A Stress Testing Benchmarking Study

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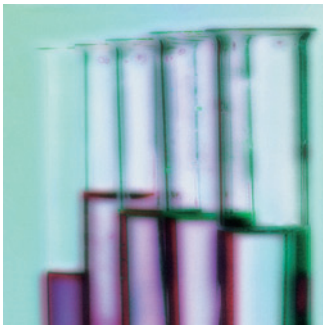

IMAGE 100

Stress testing is becoming increasingly important in testing new small-molecule drug candidates. To better understand current stress-testing practices in the pharmaceutical industry, the authors conducted a benchmarking survey to which 20 pharmaceutical companies responded. The study addressed a range of issues such as stress testing study design, types of conditions, procedures, and the company organization used to conduct stress testing. This article reviews the key findings from the survey.

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Stress testing (or forced degradation studies) is an important part of the drug development process, and the pharmaceutical industry's considerable interest in this topic has led to the publication of an article by the Pharmaceutical Research and Manufacturer's of America (PhRMA) in *Pharmaceutical Technology* (1). Although the concept of stress testing is not new to the pharmaceutical industry, the procedure was not clearly defined until the International Conference on Harmonization (ICH) provided a definition in its guidance on stability. The ICH guideline indicates that stress testing is designed to help "determine the intrinsic stability of the molecule by establishing degradation pathways in order to identify the likely degradation products and to validate the stability-indicating power of the analytical procedures used" (2).

Because the ICH definition leaves the details of the investigations to the pharmaceutical researcher, the practices that companies use to conduct stress testing studies can vary tremendously and therefore have a significant effect on the quality of the analytical methodology used throughout the industry. The intent of this study about stress testing is to survey stress testing practices in the industry and to provide a thorough comparative analysis of approaches to stress testing. The authors hope that these survey results will provide further guidance about stress testing to the industry.

Stress testing is a critical component of drug development. By generating key stress-testing samples (i.e., partially degraded samples stressed under various conditions), predictive degradation information can be obtained early in the process and can be of significant value to a drug company in terms of time and money. In addition, stress testing can help in the selection of more-stable drug substance salt forms and drug formulations.

Stress testing also is becoming increasingly important in testing new molecules. Methods developed by stress testing and the stability information gained from those methods can have a significant effect on the actual compound selected for development. Therefore, to understand the current state of stress testing in the pharmaceutical industry, a benchmarking survey focusing on the methods and practices was conducted in November 2001. The survey was sponsored by Eli Lilly and Company (Indianapolis, IN) and Pfizer Inc. (Groton, CT). KMR Group, Inc. (KMR, Chicago, IL), a management consulting firm that specializes in benchmarking, conducted the study.

The study addressed a range of issues, including

- stress testing design (i.e., how companies design stress testing studies and the approaches used)
- stress testing activity (i.e., types of stress testing conducted such as oxidative and the procedures used)
- organization (i.e., how companies are structured to oversee their stress testing activities and resources).

The survey focused on stress testing studies pertaining to small-molecule drugs (i.e., nonbiologicals or nonprotein) and did not include monoclonal antibodies. Information related to small peptides was only included if the drug was going to be registered with the Center for Drug Evaluation and Research. The study encompassed only stress testing studies, not formal stability studies such as accelerated and long-term stability studies. The survey attempted to compare general internal practices rather than the details of each exception to the general practice or outsourcing practices. Therefore, companies were asked to focus on the current predominant internal practice or method at their company. If important exceptions to the general rule existed, participants were asked to note them. Both pharmaceutical and contract laboratories were invited to participate. Twenty companies provided responses to the survey. Of these, eleven are large pharmaceutical companies, four are midsize pharmaceutical companies, and four are contract services companies.

Survey methods

The survey was conducted confidentially using a questionnaire to capture individual company responses. KMR worked closely with the sponsor companies (Eli Lilly and Pfizer) to ensure that the survey's goals would be met. A list of questions was developed by the sponsor companies as the basis for the survey. With the guidance and direction of the sponsor companies, KMR turned the list of questions into a formal, detailed survey.

KMR was responsible for distributing the final questionnaire to each participating company, and survey responses were submitted directly to KMR. To ensure comparability with companies, each company's data were reviewed to ensure consistency with the definitions and queried if needed.

All data submitted by each company remained confidential and were analyzed and presented in aggregate to maintain confidentiality. All participants received a final copy of the report.

Key findings

Stress testing as a function. More than two-thirds of the companies responded that no defined stress-testing group existed within their company. For the companies that have defined stress-testing groups, roughly two-thirds are centralized (i.e., report to a worldwide head). Regardless of whether a defined group exists, most stress testing resources report their findings within the analytical chemistry function.

Stress testing as a discipline. Most companies have a standardized approach to the design of stress testing studies. Seventy percent of these companies follow a standard operating procedure (SOP), and >50% of study participants require a protocol (see "Organization of stress testing" section).

Types of stress testing studies performed. All companies perform stress testing on the drug substance using a variety of methods, including acid–base–solution, oxidative, thermal–humidity, and photostability. Each of these methods is used on the drug substance by at least 95% of companies. Fewer companies perform stress testing on the drug product (90%), and not all methods are used with the same frequency. For example, only 60% of companies perform acid–base–solution stress testing studies on the drug product and 65% perform oxidative studies, whereas thermal–humidity and photostability studies are performed by 90% of companies.

Timing of stress testing studies. The majority of companies perform studies on the drug substance and the drug product in the preclinical stage. The practice of repeating stress testing studies varies by stage of development. Studies are repeated on the drug substance between the preclinical and registration stages, and studies are repeated on the drug product between Phase I and registration as the final commercial formulation is developed.

How stress testing studies are conducted. Seventy percent of companies generally identify the major degradation products formed during stress testing studies. Most companies attempt to induce at least 5–20% degradation of the drug substance before considering stress testing to be complete. The primary methods used to analyze stress testing studies are liquid chromatography (LC)–diode array (65%) and LC–UV (30%).

Organization of stress testing

The stress testing function is structured quite differently among the companies surveyed. A third (six) of the companies organize stress testing into a defined group. Of those six companies, four are centralized. In most companies, the personnel responsible for stress testing report their findings within the analytical chemistry function. Of the six companies with a formal, defined stress-testing group, five report to the head of analytical chemistry, and one reports to the head of early development.

All twenty companies were asked who is primarily responsible for designing and conducting stress testing studies in each phase (see Table I). *Individual scientists* was the most frequently cited primary resource responsible for both designing and conducting stress testing studies, regardless of the phase of development. However, 25% of companies have a specialized degradation group that performs stress testing studies during some phase of development, most often after preclinical development. Although none of the companies indicated that a robot system was the primary resource for either designing or conducting stress testing studies, one company selected it as a secondary resource or alternative for conducting stress testing studies in Phases II and III.

The primary reasons for conducting stress testing studies vary significantly among companies (see Figure 1). Method development was selected with the highest frequency, although it was selected by only seven companies. Other common responses were method validation, selected by four companies, and stability support and distribution, selected by three companies. Regulatory compliance was the most popular secondary response for performing stress testing studies; however, the majority of companies selected all categories as secondary reasons.

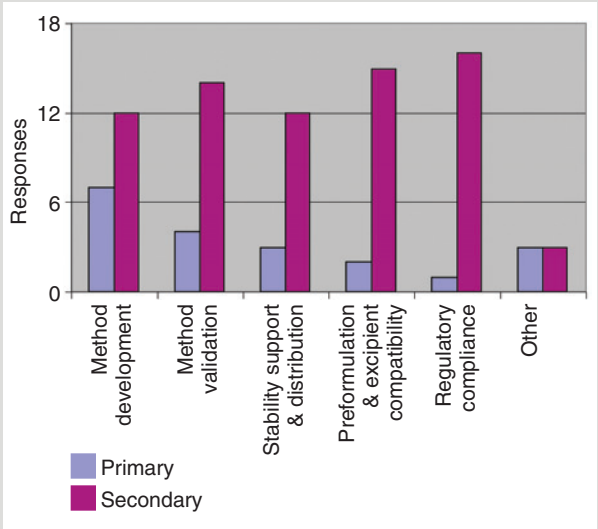

Figure 1: Predominant reasons to perform stress testing studies (n = 20).

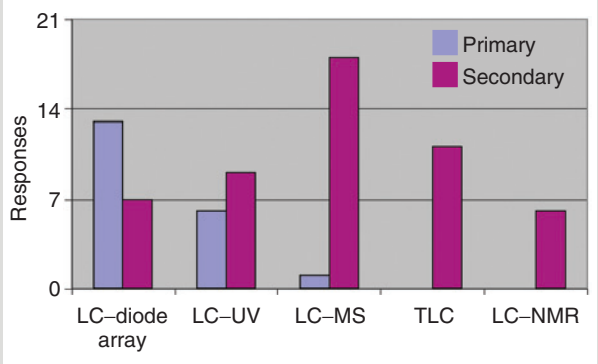

Figure 2: Methods used to analyze samples, and the top five responses (n = 20).

One company commented that choosing a single primary reason is difficult because all the reasons that were listed are important (see Figure 1).

Thirteen companies have a standardized approach to designing stress testing studies. Of the thirteen, 70% follow an SOP. Eleven companies require a protocol to conduct stress testing studies, and 70% of those use a standardized approach.

Most (eight out of nine) companies that follow SOPs also require a protocol for stress testing studies. All but one company typically generate a technical report for internal purposes. More than three quarters of respondents generate a technical report for >75% of the studies performed. One company commented that reports are generated for all new drug applications and for 50% of preclinical- or early-phase stress testing studies.

Most companies provide some version of a technical report for submission purposes. Ten companies give a summary (one as an addendum to the chemistry, manufacturing, and controls section), and four companies did not know.

Activity

This section of the survey focused on methods used to analyze stress testing samples and the appropriate stage of development to perform stress testing studies. Methods used to analyze stress testing samples included either LC–diode array or LC–UV as the primary method of analysis. Eighteen companies cited LC–mass spectrometry (MS) as a secondary method. One company stated that it uses LC–MS, capillary electrophoresis, and thin-layer chromatography (TLC) for selected samples. Another company commented that it uses LC–NMR only for specific identification projects. The typical methodologies used by respondents to analyze stressed samples are outlined in Figure 2.

Most (twelve) companies first perform stress testing studies on the drug substance in the preclinical stage. Five companies first perform stress testing in the discovery stage, and the remaining two companies first perform stress testing in Phase I and II, respectively. Seventeen companies repeat stress testing studies, and eight companies repeat stress testing studies in more than one phase. Eighteen companies (out of twenty) perform some kind of stress testing studies on the drug product. These companies perform drug product studies between discovery and Phase II, but usually in the preclinical stage. Phases in which these studies are repeated vary from Phase I to registration. Similar to the practices for drug substance studies, eight companies repeat drug product studies in more than one phase.

Fourteen companies generally identify major degradation products observed during stress testing on the drug substance even if the degradation products are not observed during stability studies (e.g., 25 °C/60% RH, 30 °C/60% RH, 40 °C/75% RH). Of the fourteen, ten companies identify all major degradation products that form in stress testing, and two companies generally identify only those approaching ICH thresholds (i.e., the degradation products that are formed during formal stability that approach ICH thresholds). One company stated that the identification effort varies from drug to drug,

Table I: Resources primarily responsible for conducting stress testing studies by phase.

Conduct Resource	Discovery	Preclinical	Phase I	Phase II	Phase III	Registration
Specialized degradation group	3	3	4	5	4	4
Robot system	0	0	0	0	0	0
Contract laboratory	0	0	0	1	1	1
Individual scientists	6	15	13	12	12	11
Other	1	0	0	0	0	0
N/A	10	2	3	2	3	4
Total	**20**	**20**	**20**	**20**	**20**	**20**

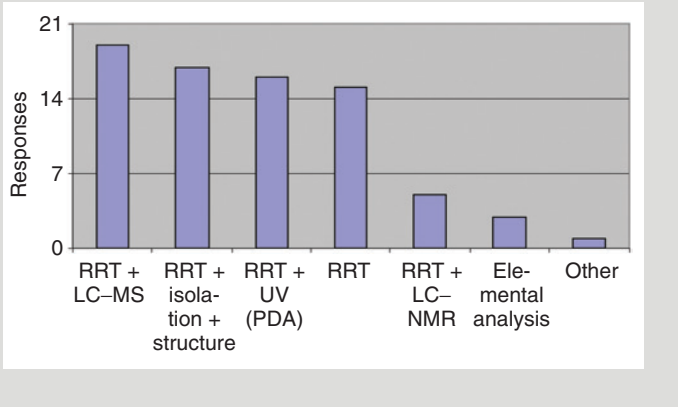

Figure 3: Typical degradant characterization methodologies (n = 20, and RRT is relative retention time).

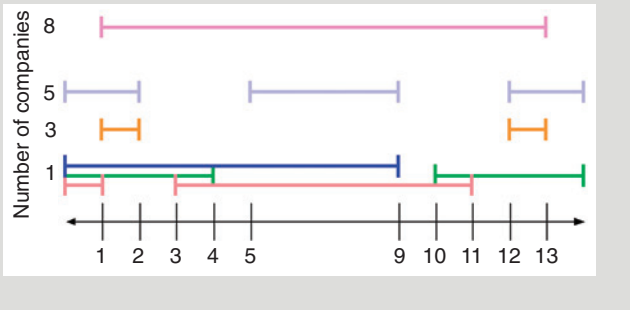

Figure 4: pH level covered In acid–base studies. Drug substance (n = 19).

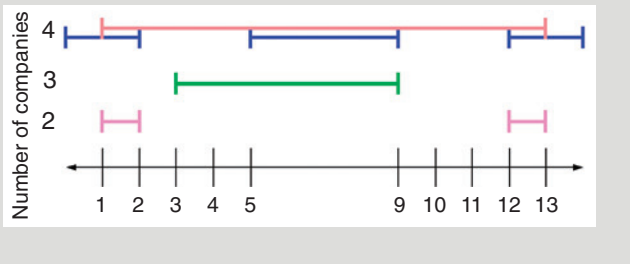

Figure 5: pH level covered In acid–base studies. Drug product (n = 13).

and another company identifies only those at or above ICH threshold limits.

Companies were then asked to indicate the typical degradation-characterization methodologies (i.e., for structure elucidation and peak tracking) that were implemented. Responses are shown in Figure 3.

Acid–base testing

Nineteen out of the twenty companies participating in the survey perform acid–base stress testing on the drug substance. Approximately 60% of companies perform acid–base testing on the drug product, and 15% perform acid–base testing on intermediates. When the desired drug product is a solution dosage form, acid–base stress testing studies are used more frequently than when the drug product is a solid oral dosage form. Figure 4 shows the various pH range combinations that companies use to perform acid–base studies on the drug substance. Nineteen companies typically perform stress testing on the drug substance in solutions at different pHs. Each color represents a range combination. Companies are classified with the combination that most accurately represents their response. For example, in Figure 4, three companies indicated using pH ranges of 1–2 and 12–13 (represented by the orange bars in Figure 4). Forty-two percent of companies cover a wide range (1–13), ~20% cover the outer ranges only, and roughly 25% cover pHs in the low (0–2), mid (5–9), and high (12–>13) ranges. Approximately 10% cover pHs in the low to mid ranges.

Figure 5 shows various pH range combinations that companies use to perform acid–base studies on drug product. Thirteen companies typically perform stress testing on drug products in solutions at different pHs. Thirty percent of these companies cover a continuous range of pHs from 1–13. Another 30% use low, mid, and high pH ranges (12–>13). Roughly 25% cover the middle ranges only, and 15% cover the outer ranges only.

For acid–base stress testing, 14 companies stress at one concentration, and four companies use multiple concentrations. Three companies indicated that they use solubility-dependent concentrations, and one company indicated that it uses compound-dependent concentrations. Two companies stated that they may use one or multiple concentrations depending on the situation. Fifteen companies use a concentration between 0.1 and 1.0 mg/mL.

Phosphate is the most common buffer used among the 11 companies that use buffers. Of these, phosphate is used by all companies to acidify solutions and used by 64% to basify solutions. One company stated that the method used to control pH depends on the drug substance.

Eighteen companies use cosolvents to help solubilize the drug substance. Acetonitrile (ACN) and methanol are the most commonly used cosolvents for acid–base stress testing. One company stated that it uses cosolvents only when necessary, which, in practice, meant routinely. The percent of studies involving the use of cosolvents varies among companies but is ⩽75%.

Most companies use low temperature ranges (ambient–70 °C) for acid–base studies on the drug substance. Only a few companies use temperatures >70 °C. Conditions used are more extreme if the drug substance does not degrade easily in acid–base studies. Companies tend to use a low (1–2) and high (12–13) pH range to promote degradation. Six companies use temperatures >90 °C if the compound does not degrade easily; however, the majority of the companies do not exceed 80 °C routinely.

The maximum time companies will stress samples if no degradation occurs varies among companies. Twenty percent of companies will stress the samples for 25 days or more. Most companies attempt to induce 5–20% degradation of the drug substance to consider the stress test complete.

Glossary

AAPH: 2,2′-azobis(2-amidopropane)dihydrochloride.
AIBN: 2,2′-azobisisobutyronitrile.
AMVN: 2,2′-azobis(2,4-dimethylvaleronitrile).
DPPH: 1,1-diphenyl-2-picrylhydrazyl.
Acid–base–solution stress testing: forced degradation studies designed to test the stability of compounds primarily by exposure to acid–base–solutions in a variety of pH conditions.
Ambient: the surrounding laboratory temperature of the environment in which the study is performed.
Confirmatory photostability studies: studies designed to determine the degree of photodegradation protection required and to provide the information necessary for handling, packaging, and labeling (see ICH Q1B glossary).
Cosolvents: an inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance or the manufacture of a new drug product.
Degradation: the change of a compound into a different chemical structure induced over time by the action of elements such as light, temperature, pH, water, or by reacting with an excipient and/or the immediate container–closure system.
Drug product: the finished dosage form (e.g., tablet, capsule, etc.) that contains a drug substance—generally, but not necessarily, in association with other active or inactive ingredients.
Drug substance: the active ingredient intended to diagnose, treat, cure, or prevent disease or affect the structure or function of the body, excluding other inactive substances used in the drug product.
Excipient: anything other than the drug substance in a dosage form.
Forced degradation studies: see stress testing.
ICH stability studies: long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the retest period of a drug substance or the shelf life of a drug product.
Intermediate: compound produced during the synthesis of the drug substance that may undergo further synthetic modification to produce the drug substance.
Neutralize: a process to prevent further reaction in acid–base–solution stress testing studies (e.g., by addition of an acid or base).
Oxidative stress testing: forced degradation studies designed to test the susceptibility of compounds to oxidative degradation.
Photostability Option 1: exposure of the sample to any light source that is designed to produce an output similar to the D65/ID65 emission standard such as an artificial daylight fluorescent lamp combining visible and UV outputs, xenon, or metal halide lamp. D65 is the internationally recognized standard for outdoor daylight, and ID65 is the equivalent indoor indirect daylight standard (see ICH Q1B glossary}.
Photostability Option 2: Exposure of the sample to a cool white fluorescent lamp designed to produce an output similar to that of ISO 10977 and to a near fluorescent lamp having a spectral distribution from 320 to 400 nm (see ICH Q1B glossary).
Photostability stress testing: Forced degradation studies (as opposed to confirmatory studies) designed to test the stability of compounds under light exposure (i.e., visible and UV light) (see ICH Q1B glossary).
Quench: a process to prevent further reaction in oxidative studies (e.g., by addition of an antioxidant).
Thermal–humidity stress testing: forced degradation studies designed to test the stability of compounds by exposing them to different thermal and humidity conditions.
Sample: the drug substance or drug product being tested.
Stress testing: studies undertaken to elucidate intrinsic stability attributes of the drug substance or drug product (see ICH Q1A definition). Also referred to as *forced degradation studies*.
Solid-state stress testing: studies that determine the solid-state stability of the drug substance or drug product.

Oxidation

Nineteen companies perform oxidative stress testing on the drug substance. Approximately 65% perform oxidative stress testing on the drug product, and 15% of companies perform oxidative stress testing on intermediates. A third of companies perform stress testing on the drug substance only. When performing oxidative stress testing, responses also show that

- Nineteen companies use peroxides as an oxidative measure.
- Five companies use a radical initiator.
- Three companies use pressured oxygen.
- Three companies use transition metals.
- Only two companies use bubbled oxygen.

Figures 6–9 show types of oxidative stress tests and their typical performance conditions. The number of companies that perform each type is shown in the center of the diagrams. Each pie chart in the figures represents a specific condition and is divided according to the number of responses for that condition. For example, in the peroxide pie chart that shows typical temperatures, 84% of the companies selected ambient–30 °C, 11% selected 31–50 °C, and only 5% selected >50 °C.

Peroxides ($n = 19$). All companies use hydrogen peroxide. The typical concentration selected by a majority of companies (63%) is 1–3%. The typical temperature range selected by most companies (84%) is ambient–30 °C. The maximum study duration selected was the same for one and seven days (37% for both) (see Figure 6).

Radical initiator ($n = 5$). The typical initiator used by four out of five companies is AIBN (see Glossary). The typical solvent used by four out of five companies is ACN–water. The typical temperature used by three out of five companies is 31–40 °C. The maximum study duration selected is 1 (one company), 7 (two companies), and 14 days (two companies) (see Figure 7).

Transition metals ($n = 3$). All three companies use both copper (Cu^{II}) and iron (Fe^{III}) as the typical metals. Two companies use similar concentrations, 0.05 and 1.0 mM, respectively, and one company uses a significantly higher concentration (25 mM). The typical solvent used by all companies is aqueous–water. The typical temperature used by two out of the three companies is 31–40 °C. The maximum study duration varies among companies from 1 to more than 14 days (see Figure 8).

Pressured oxygen ($n = 3$). The typical pressure is 150 or 300

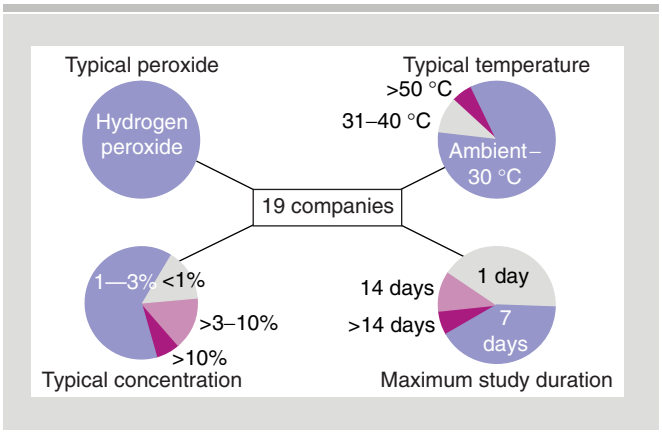

Figure 6: Responses for peroxide.

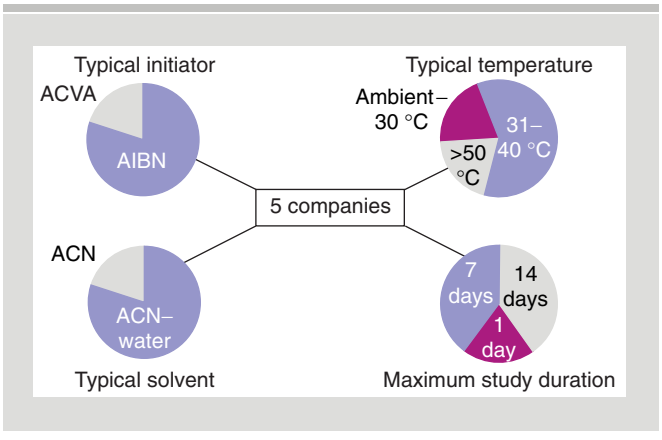

Figure 7: Responses for radical initiators.

psi. One company stated that the pressure varies. The typical temperature is >50 °C for two companies and ambient–30 °C for one company. The maximum study duration varies among the three companies from 1 to more than 14 days (see Figure 9).

Bubbled oxygen ($n = 2$). The conditions for bubbled oxygen are almost identical for both companies. The typical temperature used by both companies is ambient–30 °C. The maximum study duration is 7 days for both companies. However, the flow rate is different; one uses 5–10 cc/min, and the other uses 10 cc/min (see Figure 9).

Four companies typically quench oxidative studies. Of these four companies, three companies quench peroxide studies only and use reductants as the quenching method (e.g., sodium metabisulfite, sodium sulfite, and sodium thiosulfate). One company quenches only studies involving radical initiators and pressured oxygen using acid–chelators as the quenching method.

Thermal–humidity studies

All companies perform thermal–humidity stress testing on the drug substance, 90% of companies perform stress testing on the drug product, and 20% perform stress testing on intermediates. Two companies perform stress testing only on the drug substance. Most companies perform thermal–humidity stress testing studies in both open and closed containers; however, 20% of companies use only open containers, and two companies use only closed containers.

Thirteen companies use a variety of temperature ranges when performing typical thermal–humidity stress testing studies on the drug substance, whereas seven companies use only one range. Most companies (70%) typically test at a range of 51–70 °C. If the drug substance does not degrade easily, 50% of companies stress solid-state samples at >90 °C, and 25% of companies stress samples at 71–90 °C (see Figure 10).

When conducting thermal–humidity stress testing studies on the drug product, 72% of companies use a temperature range of 41–50 or 51–70 °C. If the drug product does not degrade easily, ~44% of companies stress solid-state samples at a range >70 °C. From these data, it can be concluded that the drug substance is stressed at higher temperature ranges than the drug product.

More than 50% of companies stress solid-state samples of the drug substance in a variety of humidity ranges (see Figure 11). Eight companies use only one range. The typical range used by most companies is 51–75%. If the drug substance does not degrade easily, ~95% of companies stress solid-state samples >51% humidity, and nine of these companies stress at >75% humidity. Only one company uses an ambient or uncontrolled humidity range. For the drug product, the typical humidity range used most often and selected by 88% of companies is 51–75%. If the drug product does not degrade easily, all companies use a humidity range of ⩾51%.

Typical duration for performing thermal–humidity studies on the drug substance varies among companies (see Figure 12). The duration selected most frequently (chosen by 40% of the companies) was >3–6 weeks; 30% selected a duration of longer than six weeks. If the drug substance does not degrade easily, 50% of companies use a duration longer than six weeks. For the drug product, 50% of companies use a range of longer than 3–6 weeks. If the drug product does not degrade easily, 67% of companies use a duration longer than six weeks.

Photostability studies

Eighteen out of nineteen companies perform photostability stress testing on the drug substance and the drug product. Roughly 16% of the companies perform photostability stress testing on intermediates. One company performs stress testing only on the drug substance, and another company performs stress testing only on the drug product. The majority of companies (63%) use the ICH standard for their typical visible-light dose range (i.e., overall illumination is ⩾1.2 million lux h) (2). Thirty-seven percent use a range greater than the ICH standard. Maximum visible-light dose ranges vary among companies (see Figure 13). Eighty-nine percent use a maximum visible-light dose range greater than the ICH standard; however, only two companies use a maximum visible-light dose range >10 times ICH.

Most companies (67%) use the ICH standard for their typical UV-light dose range (i.e., overall integrated near-UV energy of ⩾200 watt h/m^2) (see Figure 14) (2). Maximum UV-light dose ranges vary among companies; however, ~67% of companies use a UV-light dose range that is >2 times the ICH standard. Of these, two companies use a UV-light dose range >10 times ICH.

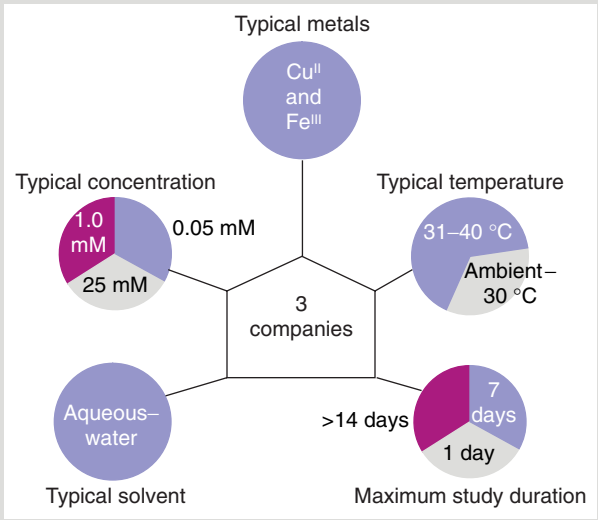

Figure 8: Responses for transition metals.

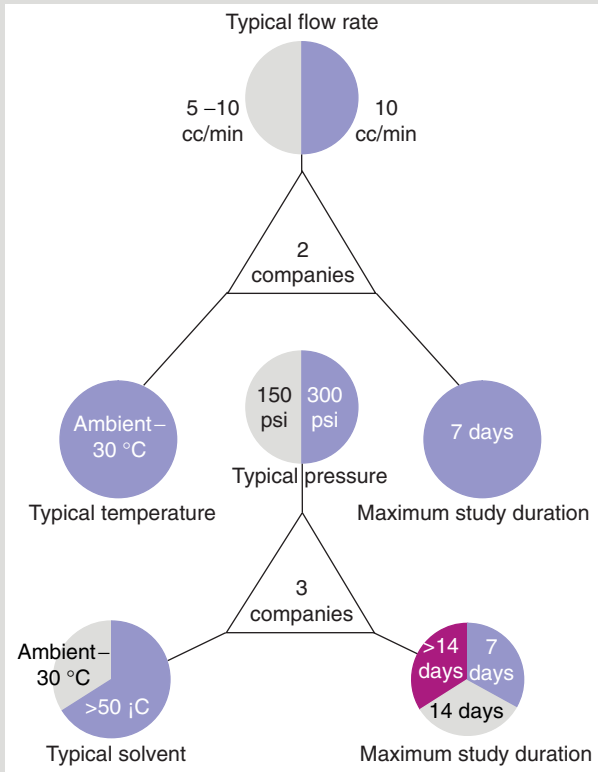

Figure 9: Responses for bubbled oxygen (top) and pressured oxygen (bottom).

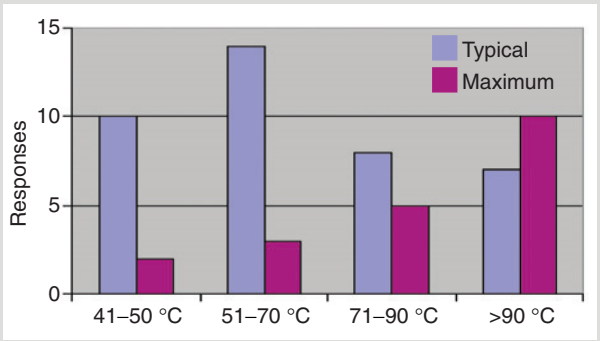

Figure 10: Temperature ranges used to stress samples. Drug substance ($n = 20$).

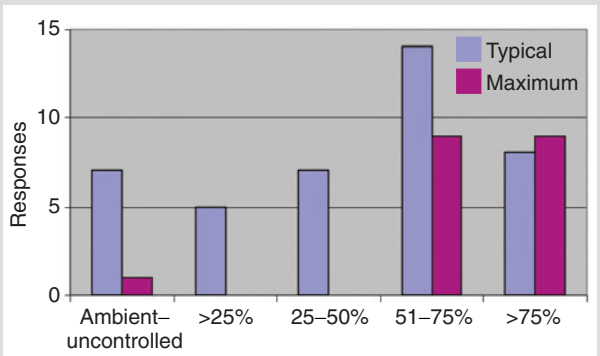

Figure 11: Relative humidity ranges used to stress samples. Drug substance ($n = 19$).

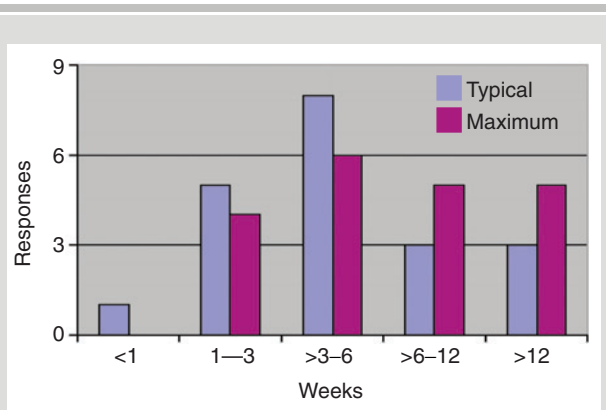

Figure 12: Thermal/humidity duration used to stress samples. Drug substance ($n = 20$).

Fourteen companies perform photostability studies on the drug substance in solution. Of these, three companies perform solution photostability stress testing only if the drug will be marketed as a solution, cream, or syrup. Five companies do not perform photostability studies in solution. Four companies expose solutions to more than one pH if the drug substance has ionizable function groups.

In an ICH comparison of Option 1 and 2 (see Glossary) for photostability stress testing:

- Eighteen companies perform photostability studies using an ICH photostability option (only one company does not use either option).
- Ten companies use ICH photostability Option 1 for >70% of their studies

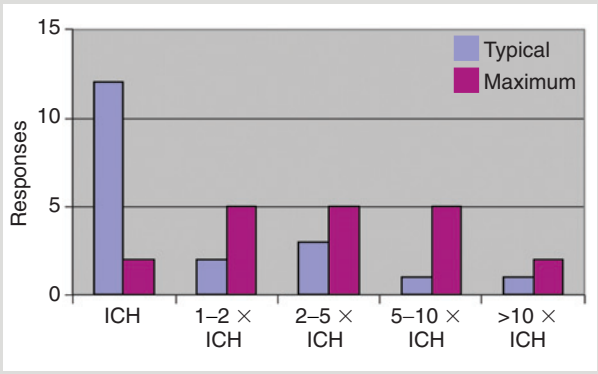

Figure 13: Typical and maximum visible-light dose ranges (ICH = 1.2 million lux h) (n = 19).

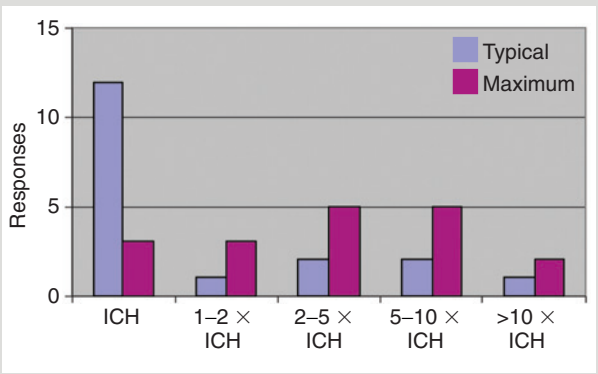

Figure 14: Typical and maximum visible-light dose ranges (ICH = 200 watt h/m^2) (n = 18).

- Six companies use ICH photostability Option 2 for >70% of their studies
- Two companies use both Option 1 and 2 for 100% of their studies.

Sixteen companies perform both stress testing and confirmatory studies. Of these, 81% use the same ICH photostability option for both stress testing and confirmatory studies. Three companies do not perform confirmatory studies.

For Option 1 photostability stress testing:

- Most companies (86%) use the Atlas manufacturer light instrument.
- One company uses a home-built model.
- One company uses a Powers Scientific model.

For Option 2, companies use more manufacturers:

- Three companies use Southern New England Lighting.
- Three companies use Environmental Specialties.
- One company uses Sanyo Gallenkamp.
- One company uses Percival Scientific.
- Two companies use home-built models.

Most companies perform light measurements using radiometers or photometers. Twelve companies use an external model, and seven companies use a built-in model.

Conclusion

Although stress testing has played a critical role in the drug development process, some have called it an "artful science" with a diversity of approaches depending greatly on the experience and background of the scientists who are conducting the studies. Although this benchmarking survey shows significantly diversified approaches among the participating companies, the diversity is not as great as one might expect based on the lack of clear guidance in literature or in regulatory guidelines. For example, it appears that most companies attempt to induce 5–20% degradation while limiting how harshly they will stress drugs (e.g., maximum temperatures, maximum and minimum pH conditions, and maximum length of time). On the other hand, the temperatures, pH conditions, and the duration of studies appear to vary considerably. Most companies are using high-performance LC with UV detection as the primary analytical methodology for stress testing studies. Fourteen companies indicate that they attempt to identify the major degradation product that occurs during stress testing, and three companies indicate that they only identify those stress testing degradation products that also are formed during formal stability studies at levels approaching or exceeding the ICH impurity threshold limits.

The authors hope that this survey will provide useful information to the pharmaceutical industry about conducting stress testing studies. It seems likely, however, that this survey will raise additional questions for the interested pharmaceutical researcher. The authors of this article recognize this potential and have proposed a follow-up conference specifically focused on stress testing.

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Reference

1. D.W. Reynolds et al., "Available Guidance and Best Practices for Conducting Forced Degradation Studies," *Pharm. Technol.* **26** (2), 48–54 (2002).
2. ICH Guideline, "Stability Testing: Photostability Testing of New Drug Substances and Products," November 1996. PT

FYI

Improved site security

Members of the Synthetic Organic Chemical Manufacturers Association (SOCMA) formally adopted the Security Code of Management Practices as part of SOCMA's Responsible Care program. Implementation of the new security code is now a condition of membership.

To help member firms implement the new security practices, SOCMA developed an on-line chemical-site Security Vulnerability Analysis methodology and a computer-based model to help enhance existing security efforts at batch and specialty chemical manufacturing facilities. The tools can be downloaded by members and nonmembers at no charge from SOCMA's Web site, www.socma.org.