SHELF LIFE AND
STABILITY STUDIES
MALE LATEX CONDOMS
8 May, 2019

Topics to be Covered

1. Definition of shelf life
2. Background
   - ISO 4074:2002 and ISO 4074:2015
   - Storage conditions, mean kinetic temperature and climatic zones
3. Practical guidance
   - Selection of lots
   - Samples and storage
   - Testing
   - Reporting
   - Minimum stability testing
   - Accelerated stability testing
   - Real time stability testing

Questions

Definition of Shelf Life

The period from date of manufacture during which the condoms will conform to the critical performance requirements of ISO 4074:2015

Background – ISO 4074:2002

- ISO 4074:2002 introduced more stringent requirements for estimating the shelf lives of condoms:
  - Minimum stability requirements based on conditioning condoms for 90 days at 50 °C and 7 days at 70 °C
  - Determination of a provisional shelf life using accelerated stability studies at elevated temperatures
  - Real time stability studies at 30 °C for the duration of the shelf life of the condom
- Burst properties tested on a lot basis after conditioning for 7 days at 70 °C (Clause 6.2)
  - Removed as a lot by lot requirement by Corrigendum 2 in 2008

ISO 4074:2015 Updated Procedures and Requirements

- Critical performance requirements defined

  - Burst properties

  - Freedom from holes

  - Package integrity

  - Other important properties such as odour, colour and ease of unrolling should also be monitored

- Same minimum stability requirements

- Major changes to procedure for estimating provisional shelf life using accelerated studies at (50 ±2) °C

  - 90 days shelf life of 2 years

  - 120 days shelf life of 3 years

  - 180 days shelf life of 5 years

- Improved description of procedures for real studies at 30 °C

Storage Conditions – Why 30 °C?

- Temperatures vary widely around the world, by season and by day and night
- Average temperatures can be easily measured
- Average temperatures do not take into account the exponential rates of change seen with chemical reactions
- Pharmaceutical Industry introduced the concepts of mean kinetic temperature (MKT) and World Climatic Zones

Mean Kinetic Temperature

- MKT is single temperature that provides the same challenge as the real life storage conditions for the product
  - MKT takes into account daily and seasonal temperature change
  - MKT takes into account the exponential change in chemical reaction rates with temperature based on the Arrhenius equation* with an activation energy of 83.144 kJ/mole
- The world can be divided into different climatic zones based on MKT

World Climatic Zones

Climatic Zone	Definition	Criteria Temperature / Humidity	Testing Conditions
I	Temperate	≤ 15°C ≤ 11 hPa	21°C 45% RH
II	Subtropical / Mediterranean	> 15° to 22°C ≤ 15 hPa	25°C 60% RH
III	Hot and dry	> 22°C > 15 to 27 hPa	30°C 35% RH
IVA	Hot and humid	> 22°C > 15 to 27 hPa	30°C 65% RH
IVB	Hot and very humid	> 22°C > 27 hPa	30°C 75% RH

Reference Conditions for Shelf Life Determination of Male Condoms

- Male condoms distributed all over the world therefore most extreme (zone IVB) conditions selected as the reference for shelf life claims

- Temperature set as 30 °C (tolerance +5/-2 °C)

- Humidity 75% ± 5%

  - Male condoms are usually distributed in impermeable aluminium laminate foil packages, humidity is not normally controlled

Practical Guidance

Practical Guidance – Selection of Lots

- All lots must have been stored for the maximum permitted bulk storage time prior to starting the study
- Minimum of 3 lots
- Lots should be typical of normal production
- Randomly selected from a period of stable production
- All elements of the stability study done on **same set of lots**
  - Real time
  - Minimum stability
  - Accelerated study at 50 °C
- Minimum stability data at 50 °C can be extracted from the accelerated study

Practical Guidance – Samples and storage

- Calculate the number of samples required and include spares
- Test condoms at start of study (condoms may have changed since date of manufacture)
  - Annex B sample sizes are recommended in ISO 4074:2015
  - As a minimum Annex A sample sizes must be used
- Follow the procedures in ISO 4074:2015 Annex I for storage conditions
- Make certain that the storage conditions meet requirements
  - Monitor and record temperatures regularly, ideally continuously
  - Maintain temperatures within the specified temperature tolerance
  - Adequate space for samples whilst maintaining good air flow
  - Have an action plan in case stability ovens/chambers breakdown

Practical Guidance - Testing

- After conditioning keep the packages at (25 ± 5) °C until tested

- Test condoms within 96 hours but not sooner than 12 hours after conditioning

- Make certain testing equipment is calibrated and working correctly

- Make sure technicians are properly trained and training records are up to date

- Make sure all testing conditions are fully documented

- Make sure results are correctly captured and recorded

Practical Guidance –Reporting

- Prepare interim reports and update as new results become available
- Monitor trends
  - Burst results
    - plot average burst volumes and pressure over time
    - Plot standard deviations over time
  - All properties
    - plot numbers of nonconforming condoms over time
  - Include statistical analyses in reports
    - Burst properties – use t-tests or ANOVA to compare results between lots and over time to determine if differences are statistically significant
    - Ensure that lower one-sided 98.5 percentile value for burst volumes remain above 20 litres and burst pressures above 1.1 kPa
    - Nonconformity rates – use Fisher Exact Test or Chi Squared Test to determine if any changes in numbers of nonconforming condoms between lots and over time are statistically significant
  - Use linear and non-linear correlation methods to determine trends and extrapolate results to end of study

Practical Guidance – Minimum Stability Testing

- Follow the procedure in ISO 4074:2015 Clause 11.2

- Determine the numbers of condoms required including spares

- Condition condoms for (168 ± 2) hours at (70 ± 2) °C and (90 ± 1) days at (50 ± 2) °C using the procedures specified in ISO 4074:2015 Annex I

- Test the condoms for:
  - Burst properties
  - Freedom from holes
  - Package integrity
  - Also inspect the condoms and packaging for discolouration, odour, unrolling properties

- Assess conformance with ISO 4074:2015 requirements

- Prepare the report

Practical Guidance – Accelerated Stability Study

- Follow the procedures in ISO 4074:2015 Clause 11.4 and Annex L (informative)

- Determine if there is a suitable control condom with a shelf life confirmed by a real time study

- Select the procedure

  - Clause L.2 no control condom

  - Clause L.3 with control condom

Practical Guidance – Accelerated Stability Study No Control Condom (Annex L.2)

- Determine the numbers of condoms required including spares

- Condition condoms at (50 ± 2) °C using the procedures specified in ISO 4074:2015 Annex I

- Remove samples for testing after specified time periods (90, 120 and 180 days)

- Test the condoms for:

  - Burst properties

  - Freedom from holes

  - Package integrity

  - Also inspect the condoms and packaging for discolouration, odour, unrolling properties

- Assess conformance with ISO 4074:2015 requirements

- Prepare the report

Practical Guidance – Accelerated Stability Study With Control Condom (Annex L.2) Step 1

- Determine the numbers of condoms required including spares
  - Minimum of 3 production lots of test condom
  - Minimum of 2 product lots for control condom
  - Minimum of 32 samples per temperature per test station
- Condition condoms at a minimum of 2 temperatures using the procedures specified in ISO 4074:2015 Annex I
- Test the condoms for burst properties
- Compare the changes in burst properties for test and control condom and choose a set of conditions (i.e. a time and temperature) that results in the same significant changes in burst properties for the test and control condoms.

Practical Guidance – Accelerated Stability Study With Control Condom (Annex L.2) Step 2

- Determine the numbers of test condoms required including spares

- Condition condoms at the selected temperature using the procedures specified in ISO 4074:2015 Annex I

- Test the condoms for:

  - Burst properties

  - Freedom from holes

  - Package integrity

  - Also inspect the condoms and packaging for discolouration, odour, unrolling properties

- Assess conformance with ISO 4074:2015 requirements

- Prepare the report

Practical Guidance – Real Time Stability Study

- Follow the procedures in ISO 4074:2015 Clause 11.3 and Annex K (normative)

- Determine the numbers of samples required including spares

  - Testing at the end of the study for burst properties, freedom from holes and package integrity

  - Monitoring of burst properties during the study (32 or 125 condoms per test)

- Condition condoms at (30 +5/-2) °C using the procedures specified in ISO 4074:2015 Annex I)

  - Remove samples for monitoring at regular intervals (one year or less)

  - After conditioning keep the packages at (25 ± 5) °C until tested

  - Within 96 hours but not sooner than 12 hours after conditioning test the condoms for burst properties

  - Assess whether it is necessary to terminate the real time study early

Practical Guidance – Real Time Stability Study (Continued)

- Continue to condition the condoms for the required shelf life period (maximum of 5 years) unless the decision is taken to terminate the study early
- Test the condoms for:
  - Burst properties
  - Freedom from holes
  - Package integrity
  - Also inspect the condoms and packaging for discolouration, odour, unrolling properties
- Assess conformance with ISO 4074:2015 requirements
- Prepare the report

Any Questions?

Thank you for your attention

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