Stability Studies

Recent Changes in Stability Testing Guidelines
Guidelines

• ICH
  – ICH Q1 A (R2) (CPMP/ICH/2736/99)
    • NfG on Stability Testing: Stability Testing of New Drug Substances and Products
      – Covering Climatic Zones I and II
  – ICH Q 1 F (CPMP/ICH/421/02)
    • NfG on Stability Data Package for Registration Applications in Climatic Zones III and IV
      – August 2003 until June 2006

• WHO
  • Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms, TRS No. 863, Annex 5, 1996
    – with revisions 2001, 2005
Recent changes

- ICH Q1F (CPMP/ICH/421/02)
  - Withdrawal in June 2006
    - Explanatory Note on the Withdrawal of ICH Q1F from the ICH Website

- WHO
  - Definition of Climatic Zones IVa and IVb
History of recent changes

• 2000
  – Discussion on harmonization between ICH and WHO with respect to
    • number of stability tests
    • stability testing conditions employed worldwide

  • Development of ICH Q1F

1 Stability Testing of Pharmaceutical Products in a Global Environment (2006), RAJ Pharma, Dr. Sabine Kopp
Copenhagen, 30 October, 2006
Dr. B. Schmauser
Stages of Harmonization

• First proposal by ICH Q1 (expert group):
  – modification of long term storage testing conditions for climatic zone IV
    • from 30°C/70%RH to 30°C/60%RH

• Resonance
  • sound scientific approach (+)
  • role of packaging material
  • too scientific and impractical (-)
  • simulation of long term storage conditions deviates from actual meteorological and physical storage conditions

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Stages of Harmonization

- Second proposal by ICH:
  - modification of long term storage testing conditions for climatic zone IV
    - from 30°C/70%RH to 30°C/65%RH
      - discussion
  - WHO guidelines for stability testing:
    - real time stability studies for zone IV
      - 30°C±2°C/65%±5%RH
    - additional stability data for special transportation and conditions outside the storage conditions

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Stages of Harmonization¹

• ASEAN response
  – conditions described in WHO and ICH guidelines not reflective of the climatic conditions prevalent in ASEAN countries
  – definition of own requirements for long term stability testing addressing hot and humid climatic zone IV:
    • $30^\circ\mathrm{C} \pm 2^\circ\mathrm{C}/75\% \pm 5\%\mathrm{RH}$
  – considerations based on principle of testing at more stressful conditions in favour of patient safety
    • identification of substances/formulations with stability problems more likely
  – implementation of decisions after a transition period

¹ Stability Testing of Pharmaceutical Products in a Global Environment (2006), RAJ Pharma, Dr. Sabine Kopp

Copenhagen, 30 October, 2006

Dr. B. Schmauser
Stages of Harmonization

- Consequences of ASEAN approach for applications in ASEAN countries
  - evaluation of stability data generated under less stressful conditions
    - complementary data for scientific evaluation
    - detected instability
    - stability data of accelerated conditions
    - protection of packing
    - commitment to generate data under the new conditions
      - 30°C±2°C/75%±5%RH
      - 40°C±2°C/75%±5%RH
  - label recommendations

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Stages of Harmonization

• WHO action to ASEAN response:
  – Consultation
    • revert to 30°C/70%RH
    • change to 30°C/75%RH
    • add a new climatic zone IVb
      – 30°C/75%RH (IVb)
      – 30°C/65%RH (IVa)

• WHO decision
  – Zone IVa and IVb to be included in the stability testing guideline
  – Member States to declare applicability of conditions in their territory (IVa or IVb)

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Stages of Harmonization

• ICH reaction (Explanatory note)
  – withdrawal of ICHQ1F
    • Divergence in global stability testing requirements
      – Initial idea not supported
        › Facilitation of access to medicines by reducing the number of different storage conditions
      – harmonized conditions not supported
        › Safety margin for medicinal products considered not adequately addressed in hot and extremely humid countries
Impact of withdrawal of ICH Q1F

• ICH Q1A (R2)
  – Intermediate testing conditions are retained
    • 30°C/65%RH
  – Use of more stringent humidity conditions is acceptable
    • e. g. 30°C/75%RH

• Prequalification project
  – Preferred long term testing conditions are
    • 30°C/65%RH
  – More stringent conditions are accepted
Impact of withdrawal of ICH Q1F

• Applicability of retest periods based on long term stability studies at
  – Zone II conditions (25°C/60%RH)
  – Zone IVa conditions (30°C/65%RH)

in countries of Zone IVb (30°C/75%RH)?

• Potential approach
  – Inclusion of cautionary statement in label
    » Keep protected from ambient humidity
    » Store below …°C (long term testing temperature)
Basic considerations

- Stability of FPPs is not only the outcome of performing stability studies under certain conditions.
- Stability is also the result of proper **pharmaceutical development**
  - taking into account the intrinsic properties of APIs elucidated by stress stability studies
  - investigation of compatibility of APIs with each other and with excipients by stress stability studies
  - development of formulation
  - development of a manufacturing procedure based on the results of all preceding studies
Guidelines to consult

• With a focus on stability:
  – Guideline on Submission of Documentation for Prequalification of Multi-source (Generic) Finished Pharmaceutical Products (FPPs) Used in the Treatment of HIV/AIDS, Malaria and Tuberculosis
    • 2.7 Stability testing of the API
    • 3.11 Stability testing of the FPP
  – Supplement 2 of this Guideline
    • Extension of the WHO List of stable APIs
  – Variation Guide
    • Annex IV, stability
Prequalification

• For further information on minimum requirements for prequalification of FPPs please visit
  – << http://mednet3.who.int/prequal/ >>

• THANK YOU FOR YOUR ATTENTION