WHO-EM/EDB/081/E

Report on the

Consultation on regional guidelines on stability studies of medicines and biologicals

Jeddah, Saudi Arabia
25–28 February 2006

World Health Organization
Regional Office for the Eastern Mediterranean

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Document WHO-EM/EDB/081/E/03.07/102

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1. INTRODUCTION

The World Health Organization's Regional Office for the Eastern Mediterranean (WHO/EMRO) held a consultation on regional guidelines on stability studies of medicines and biologicals on 25–28, February 2006 in Jeddah, Saudi Arabia. The meeting was attended by participants from 12 countries of the WHO Eastern Mediterranean Region. The objectives of the consultation were to:

- review national requirements of stability studies of medicines and biologicals;
- update participants with recent advances in stability studies of medicines and biologicals; and
- develop regional guidelines on stability studies of medicines and biologicals.

In his opening address to the meeting, Dr Hussein A. Gezairy, WHO Regional Director for the Eastern Mediterranean, noted that assuring the quality of medicines through the production, storage, supply and use cycle was one of the main components of the WHO Medicines Strategy. Medicine stability data would provide evidence for retest dates for drug substances and expiry dates for products, as well as reconstituted drug preparations. To achieve this objective, it was important to address all aspects related to drug stability and maintenance of medicine quality throughout shelf-life.

Medicine stability had an important regulatory dimension. National medicine regulatory authorities should clearly indicate the national stability requirements and should have the national expertise to validate the stability data provided, as well as monitor the quality of medicine throughout the shelf-life. In this respect, harmonization of stability requirements at regional and global levels was of great importance. The example of the GCC stability guidelines and the Arab stability guidelines were great steps forward. The meeting was expected to develop the regional guidelines which could be the basis for harmonized stability requirements in the Region. It was important to involve medicine regulatory authorities, the pharmaceutical industry and academic institutions in the finalization of the regional guidelines.

With the ongoing developments in biotechnology, many medicines in the future would be of a biological nature and might be formulated in specific and complex drug delivery systems. These new medicines and the medicine delivery system would require special attention with respect to their stability studies and requirements. Biologicals and biotechnology products were complex and were usually more subject to the various degradation mechanisms, which might be physical, chemical or microbiological. Stability testing of these products should be appropriately designed to be stability-indicating methods. He closed by emphasizing the need to develop the appropriate expertise at national and regional levels in all areas related to stability testing of new materials, medicine products, and biological and biotechnology products.

Dr Yasser El Ghamry, General Director, Eastern Health Province, delivered a message on behalf of H.E. Dr Hamed Almanee, Minister of Health, Saudi Arabia. In his message, the Minister emphasized the technical importance of developing regional guidelines on stability

studies. He highlighted some of the important activities being undertaken by the Ministry to assure the quality, safety and efficacy of medicines registered in Saudi Arabia. He also referred to the newly established Saudi Food and Drug Administration, and the growing local pharmaceutical industries in Saudi Arabia.

Dr Esmail M. Niazy (Saudi Arabia) was elected Chair of the meeting. The programme and list of participants for the meeting are included as Annexes 1 and 2, respectively. The full text of Dr Gezairy's speech is attached as Annex 3.

This report provides a summary of the presentations and discussions. A compact disc containing all the presentations and other meeting-related documents was distributed at the end of the meeting.

2. TECHNICAL PRESENTATIONS

2.1 Global perspective

Dr Abdel Aziz Saleh, WHO EMRO

The main points discussed in the consultation on stability studies in a global environment, held in Geneva on 13–14 December 2004 are as follows.

- Calculations based on meteorological data have shown that the existing long-term stability conditions in WHO guidelines for Zone IV (30 C/65%RH) do not reflect climatic conditions in many countries which have hot and very humid areas, such as Brazil, Cuba, China, India, and all of the Asian countries.
- Predicting stability under one set of long-term stability testing conditions from data generated at another set of conditions involves an element of risk. However, studies under more stressful conditions underwrite stability at less stressful conditions.
- It is desirable to achieve a single harmonized, long-term stability testing condition for Zone IV. Can this be achieved without compromising patient safety?

The following future options for the WHO guideline were proposed and discussed. These are not listed in any order:

- Revert to 30 C/70%RH as the long-term stability testing condition for Zone IV as it is likely that considerable data are already available. This might service as a potential platform for future harmonization between ICH and WHO.
- Change to 30 C/75%RH as the long-term stability testing condition for Zone IV in the interest of patient safety worldwide
- Add a new climatic Zone IVb to accommodate hot and very humid areas (30 C/75%RH). The present Zone IV (30 C/65%RH) would become Zone IVa.

As a result of the discussions in the consultation, it was recommended that the existing WHO guideline on stability testing should be reviewed in the light of new information on climatic conditions in Zone IV as raised by Asian countries.

After extensive discussion, the WHO Expert Committee on Specifications for Pharmaceutical Preparations in its meeting in Geneva on 24–28 October 2005 reached consensus that the WHO stability guidelines be amended to reflect conditions for Zone IV as follows:

Zone IVa (30 C and 65% relative humidity)
Zone IVb (30 C and 75% relative humidity)

It was agreed that each individual Member State within the former Zone IV would need to indicate which of these conditions (Zones IVa or IVb) would be applicable in its territory.

2.2 Regional perspective

Dr Abdel Aziz Saleh, WHO EMRO

The main recommendations of the last WHO intercountry workshop on the validation of expiry dates of medicines, held in Amman, Jordan, from 29 March to 1 April 1993 were as follows.

1. Medicine regulatory authorities in various countries, in close collaboration with the pharmaceutical industry, professional associations and academic institutions, should develop clear guidelines on requirements for drug stability and expiry date determination. The existing WHO guidelines and the draft ICH guidelines can be taken into consideration.

2. Ministries of health and medicine research institutions and faculties of pharmacy should conduct operational research to identify the problems related to drug stability and appropriate approaches for solutions.

3. Medicine regulatory authorities should request educational institutions, industry and professional associations to identify and play their role effectively in ensuring compliance with GSP, with a view to maintaining the stability of drugs.

4. Appropriate education on this aspect should be provided to the public by various professional organizations through the mass media.

5. WHO should collect information on the stability and shelf-life of active drug substances in relation to the shelf-life of finished products.

6. WHO should consider convening an expert meeting to discuss various issues of stability and expiry dates of raw materials.

Following this meeting, the Arab Union of Pharmaceutical Manufacturers (AUPM) in collaboration with WHO published the Arab Guidelines on Stability Testing of Pharmaceutical Products. Information collected from various countries shows that most of the countries are not following the regional guidelines.

2.3 A risk-based approach to establish stability testing conditions for Northern Africa, the Arabian Peninsula, the Middle East and Pakistan
Dr Manual Zahn, WHO Temporary Adviser

The physico-chemical background of stability studies includes discussions of:

- Mean Kinetic Temperature (MKT)
- Saturation Vapour Pressure (PS)
- Relative Humidity (RH)

The Climatic Zone concept developed out of seminal studies and research on climatic zones (Paul Schumacher), derived testing conditions (Wolfgang Grimm), revised conditions (Grimm) and Köppen's climatic classification system.

Several key principles must be followed in establishing stability testing: 1) Evaluation of climates should be based on mean meteorological data (temperature and dew points) to calculate MKT and PD; 2) The hottest and most humid place within a country, region or common market determines stability testing conditions applicable to the whole country, region or common market.

Stability risk factors include:

- Internal factors, such as reactivity of active ingredient(s), excipients, packaging material and interactions between components
- Factors relating to manufacture, such as batch size, equipment, quality of components, etc.
- External factors such as: heat and moisture, light, pH, oxygen, etc.
- Physical damage during shipment and storage.

'Built-in' safety margins are determined by conducting stability testing at more challenging conditions than climatic conditions.

The presenter discussed in more detail the climatic data of some countries of the Region and suggested the appropriate stability testing conditions for each country. Stability testing of special pharmaceutical products was also discussed, such as aqueous-based products packed in semi-permeable containers, and products packaged in impermeable containers.

2.4 Industrial perspectives on stability studies
Dr Lina Nabulsi, WHO Temporary Adviser

There are 12 principles (W. Grimm) which are decisive for stability testing and are applicable to all stages of development on the dosage forms.

- Systematic development
- Selection of batches and samples
- Test criteria

- Analytical methods
- Specifications
- Storage conditions
- Testing intervals
- Storage period
- Number of batches
- Packaging materials
- Evaluation
- Statements

The pharmaceutical industry believes that specifications and analytical methods are the most critical aspects of stability studies. Experience has shown that some protocols follow strictly the most recent guidelines while for others still more experience is needed to develop a method of analysis for related substances or degraded products.

With respect to storage conditions, while the industry performs the accelerated studies at 40ºC/75%RH for six months using a controlled chamber, long-term storage conditions are an issue that is not well resolved. Some industries still incubate long-term stability samples at ambient conditions, while long-term storage condition requires investment in a walk-in chamber.

Dr Nabulsi concluded the presentation with the following recommendations:

- Establish and declare the regional climatic zone country by country
- Finalize the storage condition for zone IV
- Establish national/regional labelling storage statements
- Emphasize the importance of ongoing stability studies
- Urge regional health authorities to focus on post-marketing sampling and analysis of drug products
- Conduct training workshops for industry and health authorities on developing, validating and evaluating specifications and analytical methods (related substances).

2.5 Stability studies and storage requirements

Dr Saleh A. H. Khalil, WHO Temporary Adviser

The presenter discussed the problems associated with transportation, distribution and storage of medicines in climatic zones III and IV, and the extent of post-marketing instability of selected drug products in climatic zones. He also recommended strategies for storage of medicines in climatic zones III and IV.

Expiry is dependent on storage conditions and deviations from the recommended storage conditions render expiry dates invalid. For example, a rise of 10 °C above recommended storage temperature can shorten the shelf-life to half its value.

Based on the result of stability studies the following storage conditions may be recommended:

- In a refrigerator at 2–8 °C
- In cool and dry place (NMT 15 °C and RH about 35%)
- At controlled room temperature (below 25 °C, below 30 °C)
- At room temperature, avoid excessive heat.

Some of the problems encountered during transportation, distribution and storage of medicines include:

- Lack of observance of good storage practices
- Lack of air-conditioning and dehumidifier systems operating 24 hours a day in some warehouses and the majority of community pharmacies
- Occasional power failure and lack of generators.

Some research studies have been conducted on representative examples of post-marketing stability of some medicines stored in climatic zones III and IV, such as aspirin tablets, cyclophosphamide vials and chloramphenicol eye drops.

To maintain post-marketing stability of medicines stored in climatic zones III and IV, the following options may be considered.

- Adoption of good storage practices during all stages of: transportation; short-term storage at ports of arrival; distribution; and long-term storage in warehouses and community pharmacies.
- Development of formulations and package system that withstand prevailing storage conditions of zones III and IV, e.g. use of Al/Al instead of PVC/Al blisters.
- Shortening of shelf lives of medicines marketed in climatic zones III and IV to half their derived values for zones I and II.
- Conducting post-marketing stability studies of medicine to ensure product quality.

2.6 Stability of pharmaceutical raw materials: drug substances and excipients

Dr Saleh A. Khalil

Conducting stability studies on raw materials is very important.

- Raw material stability is the core of finished product quality.
- Raw materials that lost one or more elements of stability and used in production, would lead to defective finished products.
- Raw material stability profiles are required for product registration in the European Union and United States of America.
- Expiration dates and retest dates are derived from stability studies.
- Some elements of stability are tested in both raw materials and finished products, for example the degradation products of some drugs and excipients.

Forms of instability of raw materials (drugs and excipients) include; physical, chemical, microbiological, toxicological and therapeutic.

3. COUNTRY PRESENTATIONS

3.1 Bahrain

Dr Sawsan Abbas Murad

The main points of the guidelines are as follows.

- Stability studies should be attested by quality assurance section and authorized by manufacturer. Stability studies should be conducted on the product in the same container-closure system intended for marketing in Bahrain.
- Stability studies should be provided for at least 3 production batches, the following should be clarified at the beginning of the document:
  - Batch numbers, dates of manufacture and dates of expiry of batches tested
  - Storage conditions of temperature and relative humidity used during the study protocols
  - Samples should be taken for analysis at certain points of time, i.e. every 3 months at least during the first year and every six months thereafter
  - Analysis method
  - Parameters tested
  - Conclusion of the studies pertinent to stability and suggested shelf-life and storage condition (the conclusion could be added at the end of the document)
- Tests should cover physical, chemical, biological and microbiological attributes.
- Conditions for accelerated stability studies testing was discussed.
- Real-time should cover at least 12 months duration at long term and at least 6 months data at intermediate storage conditions.

General conditions for long-term stability studies

Study	Storage condition	Minimum time period covered by data at submission
Long term for zones III and IV	30 ºC ± 2 and 65% RH ± 5%	12 months
For zones I and II	25 ºC ± 2 and 60% RH ± 5%	12 months
Accelerated	40 ºC ± 2ºC and 75%RH ± 5%	6 months

Conditions for refrigerated drugs

Study	Storage condition	Duration
Long-term	5 ºC ± 3 °C	12 months
Accelerated	25 ºC ± 2 ºC and 60%RH ± 5%	If change occurs between 3–6 months of accelerated stability testing, retest should be done. Period to be based on real time data. If change occurs within the first 3 months of accelerated test, more frequent testing at a shorter period should be done. No need for retesting through the 6 months period if a significant change occurred within the first 3 months.

Drugs stored in a freezer

Study	Storage condition	Duration
Long-term	–20 ºC ± 5 ºC	12 months

Single batch testing at 5 ºC±3 ºC for studies of effects of change of temperature during shipping on at least 3 production batches should be used.

- If container-closure system to be registered is superior to the one in the stability studies, then comparative stability data may not be required.
- If the product is to be registered in moisture-permeable container such as PVC or same grades of polyethylene or if the closure system allows moisture permeation, the high humidity conditions should be considered in the stability studies at the recommended temperature.
- Stability data should be generated on 3 production batches. In case data are incomplete, a commitment should be made to update the requirements for full term stability studies on 3 production batches.
- Accelerated stability studies are useful in predicting the probable stability of a new product, but this should be verified by studies on production batches in the pack intended for registration at the maximum recommended storage temperature for the full term proposed, e.g. at 30 °C, if the recommended storage temperature statement is "Store below 30°".
- Accelerated studies are done with the purpose of increasing the rate of chemical degradation and physical change of a drug by exaggerating the normal storage conditions. They include elevated temperature, high humidity, and intense light and when appropriate low temperature, freeze/thaw cycles.
- These accelerated studies help in equivalence tests of multi-source products and they are determined by the climate zone whereby the product is intended for distribution, and uses of the product and by the type of dosage forms.
- They are less suitable for semi-solid and heterogeneous formulations like emulsions. For climate zones III and IV, the conditions mostly accepted are 40 °C ± 2 °C and 75% RH ± 5% for 6 months.
- Lower temperature may be used for temperature-sensitive drug substance or product. In such cases, accelerated studies are carried out for six months at a temperature at least 15 °C above its designated long-term storage conditions with appropriate RH.
- Directions on actions to be taken if significant changes occurred were mentioned.
- Significant changes for a drug substance are defined as failure to meet its specifications such as the following:
  - If storage and transportation may occur outside the storage criteria then 3-month stability studies at 45–50 ºC and 75% RH are required
  - Stability studies should include testing of several attributes of the drug product that are susceptible to change during storage and are likely to influence quality/safety and or efficacy

– For multi-dose injectables containing antimicrobial preservative, a microbial challenge test at the end of shelf life is required in addition to the chemical assay of the preservative during the studies.

After constitution or dilution, if applicable, stability studies should be conducted to provide information for the labelling on the preparation, storage condition and in-use period of the constituted or diluted product. Such studies should be performed at initial and final time points or 12 months if full data are not available.

3.2 Egypt

Dr Marwa Hamdy Abdel Megeed

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.

Application for new product registration or otherwise registration must include a complete description and data derived from stability studies of the drug, including information pertaining to the suitability of the analytic methods used. Test results must justify the expiry date for the product.

Data must be submitted for at least three lots of each package form. When different strengths of the same formulation or variable sizes of the same container closure system are presented, it is not necessary to have a stability study for each strength or package size.

The written testing programme must include:

- The number of lots and the batch number for each including clearly the manufacturing date.
- Sample size based on statistical criteria to ensure valid estimate of stability.
- Storage conditions for temperature, humidity and/or light. The shelf stability study must embrace temperature and humidity records, at least, or seasonal intervals.

In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) to test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the length of studies chosen should be sufficient to cover storage, shipment and subsequent use.

The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed re-test period. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage conditions and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

General case

Study	Storagecondition	Minimum time period covered by data at submission
Long term	30 °C ± 2 °C/65% RH ± 5% RH	12 months
Intermediate	30 °C ± 2 °C/65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

Drug substances intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated	25 °C ± 2 °C / 60% RH ± 5% RH	6 months

Drug substances intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	–20 °C ± 5 °C	12 months

Other requirements include the following.

- Drug substances intended for storage below −20 °C should be treated on a case-by-case basis.
- Products to be reconstituted must embrace additional testing for samples reconstitutes and stored as mentioned on the label.
- A validated analytical method for the estimation of the active ingredient(s), with sufficient information proving its selective for the active ingredients(s), but not for the degradation product(s).
- When the degradation products are identified, the following information should be given: chemical nature, biological effects and the concentration likely to be encountered mechanisms of formation specifications and directions for testing their presence at the levels or concentrations expect to be present.
- The essential characteristics for each dosage form are identified.
- The frequency of investigation which must be at least 3 times every year for shelf-storage.
- For liquid and semisolid preparations, extreme temperature fluctuations (storage at 40 °C and 45 °C for at least 21 days) must be included while investigating drug strength and product characteristics every day.

Stability data should be developed for each type of container and closure proposed for marketing the medicine that differs in composition and/or design regardless of the cap liners. The possibilities of interaction between medicine and container-closure system and the

introduction of leachables into medicine formulation during storage should be assessed. Where package container sealant integrity is to be assessed higher than 75% relative humidity it may be appropriate to stress its adhesive properties at 37 °C (e.g. blister units and strip packages).

The expiration date must be written on the container accompanied with batch number and manufacturing date. In case where the three items cannot be printed, expirations date and batch number are minimal requirements. The storage requirements must be observed clearly by the consumer. Special instructions could be type written or printed in special colour or in a frame.

3.3 Islamic Republic of Iran

Dr Morteza Pirali Hamedani

The national regulations on medicine registration include requirements for stability testing on active ingredients and finished products, photo stability testing and packaging information. The registration file should include the following stability data:

- Stability summary and conclusion
- Stability testing of existing drug substances
- Maximum shelf-life for sterile products after first opening or following reconstitution
- Declaration of storage conditions
- Post-approval stability commitments
- For established drug substances in conventional dosage forms, literature data on the decomposition process and degradability of active substance are generally available together with adequate analytical methods. Thus, stability studies may be restricted.
- For the registration dossier, it is required to submit information on the accelerated and real time stability data of the final dosage from in its final container and packaging
- The stability tests are based on the international guidelines (ICH,WHO)
- Because of the 4 different climate conditions present in the country at the same time, the worst condition is suggested as the basis for stability studies (zone IV).

For pre-marketing authorization, the following are required:

- Accelerated stability data based on “stability testing on active substances and finished products” guideline for 6 months
- Intermediate stability data based on “stability testing on active substances and finished products” guideline for 1 year.
- Commitment for completing the stability data for at least 3 batches

For post-marketing authorization, reports of stability data for acceleration and long-term study at six-month intervals until expiration date for 3 production batches should be submitted to the regulatory authority.

In addition, there should be information about the suitability of containers for storage, transportation and use in pharmaceutical products. Moisture and light protection of container, compatibility with dosage form and performance should be considered.

3.4 Jordan

Dr Abeer Shaban

In Jordan the types of stability studies required are: accelerated stability studies, long term stability studies and ongoing studies.

The stability study section of any drug technical file should include the following.

- Accelerate stability study of drug product in its marketing packaging material at 40 ± 2 °C\75%RH at 6 months for prediction of shelf life with its statistical analysis for the same manufacturing site.
- Long-term stability study at storage conditions intended for use in the market (12 months) or whole shelf life or commitment.
- Batch analysis includes size of batches used in both studies, type of batch, batch number, manufacturing date, expiry date of primary package and its size.
- Results with analysis and discussion with justifications if needed.
- Study conclusion includes shelf-life of the product storage conditions and type of primary package.
- A commitment to submit long-term stability study of the first 3 production batches and ongoing stability studies.
- A commitment to submit annual report (includes stability studies covering shelf life of the product).
- Validation of stability indicating method including degradation products.
- In case of manufacturing site change, accelerated stability studies of at least 3 months for the new manufacturing site and a commitment to continue long-term stability study covering the shelf-life period should be submitted.
- If extension of shelf life is requested, chromatograms should be provided that cover the extended time asked for the shelf life.
- Method of analysis of all tests with chromatograms batch number and date of sample should be included.
- All the peaks of the chromatograms should be labelled clearly (including the solvent peak) or listed in a clearly table form.
- Internal standard used in HPLC should be stated with relative retention time.
- Chromatograms should indicate blank and standards of related substances.
- The guidelines have also identified the storage conditions, required labelled with additional labels and precautions which should be included as resulted from the stability studies accepted in JFDA.
- The guidelines also include a list of accepted precautions added to storage conditions which should not be used to cover a stability problem of the drug.

3.5 Lebanon

Dr Hala El Hout

According to the registration requirements in Lebanon, stability studies carried out by local pharmaceutical industries should include:

- Long term (real time) testing: evaluation of the organoleptic, physical, chemical, biological and microbiological characteristics of a drug product covering the expected duration of shelf-life 25 °C ± 2 °C at 60% ± 5% relative humidity covering a minimum of twelve months duration.
- Accelerated testing: designed to increase the rate of chemical degradation or physical change of a product by using exaggerated storage conditions
  - At 40 °C ± 2 °C at 75% ± 5% relative humidity covering 6 months of duration for a product to be stored long term under controlled room temperature.
  - At 25 °C ± 2 °C at 60% ± 5% relative humidity covering 6 months of duration for a product to be stored long term under refrigerated conditions.

Reports on stability studies are also requested for registration of imported drugs.

3.6 Morocco

Mr Mourad Derouiche

According to the guidelines, the objective of stability studies is the evaluation of the quality of products tested in different environmental conditions (temperature, relative humidity, etc). The purpose of the stability study is to establish storage conditions of drug substance or product and shelf life.

The guidelines detail selection of batches for: a) drug products and b) drug substances.

a) Drug product

A minimum of two primary batches (pilot) is needed to cover the proposed shelf life for the registration files and confirmed by a minimum of two production batches of 6 months (real time and accelerated storage) for the locally manufactured product. A commitment to complete stability studies for one production batch to cover the proposed shelf life should be submitted.

b) Drug substance

A minimum two primary batch (pilots) is needed for the registration file. Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing design is applied. Storage conditions during stability studies are as follows:

General case

- Long term 25 °C ± 2 °C/60 % ± 5% RH shelf life
- Intermediate 30 °C ± 2 °C/65 % ± 5% RH 12 months
- Accelerated 40 °C ± 2 °C/75% ± 5% RH 6 months

Storage in a refrigerator

- Long term 5 °C ± 3°C shelf life
- Accelerated 25 °C ± 2 °C/60% ± 5% RH 6 months

Storage in a freezer

Long term-20 °C ± 5 °C shelf life

Semi-permeable containers

- Long term 25 °C/40% RH shelf life
- Intermediate 30 °C/35% RH 12 months
- Accelerated 40 °C/65% RH 6 months

Impermeable packaging

- Stability testing can be carried out under any controlled or ambient humidity conditions

The stability guidelines have also specified the testing frequency as follows.

Real time

Product with a proposed shelf life more than year:

- every 3 months in the first year
- every 6 months in the second year
- annually thereafter.

Product with a proposed shelf life less than year:

- every 1 month in the first three months.
- every 3 months thereafter.

Accelerated condition

- 40 °C/75% RH
  minimum 3 time points including (0,3,6 months)
- Testing frequency: (intermediate storage)
- 30 °C/60% RH
  minimum 4 time points including (0,6,9, 12 months)
- Reduced designs
  matrixing or bracketing

3.7 Oman

Dr Sharifa Al-Jabri

The requirements of stability studies for medicine registrations in Oman include:

- The submitted stability study (accelerated and real time) should at least cover 3 months
- If stability study data cover 3 months ⟶ 18 months, shelf-life is granted
- If the stability data cover 6 months ⟶ 2 years, shelf-life is granted
- Any extension in shelf-life should be supported with real time stability data that cover the required shelf-life.

The manufacturer should report on any changes that may affect drug stability. These may include:

- change in formula including (active or inactive)
- change of packaging material
- change in manufacturer procedure
- change in shelf life
- change in storage condition.

3.8 Pakistan

Dr Farnaz Malik

In Pakistan, stability data are required as part of registration applications for:

- New drug molecules
- New combinations
- New dosage forms
- Imported drugs.

The format for stability studies includes the following information.

I. General product information

- Name, source, manufacturing sites, and date of manufacture of drug substance and drug or dosage form and strength, including formulation.
- Composition, type, source, size, description of container, closure, stuffers, seals, and desiccants.

II. Specifications and test methodology information

- Physical, chemical, and microbiological attributes and regulatory specifications
- Information on accuracy, precision, and suitability of the methodology
- Description of the potency test(s) for measuring biological activity, including specifications for potency determination.

III. Study design and study conditions

- Description of the sampling plan, including:
  - Batches and number selected.
  - Container and closures and number selected.
  - Number of dosage units selected
  - Sampling time points.
  - Duration of the study.
- Conditions of storage of the product under study (e.g., temperature, humidity, light, container orientation).

IV. Stability data/information

- Batch number (research, pilot, production) and associated manufacturing date.
- Analytical data, source of each data point, and date of analysis (e.g. batch, container, composite, etc).
- Tabulated data by storage condition.

V. Data analysis

- Evaluation of data, plots, and/or graphics.
- Documentation of appropriate statistical methods and formulas used.
- Results of statistical analysis and estimated expiration dating period.
- Results of statistical tests used in arriving at microbiological potency estimates.

VI. Conclusion

- Proposed expiration dating period and its justification.

3.9 Saudi Arabia

Dr Esmail M. Niazy

Guidelines for stability testing of new drug substances and products, have been prepared by the Saudi Food and Drug Authority. The draft document covers all the elements of stability testing guidelines.

The guideline defines the stability data package for a drug substance or drug product that is sufficient for refrigeration within Saudi Arabia. The guideline seeks to exemplify the core stability data package for drug substance or drug products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated. Alternative approaches may be used when there are scientifically justifiable reasons.

The guideline is intended to provide recommendations on the core stability study package required for the drug substance or drug products. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time

under the influence of a variety of environmental factors, such as temperature, humidity and light, and to establish a shelf life for the drug substance or drug product and recommended storage conditions for the drug substance or drug product.

The guideline addresses the information to be submitted in registration applications for drug substance or drug products. The choice of test conditions defined in this guideline is based on the analysis of the effects of climatic conditions in the areas of Saudi Arabia.

Drug substance

General storage conditions

Study	Storage conditions	Minimum time period covered by data at submission
Long-term	30 °C±2 °C / 65%RH ± 5%RH	12 months
Accelerated	40 °C±2 °C / 75%RH ± 5%RH	6 months

If it cannot be demonstrated that the drug substance will remain within its acceptance criteria when stored at 30 °C ± 2 °C/65%RH ± 5%RH for the duration of the proposed shelf life, the following options should be considered:

- A reduced retest period
- A more protective container closure system
- Additional cautionary statements in the labelling.

Drug substances intended for storage in a refrigerator

Study	Storage conditions	Minimum time period covered by data at submission
Long-term	5 °C ± 3 °C / 65%RH ± 5%RH	12 months
Accelerated	25 °C ± 2 °C / 60%RH ± 5%RH	6 months

Drug substances intended for storage in a freezer

Study	Storage conditions	Minimum time period covered by data at submission
Long-term	–20 °C ± 5 °C	12 months

Drug product

General storage conditions

Study	Storage conditions	Minimum time period covered by data at submission
Long-term	30 °C±2 °C / 65%RH ± 5%RH	12 months
Accelerated	40 °C±2 °C / 75%RH ± 5%RH	6 months

If it cannot be demonstrated that the drug product will remain within its acceptance criteria when stored at 30°C ± 2°C/65%RH ± 5%RH for the duration of the proposed shelf life, the following options should be considered:

- A reduced shelf life
- A more productive container closure system
- Additional cautionary statements in the labelling.

Drug products intended for storage in a refrigerator

Study	Storage conditions	Minimum time period covered by data at submission
Long-term	5 °C ± 3 °C	12 months
Accelerated	25 °C ± 2 °C / 60%RH ± 5%RH	6 months

Drug products intended for storage in a freezer

Study	Storage conditions	Minimum time period covered by data at submission
Long-term	–20 °C ± 5 °C	12 months

The draft guidelines also discuss in detail the following items:

- Test attributes, test procedures and acceptance criteria
- Testing frequency
- Microbial testing
- Bacterial endotoxines and pyrogen testing
- Analytical Methods
- Evaluation
- Statements/labelling
- Shelf life and the proposed framework of the stability report.

The guidelines also include recommendations for description of labelled conditions. When applicable, a single set of uniform storage statements is recommended to avoid different labelling.

Storage conditions	Storage statement for label
Room temperature	"Store up to 30 °C" or "Store up to 25°C" if deemed essential in some cases.
Refrigerator	"Store in refrigerator, between 2 °C and 8 °C".
Freezer	"Store in freezer between –5 °C and –20 °C".

A general precautionary statement may be included, but should not be used to cover stability problems.

Stability problem	Precautionary statement for label
For drug products that cannot tolerate refrigerating	"Do not refrigerate"
For drug products that cannot tolerate freezing	"Do not freeze"
For light sensitive drug products	"Protect from light"
For drug products sensitive to humidity	"Store in a dry place"

If applicable, recommendations should also be made as to the utilization period and storage conditions after opening and dilution or reconstitution of a solution, for example an antibiotic injection supplied as a powder for reconstitution.

3.10 Sudan

Dr Siham Abdoun Mohammed

According to the Pharmacy and Poisons Acts, it is an offence to manufacture, import, sell and offer for sale any pharmaceutical product unless registered under the provisions of the Act, and regulations and directives issued under the Act. All applicants for registration of pharmaceutical products should be familiar with all such provisions and requirements issued by the Federal Board of Pharmacy. The Directorate General of Pharmacy in the Federal Ministry of Health is the executive arm of the Board.

Stability data required for drug registration in Sudan follow WHO guidelines.

The stability report provides the results of stability testing for the formulation in each of the proposed marketed packages. The report should also include data on physical as well as chemical tests including those related to reconstitution of powder, dilution of an injection or dispersion of a tablet. The stated shelf life as well as storage conditions should be supported by the results of stability testing. It is also important to note that a stability-indicating method should be used in testing the stability of the product and complete data and information about degradation product should be submitted. With respect to both locally manufactured or imported products, additional stability studies are required whenever major modifications are made to formulation, manufacturing process, packaging or method of preparation.

Condition required for accelerated and ongoing stability studies are as follows.

Type of stability	Storage temperature (°C)	Relative humidity	Duration of study (months)
Accelerated stability studies	40 ± 2	75 ± 5	6
Real time stability studies	30 ± 2	65 ± 5	24

3.11 United Arab Emirates

Dr Easa Bin Jakka Almansoori

Stability studies are required during applications for registration of the following pharmaceutical products.

- NEC (new chemical entity)
- Generics
- Herbal
- Veterinary

Stability studies are also required with applications for variations related to composition, shelf life, storage conditions and container closure system change of the registered pharmaceutical products.

Stability studies are conducted according to the design provided by the national guidelines. Photo stability testing is required on at least one primary batch of the drug product if appropriate.

For registration purposes, stability information from accelerated and long-term studies should be provided for three primary batches. Not more than two of three batches should be of pilot scale.

Testing frequency is as follows:

- Real time: 0, 3, 6, 9, 12, 18, 24 months and annually through the proposed shelf-life
- Accelerated: 0, 3 and 6 months
- Stress test: 0, 1 and 3 months.

Bracketing may be applicable if the strengths are very closely related in composition, and if material composition of the container and type of closure are the same throughout the range.

Storage conditions

General case

Study	Storage condition	Minimum time period at submission
Long-term	30ºC ± 2ºC/65% RH ± 5% RH	6 Months to 12 months
Intermediate	30ºC ± 2ºC/65% RH ± 5% RH	Minimum 12 months
Accelerated	40ºC ± 2ºC/75% RH ± 5% RH	Minimum 6 months

Product stored in impermeable containers*

Study	Storage condition	Minimum time period at submission
Long term	30 ºC ± 2 ºC/Ambient humidity	6 months to 12 months
Intermediate	30 ºC ± 2 ºC/Ambient humidity	Minimum 12 months
Accelerated	40 ºC ± 2 ºC/Ambient humidity	Minimum 6 months

*(e.g. semi-solids in sealed aluminium tubes, solutions in sealed glass ampoules) Can be conducted under controlled or ambient humidity condition.

Products packaged in semi-permeable container

Study	Storage condition	Minimum time period at submission
Long term	30ºC ± 2ºC/35% RH ± 5% RH	6 months to 12 months
Accelerated	40ºC ± 2ºC/25% RH ± 5% RH	Minimum 6 months

Drug products intended for storage in a refrigerator

Study	Storage condition	Minimum time period at submission
Long term	5ºC ± 2ºC	6 months to 12 months
Accelerated	25ºC ± 2ºC/60% RH ± 5% RH	Minimum 6 months

Products intended for storage in a freezer

Study	Storage condition	Minimum time period at submission
Long term	20 ºC ± 2ºC	12 months

According to national requirements, stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and influence quality, safety and/or efficacy. The testing should also cover, as appropriate, the physical, chemical, biological and microbiological attributes, preservative content (e.g. antioxidant, antimicrobial preservative), and functionality tests (e.g. for a dose delivery system).

In case of incomplete stability data at time of submission, commitment should be made to continue long-term studies through the proposed shelf-life, and the accelerated studies for 6 months, and to place the first 3 production batches on real time stability studies through the proposed shelf-life and on accelerated studies for 6 months.

4. STABILITY TESTING OF BIOTECHNOLOGY PRODUCTS: A REGULATORY PERSPECTIVE

Mr Fausto Tanchella, WHO Temporary Adviser

Biotechnology products are sensitive to environmental factors such as high temperature, temperature excursion, relative humidity and light.

Due to the inherent complexity of the biotechnology products, there is no single stability-indicating parameter. A stability-indicating profile is identified to provide assurance that a change in identity, purity and potency of the product is detected. Such a context requires accurate and defined storage conditions to ensure that the product retains its full potency, purity and quality up to the expiration date.

Lyophilized products are usually studied at +25 °C ± 2 °C. In most cases, liquid products require refrigerated storage conditions, i.e. +5 °C ± 3 °C.

Stability testing of biotechnology products can be carried out in two phases: pre-approval and post-approval.

Pre-approval phase

In this phase, the following stability studies should be conducted:

- Long-term stability studies under normal storage conditions
- Accelerated stability studies to producing supporting data to establish expiration date and generate information on the product degradation profile.
- Studies under stressed conditions such as high temperature, cycling and light exposure to determine the effect of accidental exposure to extreme conditions (e.g. during shipment), to identify the specific test parameters being the best stability indicators, and to show pattern of degradation.
  - Testing frequency during these studies is decided to establish the stability profile of the product.
  - For long-term studies, the testing frequency is every 3 months during the first year, every 6 months during the second year, and then annually up to the proposed shelf-life.
  - For accelerated studies, testing should be carried out at least 4 times for a 6-month study.
- In-use stability studies for multidose products to demonstrate the compliance to the defined specification limits up to the last dose.

- Short-term studies up to the end of shelf-life to confirm product usage after exposure to higher temperatures.

Post-approval phase

In this phase, the following studies are carried out:

- Reduced post-approval stability plan can be adopted and carried out according to the approval GMP stability studies.
- Supporting stability studies designed on a case-by-case basis to provide data supporting a request for post-approval changes.

Types and duration of stability studies at different phases of drug development

When	How many	Type and duration
Phase I	1 batch	Long-term: length of Phase I 6-month accelerated
Phase II	1 batch of each formulation/ dosage/container	Long-term: length of Phase I 6-month accelerated
Phase III or process validation or technology transfer	3 batches or bracketing design	Long-term: forecasted shelf life 6-month accelerated
GMP	1 batch/year/dosage	Long-term: approved shelf life
Change of manufacturing site	3 batches or bracketing design	Long-term: approved shelf life 6-month accelerated
Change in processing parameters outside validated ranges	3 batches or bracketing design	Long-term: approved shelf life 6-month accelerated
Change to equipment of the same design	1 batch	Long-term: approved shelf life 6-month accelerated
Change to equipment of different design Change in primary packaging Change of supplier of excipient	Number of batches based on regulatory requirement and scientific justification	Long-term: approved shelf life 6-month accelerated
Deviation	Batch affected	At least 3-month accelerated

5. RECOMMENDATIONS

1. WHO in consultation with national medicine regulatory authorities should finalize the stability guidelines and submit them to the Regional Committee in 2006.

2. Pharmacy schools should revise undergraduate and postgraduate courses to include basic content of the regional guidelines, as well as stability studies for biotechnology and biological products.

3. WHO, national regulatory authorities and pharmacy schools should develop and implement regular training courses on stability studies and storage conditions.

4. National regulatory authorities and national pharmaceutical industries should organize regular training courses on stability and storage conditions.

5. National regulatory authorities should require the pharmaceutical industry to clearly indicate the appropriate storage conditions in national languages.

6. National regulatory authorities should ensure the implementation of good storage practices.

7. WHO, national regulatory authorities and pharmacy associations should develop and disseminate public education materials on good storage practices.

8. Pharmacy schools, national regulatory authorities and research institutions should carry out operational stability research and PMS studies to validate pharmaceutical product quality through out the shelf life.

Annex 1

PROGRAMME

Saturday, 25 February 2006

9:00–11:00	Opening Ceremony
	Regional Director's Address
	H.E. the Minister of Health's Message
	Objectives, Dr Abdel Aziz Saleh
	Election of Officers
11:00–12:00	Stability guidelines: global perspective, Dr Abdel Aziz Saleh
12:00–14:00	Stability guidelines: regional perspective, Dr Abdel Aziz Saleh
14:00–14:30	Stability studies: industrial perspective, Dr Lina Al Nabolssy
14:30–16:30	Country presentations
	Bahrain
	Egypt
	Islamic Republic of Iran
	Jordan
	Lebanon
	Oman

Sunday, 26 February 2006

8:30–11:00	The design of stability testing based on the climatic conditions in the Eastern Mediterranean Region, Dr Manuel Zahn
11:00–12:00	Stability studies and storage requirements, Dr Saleh Hassan Khalil
12:00–16:00	Country presentations
	Morocco
	Pakistan
	Saudi Arabia
	Sudan
	United Arab Emirates

Monday, 27 February 2006

8:30–10:30	Stability testing of biotechnology products: a regulatory perspective, Dr Fausto Tanchella
	Discussions
10:30–12:00	Stability requirements for raw materials, Dr Saleh Hassan Khalil
12:00–16:00	Discussions

Tuesday, 28 February 2006

8:30 – 11:30	Revised regional guidelines
12:00–12:30	Recommendations, Dr Abdel Aziz Saleh
12:30–14:30	Closing session

Annex 2

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Mrs Samah Abdel Aziz, Senior Secretary, WHO/EMRO
Mrs Hoda Omera, Senior Secretary, WHO/EMRO

Annex 3

ADDRESS BY THE REGIONAL DIRECTOR

Distinguished Participants, Dear Colleagues, Ladies and Gentlemen,

It gives me great pleasure to welcome you all to the Consultation on Regional Guidelines on Stability Studies of Medicines and Biologicals. I would like to thank H.E. Dr Hamad Bin Abdullah Almanee, Minister of Health of Saudi Arabia for graciously accepting to host this consultation. We are all honoured to be here and grateful for the generous hospitality that His Excellency and members of his team have extended to us. I would also like to thank Dr Tawfik Khoja, Director-General, Health Ministers' Council for the Cooperation Council States, and his team for their active participation in this consultation.

Assuring the quality of medicines through the production, storage, supply and use cycle is one of the main components of the WHO Medicines Strategy. Medicine stability data will provide evidence for retest dates for drug substances and expiry dates for products, as well as reconstituted drug preparations. To achieve this objective, it is important to address all aspects related to drug stability and maintenance of medicine quality throughout shelf-life.

The first aspect is educational. Pharmacy students should be taught, and pharmacy curricula should include the scientific principles and practical aspects of medicine stability, storage conditions and expiry dates. Such courses should include the practical aspects related to real storage conditions. This clearly indicates the importance of teaching the concept of mean kinetic temperature and the actual climatic conditions for medicines storage.

The second aspect is operational research. To ensure drug stability throughout the medicine shelf-life, there is urgent need to carry out field research on quality of medicines stored under practical conditions in each country. The results of such studies would provide important information to regulatory bodies on the national requirements for stability studies and storage conditions. A search of the regional research data base, the EMR Index Medicus, shows very few research studies have been conducted in this area.

Stability studies have another important research component. In addition to operational research studies to validate the indicated expiry date under practical storage conditions, research should also include stability of medicines following reconstitution and storage before use. Expiry dates following reconstitution should also be validated. I therefore expect schools of pharmacy and hospital pharmacies in our Region to play an active role in both teaching stability guidelines and conducting research in this important area.

Medicine stability has an important regulatory dimension. National medicine regulatory authorities should clearly indicate the national stability requirements and should have the national expertise to validate the stability data provided, as well as monitor the quality of medicine throughout the shelf-life. In this respect, harmonization of stability requirements at regional and global levels is of great importance. The example of the GCC stability guidelines and the Arab stability guidelines are great steps forward.

The present meeting is expected therefore to develop the regional guidelines which could be the basis for harmonized stability requirements in the Region. It is thus important to involve medicine regulatory authorities, the pharmaceutical industry, and academic institutions in the finalization of the regional guidelines.

There is another important dimension to medicine stability, and that is patient education. The patients should be clearly advised on how to properly store medicines, particularly reconstituted medicines. Patients should be advised to observe expiry dates of medicines, both those freshly procured and those stored in the house. Information on storage conditions, and expiry dates should be clearly labelled on medicines in national languages. Patients should also be advised on what to do with expired medicines.

With the ongoing developments in biotechnology, many medicines in future will be of a biological nature and may be formulated in specific and complex drug delivery systems. These new medicines and the medicine delivery system will require special attention with respect to their stability studies and requirements. Biologicals and biotechnology products are complex and are usually more subject to the various degradation mechanisms, which may be physical, chemical or microbiological. Stability testing of these products should be appropriately designed to be stability-indicating methods.

Your discussions and recommendations in this area will be of great value to our technical cooperation with countries of the Region. I would like to take this opportunity to thank the experts from outside the Region participating in this consultation, whose technical support is very much appreciated.

It is clear that we need to develop the appropriate expertise at national and regional levels in all areas related to stability testing of new materials, medicine products, and biological and biotechnology products. You may discuss how best we can develop our national and regional plans for human resource development in this important area.

I look forward to the outcome of this important consultation and wish you a pleasant stay in this beautiful city of Jeddah.