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WHITE PAPER

STABILITY CONTINGENCY AND DISASTER RECOVERY

MITIGATING THE RISKS INVOLVED IN STABILITY STORAGE

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Mitigating the risks involved in stability storage

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STABILITY STORAGE:
ADDRESSING POTENTIAL RISK

The risks involved with stability storage

Damage or complete loss of products that have been in stability storage for a number of years due to unforeseen or unlikely circumstances could have long term effects and repercussions for an organisation involved in pharmaceutical development. Such events that may pose a risk to the continuity of stability studies include extreme weather, flooding, fire, electrical failures, power outages, software failure or even human error and can lead to months or years of lost time with significant financial impact.

Pharmaceutical stability studies are complex. They demand considerable financial investment, time and scientific expertise. Disruption to these programs could directly affect a product's development activities, potentially impacting the product's market launch. For organisations who perform formal ICH stability programmes in-house the need to reduce risks associated with stability storage can be greatly reduced through working with specialist outsourcing partners with large capacity stability storage, who can offer responsive relief storage in the event of a disaster.

Objectives of Stability Studies

Stability studies play a fundamental role across the lifecycle of pharmaceutical products (Figure 1) and in particular, during development and IND / NDA submission activities. The main objectives of stability studies and the types of studies are listed in Figure 2. Regulatory authorities require the manufacturer to submit information on the stability of the product derived from tests on the final dosage form in its final container and packaging. Stability testing assesses how the quality of a drug substance or drug product (including its packaging) varies with time under the influence of environmental factors, including temperature, humidity and light across a variety of conditions. The process determines whether any physical, chemical or microbiological changes affect the efficiency and integrity of the final product, thereby ensuring that a pharmaceutical product is safe and effective, irrespective of where in the world it will be supplied. Moreover, stability testing establishes the shelf life and recommended storage conditions of a finished pharmaceutical product and the retest periods for a drug substance and ensures compliance with international regulations that form part of the registration process for a new drug substance or drug product.

Stability Studies Across the Drug Product Lifecycle

Preclinical Stability	IND Submission	NDA Submission	Marketed Product
Experimental Stability	API Stability	API Stability	Commercial Stability
Dosing Stability	Drug / Excipient Compatability	CTM Stability	Post-Approval Changes
	CTM Stability	Comparator Studies	ANDA Stability Studies
	Shipping Stability	NDA Stability Studies	

Figure 1 Stability Studies Across the Drug Product Lifecycle

OBJECTIVE	TYPE OF STUDY	USE
To select adequate (from the viewpoint of stability) formulations and container-closure systems	Accelerated	Development of the product
To determine shelf-life and storage conditions	Accelerated and real-time	Development of the product and of the registration dossier
To substantiate the claimed shelf-life	Real-time	Registration dossier
To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product	Accelerated and real-time	Quality assurance in general, including quality control
To determine shelf-life and storage conditions	Accelerated and real-time	Development of the product and of the registration dossier

Figure 2 Objectives of Stability Studies

Risk Management

Due to the considerable demand for resources, time and financial investment, it is important to identify all potential risks and their impact, prior to beginning a stability program. These potential risks include:

- Potential loss of valuable products that have been in stability storage for a number of years
- Disruption to the continuation and integrity of the stability trial
- Disruption to operations, downtime and productivity
- Delays associated with achieving successful regulatory approval and market launch for the product

Success in mitigating these risks is dependent on implementing a rational recovery plan in the event of a disaster or emergency for pharmaceutical stability storage. Additionally, the creation of contingency storage at a second site is an essential requirement helps to de-risk stability programs.

Business Continuity Planning (BCP) is the strategy by which an organisation will recover and restore interrupted critical operations within a predetermined time period of any disaster scenario and is particularly relevant to long term stability studies. BCP involves five main elements:

- People: key contacts with up to date contact details
- Premises: recovery operations
- Process: for returning organisation to minimum service levels
- Publicity: internal and external communications
- Providers: key contacts in the supply chain

In this case, "providers" include the stability storage providers you select. With regard to outsourcing contingency storage at a second site, your provider must be able to demonstrate continued excellence in project management and quality and provide suitable capacity in a facility that is monitored, fully validated and alarmed.

With regard to disaster recovery risk management, your storage provider must be carefully pre-selected considering the requirements for quality, efficiency and facility specifications but should also be able to implement a competent and responsive disaster recovery procedure to cover any emergency transfer of samples from your site which can deal with either individual batches to entire chambers of samples should your own stability chambers go down.

Selecting a stability storage service provider

During the selection of a storage service provider, there are some practical considerations that underpin this process which will help to secure a suitable back-up resource to your existing stability suite. Client audits are an important step to assessing this service provider and site visits are invaluable to review a company's:

- Quality systems
- Staffing capacity and employee training programme
- Corrective and preventive actions programme
- Document control

With a specific focus on stability storage, it is also prudent to consider storage providers who have a proven track record in managing stability studies. Site visits should focus on:

- Stability program administration
- Chamber capacity and storage conditions
- Chamber security, alarm and back-up systems
- Operation, maintenance and calibrations of stability chambers, freezers and refrigerators
- Environmental monitoring of stability chambers, freezers and refrigerators
- Qualification documentation (IQ/OQ/PQ)
- Each storage provider's stability disaster recovery and client notification plan
- Knowledge of relevant ICH guidelines

This last point is key. Even though stability contingency and disaster recovery is not specifically covered in the ICH guidelines relevant to stability studies (Figure 3), knowledge of the regulatory requirements of a stability program are absolutely crucial.

ICH GUIDELINES RELEVANT TO STABILITY STUDIES

- Q1A (R2) Stability Testing of New Drug Substances and Products
- Q1B Stability Testing : Photostability Testing of New Drug Substances and Products
- Q1C Stability Testing for New Dosage Forms
- Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
- Q1E Evaluation of Stability Data
- Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV
- Q5C Stability Testing of Biotechnological/ Biological Products
- US-FDA Guidance Documents: - 21CFR FDA210&211

Figure 3 ICH Guidelines relevant to stability studies

WHICH QUALITIES DEMONSTRATE EXCELLENCE OF YOUR STABILITY CONTINGENCY PARTNER?

A customized program

A contingency management plan that is customized to meet your individual company requirements should consider the nature of your samples and a wide range of other practical considerations (Figure 4). The contingency management plan should be uncomplicated, easy to execute, and ensure smooth continuity in your stability storage operations in case of an emergency.

Capacity

Your partner should offer reserved stability space available across all necessary environmental conditions, for either individual batches to entire chambers depending on your needs, should an in-house condition fail. Available capacity should take into consideration the type of products and dimensions of samples, ranging from solid dose tablets in typical containers to larger medical devices with unsual shapes or size which may require a much larger storage volume.

Excellence in project management

Project management is fundamental to addressing the range of unique regulatory, compliance, time-critical and quality related needs for smooth implementation of stability contingency and disaster recovery plans. Excellence in project management techniques and communications can effectively facilitate necessary scheduling, risk management, and control requirements in order to mitigate risks.

Quality

A stability contingency and disaster recovery partner should work closely with clients to deploy Technical Agreements and facilitate quality audits to ensure that the required documentation is in place to cover disaster recovery situations whilst demonstrating excellence in quality.

Responsiveness

Should one of your own stability chambers fail, your chosen partner should swiftly mobilise the agreed contingency plan and transfer the affected samples, avoiding significant interruption to client stability studies.

Conclusion

Ultimately, a successful study comes from a successful collaboration. The information in the stability contingency and disaster recovery plan and resulting stability protocol is paramount to success.

Evaluate your storage partner closely. Decide the details of how samples should be stored and treated before you finalise your protocol and get everything captured in one document.

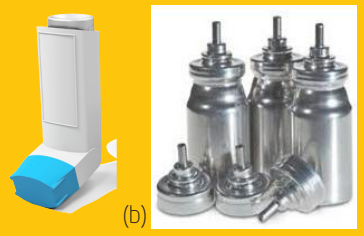
Stay in contact with the contract storage provider, keep them informed of any changes to the protocol, or documentation or protocol changes once on store.

Once you are sure that you have the right customized plan in place and that your partner can offer you the capacity, responsiveness and technical considerations you need, it is possible to mitigate risks to your stability storage operations, minimize disruption and ensure the integrity of your stability trials.

PRACTICAL CONSIDERATIONS 1: ORIENTATION

Orientation of some product types can be crucial to stability studies; is this defined in your protocol? If your samples are to be stored inverted or upright do they need support? How will this be achieved without reducing airflow?

One such example is inhalation medicines. Certain products will be affected by the orientation they are stored in and so multiple arms to the programme may be required (e.g. upright, horizontal, inverted).



(a) (b)

Should cannisters be stored upright but valve down (a), or should the canisters be removed and placed upright, valve up? (b)

PRACTICAL CONSIDERATIONS 2: TRANSPORT

Do the samples need to be transported e.g. to an analytical partner? If yes, what needs to be considered?

Do samples need to be transported in a specific orientation?

Does the temperature need to be controlled?

Does the temperature need to be monitored?

Should the delivery be time bound?

For controlled drugs, does the storage provider need an export licence or consider specific packaging requirements for customs?

Figure 4 Practical considerations

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OUR SERVICES

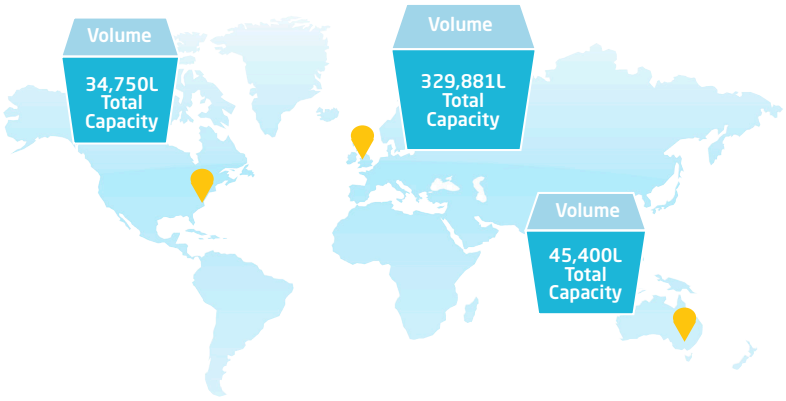
As a specialist stability outsourcing partner with large capacity stability storage we can offer responsive relief storage in the event of a disaster. Due to the high volume capacity and wide range of conditions and ability to offer storage at bespoke conditions we can respond to disaster recovery storage project for many types of pharmaceutical products and medical devices. Many of our customers also place a volume of contingency storage with us in order to de-risk their stability programmes.

With a network of ICH stability storage facilities in the UK, US and Australia, we offer an extensive capacity and a range of conditions including climatic walk in chambers, cabinets and refrigerated as well as freezer storage which monitored with back-up chambers at each site. All sites have 24 hour alarm systems with dedicated on call teams to react to the excursions from storage conditions. Our stability teams provide professionally managed Good Manufacturing Practice (cGMP) stability programs for APIs or complex of dosage forms including orally inhaled and nasal drug products (OINDP), biopharmaceuticals or medical devices.

- cGMP registration stability programs
- Design, storage and management
- Development and validation of stability indicating methods
- Stability testing for APIs, clinical trial materials, or formulated products
- Tailored reporting (timepoint and final reports)
- All ICH conditions storage
- Photostability (ICH Q1B Options 1 & 2)
- Temperature cycling, freeze-thaw and shipping studies
- Bespoke or specialised conditions
- Contingency & disaster recovery storage

Our analytical laboratory network provides development and validation of stability indicating methods through state-of-the-art technology to identify and quantify degradation products. Routine time point testing includes the usual tests such as assay and impurity analysis, dissolution, moisture, hardness, friability and disintegration.

With over 25 years of experience in stability studies integrated with a comprehensive understanding of the latest developments in regional, country and ICH stability study guidelines we offer a truly flexible stability outsourcing partnership.



MEET OUR EXPERT: STUART KIRBYSHIRE

Stuart Kirbyshire is the Stability Manager at Intertek Melbourn. He joined Melbourn Scientific in 2003 as an Analyst, and has been a Team Leader for the last five years. He brings vast experience in testing and managing studies of many pharmaceutical product types, ranging from new chemical formulations studies through to post market approval and generic product development studies

STABILITY STORAGE GLOBAL NETWORK

Intertek offers current cGMP compliant stability studies for the pharmaceutical, biopharmaceutical and consumer healthcare market. We have an extensive range of ICH stability conditions available to our customers across the Intertek network:

- Storage at -20°C, -3°C, 2-8°C, 5°C
- 15°C/50%RH
- 25°C/40%RH
- 25°C/50%RH
- 25°C/60%RH
- 30°C/25%RH
- 30°C/35%RH
- 30°C/50%RH
- 30°C/65%RH
- 30°C/75%RH
- 35°C/50%RH
- 40°C/NMT25%RH
- 40°C/75%RH
- Cabinets at 50°C, 55°C, 57°C
- Photostability (ICH Options 1 & 2)
- Specialised Conditions
- Freeze / Thaw Cycle Tests

Intertek is a leading Total Quality Assurance provider to industries worldwide. Our network of more than 1,000 laboratories and offices and over 42,000 people in more than 100 countries, delivers innovative and bespoke Assurance, Testing, Inspection and Certification solutions for our customers' operations and supply chains. Intertek Total Quality Assurance expertise, delivered consistently with precision, pace and passion, enabling our customers to power ahead safely.

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