ASAP*prime*® Software

Software to Speed Product Development and Minimize Risk

- **ASAP***prime*® is a software package available from FreeThink Technologies, Inc. The software is based on the Accelerated Stability Assessment Program (ASAP) and uses experimental data modeling to accurately determine the shelf-life of products in very short time periods.
- **ASAP***prime*® comprises **ASAP***design*™ and the main user interface.
- **ASAP***design*™ is a wizard which leads the user through questions aimed to provide an experimental plan for an ASAP study of a specific product.
- This plan is based on product knowledge, design space limitations of temperature and relative humidity (RH), data precision required, time available, and the number of samples chosen to be analyzed.
- Once the study is carried out, the results are input into the main program to build a mathematical model of the product behavior.
- The modeling uses a statistical and scientific fitting process to provide the user with the probability that a product will remain within its stability-indicating specification limits at the designated shelf-life time, based on the selected storage conditions and packaging options.
- **ASAP***prime*® differs from forced degradation since it is designed for predictive shelf-life determinations (modeling) rather than for a test of analytical method appropriateness.

ASAP*prime*® Licenses

- **ASAP***prime*® is the industry standard for pharmaceutical accelerated stability modeling and is currently licensed by the majority of large pharmaceutical companies.
- The software is fully validated and compliant with CFR Part 11 regulations. User data are isolated since the program is installed and runs locally on customer PCs. Active licensees receive all updates at no additional charge.
- Licensing options vary from one seat, one year to full site licenses for multiple years.
- **ASAP***prime*® software licenses are an exceptional value for both large and small companies conducting regular stability studies and package screening scenarios.

EXCELLENT SERVICE | QUICK START TIMES | SCIENTIFIC EXPERIENCE | QUALITY SYSTEMS

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A New, Faster Paradigm for Stability

ASAP*prime*® studies differ in many ways from traditional or even accelerated stability studies.

- In traditional stability studies, samples are placed in stability chambers (usually in packaging) with measurements occurring at various, fixed time points.
- Changes such as the growth of impurities, loss of active ingredients or other stability-indicating factors are monitored, and rates extrapolated accordingly.
- When higher temperatures/RH conditions are used, there is often significantly more degradation than at the lower, less harsh conditions.

ASAP*prime*® employs a different, more scientifically accurate paradigm.

- With **ASAP*prime*®**, the product is exposed, without package protection, to conditions and time points designed to make the product hit, but not greatly exceed, its specification limit.
- **ASAP*prime*®** determines the "time to fail" (isoconversion times) at a range of conditions; then uses these data to model the long-term behavior.
- **ASAP*prime*®** uses the open RH sensitivity of the product to calculate packaging impact.

Experimental Design - ASAP*design*™

ASAP*design*™ is a wizard within **ASAP*prime*®** that designs an optimal study for data modeling.

- **ASAP*design*™** first considers the precision of the measurements needed to determine the failure point. This defines the number of repeats needed to power the study adequately.
- The scientist determines how many analyses will be used (typically 20-30) and how long the study will last (typically 2-6 weeks). The program then populates an optimized design with respect to repeats, conditions (temp., RH) and time points.
- To get the product to hit its specification limit at as many conditions as possible, the program can incorporate any available prior knowledge about the product to establish what conditions and time points are appropriate.
- Less harsh conditions will not be used if the product is unlikely to hit its specification limit in the indicated time. The result is that when an **ASAP*prime*®** study is carried out in shorter times, there will be greater extrapolation to the long-term condition with correspondingly larger error bars.
- The program uses any product phase boundaries to limit the design space.
- Because **ASAP*design*™** uses prior knowledge, the precision and accuracy of **ASAP*prime*®** modeling for a product will increase throughout the development process.
- When the design requires RH control, **ASAP*design*™** will provide information about the appropriate saturated salts to use at each condition. These studies are carried out in individual jars containing vials of salt slurries to control the RH. These "mini-chambers" enable non-RH controlled ovens to house samples at multiple RH conditions and prevent cross-contamination within ovens.

Accurate, Predictive Data Analysis

Isoconversion

- In traditional stability studies, degradation at fixed time points (e.g., 3, 6, 12, 18, 24 months) are determined. When higher temperatures are used, degradation is generally greater. The result is a different level of conversion at each condition.
- When the degradation behavior of the product is not linear (the case in >60% of products) fitting of the data to temperature models is not predictive and is considered "non-Arrhenius".
- With **ASAP***prime*®, data are analyzed in terms of isoconversion times at each condition. In this paradigm, the conversion to degradation products is kept constant to target the specification limit, while time is varied at each condition.
- When degradation amounts at a particular condition are close to the specification limit, the estimation of the isoconversion time will have a small error bar. When extrapolation is needed, the precision will be lower.
- **ASAP***prime*® can fit the data to different curve shapes to best estimate isoconversion times.
- Normalized error bars for isoconversion times are calculated using error bars for the points themselves, typically a relative standard deviation (RSD) at higher degradation amounts and a fixed error at low degradation. Repeats are also factored in.

Modified Arrhenius Fitting

$$\ln (1/t_{iso}) = \ln A - E_a/(RT) + B(RH)$$

The isoconversion times (t_{iso}) at all conditions are fit to a moisture-corrected Arrhenius equation which has been shown to work across all chemical and most physical changes that occur as samples age (A, collision frequency; E_a, activation energy; R, gas constant; T, temperature in Kelvin; B, humidity sensitivity factor).

- Instead of using rate constants, **ASAP***prime*® uses the inverse of the isoconversion time;
- **ASAP***prime*® adds a term for the impact of RH on a degradation process.
- Error bars from the isoconversion times are propagated by Monte Carlo simulations to determine the precision in the fitting parameters. These are used to calculate the probability that a product will remain within its specification limits at the end of shelf-life.

ASAP*prime*® vs. Traditional Stability

- In traditional stability programs, samples are analyzed as soon as they are removed from chambers. This leads to systematic error based on day-to-day offsets (instrument-to-instrument, analyst-to-analyst).
- With **ASAP***prime*®, samples, including the controls, are analyzed in a batch to minimize variability.
- **ASAP***design*™ can schedule when each sample should be added and removed from chambers.
- To minimize any systematic error due to instrument drift or other causes, **ASAP***design*™ provides a randomized order for analysis. This randomized order is especially important during comparison studies (e.g., formulation screening).
- In traditional stability studies, wide latitude is allowed under the regulated conditions (e.g., 25±2°C/60±5%RH); however, with **ASAP***prime*® studies, the actual measured conditions are used in the modeling.
- The analytical results are reported even when nominally below the limit of quantitation (LOQ).

Packaging Selection Without Screening

- **ASAP*prime*®** enables determination of packaging without the need for package screening studies.
- **ASAP*prime*®** calculates the RH as a function of time inside a package using the balance of moisture transfer rates (controlled by packaging permeability) and the ability of the product to hold moisture as a function of RH (controlled by the product's moisture sorption isotherm).
- **ASAP*prime*®** uses an extensive database of both packaging material moisture permeabilities (bottles, blisters and drums) and moisture sorption isotherms of most common pharmaceutical materials that allow calculation of formulation isotherms. These determine a product, package and storage condition-specific moisture versus time behavior.
- **ASAP*prime*®** combines the RH as a function of time with the calculated moisture sensitivity of the product to determine the impact of packaging on the product shelf-life. This is expressed as a percent probability of passing.
- The software can include desiccants such as silica gel and molecular sieves. The calculations are accurate enough to determine the impact of tablet or capsule count on the shelf life of bottled products.
- **ASAP*prime*®** allows the scientist to look at many "what if" scenarios. For example, the scientist can adjust the initial water content of the product, predict what would happen if there was a shipping excursion, or consider the impact of changing climate zones.
- The ability to evaluate many packaging options using the software enables better optimization than is practical in real-time studies.
- Companies have successfully used **ASAP*prime*®** as part of cost modeling, where they balance product volumes, global distribution versus zone-specific packaging and shelf-life in different zones. This ultimately allows companies to effectively model many potential scenarios without additional testing to make decisions about packaging quality and cost.

ASAP*prime*® Regulatory Interface

- **ASAP*prime*®** is used in conjunction with, or as a replacement for, traditional ICH or accelerated stability studies.
- **ASAP*prime*®** has been successfully used in place of traditional stability, in support of use-period assignments for INDs for many country authorities including the USA FDA.
- Late stage minor changes have been justified by **ASAP*prime*®** as part of NDA filings. **ASAP*prime*®** modeling is first validated against the prior ICH data for the product before the change, then **ASAP*prime*®** is used to show that the stability does not vary with the change. This allows **ASAP*prime*®** to bridge data before and after a change in many key factors.
- **ASAP*prime*®** has been successfully used to justify post-approval changes of products that would normally require new stability programs.
- With generics, **ASAP*prime*®** justifies equivalence to the originator.
- **ASAP*prime*®** can model the impact of excursions, and thereby provide justification for acceptability of products subjected to even harsh conditions for short times.

Getting Started with ASAP*prime*®

To learn more about **ASAP*prime*®** software or **ASAP*prime*®** laboratory studies conducted by FreeThink, visit www.freethinktech.com.

FreeThink has scientific experts around the globe to assist you!

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