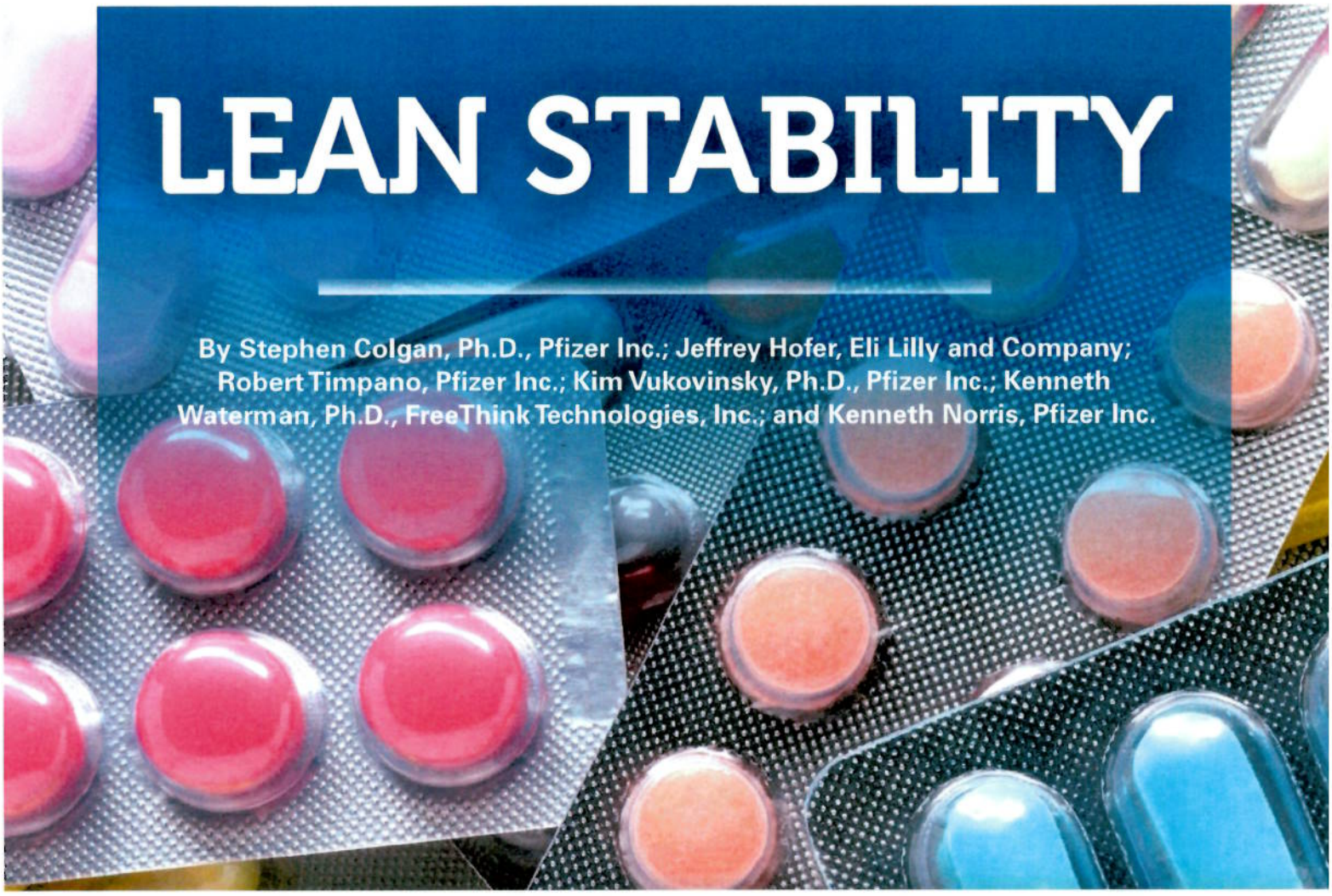
# LEAN STABILITY

By Stephen Colgan, Ph.D., Pfizer Inc.; Jeffrey Hofer, Eli Lilly and Company; Robert Timpano, Pfizer Inc.; Kim Vukovinsky, Ph.D., Pfizer Inc.; Kenneth Waterman, Ph.D., FreeThink Technologies, Inc.; and Kenneth Norris, Pfizer Inc.



We know so much about the manufacturing process, our product, and its stability, that when it is properly packaged and stored, we can guarantee that the product will be within specification at the end of shelf-life, and testing to prove it is not justified. Quite a bold statement! Industry is moving in this direction, away from the practice of overtesting "just to be sure," and a lean stability philosophy is a vehicle to move this forward.

A lean stability strategy is science- and risk-based, providing focus on meaningful attributes and time points. A lean strategy could include technical adjustments to stability protocols or strategies to improve efficiency and expedite results without impacting safety, efficacy, or quality of the product. It does not reduce knowledge or put the patient at risk. Lean stability strategies could result in less frequent and/or delayed pull points, fewer stability conditions, and streamlined analytical test profiles that focus on the individual product's stability-related quality attributes (SRQAs) and ideally include only the shelf-life limiting attributes (SLLAs). Lean strategies can facilitate the development and approval of new and improved medicines by emphasizing the key elements that contribute to quality, safety, and efficacy while deemphasizing elements that do not.

Although lean stability is not specifically mentioned in regulatory guidance, International Conference on Harmonisation (ICH), World Health Organization, and other guidance do permit alternative approaches if adequately justified. Lean stability strategies do not represent any deviation from what is currently allowed and represent an evolution of thinking, not a revolution.

## LEAN STABILITY STATISTICAL CONSIDERATIONS

Leaner stability studies allow companies to focus resources on the quality attributes that are the most informative about product quality, i.e., where the amount of change with respect to the specification limits is large relative to the measurement uncertainty, and thereby provide the best discrimination of potential changes over the shelf-life.

Traditionally, many quality attributes have been monitored on stability. Some attributes display little or no change, which indicates that the attributes are consistent over time. If a quality attribute is very stable or the change is very small relative to the measurement variability, the probability of generating an out of specification (OOS) event is essentially the same when tested at the time of manufacture and at each subsequent stability test point. It is desirable to reduce the stability testing as it provides little insight into product quality and only increases the potential for a random OOS result. Such OOS results are often due to tight specifications relative to measurement variability and likely have no assignable cause, yet these situations must be thoroughly investigated, which

*The Analysis and Pharmaceutical Quality section submitted this article.*


adds complexity and burdens the quality system. For such attributes, stability trending is not value added; a lean effort focuses on analyzing historical data, identifying stable attributes, and removing requirements on continued data collection. These attributes can be identified at the time of filing or for products on the market. For attributes with historical data that do not change over time, a statistical analysis can assist in providing quantification of the risk of decreasing or discontinuing testing of the attribute. Monitoring of drug substance assay provides a common example of this case.

In another case, the amount of variability in the attribute might be large, resulting in only substantial changes in stability being reliably detected. For example, consider a very stable small molecule drug product. Regulatory criteria for drug product assay are commonly 95.0–105.0 percent of label claim. For measurement of assay, even with composite analyses to average the content uniformity variability, a method standard deviation of 1.25 percent is not uncommon. Historical stability data can be used to provide insight on the fundamental stability of the assay attribute and to confirm that there is low likelihood of an OOS result. However, continued monitoring of the attribute in an attempt to identify changes in product quality is inefficient. Rather, an attribute that is more precise, such as the degradation product test, would be more useful to identify changes in product quality. If a new degradation product peak of a magnitude such as 0.2–0.4 percent were to grow or the growth of existing peaks were to increase by such an amount, it would be nearly impossible to confidently identify this true stability change with the assay. However, this same increase of 0.2 percent in a degradation product would be readily detected by the impurity test, where the standard deviation is often less than 0.05 percent. Given this, it makes little statistical sense to perform the assay test on stability when the goal is to detect such small (but important) potential changes. The lean stability approach would remove measurement of assay on stability and focus on purity or degradation. Similar rationales for limited or modified stability testing could be made for other common attributes.[1]

Additionally, design of stability monitoring studies could be modified. The traditional stability test time points—every three months during the first year, then every six months the second year, and annually thereafter—may not be the best time points to test. Depending upon the goals of the stability protocol, the specific risk profile of a given quality attribute, the amount of measurement variability, and the magnitude of the stability change over the shelf life, the early time point testing may have limited ability to detect meaningful stability profile changes.

To this end, establishing a good initial starting value for a quality attribute by adding two or more independent tests at the initial time point could be considered. This additional up-front testing can lead to

| Packaging | Storage Conditions | Percentage of simulations where degradant <0.50% at 2 years |
|---|---|---|
| 60-cc HDPE bottle, 20 tablets | 25°C/60%RH<br>30°C/65%RH | 100.0%<br>82.5% |
| 60-cc HDPE bottle, 20 tablets + 0.5 g silica desiccant | 30°C/65%RH | 100.0% |
| 60-cc HDPE bottle, 60 tablets | 25°C/60%RH<br>30°C/65%RH | 100.0%<br>100.0% |

**Table 1. ASAP*prime*[3] calculations on a drug product (tablet) showing that the impact of different packaging and storage conditions can determined.**

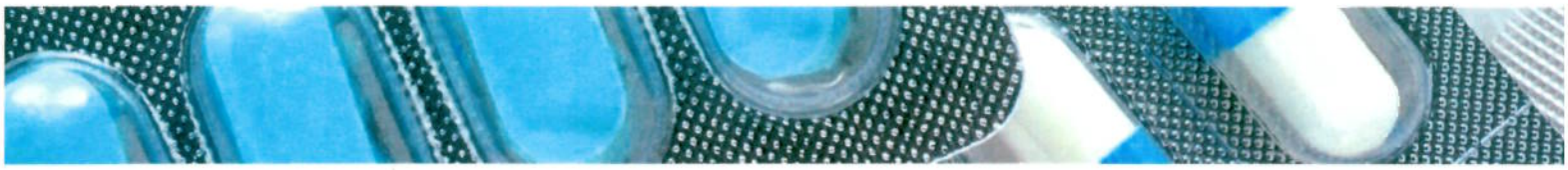
the elimination of one or more subsequent time points with little or no loss in the quality of the estimate of stability change. In fact, testing later in the stability protocol may have more likelihood of reliably identifying that a change has occurred; increasing time provides the best chance that the difference is larger relative to the test variability. Here, a reduced number of and alternative testing pull times could improve the ability to estimate the change across the stability program and allow for a better use of limited storage and analytical resources. These considerations, however, must be balanced against regulatory expectations, which vary between regions.

## SCIENTIFIC STABILITY MODELING AND LEAN STABILITY

The Accelerated Stability Assessment Program (ASAP) has gained broad acceptance as an alternate, more scientific process for determining shelf life. In this approach, unpackaged drug product samples are exposed to a range of controlled temperature (T) and relative humidity (RH) conditions designed to push the material to its failure point based on the specification limits. This "isoconversion" process allows propagation of the failure time (shelf life) to other conditions independent of the actual kinetic form of the degradation involved. Isoconversion enables very accurate stability modeling across a wide range of temperature conditions, provided there are no phase transitions within that range. A second factor for solid dosage forms is the use of the moisture-modified Arrhenius equation shown below.[2]

$$\ln(1/\text{isoconversion time}) = \ln A - E_a/(RT) + B(RH)$$

Here isoconversion time is the time to exceed the specification limit at each T and RH, A is the collision frequency, $E_a$ is the activation energy, R is the gas constant, and B is the humidity sensitivity factor. Solving this equation enables the explicit T and RH dependence of stability-indicating changes to be determined. Moreover, since the in-package RH as a function of time can be accurately modeled (using the moisture sorption isotherm of the drug product, any desiccants, and the package permeability), the behavior in packaging can be accurately predicted.



An ASAP experimental design ranges from a minimum of five conditions with one time point at each condition (appropriate for screening of solids) to more commonly eight conditions with three time points at each condition. Often the tests are conducted in a period of two to six weeks, with all samples analyzed as a batch to reduce the measurement variability. The measurements can involve such attributes as growth of degradation products (related substances), loss of potency (assay), color change, and in some cases, change in dissolution. Once data are generated, commercial software[3] or internal calculations can be used to provide an estimation of the confidence that a specification limit will not be exceeded at the end of shelf life with a given packaging and storage condition.

ASAP uses a large amount of data at designed conditions to model the behavior of drug substances or drug products with respect to stability. In many cases, the ASAP modeling is validated against long-term (in-package) data showing that the model is in fact reliable with that particular product. The intersection with lean stability comes from the product understanding inherent in this scientific and statistical modeling: the impact of specific packaging, storage conditions, and excursions can all be calculated with confidence without additional experiments. In addition, the impact of any process or raw material changes can be rapidly assessed by comparison with the original ASAP model. Lean stability using ASAP allows for the elimination of testing of a drug product in multiple packaging and storage conditions when the science allows confident determination of the outcome of these changes. As an example, Table 1 shows the impact of a drug product having a high RH sensitivity (high B term) stored in bottles with different sizes and different tablet counts at two different storage conditions. Once the model is validated, a company should be able to make changes to the packaging provided those changes do not decrease the shelf life below a threshold of 95 percent probability.

Another potential benefit of ASAP is that a company developing a new drug product could get that product into the clinic earlier using the model calculations to identify which shelf life limiting attributes are appropriate for stability tests to monitor and to justify a use period for the clinical supplies. Figure 1 highlights that, based on the ASAP predictions, there is little change in assay over time (though as discussed above, the variability in assay measurements can give random failures, especially for lots released near the lower limit of the stability specification), while formation of a degradation product could breach its specification limit depending on the specific storage condition and packaging.

## HOW LEAN STRATEGIES ARE USED IN PRACTICE

Throughout clinical development of a new chemical entity, lean stability strategies have been used in clinical trial applications (CTAs) leveraging science- and risk-based approaches. Examples of these strategies include:

- minimizing or eliminating non-value-added tests, conditions, and pull points on stability;
- leveraging scientific modeling tools and data from accelerated studies such as ASAP in lieu of traditional ICH-like stability data to assess changes in drug substance and/or drug product manufacturing and packaging configurations to determine if additional stability studies are needed; and
- use of ASAP data and modeling in lieu of traditional real-time stability data to underwrite initial clinical use period assignments and storage conditions in CTAs, while continuing to monitor stability on clinical supplies to confirm and extend use period assignments.

The lean stability strategies noted above have been used in CTAs for more than five years in many regions including the United States, Europe, and emerging markets. These lean stability approaches "have been widely accepted by regulatory agencies in varying countries/regions through the standard CTA filing and query response process." Further collaboration between industry and regulators is needed to advance the acceptance of lean stability strategies throughout the development lifecycle.[4]

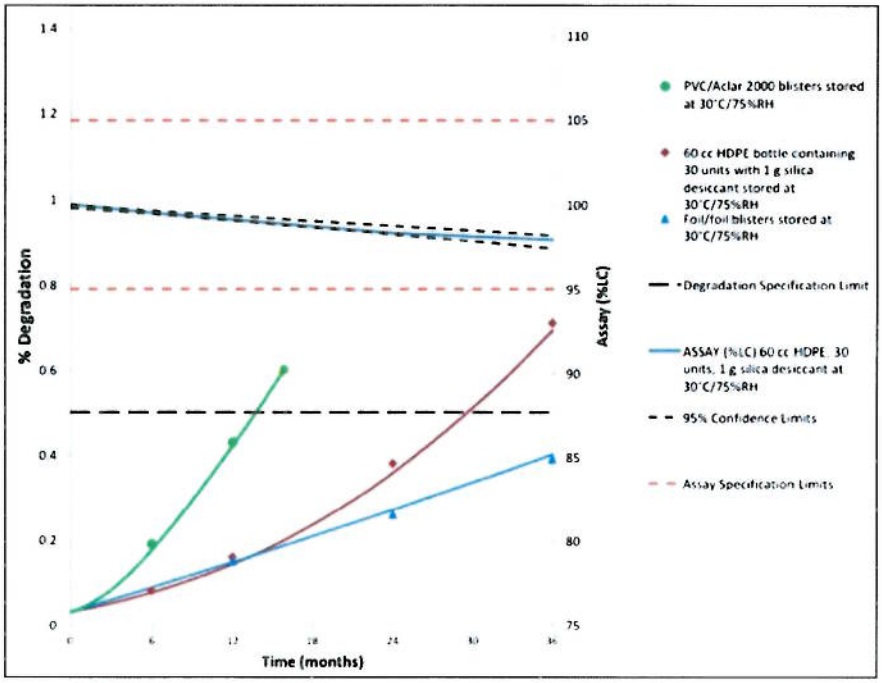



**Figure 1: ASAP-calculated and real-time measured values for a drug product over a three-year time period.**

# LEAN STABILITY

For registration stability studies used to support a product's commercial application, lean stability studies can potentially allow applicants to leverage long-term and model data to demonstrate that certain factors do not in fact influence the product shelf life. Examples of this include changes in dosage form shape, color of coating, excipient source, packaging changes, scale of manufacturing, and other minor processing changes. Both lean and traditional stability studies are designed to confirm and support the applicant's understanding of a product's stability behavior while also de-risking regulatory concerns. Bracketed and matrixed strategies (strengths, lots, markings, container closure combinations, etc.) are examples of lean stability strategies that have been used for years in certain regions/markets. With the advancement of more sophisticated modeling such as ASAP, the implementation of quality by design, and increased use of statistical methods, greater use of lean stability approaches in the future are anticipated. In addition, with the wealth of stability knowledge gained during development, the applicant should be in a better position to support lean postapproval stability commitments, if warranted, and to support justification of extended shelf-life assignments at approval when limited real-time data (e.g., six months) is available at the time of the filing. This becomes important for breakthrough therapies, which will need supply chains that can reliably and consistently provide medicines critically needed by very sick patients.

Since 2012, lean stability strategies have been used in global commercial applications for several products. The understanding of the SRQA and SLLA obtained during development and confirmed at registration facilitated lean proposals for the following examples.[2]

- For stable drug substances, appearance and purity were the only tests proposed for the first three commercial batches as well as the annual stability commitment, since these were demonstrated to be appropriate SLLA. In addition, only annual testing at the long-term storage condition was proposed. Global acceptance of the lean protocol was received for one compound, while there was mixed feedback received for a similarly stable second drug substance. Two boards of health mandated inclusion of active pharmaceutical ingredient (API) assay as part of the postapproval protocols.
- A stable solid oral drug product with 24 months of real-time stability data was filed. Based on the confirmed SLLA, the only proposed testing for both postapproval and annual stability commitment protocols were appearance, degradation products, and dissolution. In addition, the stability protocols included only annual testing starting at twelve months. While the strategy was accepted by the vast majority of regions/markets, some markets required the addition of several early time points and storage conditions as well as a mandate to include both assay and microbial testing.

## CONCLUSIONS AND PATH FORWARD

Lean stability concepts can be applied at all stages of development (clinical, at registration, and postapproval) and to all product types (API, drug product, small molecules, biologics, vitamins, etc.). For products with a rich historical database, the ability to evaluate which quality attributes provide the most discriminatory power to identify stability changes can be established via analysis of these data. Attributes whose values remain consistent over time could either be eliminated from stability testing or significantly reduced in their test protocols. While the regulatory acceptance of these strategies is variable, industry and regulatory authorities should collaborate to advance these concepts, as all parties will ultimately benefit.[5]

## DISCUSSION POINT

We want to know your opinion!

Please discuss the following question with your colleagues via the *AAPS Blog*. To find the blog entry associated with this article, visit http://aapsblog.aaps.org/tag/aaps-newsmagazine.

*What challenges do you see related to the use of lean stability strategies in regulatory filings, and how would you address them?*

Learn more about the AAPS Analysis and Pharmaceutical Quality section; visit the section's webpage at www.aaps.org/APQ.

## REFERENCES


1. Gorog S. The sacred cow: the questionable role of assay methods in characterizing the quality of bulk pharmaceuticals. *J Pharm Biomed Anal.* 2005;36(5):931–937.
2. Colgan ST, Timpano RJ, Diaz D, et al. Opportunities for lean stability strategies. *J Pharm Innov.* 2014;9:259–271.
3. ASAPprime software is available from FreeThink Technologies, Inc.
4. Freed AL, Clement E, Timpano R. Regulatory responses to the use of various lean stability strategies in early drug development. *Regul Rapporteur.* 2014;11(7/8):5–8.
5. The IQ Consortium (https://iqconsortium.org) has endorsed the formation of a new ASAP Working Group which has a goal to facilitate the identification of best practices related to ASAP and to work to align expectations between industry and the regulators.