

Setting-up a Functional Stability Unit

In setting-up a stability unit it is necessary to highlight some current deficiencies found in Pharmaceutical Stability Departments, as well as indicating the necessary control structures required for the efficient operation of a functional Stability Department. The structure of a practical and operational proven stability department is herewith described.

Stability Control.

Stability control is achieved through standard operational *systems* - namely proper stability *documentation*, sufficient control *SOPs* and acceptable monitoring equipment and laboratory *facilities*.

The analytical testing section (personnel and equipment) must be of sufficient size to adequately perform the stability tests in the **required time**. Stability testing depends on good timing. Consistently late drug product testing is of little scientific or regulatory value.

Number of SOPs required

Stability SOPs number about 45 to 50 for a well managed and organized stability department to operate efficiently within current GMP.

A comprehensive list of the stability control SOPs and some SOP summaries, controlling key functions are included in this issue to *highlight* the many operational *details* required.

In Generic and Researched-based analytical laboratories, stability testing is performed in three target areas. Each area is fundamental to the long-term success of the firms products, whether the products are New Drugs, ANDAs or simply OTCs.

Departments Impacted

The stability department(s) must service the **Development** Department (or **R&D**), the **Regulatory** Batches (those submitted to the authorities) and the **Production** Department (where each commercial product is placed on stability once a year - i.e. only one batch of each strength and largest pack size).

The Stability Requirements

The main stability operations are:

■ **Development Stability**

- Stability testing during the key product development stages (i.e. stability testing *prior* to the pivotal batch used for regulatory filing).

■ **Regulatory Stability**

Stability testing of ANDA / AADA FDA *filed* batch(es):-

- Original Generic Applications submitted to FDA.
- Amended Applications (*before* file approval.)
- Supplementary Applications (changes *after* approval.)

■ **Production Stability**

Stability testing - annually on a representative full production batch. One production batch *per* product, *per* strength, *per* year.

Annual Reports - ongoing stability commitments *per filed* application.

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Stability Facilities

Adequate stability facilities are required. The number of stability tests increase every year. Thus facilities are required to be sufficiently large in order to accommodate the annual growth. Firms need to invest adequately in the stability department facilities and equipment.

The stability data on development, regulatory, or production lots constitute critical review data during ANDA file review and Pre-approval Inspections (PAIs.)

The minimum stability facilities required are:

The environmental system:

- A large 25°C - 30°C controlled environment stability room with **generous** multilevel shelving.
- dedicated controlled temperature room(s)
- continuous recording of temperature and humidity in the stability room(s)
- a validated environment - (room probes and periodic room validation)
- 30° and 40°C climatic chamber cabinets with automatic recorders.
- a light chamber cabinet (optional)

Drug Products need to be properly *exposed* to the controlled environment - this requires *orderly* storage on appropriate and spacious shelving

Products may not be stored indiscriminately in cardboard boxes].

The Minimum Set-up requirements

The Computer system

- A stability computer (Pentium) with a *validated* stability software program.
- A computer back-up system (e.g. tape or disc system).
- A rapid printer with continuous paper or sheet feed .

This is a minimum acceptable system. Review chemists and Scientific Officers conducting GMP or pre-approval inspections regard a suitable structured and efficiently established stability department as a critical factor in the evaluation program.

Therefore the following areas should be properly reviewed:

- **Correctly** formatted Stability Reports (for agency review chemists).
- **Adequate** environmental control on temperature and humidity (review of recording graphs) - Environmental controls are reviewed by PAI site inspectors.
- **Skilfully** written Stability SOPs - for efficient daily operation (reviewed during PAI site visits).
- **Meticulous** care is necessary to pass a ANDA product specific pre-approval site inspection.☐

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Do's & Don'ts for Managing Stability Departments.

Formal SOP monitoring

Do - insure that Stability SOPs are regularly updated annually or bi-annually.

Do - monitor and approve proposed changes to Stability SOPs.

(Avoid stability and quality control laboratory personnel displaying a non-awareness of the departmental SOPs in their essential day-to-day work).

Do - train and re-train staff in the correct use and understanding of current SOPs.

Do's & Don'ts for Stability Departments.

Do - check the firms SOPs adequately cover all aspects of stability operations required by the FDA or Agency.

Do - insure the instructions and details in the SOPs are adequate and

sufficient to assure consistent and repeated operation by staff, reading the SOPs.

Do - check staff are aware of latest *edition* of the Stability SOPs, affecting their day-to-day work.

Do - provide frequent departmental training in 'reviewing and understanding' the principles of the SOPs.

ALWAYS
KEEP
DEPARTMENT
SOPs
ON SITE

Do - insure operational personnel are aware of the latest editions of the SOPs and where they can be located in their stability department (All SOPs on Site).

Do - insure they are able to refer to the SOPs for rapid guidance in performing their routine daily duties and tasks.

Do - insure supervisors and personnel have signed a '*Read and Understood*' form annually indicating full awareness of the SOP contents.

Do - insure SOP distribution is adequate and the SOP Change Control System really works and is consistently *on time*.

Do - insure the 25°C *climatic* area for storing the ANDA / NDA and OTC stability samples at 25° C ($\pm 2^\circ$) is a **controlled** environment room.

Do - insure access is through an controlled-access door, that does not affect the environmental temperature - every time the door is opened.

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Don't - allow the stability room to be used as a stability office, where personnel are continually entering and leaving the controlled facility.

Don't - allow an air-conditioned 22° -25°C *stability office* to function as a 25°C climatic room.

Don't - store the 25°C long term stability samples in an office.

(In terms of GMP compliance such a facility is inadequate and the environment cannot be controlled).

Don't - install unreadable chart temperature recorders due to the smallness of the rotating chart.

(Out-of-specifications temperatures are not adequately shown on these charts, as the range divisions on the chart are cramped and often too small. Narrow chart sensitivity scales are generally unsuitable and unreadable. The compliance value of such a temperature recording system is of minimal value and open to agency challenge).

Do - insist that current recording devices are fitted with larger chart recorder so that the daily temperatures and OOS values can be read with accuracy and precision.

Do - insure there is a system for 60% RH control (environmental humidity).

Do - insure the stability room has sufficient temperature probes at the *upper and lower* levels of the room

where the stability samples are being stored.

Do construct a dedicated stability room with controlled environmental facilities that maintain the temperature at 25 °C ($\pm 2^\circ$ C) and the relative humidity at 60 % RH ($\pm 5\%$).

Do install the 30° and 40° C climatic chamber units *inside* the controlled stability areas or rooms.

Don't - allow stability samples for ANDA/NDA and OTC (development, or production samples) to be stored in cardboard boxes on cramped shelving (i.e. stacked one on top of the other).

(Reason - the samples are not exposed to the environment uniformly as they are protected by the insulating cardboard boxes in which they are stored.

Thus the lower samples are screened by the newer samples and a uniform controlled exposure to temperature *and* humidity is not generally achieved.

The older stability samples at the bottom of the cardboard box will be temperature and humidity screened by the several upper sample layers.)

Do avoid product exposure to large seasonal variations which do not keep the temperature in (non-insulated) stability rooms within a $\pm 2^\circ$ C range of 25° C, in either winter or summer.

Do avoid *uneven* room temperature *exposures* (near doorways, vents, fans.)

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Do insure the samples are arranged on the shelving in a neat, orderly manner.

Do insure there is not a large *across* room-variation in temperature and humidity. Both these variables must be adequately controlled (<5 %).

Do insure the upper and lower shelves have been challenged for temperature compliance. (A single chart recorder probe does not record the temperature accurately at which all the stability samples are stored. Multiple probes are necessary - i.e. > 2 upper and 2 lower.

Do insure the room temperature validation studies have been conducted to insure the firm is aware of the actual storage parameters of the stability ANDA/NDA and OTC test samples.

Do - insure there is a substantive review and control of stability temperature *recorders or charts*.

Do - insure temperature/RH charts are reviewed for out-of-specification (OOS) temperature and RH values.

Review Recording Charts for OOS Values - Daily

Do - insure the monitoring control charts are adequately signed and filed in an rapid retrieval system.

Do - insure adequate quality assurance evaluation is performed on the recording charts.

Do - insure there is corrective action taken when the stability temperature goes out of the specifications (OOS).

Do - insure that is possible for the firm to conclusively assure the FDA that the filed drugs were held at 25° C, 40° C ($\pm 2^{\circ}$ C) for the required storage periods of 3, 6, 9, 12, 18, + etc. months.

Do - insure a corrective action SOP exists - to determine the procedures to follow after a failure of the recording equipment or power supply during an ongoing stability study.

Do - insure corrective actions are carried out, documented and *closed*.

Have emergency procedures in place

Do - insure there are written emergency procedures for the use of *calibrated* hand-thermometers and recording logbooks due to recorder or stability probe failures.

Do - insure air-condition failures or equipment shutdowns are recorded.

Do - insure periodic revalidation and temperature distribution studies of the climatic chambers are carried out (every two years or when there is a change).

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Do - insure Original Data Summary Sheets are never replaced with unauthorized "corrected versions".

Do - outlaw the use of "White-Out tapes or liquids" in stability and other reports.

Do - review of the annual report prepared for the FDA to show that the ongoing stability testing has been met, as per the filed ANDA commitment.

Agency Case-History I. - Data values go unrecorded.

Investigations highlighted that one set of data values had not been recorded. The appearance that the stability data sheets are a direct and accurate transfer procedure of the raw data in the laboratory notebooks is open to question and further investigation.

This technique appears to be used to alter raw data when the original worksheet data was not in compliance.

Case History II - Lost raw data

The 6 month data point for the product potency was required to be evaluated by microbial assay. However the raw data to support this assay value in the stability data sheet was not able to be found. Further investigation highlighted that this raw data was untraceable.

Do - insure there is no lost data and full *traceability* of stability test points.

Do - insure summary data sheets

containing 'failed analysis results' are meticulously signed and filed.

Do - insure there exists a well documented reporting system for the **repeat** testing of stability data, according to written SOPs.

Do - insure traceability of ALL tests performed via the laboratory worksheets, resulting in credibility of the laboratory test results.

Do - investigate thoroughly if it appears that the stability data is tested and repeat tested *until* it passes.

Do - insure established procedures for investigating abnormal assay fluctuations or out-of-specification (OOS) results in the analytical and microbial stability testing program, is both operational and functional.

Do - insure OOS SOPs are written and the principles of the Judge Wolin's decisions are followed and properly investigated.

Do - review and audit stability documentation in order to establish the authenticity of the stability test results reported to the FDA in ANDAs or Supplements or Annual Reports.

Do Insure there is a *formal pre-submission* internal auditing program

Do - insure the firms does verify the 100% transfer of raw data readings and results obtained from the individual laboratory workbooks to the final computer stability print-out reports.

(Where *intermediate* summary sheets and analysis request forms

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are used, these intermediate data sheets should be *signed and stamped* as bona fide and accurate by Quality Assurance).

Do - insure the final stability study is signed off by the Director of Quality Control and the firm has a SOP specifying the *acceptance and sign-off* procedure for a completed stability study, to ensure that the study is complete and accurate.

Do - insure that no laboratory raw data is unavailable or missing in support of the Stability Summary Data Reports.

Do - insure proper *cross-referencing* of laboratory notebooks and worksheets with computerized documentation prior to data being submitted to the FDA.

Do - insure retrospective audits trails of ANDA stability reports to summary data sheets and back to laboratory workbooks clarify that the FDA filed data can be supported by the raw laboratory test data.

Do - insure the firm does have a comprehensive and functional laboratory data reporting system for test results.

Do - insure that data points are not missing (e.g. pH values; missing potency from crimp-end of semi solid tubes etc.).

Do - insure stability test values are not different from the filed values.

Do - insure the use of *bound and numbered* laboratory notebooks.

Note - The use of unnumbered analytical worksheets for recording analytical data should be discontinued and is not in GMP compliance).

Do - insure that stability data is not **selectively** screened prior to computerisation.

Do - insure the absence of discrepancies and different values in ANDA Annual Reports and the original laboratory raw data.

Do -[Case study:- Review of the annual report prepared for the FDA showed that the ongoing stability testing as per ANDA commitment showed an original report in the stability files with a test data line covered with "white tape". This data report was photocopied and sent to the FDA. The photocopy did not reveal the 'white-out' data in question.]

Do - insure traceability of workbook reference page numbers and dates relating to the original raw data in laboratory workbooks.

Do - insure the traceability of any repeat testing performed on the stability samples is clearly referenced on the stability documentation used to prepare the computerized stability reports.

Do - insure the need to prepare an SOP for cross-referencing laboratory note-book data with computerised stability test result documentation.

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Do - insure all repeat testing performed at the same test interval is cross-referenced *together* with all the tests conducted.

Note: a reviewer requires to audit *all* testing performed on the stability test sample and not only the raw data in the laboratory notebooks that *passed* the stability check specifications.

Do - insure all stability data points are present and are in full compliance with the *pre-written* stability protocol.

Do - insure a full review of the stability protocol and a comparison of the test procedures carried out on the stability samples - at *each* test station -in order to highlight any incidence where stability data points may be absent or OOS.

Do - insure that no raw data is **omitted** from the stability reports or in the Annual Reports submitted to the FDA.

Do - insure stability SOPs are adequate and routinely reviewed for GMP compliance by written *in-house* audits.

Do - insure the existing SOPs do control the functions of the stability department. (45-50 SOPs presented are a prerequisite to operate a stability department for an innovative or generic drug manufacturing company).

Do - insure that SOPs are not deficient both in the **content** and **detail**.

The lack of suitable SOPs in a stability department may result that much of the stability management and testing of the stability samples are erratic and *out-of-control* resulting in a future failed PAI review

Do - insure that SOPs are readily available and routinely followed and updated (i.e. after a change or annually).

The lack of a full set of stability SOPs and the fact that the SOPs are incomplete or that stability personnel are poorly trained on the contents of the SOPs is strong evidence to an agency that the firm's stability testing program is not in current GMP compliance.

Do - insure samples are analyzed on time using; *First-In-First-Out* (FIFO).

Do - insure that it is not possible, for a sample in a stability program to remain untested after the 'due date' and thus skip the designated 'testing interval'.

Do - insure the Certificate of Analyses are not *out of date* for time zero when the sample is eventually placed on stability at a 'start date' several months after the initial C-of-A. was performed.

[Reason - the sample assay value potency may have *degraded* by several months aging which would not be reflected by the *initial* certificate of analysis - some time earlier].

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Do - insure the presence of stability SOPs controlling the maximum time period [30 days] between initial testing (Certificate of Analysis at time zero) and the 'Start Date' of the stability study in order not to invalidate the initial stability results.

Do - insure that all the stability SOPs are regularly updated according to the firm's SOP index.



OBSERVATIONS

Recent PAI observations associated with stability units are shown giving the reader a brief overview of agency observations

- Traceability of **retested** stability samples difficult and inconsistent.
- Traceability of raw data **inconsistent**.
- No written procedures for reporting stability results precisely.
- 'Corrected' data substituted on FDA summary data sheets.
- Use of 'white-out liquid' in stability reports to obscure test results.
- Annual reports to FDA **not** accurate or authentic.
- Lack of stability and analytical SOPs to insure GMP compliance.
- Stability data reports not internally audited and reviewed.
- Data transfer from raw documents to final report not verified.
- No review of temperature / RH

charts.

- Uncontrolled storage of charts makes retrospective temperature / RH chart review, difficult and time consuming.

- No written emergency procedures after equipment breakdowns.

- No corrective action taken after stability system failures.

- Stability storage recording temperature procedures not in cGMP compliance.

- Stability climatic room must be dedicated to stability sample storage.

- Stability room general office area for multipurpose use.

- Single-probe recorders are not suitable for temperature control.

- No *periodic* revalidation of stability chambers.

- Inadequate temperature validation studies performed in stability room.

- Uneven temperature distribution - and temperatures are out of the stated specification range in stability rooms.

- No controlled storage of stability samples before testing.

- Upper and lower sample room temperatures have not been validated.

- Overall stability facilities in violation GMP compliance.

- Absent pH values and missing data test points.

- Sample re-tests and to-be-repeated procedures violate Wolin's rules.

- Missing data points with only passing stability test values *selected*.

Stability reports not signed of by QA Director.

- Stability Room for 25^o C samples used as a working office with inadequate environmental controls.
- No substantive review of stability temperature recorders or charts.
- Original Data Summary Sheets replaced with "corrected versions" - including the use of "White-Out tape" in stability reports.
- Laboratory raw data unavailable or missing to support the Stability Summary Data Reports.
- Discrepancies and different values in Annual Reports and laboratory raw data of ANDA tested product.
- Stability data points are not in compliance with stability protocol.
- Inadequate controls on the overall stability testing program.

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