well as documented evidence that the procedures have been followed. In a preapproval inspection (PAI), the inspector looks at specific stability studies, lots, and/or package types. It is also common for an inspector to trace samples from either upstream (batch record) or downstream (test data). General CGMP inspections by FDA, typically scheduled at least every two years, may cover any or all of one's systems. Ensure they are looking for compliance to the systems and procedures in place. Remember the adage, "if it isn't written down, it didn't happen."

There are as many ways to achieve sample traceability as there are storage facilities and the people running them. The key elements for success and compliance include the following.

Validated storage conditions. This includes installation, operational, and performance qualifications (IQ/OQ/PQ), including temperature and humidity mapping. FDA appreciates summary reports of these activities with conclusions at the front of an easy to find, well-organized binder containing protocols, plans, and raw data.

Validated computer systems and

software applications: 21 *CFR* Part 11 compliance. Computerized systems are not necessarily required. Paper systems can suffice. However, if computer system are used, then they should be validated and be 21 *CFR* Part 11 compliant or part of a plan to be compliant soon.

Calibrated monitoring devices. Calibrations should occur on a regular schedule according to a written plan.

Perpetual inventory system. This system should track samples from receipt through final disposition.

Protocol documentation with audit trails. The protocol drives the stability study activities. Be sure the most current approved version is being used. "You only get one chance to get it right the first time."

Adequate number of qualified/ trained personnel.

Written SOPs that are easily accessed by staff.

Secured access. Control who has access to chambers and their contents.

Disaster recovery plan. Plan responses to power failure, chamber failure, monitoring system failure, all of the above simultaneously, natural disasters, and so forth.

Fail-safe provisions. Webster's defines *fail-safe* as "incorporating some feature(s) for automatically counteracting the effect of anticipated possible sources of failure." Fail-safe may include redundant monitoring devices, back-up power generator, UPS for critical computer components, supply of critical equipment components, back-up water supply for humidity generators, frequent/routine facility inspections, back-up copies of historical storage data, verification of critical job functions such as setting studies and pulling samples, and so forth.

Conclusion

A successful stability operation will accomplish the following:

- getting the right quantities of the right lots into the right storage conditions the first time, every-time
- sustaining storage conditions within specifications in an uninterrupted manner
- pulling the right quantity of the right lots from the right storage conditions, on-schedule, and label samples in a way to ensure accuracy and prevent mix-up downstream
- testing samples according to the protocol and in a timely manner
- sustaining records that verify the accuracy of all actions.

Stability testing is a complex, ever-changing discipline, and there is no way to cover all the aspects in this brief chapter. Analysts should participate in training, seminars, and discussion groups, as well as network with professionals as part of the learning process. The Pharmaceutical Stability Discussion Group is a valuable resource. It can be contacted at psdg@erols.com. **PT**