packaging

Stability modeling and package selection

Matthew Knopp
Editor

To save time and get to market faster, pharmaceutical manufacturers use computer modeling and simulations that assess product stability and propose packaging options.

There's no getting around stability testing. To gain FDA approval, every drug product must be tested according to protocols established by the International Conference on Harmonization (ICH). Those tests can take 6 to 18 months or even longer if the manufacturer is seeking a longer shelf-life for its product.

Computer models and simulations, however, can predict product stability and recommend packaging in weeks. Many large manufacturers conduct computer modeling in-house, while others seek help from specialists, including Bilcare Research of Delaware City, DE; FreeThink Technologies of Branford, CT; and Multisorb Technologies of Buffalo, NY.

Bilcare

Ajith Nair is head of research at Bilcare, a supplier of barrier films for blister packages. He developed the company's stability modeling service, BilcareOptima, in 2001. "When we started our research, we focused on what I call the drug stabilization process. We wanted to quantitatively understand the environmental variables that are causing the drug deterioration and then develop a package that will prevent the product from reaching that level of failure."

Moisture, light, oxygen, temperature, and time are the primary factors that lead to degradation, and the Optima service quantifies each factor's influence on the physico-chemical properties of tablets and capsules through forced degradation studies. With that data, Bilcare can predict how the product will perform in stability tests and real-time conditions and recommend packaging. The process takes about 6 weeks, much faster than real-life stability tests. "Why go into a stability study with a blindfold?" Nair said. "Why use a trial-and-error method to understand what package is going to stabilize a product when you can use a service and identify the optimum package?"

From modeling in excess of 400 formulations, Bilcare has learned that in more than 95 percent of the cases, products fail due to their physical attributes before they fail due to their chemical assay or impurity profiles. "That makes packaging development easier because doing so many chemical analyses is the most difficult part of any project." They're also expensive and have become unnecessary in determining the package, he said. "Without doing the chemical analysis, we can still develop the optimal package that's going to pass the stability study in all respects.

"We take a holistic approach to the drug stabilization process, which is more than just predicting the failure in chemical assay or in the impurity level using Arrhenius or modified Arrhenius equations," Nair said. "We study all the physical attributes—hardness, friability, drug release, disintegration and dissolution times—and define critical quality attributes of the product." He said that the FDA is focused on assay and impurity, "but they don't like it when a product fails to release the drug properly even if the assay is correct."

Degradation studies and package modeling also align with Quality-by-Design principles. "The FDA is saying to incorporate your quality not by testing but by understanding the process, understanding why you select a specific package. The report that we provide is in line with Quality by Design, and customers use that in their filing."

Currently, regulators won't accept modeling results as a replacement for real-life ICH stability studies, but they will eventually, Nair said. "There is a long way to go but if they're really looking to speed up development, then they have to do it. It's a way to reduce healthcare costs by reducing the cost of manufacturing the medicines."

Companies also want to understand whether temperature or moisture excursions will impair their products.

Other kinds of modeling are also gaining acceptance, including for dissolution. "It's not just about assay. If your product becomes hard and it does not dissolve on time, that's a failure. Especially with a blister pack: If the hardness goes below the push-through force of the product and it breaks when patients push it through, that's a failure. I'm happy to see people working on [models for] that."

Bilcare also offers FastPack, a package-design service that takes just 15 days. "The customer doesn't have to do anything except send us the tablet," Nair said. After that, the company provides the package's specifications and a drawing of the tooling required to make it. The barrier properties of the film are paramount, but the size and shape of the tablet also influence its in-package stability. "If you use the same film formed in a different way or drawn to different sizes, then you end up getting a different barrier," Nair said.

Even small differences between the R&D and commercial packages can be important. "It can happen when you develop the package using an R&D pilot machine, do the stability study, and then write a [blister] specification on that basis," Nair said. "Then, when the production batch is run on a commercial machine using a different tool, the stability can fail, and they wonder why there's a problem, so they come to us. What we find is that the moisture permeation of the formed cavity was different from what they used for the stability study, even though the film had the same specifications." The Optima and FastPack services are available to any company.

FreeThink Technologies

Founded by Ken Waterman in 2011, FreeThink Technologies offers its stability and formulation modeling software, ASAPprime, under license. Or it will do the work in-house on behalf of customers. The focus is on the product, not the package, Waterman said. "The package is important but it's only one of the things you might do with [the data]. You might want to see whether your generic product is as good as the originator. Or is a tablet as good as a capsule? Or is this capsule better than that capsule? It's not just packaging that people are interested in, but 'What formulation should be used? How do we make a tablet?'"

That requires understanding a formulation's excipients. "We offer a process so you can make a tablet or capsule formulation in a much shorter time than the traditional way," Waterman said. "We don't do excipient compatibility studies the old-fashioned way, so we've been able to speed the process up significantly." Results are typically ready in 3 weeks.

By using data based on a range of exposure conditions, FreeThink's modeling often represents reality better than extrapolations from long-term stability tests, Waterman said. Those tests, he said, can be "noisy" because each analysis is done independently and often involves different analysts and instrumentation. ASAPprime is also more accurate because it doesn't assume linearity, as the ICH tests do. "They assume whatever happened in 6 months you can just double and see what would happen in 1 year,

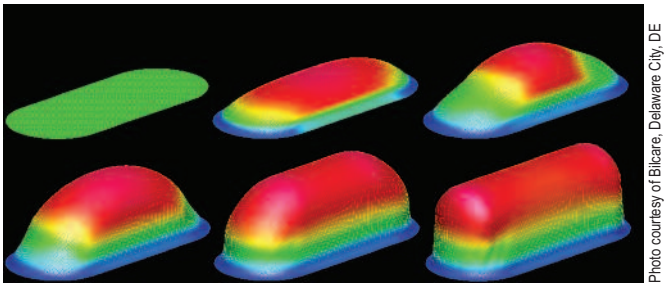
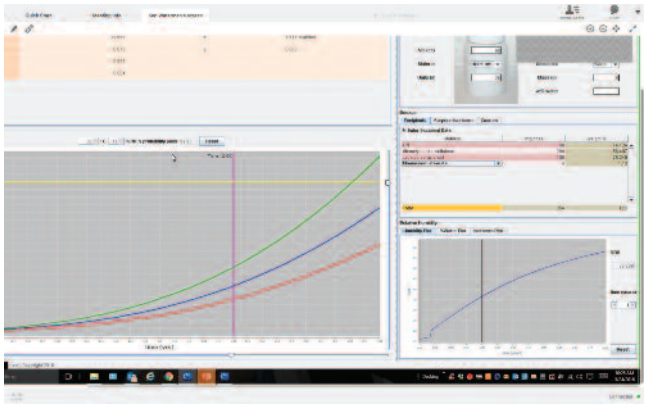


Photo courtesy of Bilcare, Delaware City, DE

Bilcare's Optima service identifies what packaging is needed to preserve stability. Its FastPack service specifies the package and designs the tooling required to form the blister.



A screenshot of FreeThink's ASAPprime modeling software.

which is not correct." He also said ICH tests allow too much variability in the ranges: ±2°C and ±5 percent humidity. "A 10 percent humidity range is dramatic. We're much more careful about it."

FreeThink operates several environmental chambers to conduct long-term testing in its lab, but Waterman predicted that modeling will change how formulation and package development are undertaken and reduce the number of candidates in stability studies. "A number of companies have stopped doing package screening. They just call it package confirmation," he said. "You still need to do long-term stability, but instead of doing five or six configurations of different packaging, you do one or two. That saves a lot of money."

Understanding how unexpected temperature or moisture extremes affect the product can also save money, he said. "Companies like to understand what happens if there's an excursion. Maybe initially it was at 22°C, 50 percent humidity for 60 days and then on day 61 it went up to 52°C at 78 percent humidity for a week. At that point, companies don't know whether the product is still acceptable, so they often discard it and sacrifice the money. We can give them support to make a better decision one way or the other." While it doesn't offer packaging, FreeThink's has marketing agreements with Klockner Pentaplast, a supplier of barrier films, and Clariant, a supplier of desiccants.

Multisorb Technologies

Multisorb Technolgies sells desiccants and oxygen absorbers, as well as equipment that inserts them into the final commercial packages. Its testing services are free of charge to customers. "We will recommend a solution based on the options that we provide," said Chris Gilmor, the company's commercial director, Americas, for healthcare.

Its modeling is based on the same science that other companies use and is reliable. "We've provided simulations for over 1,000 different packaging presentations, and the FDA and our customers have gotten very comfortable with our recommendations," Gilmor said. He said repeat customers have used its recommendations to go directly to registration batches. The company can simulate the performance of any packaging, including bulk packages and blister packs, and the results are usually ready in a month.

Multisorb relies on the customer to provide information about its proposed packaging, such as bottle drawings that show surface area, wall thickness, and the moisture vapor transmission rate (MVTR) of the polymer resin or barrier film. HDPE bottles are the most common type, but if a customer is unsure about what package it will use and wants simulation data quickly, Multisorb's simulations can be based on industry-standard bottle designs and blister films.

The customer typically supplies samples of the tablet or capsule so Multisorb can generate empirically based data to use as inputs. If the active is a controlled substance, a placebo that includes everything but the active will suffice, Gilmor said. Or Multisorb will tell customers how to test the product and have them send the data file to Multisorb.

Gilmor said Multisorb's work figured prominently in a customer's success in formulating a generic version of a blockbuster drug product. "The API was off patent so everyone could make a generic version," he said. "But there was still another patent on the organic acids used to stabilize it." To get around that patent, Multisorb spent a month on simulations and demonstrated a different way to stabilize the drug product. As a result, its customer won 6 months of exclusivity in a market valued at more than $1 billion.

Customers also ask Multisorb to reevaluate packaging. "If there is any change to a packaging presentation, people often come back and reevaluate that with us," Gilmor said. "Or maybe you need to evaluate a different ICH climatic zone. While a product normally sold in Canada and the USA may not use a desiccant, once it's sold into Mexico or farther south, it could need one."

Changing the tablet count or using a bottle with a different wall thickness also justifies reevaluation. Gilmor said physician's samples are among the most difficult to stabilize because they contain few tablets. "You can have the same amount of moisture coming in your bottle but it might be affecting five tablets versus 30 tablets." Customers also reevaluate the package if they learn of problems in the field or if they decide to source their packaging materials from a different vendor. *T&C*

Photo courtesy of Multisorb, Buffalo, NY

Multisorb supplies desiccants, oxygen scavengers, and the equipment to insert them.

Bilcare Research, Delaware City, DE.
Tel. 302 838 3200
www.bilcaresolutions.com

FreeThink Technologies, Branford, CT.
Tel. 860 237 5800
www.freethinktech.com

Multisorb Technologies, Buffalo, NY.
Tel. 716 824 8900
www.multisorb.com