DESIGN OPTIMIZATION AND RAPID PROTOTYPING SOLUTIONS FOR BLISTER PACK DESIGN, DEVELOPMENT, AND TESTING

a four-part series of white papers

INTRODUCTION

The first paper in this series gave an overview of the new tools and strategies in blister pack development and testing that make rapid prototyping of package designs possible. Rapid prototyping allows pharmaceutical companies to save time and money, and to speed their products to market, by greatly accelerating progress from initial design through stability shelf tests in blister packaging. In subsequent papers, we will discuss the new generation of virtual design tools, and the new generation of blister machines that accelerate prototyping. In this paper, we discuss an essential and innovative first step that lays the groundwork for that acceleration.

Good packaging design, design that anticipates and addresses the product requirements for stability performance (and that speeds the development and testing), depends on good information going in. With detailed information about product susceptibility to moisture and oxygen exposure under various conditions, packaging designers can move much more briskly toward materials and designs that meet the demands of the product application. A major new development in product stability evaluation is now making that kind of detailed pre-design knowledge possible.

In the first paper, we described the packaging performance parameters for an example pharmaceutical product:

Specification for Lozenge
Highly Moisture Sensitive (Estimated permeability < 0.5 mg/day at 40°C & 75% Relative Humidity storage)
Highly Oxygen Sensitive (Estimated permeability < 2 mm3/day at 23°C & 50% Relative Humidity storage)
Highly Light Sensitive (Sensitive to light in the 290–450 nm range)

The current paper gives the background on how stability parameters like these have traditionally been developed, and how innovative new approaches are now making them more refined, more exacting, and more fully integrated into the process of package design and prototyping.

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PAPER II:
ACCELERATED STABILITY ASSESSMENT OF DRUG COMPOUNDS FOR PHARMACEUTICAL BLISTER PACKAGING

TRADITIONAL REAL-TIME TESTING

Stability testing is an ongoing consideration in the drug development process, often taking place in real time over the course of years as the drug is developed and put through trials. As part of that process, pharmaceutical manufacturers must assure the public and regulatory authorities that a drug product at the end of its labeled shelf-life is still safe and effective. To meet these obligations, manufacturers have employed a range of strategies. Traditional procedures for conducting stability testing involved using real-time, massive line studies that would subject the products to a range of temperatures and relative humidities over a range of timeframes. In order for the product to meet approval guidelines, each country authority expected data for very specific conditions. In order to test a drug product for stability issues, generating appropriate data could take in excess of six months. Establishing the actual shelf-life could take more than two years.

Another factor slowing time to market was the fact that separate testing runs were necessary for different stages of drug development. Since the packaging for a drug product in the clinical trial phase is often modified as the product is registered for commercial use, further time-consuming stability testing is often carried out at late stages of product development. Also, since new product registration requires commercial line packaging, examining multiple packaging options to maximize performance while minimizing cost can be quite expensive.

ASAP

Stability protocols, such as those defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), were developed to bring consistency across different regulatory agencies and thereby speed some of those testing times. As part of the ICH standards, drug products can be exposed to moderately more extreme conditions, and those accelerated conditions can be taken as standing for longer exposures under actual storage conditions. For example, testing for six months at 40°C and 75% Relative Humidity might be equivalent to two years at 25°C/60%RH. But these "accelerated" guidelines were not necessarily science-based, and, ultimately, the product must still pass acceptance criteria at the prescribed storage conditions.

It has recently become understood that these ICH "accelerated" protocols can be improved upon, both in terms of speed and scientific accuracy. In 2011 a Connecticut company named FreeThink Technologies came on the market with laboratory services and a software product called ASAP*prime*® that represented a major step forward in stability assessment of drug substances and drug products. The software was developed by FreeThink founder and CEO Dr. Kenneth Waterman, a senior research chemist with a dozen years' experience working on drug stability and the science underlying ASAP (Accelerated Stability Assessment Program) while at Pfizer. Waterman's ASAP*prime*® software utilizes laboratory-derived data to construct a robust statistical stability model of the drug product or substance in question. According to Mark Kastan, co-Founder with Waterman of FreeThink: "Ken studied the existing science and came up with some insights using his breadth of knowledge about physics,

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chemistry, and statistics. What he developed was a new approach that can get the customer a better answer in 2 to 4 weeks than could be gotten in the 6 to 12 months of traditional stability assessment."

One of Waterman's key innovations is to increase the temperature stress on the substance being tested while controlling and monitoring the relative humidity exposure. Kastan points out the way that FreeThink addresses one of the central questions of accelerated protocols: "What do people mean by accelerated conditions? Most people in the industry are referring to accelerated conditions at temperatures between 25° and 40°C. Whereas we play in the 60° to 80°C range." That increase in the environmental stress brought to bear on the product means less time is needed to produce results that can be modeled as predictions.

FreeThink's ASAP*prime*® also takes in to account more than just temperature effects. "The other issue in accelerated protocols, and this was Ken's major insight, is the effect of humidity," says Kastan. "Most people will stress the product at 30-40°C in packaging. Whereas in what we do the product is open to the conditions, the temperature and the humidity, and that's where we get the data to form the model."

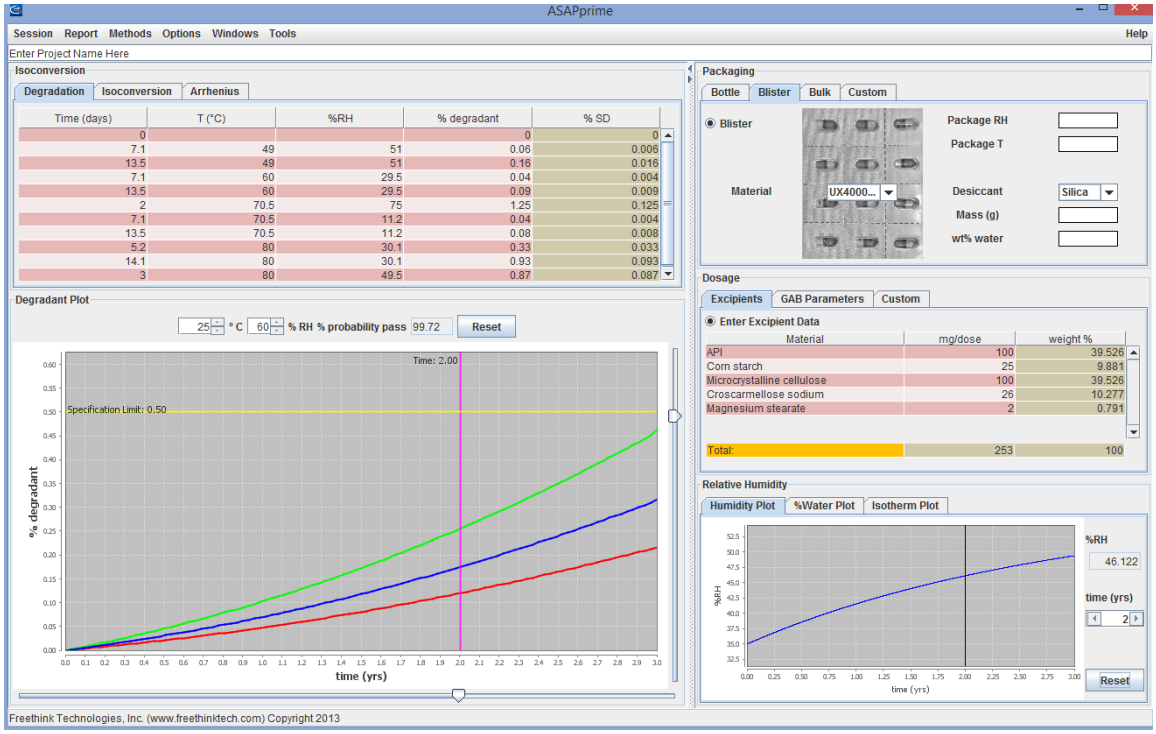

Figure 1: FreeThink's ASAPprime® software models moisture levels over time with a given packaging and storage condition, then couples this with the product's specific moisture sensitivity to statistically determine the shelf-life.

The resulting data are produced more quickly, and contain a richer set of data points than traditional testing can produce. The final step in the FreeThink approach is to bring to bear sophisticated statistical modeling to work with that data. An example of the output is seen in Figure 1, above. In this example, based on a two-week ASAP study, a product stored in Pentapharm® ACLAR® PA400/02 blister packaging is shown to have a probability of passing a two-year shelf-life at 25°C/60%RH of 99.7%.

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ASAP*prime*® stability modeling can be keyed either to the degradation of the drug into secondary substances, or to the predictions can focus on loss of potency. The software was designed to model and evaluate either of those pathways. "After we have stressed the drug product in various temperatures and humidities," says Kastan, "we are looking for either formation of degradant or loss of potency. We measure that after the stress period is over, and use that combination of temperature, humidity, time to form a statistical model using ASAP*prime*®."

FROM EARLY PHASES TO PHASE 4

Until very recently, accelerated stability assessments had been used exclusively for evaluating the viability of a compound as a pharmaceutical candidate. At the early phases of the drug development process, pharma scientists actively explore the possible therapeutic applications of a candidate molecule, its appropriate formulations, its possible delivery mechanisms, and, eventually, its efficacy in human trials. Part of that evaluation is to understand the molecule's stability—how long before its effectiveness degrades, what environmental conditions can it tolerate, does it react with any potential excipients to produce unwanted secondary substances? Mark Kastan explains that FreeThink's original goal was to speed drugs at this state of development: "the first focus was on early stage development—how to get a product into Phase 1 and Phase 1a sooner."

Packaging engineers have traditionally come into the process of drug development later in phase 4 as the marketing for the product was being developed. Since their work was considered primarily a marketing function, they did not necessarily have access to the stability information generated by earlier phases of drug development. This led to duplication, with packaging manufacturers running their own series of stability tests to evaluate package performance.

In 2013, engineers at Klöckner Pentaplast's (kp) Blister Technology Center began to explore the possibility of using FreeThink's testing results to augment their work in speeding development times for package prototypes. According to Daniel Stagnaro, Director of Pharmaceutical Films, America at kp, "for a number of years, FreeThink has been working with some of the major pharmaceutical companies to provide stability testing for early-phase drug development. What we realized was that no one in our market was applying that work to packaging."

That insight has led to a technology partnership between the two firms which brings together the stability modeling of ASAP*prime*® with the blister performance modeling of kp's BlisterPro® software (described in detail in paper 3 of this series). The partnership allows packaging engineers to model and predict blister performance with unprecedented detail and accuracy, in many cases bypassing (or greatly shortening) the need for extended preliminary testing of prototypes.

"We are running the validation studies again, in short form, as we're developing the packaging and before the final stability studies for filing," says Stagnaro. "This lets us validate that the marriage of the packaging solution with the product's properties indeed produces a stable product. At the end of the ASAP*prime*® simulation we can tell you with a very high degree of certainty if this drug product is going to pass stability under specific conditions. This is something that we can do now with a three to four week study and predict the results of a stability test two years in advance."

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VALUE ADDED BY FREETHINK

The introduction of FreeThink's ASAP*prime*® software into the packaging marketplace brings a new level of rigor and speed to the blister development process. Not only does ASAP*prime*® predict drug product stability faster and more accurately, it can also be extended to model interactions between the drug and the packaging materials, or even to model drug degradation by shipping, handling, and storage effects under different environmental conditions.

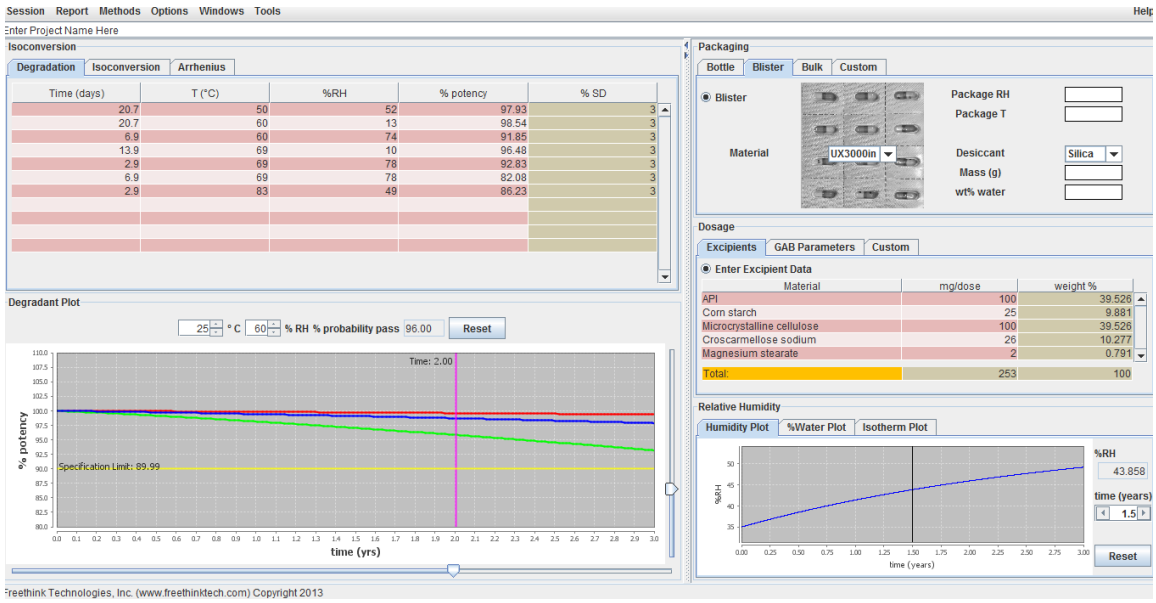

Figure 2: ASAPprime® modeling of potency loss over time. For this product, packaged in Pentapharm® ACLAR® PA300/02, the probability of achieving a two-year shelf-life at 25°C/60%RH is 95.8%.

Making that level of detailed prediction available to packaging engineers allows for a rapid cycle of design iterations as the packaging is being developed. Blister cavity shapes, alternative blister films, blister card configurations can all be prototyped and evaluated virtually, with a minimum of new testing. Blister packs can now be much more precisely optimized for the needs of the drug product application, with the result of more rapid time to market and a more efficient and cost effective package development process. A film manufacturer such as kp offers over 30 types of barrier films for blister packaging, each of which carries different costs and performance. Testing a full range of package prototypes would be prohibitive. With ASAP*prime*®, packaging options can be easily modeled, giving the customer a more timely, refined, and cost effective set of options.

According to Stagnaro, "before FreeThink Technologies, the only way for blister engineers to have stability data for a design was to actually test it. They would shelf test their designs with low barrier, middle barrier, high barrier, and ultra-high barrier films. It was adequate but not optimal. Sometimes, in favor of speed and to reduce testing costs, the customer would choose to over-package—they would buy time with greater expense on materials. And often that expense is high, because over-designed packaging can involve added operations to the process, such as pouches and desiccants, which are unnecessarily expensive." Moreover, this expense will be borne for many years to come. FreeThink, says Stagnaro, has streamlined the blister design process.

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CONCLUSION

In a first-of-its-kind collaboration, FreeThink Technologies and kp's Blister Technology Center have formed an exclusive alliance to bring accelerated stability assessment models fully into the package design process. This allows packaging engineers to begin the process of blister design with considerable detailed knowledge about the drug product and about the barrier performance required of the packaging. It minimizes the need for time-consuming line testing of package prototypes, and it allows for virtual modeling of package performance. That new potential for virtual prototyping, a marriage between FreeThink's ASAP*prime*® and kp's blister design software BlisterPro®, is the subject of the next paper in this series.

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