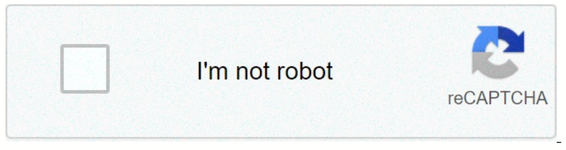


I am not robot!

Ich guideline for accelerated stability studies.

1. STABILITY STUDIES ICH Guidelines Q1A-Q1F Prepared By: Aman Dhamrait Pa 2. Objective of Stability testing Scope of Stability testing Rationale of stability studies Advantages of stability studies Variables affecting the stability Adverse effects of instability of drugs Stability Testing Terminologies ICH Q1A(R2) ICH Q1B ICH Q1C ICH Q1D ICH Q1E References 2 4. 4 “A measure of how pharmaceutical products maintains its quality attribute over a time.” 5. "..... 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 & light, & enables recommended storage conditions, re-test periods & shelf lives to be established” (ICH) 5 6. • Provide evidence as to how the quality of the drug product varies with time. • Establish shelf life for the drug product. • Determine recommended storage conditions. • Determine container closure system suitability. 6 7. • Chemical degradation of the product leads to lowering of the concentration of the drug in the dosage form. • Toxic products may be formed , due to chemical degradation of the active ingredient. 7 8. • Assurance to the patient • Economic considerations • Legal requirement 8 9. Formulation Packaging Site and method of manufacture ◦ API ◦ Finished product Batch size Batch to batch variability ◦ Process validation ◦ Quality risk management Container labelling Changes to product 9 10. Loss of active drug (e.g. aspirin hydrolysis, oxidation of adrenaline) Loss of vehicle (e.g. evaporation of water from o/w creams, evaporation of alcohol from alcoholic mixtures) Loss of content uniformity (e.g. creaming of emulsions, impaction of suspensions) Loss of elegance (e.g. fading of tablets and colored solutions) Reduction in bioavailability (e.g. ageing of tablets resulting in a change in dissolution profile) Production of potential toxic materials (e.g. breakdown products from drug degradation) 10 12. • CHEMICAL: Each active ingredient retains its chemical integrity and labeled potency within the specified limit. • PHYSICAL: The physical stability properties includes appearance, palatability, uniformity, dissolution and suspend ability are retained. • MICROBIOLOGICAL: Sterility or resistance to microbial growth is retained according to specified requirement. • THERAPEUTIC: Therapeutic activity remains unchanged . • TOXICOLOGIC: No significant increase in toxicity occurs. 12 13. STAGE 1- Early stage stress and accelerated testing with drug substances. STAGE 2- Stability on pre-formulation batches. STAGE 3- Stress testing on scale-up batches. STAGE 4- Accelerated and long term testing for registration purposes. STAGE 5- On-going stability testing STAGE 6- Follow-up stabilities 13 14. Development studies • Characterise compatibility with common excipients. • Characterise stability profile of API (E.g. susceptibility to acid, base, light, oxygen etc) • Characterise stability profile of early formulations (Especially susceptibility to heat, humidity & light) Confirmatory studies • Long term & accelerated studies on the product as it is to be registered 14 15. The ICH has so far released six guidelines for stability studies as indicated in table : 15 ICH GUIDELINES TITLE Q 1 A Stability testing of new drug substances and products (second revision) Q1B Stability testing : photo stability testing of new drug substance and products. Q1C Stability testing for new dosage forms Q1D Bracketing and matrixing designs for stability testing of drug substances and products Q1E Evaluation of stability data Q1F Stability data package for registration application in climatic zones III and IV 16. • Production batch • Pilot scale batch • Re-test period(API) • Accelerated testing • Intermediate testing • Stress testing • Bracketing • Matrixing 16 17. • Partition of the world into four temperature classes based on kinetic averaging of monthly temperatures, • Zones (Futscher & Schumacher 1972): I Temperate (21oC/45%RH) II Subtropical (25oC/60%RH with possibly high RH) III Hot & dry (30oC/35%RH) IV Hot & wet (30oC/70%RH) • The temperatures above are kinetic averages. 17 19. Region Zone I & II Countries Zone III & IV Countries Europe All Countries ---- America Argentia, Canada,Bolivia etc. Barbodas, Brazil, Venezuela, Panama etc (IV) Asia Japan, Afganistan, Israel etc Bangladesh, Hong Kong, India etc Africa Egypt, South Africa, Zimbabwe etc Mali, Uganda, Nigeria etc Australian/Oceanic Australia, New Zealand Papua-New Guinea, Fiji etc 19 21. • General • Stress Testing • Selection of Batches • Container Closure System • Specification • Testing Frequency • Storage Conditions • Stability Commitment • Evaluation • Statements/Labelling 21 22. Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation. 22 23. Main tool that predict the stability problems. Foundation for developing and validating analytical methods. For an API the following approaches may be used: When available, it is acceptable to provide relevant data published in the scientific literature to support the identified degradation pathways and products. When no data is available, stress testing should be performed. The nature of the stress testing will depend on the individual active substance and the type of pharmaceutical product involved. 23 24. Stress testing of the active substance can help in Identification of degradants Identification of degradation pathways Determination of which type(s) of stress affect the molecule: ◦ Photo-stability ◦ High Temperature ◦ Low Temperature ◦ Oxidation ◦ pH extremes ◦ Water 24 25. Oxidation: Typically done by placing the drug substance in aqueous solution of hydrogen peroxide. Goal is significant degradation (typically 10-30% of API) ◦ Can identify degradants ◦ Determine whether protective packaging is required ◦ Determine if an antioxidant should be considered for the drug product formulation. pH: Typically done by adding drug substance to buffered aqueous solutions at pH values from 1-10 ◦ Decide if the molecule will survive passage through the stomach Is enteric coating necessary? Should the drug be given by injection? 25 26. 26 Stress factor Conditions Heat 10°C increments Humidity 75%RH or greater Acid 0.1N Hcl Base 0.1N NaOH Oxidative 3%H2O2 Photolytic Xenon,Metal hailde lamp or Near UV,White florescent lamp 27. Data from formal stability studies should be provided on at least three primary batches of the active substance. The batches should be manufactured to a minimum of pilot scale by the same synthetic route as, and using a method of manufacture and procedure that simulates the final process to be used for, production batches. 27 28.

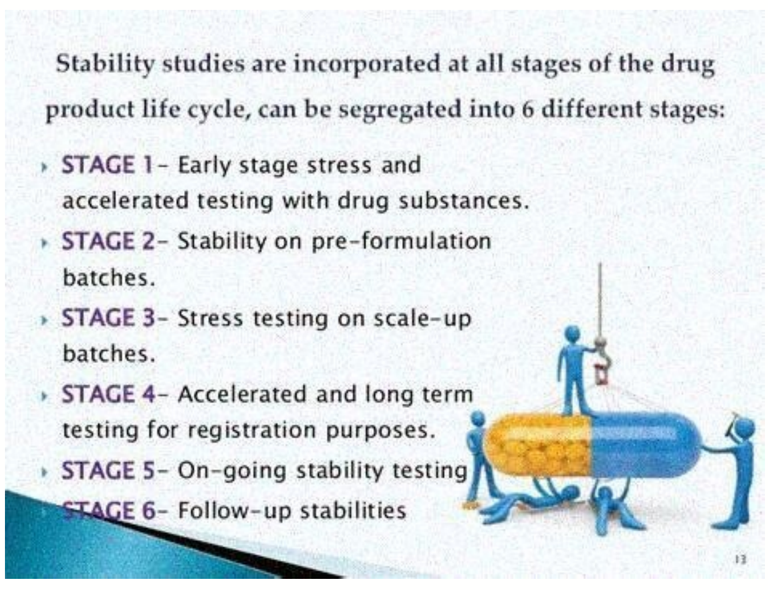
The stability studies should be conducted on the active substance packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.

28 29. • Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. • The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes. e.g. appearance, assay, degradation. 29 30. For long term studies: Year 1: every 3 months Year 2: every 6 months Subsequent years: annually At accelerated storage conditions: (6 month study) Minimum three points including t0 and tfinal, e.g. 0 3 6 (initial) (final) At intermediate storage conditions: (12 month study) Four points including t0 and tfinal, e.g. 0 6 9 12 (initial) (final) 30 31. A drug substance should be evaluated • To test its thermal stability • Its sensitivity to moisture(if applicable) • The long-term testing (minimum of 12 months) on at least 3 primary batches at the time of submission and • should be continued for a period of time sufficient to cover the proposed re-test period. 31 32. If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and “significant change” occurs at any time during six months’ testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. significant change – failure to meet its specification 32 Study Storage condition Minimum time period covered by data at submission Long Term* (Ambient) 25º C ± 2º C 60%RH ± 5% 12 months Intermediate** (controlled) 30º C ± 2º C 65%RH ± 5% 6 months Accelerated 40º C ± 2º C 75%RH ± 5% 6 months 33. If significant change occurs between 3 and 6 months testing at the accelerated storage condition, the proposed re-test period should be based on the real time data available at the long term storage condition.

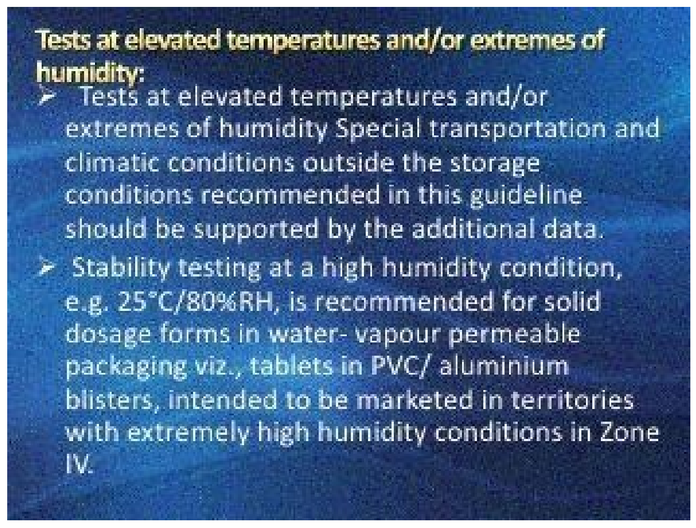
33 Study Storage condition Minimum time period covered by data at submission Long Term 5º C ± 3º C 12 months Accelerated 25º C ± 2º C 60%RH ± 5% 6 months 34. In the absence of an accelerated storage condition for active substances intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. 5°C ± 3°C or 25°C ± 2°C or 30°C ± 2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition. e.g., during shipping or handling 34 Study Storage condition Minimum time period covered by data at submission Long Term -20º C ± 5º C 12 months 35. • When available long-term stability data does not cover the proposed re-test period, a commitment should be made to continue stability studies in order to firmly establish the re-test period. • Where the data submitted is from fewer than 3 production batches, a commitment should be made to continue the long-term studies with additional production batches, to a total of at least 3. • If the submission does not include stability data on production batches, a commitment should be made to place the first 3 production batches on long-term studies through the proposed re- test period. 35 36.

Minimum of 3 batches of drug substance is tested. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned re-test period. The analyst must found the batch to batch variability & if it is small than only it is accepted & it can be done by different statistical test's (P value for level of significance for rejection). Where the data show so little degradation and so little variability then it is normally unnecessary to go through the statistical analysis; providing a justification for the omission should be sufficient. 36 37. A storage statement should be established for the labelling based on the stability evaluation of the active substance. Where applicable, specific instructions should be provided, particularly for active substances that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” must be avoided. 37 38. • General • Selection of Batches • Container Closure System • Specification • Testing Frequency • Storage Conditions • Stability Commitment • Evaluation • Statements/Labelling 38 39. The design of the formal stability studies for the pharmaceutical product should be based on knowledge of the behavior and properties of the active substance, from stability studies on the active substance, and on experience gained from clinical formulation studies. 39 40.

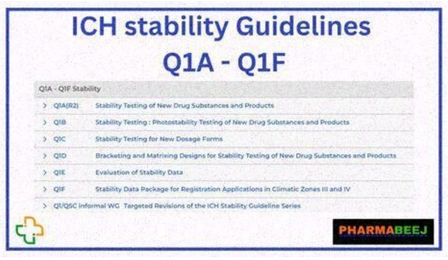
Data from stability studies should be provided on at least three primary batches of the pharmaceutical product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing.



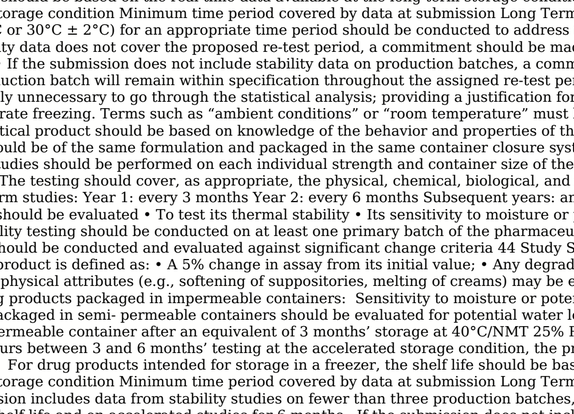
• Determine recommended storage conditions. • Determine container closure system suitability. 6 7. • Chemical degradation of the product leads to lowering of the concentration of the drug in the dosage form. • Toxic products may be formed , due to chemical degradation of the active ingredient. 7 8. • Assurance to the patient • Economic considerations • Legal requirement 8 9. Formulation Packaging Site and method of manufacture ◦ API ◦ Finished product Batch size Batch to batch variability ◦ Process validation ◦ Quality risk management Container labelling Changes to product 9 10. Loss of active drug (e.g. aspirin hydrolysis, oxidation of adrenaline) Loss of vehicle (e.g. evaporation of water from o/w creams, evaporation of alcohol from alcoholic mixtures) Loss of content uniformity (e.g. creaming of emulsions, impaction of suspensions) Loss of elegance (e.g. fading of tablets and colored solutions) Reduction in bioavailability (e.g. ageing of tablets resulting in a change in dissolution profile) Production of potential toxic materials (e.g. breakdown products from drug degradation) 10 12. • CHEMICAL: Each active ingredient retains its chemical integrity and labeled potency within the specified limit. • PHYSICAL: The physical stability properties includes appearance, palatability, uniformity, dissolution and suspend ability are retained. • MICROBIOLOGICAL: Sterility or resistance to microbial growth is retained according to specified requirement.



• Determine recommended storage conditions. • Determine container closure system suitability. 6 7. • Chemical degradation of the product leads to lowering of the concentration of the drug in the dosage form. • Toxic products may be formed , due to chemical degradation of the active ingredient. 7 8. • Assurance to the patient • Economic considerations • Legal requirement 8 9. Formulation Packaging Site and method of manufacture ◦ API ◦ Finished product Batch size Batch to batch variability ◦ Process validation ◦ Quality risk management Container labelling Changes to product 9 10. Loss of active drug (e.g. aspirin hydrolysis, oxidation of adrenaline) Loss of vehicle (e.g. evaporation of water from o/w creams, evaporation of alcohol from alcoholic mixtures) Loss of content uniformity (e.g. creaming of emulsions, impaction of suspensions) Loss of elegance (e.g. fading of tablets and colored solutions) Reduction in bioavailability (e.g. ageing of tablets resulting in a change in dissolution profile) Production of potential toxic materials (e.g. breakdown products from drug degradation) 10 12. • CHEMICAL: Each active ingredient retains its chemical integrity and labeled potency within the specified limit. • PHYSICAL: The physical stability properties includes appearance, palatability, uniformity, dissolution and suspend ability are retained.



• Determine container closure system suitability. 6 7. • Chemical degradation of the product leads to lowering of the concentration of the drug in the dosage form. • Toxic products may be formed , due to chemical degradation of the active ingredient. 7 8. • Assurance to the patient • Economic considerations • Legal requirement 8 9. Formulation Packaging Site and method of manufacture ◦ API ◦ Finished product Batch size Batch to batch variability ◦ Process validation ◦ Quality risk management Container labelling Changes to product 9 10. Loss of active drug (e.g. aspirin hydrolysis, oxidation of adrenaline) Loss of vehicle (e.g. evaporation of water from o/w creams, evaporation of alcohol from alcoholic mixtures) Loss of content uniformity (e.g. creaming of emulsions, impaction of suspensions) Loss of elegance (e.g. fading of tablets and colored solutions) Reduction in bioavailability (e.g. ageing of tablets resulting in a change in dissolution profile) Production of potential toxic materials (e.g. breakdown products from drug degradation) 10 12. • CHEMICAL: Each active ingredient retains its chemical integrity and labeled potency within the specified limit. • PHYSICAL: The physical stability properties includes appearance, palatability, uniformity, dissolution and suspend ability are retained. • MICROBIOLOGICAL: Sterility or resistance to microbial growth is retained according to specified requirement. • THERAPEUTIC: Therapeutic activity remains unchanged . • TOXICOLOGIC: No significant increase in toxicity occurs. 12 13. STAGE 1- Early stage stress and accelerated testing with drug substances. STAGE 2- Stability on pre-formulation batches. STAGE 3- Stress testing on scale-up batches. STAGE 4- Accelerated and long term testing for registration purposes. STAGE 5- On-going stability testing STAGE 6- Follow-up stabilities 13 14.



"..... 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 & light, & enables recommended storage conditions, re-test periods & shelf lives to be established" (ICH) 5 6. • Provide evidence as to how the quality of the drug product varies with time. • Establish shelf life for the drug product.

• Determine recommended storage conditions. • Determine container closure system suitability. 6 7. • Chemical degradation of the product leads to lowering of the concentration of the drug in the dosage form. • Toxic products may be formed , due to chemical degradation of the active ingredient. 7 8. • Assurance to the patient • Economic considerations • Legal requirement 8 9. Formulation Packaging Site and method of manufacture ◦ API ◦ Finished product Batch size Batch to batch variability ◦ Process validation ◦ Quality risk management Container labelling Changes to product 9 10. Loss of active drug (e.g. aspirin hydrolysis, oxidation of adrenaline) Loss of vehicle (e.g. evaporation of water from o/w creams, evaporation of alcohol from alcoholic mixtures) Loss of content uniformity (e.g. creaming of emulsions, impaction of suspensions) Loss of elegance (e.g. fading of tablets and colored solutions) Reduction in bioavailability (e.g. ageing of tablets resulting in a change in dissolution profile) Production of potential toxic materials (e.g. breakdown products from drug degradation) 10 12. • CHEMICAL: Each active ingredient retains its chemical integrity and labeled potency within the specified limit. • PHYSICAL: The physical stability properties includes appearance, palatability, uniformity, dissolution and suspend ability are retained. • MICROBIOLOGICAL: Sterility or resistance to microbial growth is retained according to specified requirement. • THERAPEUTIC: Therapeutic activity remains unchanged . • TOXICOLOGIC: No significant increase in toxicity occurs. 12 13. STAGE 1- Early stage stress and accelerated testing with drug substances. STAGE 2- Stability on pre-formulation batches. STAGE 3- Stress testing on scale-up batches. STAGE 4- Accelerated and long term testing for registration purposes. STAGE 5- On-going stability testing STAGE 6- Follow-up stabilities 13 14. Development studies • Characterise compatibility with common excipients. • Characterise stability profile of API (E.g. susceptibility to acid, base, light, oxygen etc) • Characterise stability profile of early formulations (Especially susceptibility to heat, humidity & light) Confirmatory studies • Long term & accelerated studies on the product as it is to be registered 14 15. The ICH has so far released six guidelines for stability studies as indicated in table : 15 ICH GUIDELINES TITLE Q 1 A Stability testing of new drug substances and products (second revision) Q1B Stability testing : photo stability testing of new drug substance and products. Q1C Stability testing for new dosage forms Q1D Bracketing and matrixing designs for stability testing of drug substances and products Q1E Evaluation of stability data Q1F Stability data package for registration application in climatic zones III and IV 16. • Production batch • Pilot scale batch • Re-test period(API) • Accelerated testing • Intermediate testing • Stress testing • Bracketing • Matrixing 16 17. • Partition of the world into four temperature classes based on kinetic averaging of monthly temperatures, • Zones (Futscher & Schumacher 1972): I Temperate (21oC/45%RH) II Subtropical (25oC/60%RH with possibly high RH) III Hot & dry (30oC/35%RH) IV Hot & wet (30oC/70%RH) • The temperatures above are kinetic averages. 17 19. Region Zone I & II Countries Zone III & IV Countries Europe All Countries ---- America Argentia, Canada,Bolivia etc. Barbodas, Brazil, Venezuela, Panama etc (IV) Asia Japan, Afganistan, Israel etc Bangladesh, Hong Kong, India etc Africa Egypt, South Africa, Zimbabwe etc Mali, Uganda, Nigeria etc Australian/Oceanic Australia, New Zealand Papua-New Guinea, Fiji etc 19 21. • General • Stress Testing • Selection of Batches • Container Closure System • Specification • Testing Frequency • Storage Conditions • Stability Commitment • Evaluation • Statements/Labelling 21 22. Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation. 22 23. Main tool that predict the stability problems. Foundation for developing and validating analytical methods. For an API the following approaches may be used: When available, it is acceptable to provide relevant data published in the scientific literature to support the identified degradation pathways and products.
When no data is available, stress testing should be performed.
The nature of the stress testing will depend on the individual active substance and the type of pharmaceutical product involved. 23 24. Stress testing of the active substance can help in Identification of degradants Identification of degradation pathways Determination of which type(s) of stress affect the molecule: ◦ Photo-stability ◦ High Temperature ◦ Low Temperature ◦ Oxidation ◦ pH extremes ◦ Water 24 25. Oxidation: Typically done by placing the drug substance in aqueous solution of hydrogen peroxide. Goal is significant degradation (typically 10-30% of API) ◦ Can identify degradants ◦ Determine whether protective packaging is required ◦ Determine if an antioxidant should be considered for the drug product formulation. pH: Typically done by adding drug substance to buffered aqueous solutions at pH values from 1-10 ◦ Decide if the molecule will survive passage through the stomach Is enteric coating necessary? Should the drug be given by injection? 25 26. 26 Stress factor Conditions Heat 10°C increments Humidity 75%RH or greater Acid 0.1N Hcl Base 0.1N NaOH Oxidative 3%H2O2 Photolytic Xenon,Metal hailde lamp or Near UV,White florescent lamp 27. Data from formal stability studies should be provided on at least three primary batches of the active substance. The batches should be manufactured to a minimum of pilot scale by the same synthetic route as, and using a method of manufacture and procedure that simulates the final process to be used for, production batches. 27 28. The stability studies should be conducted on the active substance packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution. 28 29. • Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. • The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes. e.g. appearance, assay, degradation.
29 30. For long term studies: Year 1: every 3 months Year 2: every 6 months Subsequent years: annually At accelerated storage conditions: (6 month study) Minimum three points including t0 and tfinal, e.g. 0 3 6 (initial) (final) At intermediate storage conditions: (12 month study) Four points including t0 and tfinal, e.g. 0 6 9 12 (initial) (final) 30 31. A drug substance should be evaluated • To test its thermal stability • Its sensitivity to moisture(if applicable) • The long-term testing (minimum of 12 months) on at least 3 primary batches at the time of submission and • should be continued for a period of time sufficient to cover the proposed re-test period. 31 32. If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during six months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. significant change – failure to meet its specification 32 Study Storage condition Minimum time period covered by data at submission Long Term* (Ambient) 25º C ± 2º C 60%RH ± 5% 12 months Intermediate** (controlled) 30º C ± 2º C 65%RH ± 5% 6 months Accelerated 40º C ± 2º C 75%RH ± 5% 6 months 33. If significant change occurs between 3 and 6 months testing at the accelerated storage condition, the proposed re-test period should be based on the real time data available at the long term storage condition.
33 Study Storage condition Minimum time period covered by data at submission Long Term 5º C ± 3º C 12 months Accelerated 25º C ± 2º C 60%RH ± 5% 6 months 34. In the absence of an accelerated storage condition for active substances intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. 5°C ± 3°C or 25°C ± 2°C or 30°C ± 2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition. e.g., during shipping or handling 34 Study Storage condition Minimum time period covered by data at submission Long Term -20º C ± 5º C 12 months 35. • When available long-term stability data does not cover the proposed re-test period, a commitment should be made to continue stability studies in order to firmly establish the re-test period. • Where the data submitted is from fewer than 3 production batches, a commitment should be made to continue the long-term studies with additional production batches, to a total of at least 3. • If the submission does not include stability data on production batches, a commitment should be made to place the first 3 production batches on long-term studies through the proposed re- test period. 35 36. Minimum of 3 batches of drug substance is tested. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned re-test period. The analyst must found the batch to batch variability & if it is small than only it is accepted & it can be done by different statistical test's (P value for level of significance for rejection). Where the data show so little degradation and so little variability then it is normally unnecessary to go through the statistical analysis; providing a justification for the omission should be sufficient. 36 37. A storage statement should be established for the labelling based on the stability evaluation of the active substance. Where applicable, specific instructions should be provided, particularly for active substances that cannot tolerate freezing. Terms such as "ambient conditions" or "room temperature" must be avoided. 37 38. • General • Selection of Batches • Container Closure System • Specification • Testing Frequency • Storage Conditions • Stability Commitment • Evaluation • Statements/Labelling 38 39. The design of the formal stability studies for the pharmaceutical product should be based on knowledge of the behavior and properties of the active substance, from stability studies on the active substance, and on experience gained from clinical formulation studies. 39 40. Data from stability studies should be provided on at least three primary batches of the pharmaceutical product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. Two of the three batches should be at least pilot scale batches and the third one can be smaller, if justified.
Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied. 40 41. Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). 41 •The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g. antioxidant, antimicrobial preservative). • Analytical procedures should be fully validated, and stability indicating. SPECIFICATIONS 42.
For long term studies: Year 1: every 3 months Year 2: every 6 months Subsequent years: annually At accelerated storage conditions: (6 month study) Minimum three points including t0 and tfinal, e.g. 0 3 6 (initial) (final) At intermediate storage conditions : (12 month study) Four points including t0 and tfinal, e.g. 0 6 9 12 (initial) (final) 42 43. A drug substance should be evaluated • To test its thermal stability • Its sensitivity to moisture or potential for solvent loss(if applicable) The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use with due regard to the climatic zone(s) in which the product is intended to be marketed.
Photostability testing should be conducted on at least one primary batch of the pharmaceutical product if appropriate. 43 44. If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria 44 Study Storage condition Minimum time period covered by data at submission Long Term* 25º C ± 2º C 60%RH ± 5% 12 months Intermediate** 30º C ± 2º C 65%RH ± 5% 6 months Accelerated 40º C ± 2º C 75%RH ± 5% 6 months 45. In general, "significant change" for a drug product is defined as: • A 5% change in assay from its initial value; • Any degradation product's exceeding its acceptance criterion; • Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions; and, as appropriate for the dosage form: • Failure to meet the acceptance criterion for pH; or • Failure to meet the acceptance criteria for dissolution for 12 dosage units.
45 46. Drug products packaged in impermeable containers: Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers. Thus, stability studies can be conducted under any controlled or ambient humidity condition. Drug products packaged in semi-permeable containers: Aqueous-based products packaged in semi- permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity. 46 47. A 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of 3 months' storage at 40°C/NMT 25% RH. 47 Study Storage condition Minimum time period covered by data at submission Long Term* 25º C ± 2º C 40%RH ± 5% 12 months Intermediate** 30º C ± 2º C 65%RH ± 5% 6 months Accelerated 40º C ± 2º C NMT25%RH 6 months 48. If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long term storage condition. 48 Study Storage condition Minimum time period covered by data at submission Long Term 5º C ± 3º C 12 months Accelerated 25º C ± 2º C 60%RH ± 5% 6 months 49. For drug products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long term storage condition.
49 Study Storage condition Minimum time period covered by data at submission Long Term -20º C ± 5º C 12 months 50. If the submission includes data from stability studies on at least 3 production batches, a commitment should be made to continue the long term studies through the proposed shelf life and the accelerated studies for 6 months. If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue the long term studies through the proposed shelf life and the accelerated studies for 6 months, and to place additional production batches, to a total of at least three, on long term stability studies through the proposed shelf life and on accelerated studies for 6 months. 50 51. A systematic approach should be adopted in the presentation and evaluation of the stability information. Minimum of 3 batches of drug product was tested The analyst must found the batch to batch variability & if it is small than only it is accepted & it can be done by different statistical test's (P value for level of significance for rejection). Where the data show so little degradation and so little variability then it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient. 51 52. • Purpose: to monitor and determine that API/FPP remains within specifications under the storage conditions, within the re-test period/shelf life in all future batches. • The programme should be described in a written protocol. • The programme should include at least one production batch per year, tested at least annually. • An ongoing study should be conducted after any significant change to the synthetic route/manufacturing process or container which may impact stability. 52 53. Stability studies should include testing of those attributes of the Drug product that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. For instance, in case of tablets: appearance hardness friability moisture content dissolution time degradants assay microbial purity 53 54. 54 Dosage form Evaluation Tablets Appearance, colour, odour, assay, degradation products, dissolution, moisture and friability. Hard gelatin capsules Appearance, colour, odour, assay, degradation products, dissolution, moisture and microbial limits Soft gelatin capsules Appearance, colour, odour, assay, degradation products, dissolution, moisture and microbial limits, pH, leakage. Emulsions Appearance, colour,odour,assay, degradation products, microbial limits ,pH, viscosity ,preservative content and distribution of dispersed phase globules. 55.
55 Dosage form Evaluation Oral solutions Appearance,colour,odour,assay,degrad ation products, PH,microbial limits, preservative content. Oral suspensions Appearance,colour,odour,assay,degrad ation products, PH,microbial limits, preservative content,redispersibility,rheological properties, mean size and distribution of particle. Oral powders Appearance,colour,moisture,and reconstitution time. Inhalations and nasal sprays Appearance,colour,odour,assay,degrad ation products, dose content uniformity, microscopic evalution,water content, leak rate, microbial limits. 56. 56 Dosage form Evaluation Topical,opthalamic,ointments ,creams, lotions,pastes,gels,solutions. Appearance,clarity,colour, homgeneity,odour,pH,resuspendibility,v iscosity,particle size distribution, assay, degradation products,preservatives, microbial limits, weight loss Small volume parenterals Appearance,colour,clarity, assay,presarvative content, degradation products, particulate matter, sterility, Large volume parenterals Appearance,colour,clarity, assay,presarvative content,degradation products,particulate matter,sterility,pH,pyrogenicity, volume. 57.
• This stability study run under more stressful conditions than expected for long term storage to account for any changes outside the label storage conditions • The goal is to get a quick understanding of what may be expected from a long term study. 57 59. Photo-stability testing studies include: (Single batch) (no photo-stability studies after administration) • Test on drug substance. • Test on exposed drug product outside the immediate pack. • Test on drug product in the immediate pack. • Test on drug product in the marketing pack. Light source Option 1: Artificial daylight lamp combining both visible & UV output similar to D65 & ID65. Option 2: Cool white fluorescent & near UV lamp(320-400nm) 59 output similar to that specified in ISO 10977 max. energy emission between 350-370 nm 60.
E.g.: Quinine chemical actinometry: 2%w/v aq.solution of quinine monohydrochloride dihydrate 60 10ml of sol. in a 20 ml colorless ampoule (SAMPLE) 10ml of sol. in a 20 ml colorless ampoule wraped in aluminum foil (CONTROL) Expose to the light source determine the absorbances of the sample (AT) and the control (Ao) at 400 nm using a 1 centimeter (cm) path length. Change in absorbance calculated by Δ A = AT - Ao. 63. This document is an annex to the ICH parent stability guideline and addresses the recommendations on what should be submitted regarding stability of new dosage forms by the owner of the original application, after the original submission for new drug substances and products A new dosage form is defined as a drug product which is a different pharmaceutical product type, but contains the same active substance as included in the existing drug product approved by the pertinent regulatory authority. Stability protocols for new dosage forms should follow the guidance in the parent stability guideline in principle. However, a reduced stability database at submission time may be acceptable in certain justified cases. 63 65. It is the design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all time points as in a full design.
The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition. e.g.: for a tablet range made with different compression weights of a similar basic granulation. Bracketing can be applied to different container sizes or different fills in the same container closure system. 65 66. 66 Pack type Label strength and batch numbers (X,Y,Z) 10 mg 20mg 30mg X Y Z X Y Z X Y Z Alu/Alu blister cards of 10 tablets + + + - - - + + + HDPE pack of 30 tablets + + + - - - + + + HDPE pack of 100 tablets - - - - - - - - - HDPE pack of 1000 tablets + + + - - - + + + 67. It is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point.
At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. 67 68. One half reduction One third reduction 68 69. Example of Matrixing Design on Time Points for a Product with Two Strengths + indicates- Sample tested 69 one-half reduction Time points (months) 0 3 6 9 12 18 24 36 S1 Batch 1 + + - - + - + + Batch 2 + - + + + - + + Batch 3 + - + - + + - + S2 Batch 1 + - + + + + - + Batch 2 + + - - + + - + Batch 3 + + - + + - + + 71. Data Presentation- • Data for all attributes should be presented in an appropriate format (e.g., tabular, graphical, narrative) and an evaluation of such data should be included in the application. • The values of quantitative attributes at all time points should be reported as measured (e.g., assay as percent of label claim). • If a statistical analysis is performed, the procedure used and the assumptions underlying the model should be stated and justified. • A tabulated summary of the outcome of statistical analysis and/or graphical presentation of the long-term data should be included. 71 72. • Extrapolation is the practice of using a known data set to infer information about future data (e.g. by using regression line analysis) • Extrapolation to extend the retest period or shelf life beyond the period covered by long-term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition. 72 73. No significant change at accelerated condition Where no significant change occurs at the accelerated condition, the retest period or shelf life would depend on the nature of the long-term and accelerated data.
Long-term and accelerated data showing little or no change over time and little or no variability Where the long-term data and accelerated data for an attribute show little or no change over time and little or no variability, it might be apparent that the drug substance or product will remain well within the acceptance criteria for that attribute during the proposed retest period or shelf life. The proposed retest period or shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data. 73 74. Data not amenable to statistical analysis Where long-term data are not amenable to statistical analysis, but relevant supporting data are provided, the proposed retest period or shelf life can be up to one and-a-half times, but should not be more than 6 months beyond, the period covered by long-term data.
Data amenable to statistical analysis If long-term data are amenable to statistical analysis but no analysis is performed, the extent of extrapolation should be the same as when data are not amenable to statistical analysis However, if a statistical analysis is performed, it can be appropriate to propose a retest period or shelf life of up to twice, but not more than 12 months beyond, the period covered by long-term data, 74 75. Significant change at accelerated conditions Where significant change occurs at the accelerated condition, the retest period or shelf life would depend on the outcome of stability testing at the intermediate condition as well as at the long-term condition. No significant change at intermediate condition Where no significant change occurs at the intermediate condition, the retest period or shelf life would depend on the nature of the long-term and intermediate data. Data not amenable to statistical analysis When the long-term data for an attribute are not amenable to statistical analysis, the proposed retest period or shelf life can be up to 3 months beyond the period covered by long-term data. 75 76. If long-term data are amenable to statistical analysis but no analysis is performed, the extent of extrapolation should be the same as when data are not amenable to statistical analysis However, if a statistical analysis is performed, it can be appropriate to propose a retest period or shelf life of up to one & half times, but not more than 6 months beyond, the period covered by long-term data, SIGNIFICANT CHANGE AT INTERMEDIATE CONDITIONS Where significant change observed at intermediate conditions, the proposed retest period or shelf life should not be more than period covered by long term study. In addition a retest period or shelf life shorter than data covered by long term study may be called for. 76 77. THE FOLLOWING ICH GUIDELINES MAY BE CONSULTED IN THE CONTEXT OF STABILITY TESTING: 1) ICH Q1A (R2): Stability testing of new drug substances and products (MEDIA419.pdf). 2) ICH Q1B: Photostability testing of new drug substances and products (MEDIA412.pdf). 3) ICH Q1C: Stability testing of new dosage forms (. 4) ICH Q1D: Bracketing and matrixing designs for stability testing of new drug substances and products (. 5) ICH Q1E: Evaluation for stability data (. 6) V.SAI KISHORE's Drug regulatory affairs (pg no 227-288) 77 HumanScientific guidelinesThis document defines the stability data package for a new drug substance or drug product that is sufficient for a registration application within the ICH regions. It does not cover the information to be submitted for abbreviated or abridged applications, variations and clinical trial applications.Keywords: Stability, stability testing, stability data, chemical active substance, finished product, specification, storage conditionsICH: Q 1 A (R2): Stability testing of new drug substances and products - Step 5 English (EN) (248.29 KB - PDF)View