

# Laboratory Services



## The Thinking CRO

FreeThink laboratories in Connecticut (U.S.) routinely support product development for large and small pharmaceutical (new, generic, OTC), medical product, nutraceutical, food, consumer product and cosmetic companies.

- FreeThink can work with most materials including controlled substances (Schedule I-V).
- Current clients range from large multinational companies to small virtual companies –all of whom depend on FreeThink laboratory services to help solve some of their most difficult analytical, formulation, packaging and development challenges.
- FreeThink is *The Thinking CRO*, with a team of industry-leading scientific experts focused on providing creative, scientifically-sound solutions and exceptional customer service.
- The FreeThink motto, “Yes we can!” reflects the company’s client-centric culture, commitment to excellence, and desire to tackle the most difficult technical challenges.



EXCELLENT SERVICE

QUICK START TIMES

SCIENTIFIC EXPERIENCE

QUALITY SYSTEMS



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# Analytical

## Stability Indicating Method Development

A critical aspect in the development of new products is the demonstration of adequate stability. Shelf-life is based on either (or both) increases in the level of something undesirable (e.g., degradation products, color) or decreases in something desirable (e.g., activity or potency, dissolution rate). This requires an appropriate analytical method for quantitatively detecting these changes.

- Some analytical methods—including methods used to detect synthetic process impurities—are not necessarily stability indicating.
- The level of growth or loss that dictates the end-point is considered the specification limit, which is set by guidelines or according to a company's quality standards.
- One aspect of developing a stability-indicating method is to expose the product to harsh conditions. FreeThink works with customers to design these forced degradation studies to produce changes in excess of anything likely to be seen in long-term storage (generally targeting 10- 15% loss of active).
- Study conditions include:
  - hydrolytic (solution samples under acidic and basic conditions)
  - oxidative (exposure to peroxides and free radicals)
  - thermal (high temperatures and humidities, with excipients, when appropriate)
  - photolytic (exposure to ultraviolet and visible light).
- FreeThink scientists establish that the analytical method can adequately separate the observed degradants, and the loss of active corresponds to rough balance of degradation product formation (mass balance).
- These studies help to prove that an analytical method is stability indicating, and also provide insight into the sensitivity of the active ingredient to environmental factors, which can inform formulation development.



## Degradant Structure Elucidation

It is often valuable to determine the chemical structure of degradation products. This can help with setting specification limits and developing mitigation strategies. FreeThink scientists can identify unknown degradation products using a range of analytical methodologies including:

- Using instrumentation at nearby Yale University for:
  - Liquid or gas chromatography with mass spectrometry (LC-MS, GC-MS)
  - Nuclear magnetic resonance (NMR) spectroscopy
- Using preferred vendors to synthesize the molecule and confirm the identity by co-elution

FreeThink's professional scientific staff is particularly adept at proposing mechanisms for formation of degradation products through their knowledge of organic chemistry and the scientific literature. They routinely design appropriate experiments to confirm mechanisms and use these mechanistic understandings to enable stabilization strategies.

# Analytical



## Extraction/Sample Preparation



For most products, active substances are mixed with inactive ingredients (e.g., excipients for pharmaceutical products). To determine whether any degradation products are formed or whether the level of the active has declined over the shelf-life, it is often necessary to extract the active and its degradation products from this matrix.

- FreeThink has the expertise to develop the sample preparation method, by first identifying solvents with the right solvation tendencies.
- Some form of energy is applied to the material (especially for solids) to help speed the dissolution. Filtration or centrifugation separates active and degradants from insoluble materials. The extraction method is tested to assure quantitative recovery.
- These methods can be performed to demonstrate scientific reliability only or can include a full cGMP validation process.

## Analytical Method Development


FreeThink can develop stability-indicating methods for a wide variety of pharmaceutical and non-pharmaceutical products, including those with multiple actives, actives with no chromophores, and materials with difficult separations.

- The decision about which technique is employed (HPLC/UPLC/GC) is made with full client consultation.
- When developing LC methods, FreeThink scientists often screen multiple column chemistries based on their expertise in this field. This approach includes varying eluting solvents and gradients to achieve separations based on a phase-appropriate approach:
  - for early product development, a method is acceptable with minimal optimization;
  - for late-stage product development, the method is optimized for separation, linearity, run time, and column robustness.
- When the active has no chromophore, FreeThink uses charged aerosol detector (CAD), evaporative light scattering (ELS) or MS detection adjusting the eluting solvents accordingly.

For tablets and capsules, a key quality attribute is the dissolution behavior.

- In developing dissolution methods at FreeThink, regulatory requirements for discrimination and biorelevance are key considerations.
- In some cases, the dissolution method will mostly be a check on the product consistency and therefore needs to be able to discriminate when manufacturing changes are made.
- The solubility of the active as a function of pH establishes whether solubilization is necessary for the method to be considered “sink” (e.g., the active is well-below saturation at all times).
- When necessary, appropriate solubilizing agents (e.g., surfactants) are added.
- Analysis of the active by UV-visible absorption spectroscopy is preferable; however, in many cases, an HPLC potency assay is used.
- Most often, at FreeThink, dissolution testing methods are developed using baskets (USP method I) or paddles (USP method II).
- FreeThink will work with the sponsor company to establish specification limits (“Q-values”).

FreeThink scientists can fully validate a method, or work with a manufacturer to validate as part of the method transfer. Methods can usually be developed very quickly, even for the most challenging projects.





# Analytical

## ASAP<sup>prime</sup>® Studies

ASAP<sup>prime</sup>® is a software package developed by FreeThink Technologies, Inc. in which experimental data are used to model the shelf-life of products in very short time periods. The software helps the user develop an experimental plan for the study of a specific product based on any prior knowledge, design space limitations of temperature and relative humidity (RH), data precision, available time, and the number of samples to be analyzed. The experimental data are used to build a mathematical model about the product. ASAP<sup>prime</sup>® differs from forced degradation in that it is designed for predictive shelf-life determinations (modeling) rather than for a test of analytical method appropriateness.

FreeThink scientists are the global experts at conducting ASAP<sup>prime</sup>® laboratory studies. In most cases, studies can be completed in as little as four weeks, with greater accuracy than traditional (ICH) six-month studies. FreeThink conducts ASAP<sup>prime</sup>® studies on:

- **Solids** (tablets, capsules, powders)
- **Liquids** (including volatile components and liquids with viscosity and color stability issues)
- **Amorphous and other high-energy solids** (solids such as spray dried dispersions and co-crystals can be modeled using an accelerated kinetic solubility technique sensitive to changes even in dilute formulations)
- **Lyophiles** (special attention is paid to moisture behavior)
- **Peptides and oligonucleotides** (with stability-model predictions ranging from refrigerated to ambient storage)
- **Medical devices** (for drug-device combinations based on chemical stability or risk of microbial contamination)

In addition to temperature and humidity sensitivity for chemical degradation, FreeThink can evaluate other parameters in accelerated studies:

- **Oxygen sensitivity** (including simultaneous modeling of the impact of oxygen, moisture and temperature)
- **Appearance** (for color and appearance stability for tablets, powders, liquids, and other dosage forms)
- **Dissolution** (for tablets and capsules based on FreeThink's novel technology)

## cGMP ASAP<sup>prime</sup>® Laboratory Studies

FreeThink offers ASAP<sup>prime</sup>® laboratory studies with three levels of quality review:

**1 Standard Level ASAP<sup>prime</sup>® Studies** are done to a high standard of scientific integrity. Analytical methods provided by the client are verified for use, but do not require a formal method transfer or validation. In some cases, methods are altered to make them more appropriate for the intended studies (with client approval). A report includes an introduction to the problem, the description of the methods employed, the experimental procedures, the analytical and ASAP<sup>prime</sup>® modeling results, interpretations and recommendations based on those results. Reports are thorough and support decision-making and explanations in regulatory filings.

**2 Quality Assurance Reviews** maintain the high scientific integrity provided at the Standard Level, and also include a Quality Assurance (QA) review of all data used in the report. FreeThink's QA team checks all entries used for data integrity and provides an additional signature on the report. This level of reporting has been used in regulatory filings where a full cGMP study is not deemed necessary.

**3 A Full cGMP ASAP<sup>prime</sup>® Study and Report** is the highest level of quality offered. In this case, all the analytical work is carried out according to FreeThink's SOPs, with customer prior approval. Analytical methods are transferred according to a formal protocol, often using co-validation. Samples are analyzed based on the protocol according to the appropriate SOPs for each step. All instruments are certified based on their qualification (IQ/OQ/PQ) and calibration documentation, and software has appropriate qualification documentation. All data used, and all reports generated are reviewed by FreeThink's experienced QA staff. This level of reporting is recommended when customers want to provide a cGMP-level of quality in their regulatory filings and are more common with late-stage and post-approval applications.

# Analytical

## Traditional Stability Studies

**ASAPprime**® laboratory studies can determine a product's stability and assist with packaging selection. However, in some cases, long-term stability studies may be required, especially in support of regulatory filings.

- FreeThink conducts long-term studies to validate the **ASAPprime**® modeling or in-place of **ASAPprime**® studies when appropriate.
- FreeThink's qualified chambers can store products at ICH (25°C/60%RH, 30°C/65%RH), accelerated (40°C/75%RH), Zone IVb (30°C/75%RH) and refrigerated (5°C) conditions.
- Packaging of small-scale batches of products (bottles, blisters) for testing is available, and can be done based on customer-approved protocols with completed studies and reporting for information only (with scientific integrity) or based on FreeThink's cGMP SOPs.
- When testing under cGMP protocols, all instrumentation used are fully validated, and all appropriate staff are fully trained in the details and applications of FreeThink's SOPs.
- Data are handled to assure data integrity (HPLC work uses the Empower 3 system).

- Customers are invited to audit FreeThink's quality systems and meet the scientists and QA professional staff.
- Analytical testing includes most standard techniques (e.g., HPLC, dissolution, Karl Fisher).

The FreeThink Quality Management System was designed to guide and implement cGMP studies using the most modern quality systems and risk management approaches. This system

- Ensures adherence to the requirements of the U.S. FDA's (cGMP) regulations.
- Guarantees high-quality and fully-verified data for each cGMP study to assist in regulatory filings.
- Revolves around support and feedback from Analytical Sciences (Quality Control), QA, Executive Management and outside stakeholders who frame FreeThink's quality processes, standards, and controls.

FreeThink's experienced staff recognizes the need for any given program to meet global compliance and is knowledgeable in international regulations and guidelines.





# Problem Solving



While many CROs can carry out method development and traditional stability studies, FreeThink scientists are especially adept at quickly solving the most challenging development problems. As *The Thinking CRO*, FreeThink scientists pride themselves on finding solutions where many others have failed. Customer examples of problems solved:

- When an unexpected stability failure occurred in late-stage development that was not seen in any earlier development stages, FreeThink correctly identified a problem with the analytical method, not the product itself. In this case, the customer's development laboratory had protected analytical samples from light (amber glass) but did not note this when the method was transferred to the production site.
- FreeThink showed that commercial-scale production of a drug-layered bead caused formation of amorphous active which was unstable. By incorporating a process adaptation to induce recrystallization, stabilization was achieved.
- FreeThink found that a customer's tablet dissolution instability was linked to deliquescence (picking up water in the air to form a solution) by the drug itself and could only be remedied by packaging. This halted the company's significant efforts at reformulation.

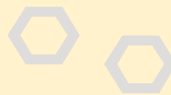


## Reports

FreeThink takes pride in delivering customer reports that are rich in content, conclusions and recommendations.

- Many CROs provide detailed "data dumps" with little or no insight for problem-solving and decision-making.
- As *The Thinking CRO*, FreeThink's senior scientists and project teams spend the necessary time to interpret what the data mean to customers and their products –enabling them to make better, more informed decisions.
- With FreeThink's scientific expertise and consultative approach, teams often make suggestions and introduce opportunities beyond the original project scope to give a company's project the best chance for success!





# Formulation Development

FreeThink is *not* a Contract Manufacturer Organization (CMO). We develop formulations and analytical methods which are owned by the sponsor companies. This provides flexibility to bid the manufacturing operation with multiple CMOs, often reducing long-term costs. FreeThink can assist in finding an appropriate CMO and manage the technology transfer process. FreeThink's scientific experts will work to find the best formulation and process solution for the project and are not constrained by a specific manufacturing approach or technology.

FreeThink scientists are leaders in the adoption of a "tiered" approach to formulation development, with an emphasis on stability enabled by **ASAPprime**®.

- Traditional excipient compatibility studies correlate poorly with final product stability and require a significant investment of time and resources.
- In the tiered approach, FreeThink's scientists prepare two to three standard formulations of actives in tablets, capsules, or other dosage forms.
- These formulations are evaluated using **ASAPprime**® to see if one or more of the formulations is acceptable for stability—not just rank-ordered.
- If deemed acceptable, the formulations can be developed rapidly. If none of the formulations reach the desired stability targets, a second-tier study is initiated.
- These second-tier formulations may include such stabilizers as antioxidants or pH modifiers.
- A final formulation is generally achieved in less than four months.
- For all formulation development, FreeThink brings its knowledge of stability to the process, enabling stable liquid and solid formulations even for unstable actives.

FreeThink scientists can establish the maximum absorbable dose (MAD), for oral absorption and use this to determine the most appropriate technology to provide adequate drug absorption.

- FreeThink can help facilitate the development of appropriate technologies through our partner companies, including:
  - Particle size reduction (for drugs that are dissolution limited rather than solubility limited)
  - Salt formation and amorphous drug forms (using spray dried dispersions, SDDs, or hot melt extrusions, HMEs).
- Our scientists have experience in product development for very lipophilic drugs in the form of oils and emulsified dispersions (e.g., self-emulsifying dispersion systems, SEDDS and self-emulsifying microdispersion systems, SMEDDS).
- These formulation options can be combined with hard (gelatin or HPMC) or soft gelatin capsules, when appropriate.

FreeThink has particular expertise in the development of oral controlled release dosage forms.

- Working with the sponsor company, a dosage form Target Product Profile (TPP) is established and used to select the primary dosage form to be developed.
- For many technologies, FreeThink scientist can develop appropriate formulations and dosage forms internally.
- In some cases, FreeThink will coordinate work through one of its partner companies.
- When the TPP requires a very high dose, FreeThink has expertise in complex tablet and chewable formulations and processes (including external lubrication technology).



# Packaging

FreeThink can determine the appropriate packaging for products based on permeability to moisture and oxygen, and product physical sensitivity. By specific knowledge of product protection needs, companies are able to optimize for cost-effective packaging.

## Moisture Sorption Isotherms

One element in the determination of packaging for solids (and some liquids) is understanding how moisture equilibrates as a function of relative humidity.

- FreeThink scientists determine moisture sorption isotherms using a Dynamic Vapor Sorption (DVS) apparatus.
- This can measure a wide range of materials and provide insight into how moisture is sorbed into a substance or product.

## Moisture and Oxygen Permeability

Another critical component in the determination of packaging's impact on product stability involves assessing the package permeability to key elements, including moisture and oxygen.

- FreeThink can determine the Moisture Vapor Transmission Rate (MVTR) and Oxygen Transmission Rate (OTR) for customer packaging.
- This is done on the actual packaging rather than flat sheets using gravimetric (for moisture) or sensor-based (for oxygen) methods.
- Through an extensive database of packaging permeability, and measuring these permeabilities as a function of temperature, various storage conditions and their effect on the internal packaging environment over time can be studied.



## Packaging Determination

Designed accelerated stability studies on loss of assay, formation of degradation products, change in appearance or change in dissolution can be rapidly completed at the FreeThink laboratories.

- The results of these studies are used to develop a mathematical/statistical model for the impact of temperature, relative humidity and oxygen.
- Experimental results are analyzed using FreeThink's proprietary **ASAPprime**® software to determine the direct impact of packaging on shelf-life, based on how the packaging provides protection from these elements.
- Calculations determine which specific options of bottles (size, type, tablet or capsule count, presence of desiccants or oxygen absorbers), blisters (material) or other storage containers will provide adequate shelf-life in each climatic zone.
- The FreeThink approach reduces the amount of active (drug) required in packaging determination in addition to reducing the time needed.
- FreeThink offers extensive experience in how best to use packaging for appropriate stability; but also remains conscious of the implications of packaging costs for the sponsor company.
- By streamlining package selection, product development can be accelerated and made more efficient. Package screening is no longer needed, only package confirmation.
- Companies have successfully used this **ASAPprime**® approach for regulatory filings.

## Package Testing

FreeThink can package products (non-GMP) for small-scale testing. Capabilities include bottles, ampoules, blisters and pouches. Packaging screening/confirmation studies at FreeThink can often be started very quickly, require relatively little product, and cost less than studies carried out at commercial packaging facilities. In addition, FreeThink studies can control many factors such as oxygen level, bottle cap torque and secondary packaging materials.