

# THE TEST OF TIME:

## SATISFYING STABILITY AND PHOTOSTABILITY REQUIREMENTS

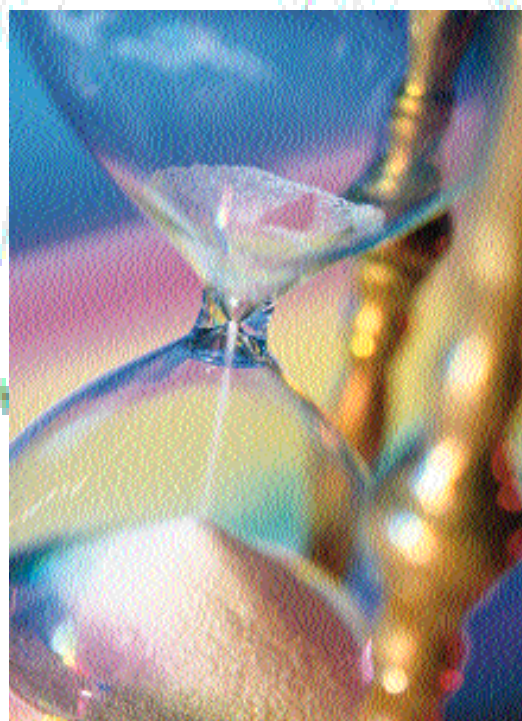
While regulatory agencies require stability testing to ensure product quality, there are advantages to considering stability and photostability early in the development process. Planning in the R&D phase for these tests typically yields formulations with the longest shelf life and once experiments are in progress, controlled environmental conditions can help propel the pace of drug development.

by Bob Dotterer

**K**nowing how a drug will perform in the body is but one set of considerations in its formulation and development process. During the 12 years and \$359 million<sup>1</sup> that are often required for a new pharmaceutical formulation to reach the market, it will be tested for moisture content, pH level, appearance, dissolution and content uniformity. The product will endure microbiological testing and its packaging will be assessed for potential contamination. One of the most time-consuming elements of these vigorous tests is determining the shelf-life of the product and its behavior relative to its packaging over a period of time.

When developing a drug under the pressure of time and in consideration of available resources, an understanding of the performance of the drug formulation is of paramount importance to researchers, while stability testing is key to establishing and sustaining high quality product. The backbone to maintaining a stability program is performing the tests within a controlled, strategically monitored environment. Subjecting the product and packaging to stress in environmental chambers, such as those shown on the following page, provides the researcher with an indication of drug quality and stability before it reaches the hands of consumers.

Stability, as defined by the World Health Organization, is “the ability of a



<sup>1</sup> Elizabeth M Rugherford. “The FDA and Privatization—The Drug Approval Process.” 50 Food & Drug L.J. 203, n.2 (1995), citing Pharmaceutical Research & Mfrs. of Am., Modern Medicines: Saving Lives and Money 4 (1994)

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Caron Products model 6010 10ft<sup>3</sup> stackable and model 6030 30 ft<sup>3</sup> upright chambers

pharmaceutical product to retain its properties within specified limits throughout its shelf life.”<sup>2</sup> The formulation’s chemical, physical, microbiological and biopharmaceutical aspects are all to be considered. Testing for stability provides evidence of how pharmaceutical quality varies with time under the influence of different environmental factors. For drug substances and drug products, these environmental factors focus on temperature, humidity and light<sup>3</sup>.

Testing for stability is required by regulatory agencies to ensure high drug quality. Data from stability testing can identify adequate formula-

tions and container closure or packaging systems. In addition, stability testing determines drug shelf life as well as proper storage and shipping conditions. Substantiation of these results may be required with further testing for use in the registration dossier. Once in general production, stability testing is performed to verify that no formulation or manufacturing process changes have occurred to adversely affect product stability.

## TESTING SNAPSHOT

Photostability is the subset of stability pertaining specifically to light. During photostability testing, a substance or compound is subjected to radiation or light, and the results show whether light exposure affects an unacceptable change<sup>4</sup>. This process is especially important for new molecular entities and associate drug products. Common photostability objectives are material characterization of APIs, product development, pre-clinical photoactivity determination, shelf-life stability and environmental fate<sup>5</sup>. Applications include stress and confirmatory testing.

While regulatory agencies require stability testing to ensure product quality, there are advantages to considering stability and photostability early in the development process. Planning in the R&D phase for these tests typically yields formulations with the longest shelf life. The optimal product and package design ultimately affect manufactures’ expenses and profitability. By subjecting various packaging methods to stability testing during product development, packaging that is functional yet inexpensive can be identified. In addition, stability testing with different production techniques also may help qualify less expensive manufacturing processes and procedures.

Testing for stability can be performed in-house

<sup>2</sup> WHO, *WHO Guidelines on Stability Testing of Pharmaceutical Products Containing Well-established Drug Substances in Conventional Dosage Forms* (World Health Organization) WHO/PHARM/94.565/rev. 1.

<sup>3</sup> ICH, *Stability Testing of New Drug Substances and Products* (International Conference on Harmonization, Geneva, October 1993).

<sup>4</sup> International Conference on Harmonization, *Guidelines for the Photostability Testing of New Drug Substances and Products*. Fed. Reg., 62, No. 95, 27116, May 16, 1997.

<sup>5</sup> Timothy D. Rhines, “Pharmaceuticals Design Photostability Studies within FDA and ICH Guidelines” presented at Regulatory Compliance and Expedited Design and Execution of International Stability Programs, June 2000.

TABLE 1—REGULATORY BODIES

Regulatory Agency Co-Sponsor	Region
US Food & Drug Administration (FDA)	United States
European Commission (EC) of the European Union	European Union
Ministry of Health and Welfare (MHW)	Japan
Pharmaceutical Industry Association Co-Sponsor	Region
Pharmaceutical and Research Manufacturers Association (PhRMA)	United States
European Federation of Pharmaceutical Industries’ Associations (EFPIA)	European Union
Japan Pharmaceutical Manufacturers Association (JPMA)	Japan

TABLE 2—GUIDELINE-RELATED WEB SITES

US Food and Drug Administration Home Page	www.fda.gov
Center for Drug Evaluation and Research	www.fda.gov/cder
Center for Biologics Evaluation and Research	www.fda.gov/cber
Center for Veterinary Medicine	www.fda.gov/cvm
Center for Devices and Radiological Health	www.fda.gov/cdrh
Office of Regulatory Affairs	www.fda.gov/ora
ICH guidelines	www.ifpma.org/ich1.html
United Kingdom Medicines Control Agency	www.open.gov.uk/mca
European Medicines Evaluation Agency (EMA)	www.emea.eu.int
European Union (EU)	www.eudra.org
Human Drugs—Documents and Guidelines	www.eudra.org/document.htm
Pharmaceutical Research and Manufacturers of America (PhRMA)	www.phrma.org
European Federation of Pharmaceutical Industries' Association (EFPIA)	www.efpia.org
Japanese Pharmaceutical Manufacturers Association (JPMA)	www.jpma.or.jp/12english/index.html
Drug Information Association	www.diahome.org
Institute for International Research	www.iir-ny.com
Pharmaceutical Education & Research Institute (PERI)	www.peri.org
Healthlinks.Net	www.healthlinks.net

The above URLs are posted as live links at [www.pharmaquality.com](http://www.pharmaquality.com)

or at an independent lab. In-house testing offers the convenience of direct access to test specimens as well as close sample monitoring. This may be especially beneficial to the product development team during the early product development phase. This flexibility and control, however, may require substantial investments in capital and labor to perform and monitor such tests. An independent lab can defer some of these initial costs while shouldering responsibility.

There are many agencies and regulatory bodies setting standards and guidelines for drug stability. Perhaps most widely used is the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines. Established in 1990 and commissioned to negotiate common standards for regulation of pharmaceutical products in the US, European Union and Japan, ICH aims to produce a single set of technical registration requirements for new drug products<sup>6</sup>. ICH is co-sponsored by the regulatory bodies that oversee drug approval and pharmaceutical trade associations in these regions. See Table 1 for co-sponsors from each region.

While ICH covers the US, European Union and Japan, World Health Organization offers assistance to small drug regulatory authorities for established generic drugs. WHO also differs from ICH by addressing the international market. It also specifies drug product testing for stability according to the climatic zone of its intended market. In addition, WHO addresses only established generic drugs in their final dosage form, not new chemical entities.

Similar in nature to ICH, the International Cooperation on Harmonization of Veterinary Medical Products sets guidelines for regulation of veterinary drugs throughout the US, European Union and Japan. Other regulatory agencies and associations exist such as Therapeutic Products Programme, Health Canada, and the European Free Trade Association. Table 2 provides sources of further information for these and related agencies.

#### COMMON THREADS

While stability requirements and testing depend upon the regulatory agency of that region, some elements are common throughout the organizations. Real-time or long term tests can run months or even years. When long test times are undesirable, accelerated stability tests fill the void. Accelerated stress conditions rapidly age the product and yield product changes faster. This involves raising the temperature and/or humidity levels exposed to the product. Table 3 (p. 30) summarizes ICH stability test conditions for drug substances and drug products.

The pillar of stability testing is conducting experiments under controlled conditions, such as an environmental chamber, in which temperature and humidity is controlled within limited space and with specific light sources. A variety of configurations, options and accessories are readily available to satisfy scientific sophistication and budgetary constraints. Two basic classes of environmental control systems are reach-in chambers and walk-in rooms.

Reach-in chambers range in size from benchtop

<sup>6</sup> Dr. Caroline Nutley, "Value and Benefit" The Value and Benefits of ICH to Industry, January 2000.

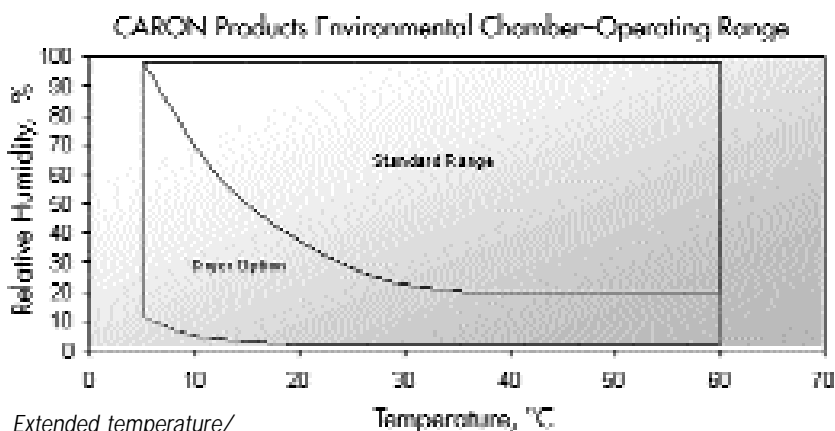
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to large upright models. Interior composition is usually stainless steel, wire shelves and a solid or glass door. For most drug stability testing, a temperature range of 5 to 50°C and a relative humidity range of 20% to 80% is sufficient. Extended ranges are readily available. Shown is the extended temperature/humidity range of a Caron Products environmental chamber attainable with a

chemical dryer. Environmental chambers have internal air circulation to enhance temperature and humidity uniformity and can include alarms, access and fresh air ports.

Standard protocol for any stability testing is an accurate log of internal chamber conditions. A circular or strip chart recorder provides clear hardcopies of chamber performance. Also, digital data-logging may be accomplished through computer communications such as RS-485. Communications also allow the user to remotely program and monitor test conditions. For applications requiring temperature or humidity profiles, a programmable controller fits the task. Most chambers offer internal electrical outlets, timed lighting and defrost packages. Manufacturers also provide options that ease laboratory setup, including self-contained water delivery systems that also filter and recycle water, which can be used when an in-house water supply or drain is unavailable for the chamber's humidity system.

An environmental chamber should be validated and calibrated. SOPs incorporating cGMPs should specify routine validation and calibration checks at logical intervals. Typical calibration includes comparing temperature and humidity readings



Extended temperature/humidity range of a Caron Products environmental chamber with chemical dryer

TABLE 3 – STABILITY TEST CONDITIONS

Study	Temperature, °C	% Relative Humidity	Light Type	Minimum Time, Months
<b>General</b>				
Long Term	25 ± 2	60 ± 5	None	12
Intermediate	30 ± 2	60 ± 5	None	6
Accelerated	40 ± 2	75 ± 5	None	6
<b>†Impermeable container</b>				
Long Term	25 ± 2	Any	None	12
Intermediate	30 ± 2	Any	None	6
Accelerated	40 ± 2	Any	None	6
<b>†Semi-permeable container</b>				
Long Term	25 ± 2	*40 ± 5	None	12
Intermediate	30 ± 2	60 ± 5	None	6
Accelerated	40 ± 2	*≤ 25	None	6
<b>Refrigerator</b>				
Long Term	5 ± 3	Any	None	12
Accelerated	25 ± 2	60 ± 5	None	6
<b>Freezer</b>				
Long term	-20 ± 5	Any	None	12
<b>Photostability</b>				
General	**As appropriate	Any	D65/ID65 or equivalent	1.2 million lux hrs & 200 watt hrs/m <sup>2</sup>

† Drug product testing only

\* Higher humidity levels may be used

\*\* Usually 20 to 25°C or a dark control must be maintained (Drug Information Association).

traceable to the National Institute of Standards and Technology. A validation procedure should incorporate chamber mapping, a method of taking simultaneous temperature and humidity measurements throughout the chamber to verify uniform conditions. Validating and calibrating a chamber is most accurate if performed while the chamber is installed on-site and in the same conditions under which it will be used. Independent third-party companies specialize in validating and calibrating environmental chambers and provide IQ/OQ reports.

With the high cost of time and resources required to develop new pharmaceutical products, a crucial component to establishing a stable product is being able to do it effectively in the least amount of time. When priority is placed on stability testing, the insight into a drug product that results from the tests supports a manufacturer's expiration date assignment and it dictates proper storage conditions. A stable product, in turn, is one of the key components to establishing and maintaining high drug quality, which contributes to a greater assurance for manufacturers—and ultimately, consumers—as new products move from the laboratory to the marketplace. ■

Caron Products & Services Inc.  
Marietta, OH  
740-373-6809  
www.caronproducts.com  
*Circle 270 on the RS card*

*Bob Dotterer is Applications Engineer with Caron Products & Services.*

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