



## Preformulation screening and stability testing



### Stability testing as part of the development and approval of pharmaceutical and cosmetic products

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#### Summary

Across Barriers GmbH offers a comprehensive range of stability testing services. The company develops test methods that span the entire life cycle of a drug or cosmetic product - from the development phase through to manufacture and product testing. In the early preformulation phases, Across Barriers offers fast and economical screening procedures to assess the stress stability of active ingredients and test mixtures. During the later stages of the drug development and manufacturing process or when testing clinical samples or products already on the market, long-term stability testing can be carried out.

A dedicated and experienced team combined with an impressive equipment inventory, particularly in the field of analytics, makes us ideally suited to perform state-of-the-art stability testing. With a quality assurance system that complies with the GLP/GMP guidelines, Across Barriers ensures that the necessary quality standards are met. By making use of these services, customers can free up internal capacity and prevent bottlenecks during peak periods.

## Stability of active ingredients

### Stress tests to examine chemical stability

Stress testing aims to evaluate the intrinsic stability of molecules, to elucidate possible degradation pathways and to identify decomposition products. The design of a stability test depends on the nature of the substance and on the dosage form. Testing covers such areas as sensitivity to temperature, humidity and pH, and examines the oxidative and photostability of the test substance. Depending on the questions to be addressed, Across Barriers can conduct initial tests to establish an outline stability profile or can carry out definitive studies that comply with customer specifications or the relevant regulatory guidelines. Preliminary in vivo studies enable us to investigate questions regarding the stability of test formulations for parenteral administration, or the stability of products to gastric and intestinal fluids or to other physiological media.

### Stability screening to examine chemical stability

To customers who wish to examine larger numbers of drug candidates or who require an initial impression of chemical stability in the very early phases of the drug development chain, Across Barriers offers a stability screening procedure. The drug substance is subjected to stress testing to determine its stability to oxidation and to acid and base-catalyzed hydrolysis. In addition, impurity profiles are recorded. If a stability indication method is already available, it can be adopted. Total impurities are listed in a short report and degradation pathways and products can be identified on request. One milligram of test substance is required per test condition. Customers receive the results of the stress stability testing within ten working days.

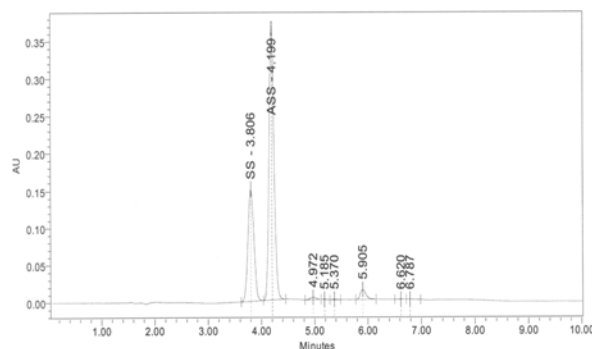


Fig. 1: Decomposition profile of acetylsalicylic acid in 0.1 M NaOH (stability to base hydrolysis)

## Compatibility testing

### Conventional compatibility studies

In addition to information on the intrinsic stability of the active ingredient, it is also important to know how the various excipients used in a drug or cosmetic formulation can affect the stability of the active ingredient. Once stress stability tests have been carried out, the conventional approach to studying compatibility involves preparing mixtures of the active ingredient with various excipients. The composition of these test mixtures or the number of components included in a mixture will depend on the nature of the formulation required. These mixtures are then stored for long periods under different temperature and humidity conditions, removed at predefined intervals and analyzed. Across Barriers can store and analyze not only prepared mixtures but also intermediates such as granules under ICH-compliant conditions.

### Compatibility screening

As the conventional compatibility studies described above require relatively large amounts of the test substance to be made available and involve relatively long storage periods, Across Barriers has developed a screening technique that generates information on incompatibilities within a few days. In the first stage of the two-phase compatibility screening process, the stress stability of the active ingredient is determined as described above. In the second stage, 1:1 or other mixtures of the active ingredient and excipients are prepared and then subjected to hydrolytic stress testing. For each mixture, 1 mg of the active ingredient is required.

The entire sample is then processed and the impurity profile recorded chromatographically. This rapid

screening method is suitable for the preformulation phase of the development process and can be applied to both solid and liquid delivery forms. The preliminary information required for compatibility screening includes solubility, purity and the physical state of the substance (crystal-line or amorphous). To investigate the compatibility of one active ingredient with twenty excipients, 30 mg of the test substance are required. Results are available within ten working days.

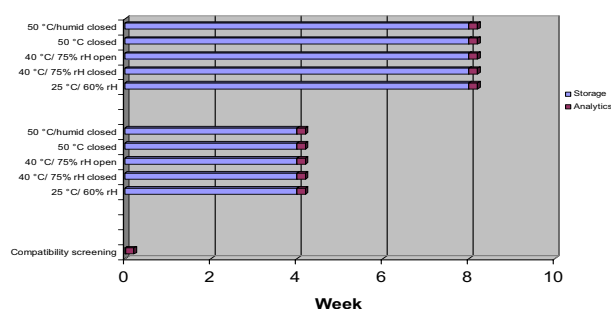


Fig. 2: Time savings achieved by using compatibility screening techniques

## Stability testing

### Storage facilities

The following storage and stress-testing conditions are available for stability and/or compatibility studies:

- -20 °C
- 5 °C
- 25 °C/ 60 % RH
- 30 °C/ 60 % RH and 30 °C/ 65 % RH
- 40 °C/ 75 % RH
- Photostability
- Freeze-thaw cycles
- specific stress testing on semisolid and liquid formulations



Fig. 3: Climate chamber for storing stability samples

## Experience of stability testing

With years of experience in the pharmaceutical and cosmetic industries, the scientific team at Across Barriers is fully acquainted with the development and execution of test procedures in all phases of the drug life cycle.

### Delivery systems and substances

- Solid dosage forms (tablets, capsules)
- Semi-solid dosage forms
- Suppositories
- Dermal patches
- Liquid dosage forms
- Trial formulations for initial in vivo studies
- Anesthetics
- Cytostatics

### Previous stability studies performed by Across Barriers

- Stress stability
- Short-term stability testing
- Batch release tests
- Clinical test samples
- Studies as part of drug approval and re-approval procedures
- Packaging studies
- Follow-up stability
- Assessment and selection of manufacturing processes
- Shelf-life determinations
- Stability after opening

### Equipment and methods available at Across Barriers

#### Drug testing

Drug stability testing requires a broad range of methods for examining the delivery system. Across Barriers can perform the following methods:

- |                          |                             |
|--------------------------|-----------------------------|
| - Karl-Fischer titration | - Hardness                  |
| - Disintegration         | - Friability                |
| - Particle counting      | - Purity, assays            |
| - Residual solvent       | - Heavy metals              |
| - UV spectroscopy        | - Melting point             |
| - Drying loss            | - Thin-layer chromatography |

Microbiological stability testing is carried out in collaboration with qualified professional partners.

### Dissolution measurements

Dissolution measurements form an important part of stability testing. Across Barriers has USP apparatus 1 and 2 for dissolution testing. This equipment can be used to perform and develop online UV-based methods. Techniques for measuring the dissolution and stability of almost any type of dosage form (e.g. dermal patches) and in a wide range of media can be developed and validated to meet a customer's specific requirements. Across Barriers can also provide assistance in optimizing existing methods or in modifying them to comply with the specifications laid down by the regulatory authorities. We can also help in designing more efficient testing protocols.

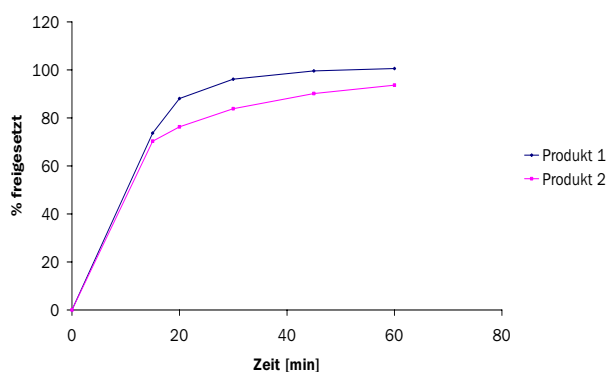


Fig. 4: Dissolution profiles of a number of products

### Analytical equipment

An extensive range of analytical detection methods (e.g. UV-VIS spectroscopy, photodiode array, fluorescence and electrochemical techniques) are available for use in stability testing. Across Barriers also makes use of the following chromatographic techniques: LC-ESI-MS coupled with PDA, and LC-MS-MS coupled with UV detection. Our analytical team can apply a customer's own stability-indicating method and can also provide support in optimizing, adapting or developing appropriate analytical methods to address a customer's specific needs. All methods used comply either with client specifications or with the relevant regulatory guidelines

### Quality assurance

All laboratory test apparatus and instruments are monitored in accordance with the GLP and GMP guidelines and are in a validated state. Personnel at Across Barriers undergo extensive internal and external training and skills development programs.

The temperature and humidity of our labs, climate cabinets and climate chambers are subject to continuous electronic monitoring. An alarm system (incorporating e-mail and SMS alerts) ensures that our systems are under control overnight and during weekends.

In the event of a failure, we have sufficient back-up systems including an emergency generator and additional climate cabinets.

All data that we record as part of our monitoring and validation procedures as well as all raw data are subjected to rigorous checks.

Reports are first checked by our quality assurance unit and then sent in draft form to the project sponsor. Once the sponsor has approved the report, final versions are compiled and issued.

### Guidelines

CPMP/ICH/2736/99  
Stability Testing of New Drugs and Products

CPMP/ICH/280/95  
Stability Testing for New Dosage Forms

CPMP/ICH/279/95  
Photostability Testing of New Drug Substances and Products

CPMP/ICH/381/95  
Text on Validation of Analytical Procedures

CPMP/ICH281/95  
Validation of Analytical Procedures : Methodology

ICH Guideline Q3A(R)  
Impurities in New Drug Substances

CPMP/ICH/2738/99  
Impurities in New Drug Substances

FIP Guidelines for Dissolution Testing of Solid Oral Products, Die Pharmazeutische Industrie 59:760 – 766 (1997) and Dissolution Technologies 4:5-14 November (1997).

FDA Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms

EC Guidelines on Good Manufacturing Practice