Session 5:

ISO 4074, the WHO Specification, and Related Standards

World Health Organization

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Session Objectives

- Understand why ISO standards and the WHO specification are requirements for prequalification
- Identify relevant ISO standards
- Introduce the WHO model specification
- Identify which requirements in each document can be altered

ISO Standards and Prequalification

ISO standards address:

- Product safety and performance (ISO 4074, 10993)
- Test methods to verify compliance (ISO 4074)
- Good manufacturing practices and quality assurance (ISO 9000 series, 13485)
- Minimum quality requirements (ISO 4074, 2859)
- Package labeling (ISO 4074, 780, 15223. EN980)

Specifications and Prequalification

Specifications address:

- Buyer's requirements
- More detailed packaging issues
- Design requirements not covered in standards

Relevant International Standards

- ISO 4074: Natural latex rubber condoms—requirements and test methods
- ISO 10993: Biocompatibility safety assessment of medical devices
- ISO 2859-1: Sampling procedures for inspection by attributes
- ISO 780: Packaging—pictorial marking for handling of goods

Relevant International Standards (continued)

- ISO 9000 Series: Quality management and QA standards
- ISO 13485: Medical devices—quality management systems

The WHO Model Specification

- Based on ISO 4074 and other international standards
- Specifies additional requirements:
  - General requirements
  - Performance requirements
  - Design requirements
  - Packaging requirements

Major Condom Standards

- ISO/EN 4074:2002
- EN600 (obsolete)
- Chinese standard
- Russian standard
- ASTM D 3492
- South American standard
- Indian standard

ISO 4074 Clause 4: Quality Verification

- Testing done on a sample of each lot
- ISO 2859-1 gives “basic sampling plans”
- Purchasers should look at quality system
- Two sampling schemes, depending on whether tests are continuing or isolated
- Note handling and storage conditions when sampling
- Lot size is part of quality system

ISO 4074 Clause 5: Design

- Integral bead
- Lubrication: Method for determination
- Length: > 160 mm
- Width: Nominal ± 2 mm
- Thickness: Method for determination

ISO 4074 Clause 6: Inflation Testing

- Inflation test for untreated condoms
- Inflation test for oven-treated condoms
- Requirements for extra-strong condoms

Air Inflation Test

- Inflates 150 mm of the condom until burst
- Limits on burst pressure and volume
- AQL for burst properties is 1.5%

ISO 4074 Clause 7: Shelf Life

- Shelf-life data to be available to regulator
- Tests:
  - Minimum stability requirements
  - Real-time studies
  - Accelerated studies
- Must do real-time and minimum stability tests; if real-time not completed, must do accelerated

ISO 4074 Clause 8: Holes

- Two alternative methods for freedom from holes test:
  - Water leak
  - Electrical
- Maximum allowable hole level: 0.25%

ISO Water Leak Test

- Fill condom with water, examine, close and roll on absorbent paper (ISO)
- Stringent limit on number allowed (AQL of 0.25%)
- Small holes not 100% detectable
- Holes hardest to find near closed end
- Currently under review by ISO

ISO Electrical Test

- Fill condom with NaCl solution, dip in NaCl solution, measure the resistance
- Minimum resistance allowed: 1.99 MΩ
- Roll non-compliers to confirm
- Stringent limit on number allowed (AQL 0.25%)
- Small holes not 100% detectable
- Currently under review by ISO

ISO 4074 Clause 9: Visible Defects

- Visible defects assessed during holes test
- Only broken beads, missing or severely distorted beads, and permanent creases with adhesion of film are considered

ISO 4074 Clause 10: Package Integrity

- Package integrity test method, to be applied if required
- Pack is immersed in water with vacuum. Endpoints are:
  - Bubbles leaking from pack, or
  - Water penetrating into pack

ISO 4074 Clause 11: Packaging and Labeling

- Packaging and labeling requirements for the individual pack and the consumer pack
- Specifications may impose additional requirements

Annexes A and B: Sampling

- Annex A is for continuing sampling (e.g., final release testing in a factory)
- Annex B is for isolated lots (e.g., prequalification sampling)
- Both annexes refer specifically to ISO 2859-1

Annexes C to M

- Describe test methods and testing equipment

WHO Requirements

ISO 4074 PLUS…..

- General requirements
- Performance requirements
- Design requirements
- Packaging requirements

WHO General Requirements

- Shall not liberate toxic or otherwise harmful substances that can be harmful to the user
- Must have ISO 10993 assessment
- Minimize water-extractable proteins
- Use an acceptable powder; WHO does not allow lycopodium and talc

ISO 10993: Biocompatibility

- Part 1: Selection and evaluation of tests
- Part 5: Cytotoxicity
- Part 10: Irritation and sensitization
- Results must be interpreted—no fixed limits
- If you use no new materials or processes, you may not need to do tests

WHO Performance Requirements

- Same as ISO, BUT…..
- They may specify additional visible defects

WHO Design Requirements

- Shape and texture
- Color: pigments must be suitable
- Smell: no bad smell
- Width: added requirement on lot mean
- Length: longer than ISO requirement
- Thickness: 0.05 to 0.08 mm
- Lubricant: 400 to 700 mg

WHO Packaging Requirements

- Requires aluminum foil laminate for pack
- Specific thickness requirements on foil materials
- No leakage, outside clean
- No delamination
- Easy to separate and open

WHO Shipment Packing Requirements

- Inner boxes—suitably constructed, labeled
- Exterior shipping cartons—minimum burst strength of 1900 kPa
- Adequately glued
- Labeled as specified

Quality Systems Standards

- ISO 9000: Quality management systems
- ISO 13485:
  - Specifically for medical devices
  - More prescriptive
  - More emphasis on risk assessment

ISO 13485

- Clause 4: The quality management system
- Clause 5: Management responsibility
- Clause 6: Resource management
- Clause 7: Product realisation
- Clause 8: Measurement, analysis, and improvement

Small Group Exercise

1. Where is there a difference between the requirements in ISO 4074 and the WHO specifications?
2. Which requirements can be altered in ISO 4074 and the WHO specifications?

Principal Differences Between the WHO Specification and the ISO Standard

General

The WHO Specification is contained in a document called "The Male Latex Condom." It is a model that purchasers can use to tell potential suppliers exactly what they want. This includes some "performance requirements" which reiterate the ISO standard requirements, some general requirements and some design requirements. It is intended for use by public sector procurement agencies.

Originally, the WHO Specification was more restrictive in terms of design options than it is today. Now, it allows the purchaser to change many aspects of the design (for example size, shape, texture, colour, flavour).

The ISO standard is an internationally agreed set of requirements for condoms. It is adopted by many countries; others, such as the USA, have very similar requirements. In some countries, compliance with ISO 4074 is mandatory, in others it is not.

The ISO standard mainly focuses on issues that relate to safety and efficacy of the condoms. It is intended to cover all known designs of natural latex condom, but some newer designs, for example, the Theyfit series, have not been incorporated.

The details below follow the order of the WHO document, and are confined to the more significant differences.

Specific Differences

General Requirements

The ISO standard concentrates on physical properties. The WHO specification requires:

> The condoms shall not liberate toxic or otherwise harmful substances in amounts that can be irritating, sensitizing or otherwise harmful to the user of the condom under normal conditions of use.

While this requirement is difficult to test for, it puts the responsibility on the manufacturer to ensure safety of the product.

ISO 4074 mentions ISO 10993 (biological compatibility) only in the non-mandatory foreword. The WHO specification requires an assessment to be conducted.

The WHO specification requires manufacturers to minimize the level of water-extractable proteins in the condoms. ISO has no requirement.

WHO stipulates that talc and lycopodium spores shall not be used for powdering and suggests a maximum of 50 mg per condom.

Shelf-life

WHO requires compliance with all performance requirements of the *Model Specification* throughout the stated shelf-life of the condom. This shelf-life shall be not less than three years and not more than five years.

The ISO standard presently requires only compliance with the inflation test, but it is anticipated that the new edition (2009 or 2010) will require compliance with freedom from holes as well.

WHO requires that if at any time during the real-time studies the manufacturer becomes aware that the shelf-life estimates made using the accelerated studies are incorrect, the purchasers must be notified immediately.

Performance Requirements

Freedom from Holes and Visible Defects

The main text of the WHO specification follows the ISO standard, but there is an additional chapter on visible defects (Chapter 3). This makes the WHO requirements ambiguous unless individual specifications refer specifically to requirements and descriptions noted in the chapter.

ISO specifies only 4 types of visible defects: Broken, missing or severely distorted rim and permanent creases with adhesion of the film.

Chapter 3 of the WHO specification has a much more extensive set of definitions of visible defects, separated into critical and non-critical.

Critical defects:
Pleat/Crease
Visible Holes under the Bead
Blister/Bubble
Coagulum
Embedded Particle(s)
Faulty Bead (Rim)
Crack Marks
Delamination
Thin Spots

Non-critical defects:
Coagulum
Embedded Particle(s)
Faulty Bead (Rim)
Crack Marks
Irregularly Formed Teat
Surface Discoloration/Streaks

The treatment of visible defects in contracts thus needs careful attention from both parties, since mere compliance with the WHO requirements does not define what is acceptable and what is not.

Note the differences in terminology between the WHO and ISO documents.

Design Requirements – Can be varied in contract

Shape and Texture - WHO default

The surface of the condoms shall be non-textured throughout.
The recommended condom should have straight and parallel sides, without constrictions, and with a visible shoulder leading to a reservoir tip.

There is no ISO requirement

Colour - WHO default

The recommended condom should be translucent and without added colouring.
If coloured condoms are desired, pigments must be suitable for use in medical devices.

There is no ISO requirement

Scents and Flavouring

WHO requires that the condoms shall not give off an unpleasant odour when the package is opened at any time after manufacture and for the shelf-life of the product. (Condoms have a characteristic odour of rubber, which tends to dissipate quickly once the package is opened.) In principle, this is mandatory.

The default design is free from added fragrance and flavouring agents.

Width

The default width is 53 mm. In addition to the ISO requirements for width, there is a tolerance of ± 1 mm for the mean of the LOT.

Length

ISO requires a minimum length of 160 mm. WHO requires:

A minimum of 170 mm for condoms with widths less than 50.0 mm.
A minimum of 180 mm for condoms with widths of 50.0 mm up to 56.0 mm.
A minimum of 190 mm for condoms with widths greater than 56.0 mm.

BUT other lengths may be specified based on the best available data on the target population.

Thickness

ISO has no requirement.

WHO requires that the mean single-wall thickness (calculated from the three individual measurements) for each condom shall be 0.065 ± 0.015 mm.

Departure from this range is not recommended.

Lubricant Including Powder

ISO has no requirement. WHO says:

The condom shall be lubricated with a quantity of silicone fluid having a viscosity between 200 and 350 centistokes.

Other lubricants such as glycols and water-based lubricants may be used. Oil-based lubricants should NOT be used

The quantity of lubricant, including powder, in the package should be 550 ± 150 mg. Lower lubricant levels may be used, but the minimum recommended quantity is 250 mg.

Individual Package Materials and Markings

ISO has specific labeling requirements to show the identity of the manufacturer, the lot number and the expiry date. WHO also requires the manufacturing date and the labeling of the dates. It requires that the lot number be printed at the time of foiling.

WHO has requirements for the package design, including the inclusion of a layer of aluminum foil (or use of an equivalent barrier) It also requires specifically that:

- There shall be no evidence of leakage.
- The outside surface of the package shall be clean.
- There shall be no separation of the layers of laminate.

- If the sealed packages are in strips, the individual packages are separated by perforations or other means that allow the packages to be separated by hand without interfering with the seals.
- The package must be easy to open without damaging the condom.

Consumer Packs

WHO has no requirement for consumer packs (as these are usually not supplied). ISO has labeling requirements.

Packing for Shipment

WHO has detailed requirements, ISO has none.

Overview of Condom Standards and Requirements

History of some condom standards

- Sweden began regulating and testing condoms in 1950.
- First British standard on condoms published in 1964.
- First US standard published in 1976.
- First ISO standard published in 1990. Revised in 1996 and 2002.
- First European standard published in 1996, and is now identical to the ISO standard.
- Chinese standard made identical to ISO in 2004.

ASTM Standard D 3492

- Similar requirements to ISO.
- Limits on condom width.
- Leaks test different.
    - Electrical test not accepted.
    - Water leaks test different (squeeze, not roll).
- Mainly used in USA, but FDA also recognizes ISO 4074 (see below)

USFDA requirements

- To market a condom in the USA, you must have a 510(k) approval.
- Originally you only had to show that your product was identical to one available before 1976.
- Now, condoms are handled under the "accelerated" 510(k) system.
- Application forms are available at: www.fda.gov.
- Suppliers may be subject to USFDA audit later.
- For the accelerated 510(k), you need to declare that your product passes ASTM D3492 or equivalent (ISO 4074 should be accepted).
- You also need to declare that the product has been tested according to ISO 10993.
- The FDA does random checks for holes on incoming product; they use the ISO visual method.

European requirements

- The product standard is ISO 4074.
- There was a long phasing-in period during which the old standard (EN 600-1996) was also acceptable.
- You must have a CE [Conformite Europeene] marking, which applies to individual products.
- You must have a representative in the European Union, who takes responsibility for non-compliance.

Meeting CE requirements

You must comply with the essential principles of safety and efficacy of your device according to the Medical Device Directive (MDD).

You are assumed to comply if you:

- Have a product that complies with a "harmonized standard."
- Meet the requirements of one of four annexes to the Directive.

The annexes to the Medical Device Directive

Four options are available:

- You have a fully audited quality system covering all aspects of design production and testing—almost no independent testing required.
- You have a type examination and you have every batch tested independently.
- You have a quality system covering production and testing, and some independent surveillance testing, and a type examination.
- You have a quality system covering testing, and some independent surveillance testing and a type examination.

South American Specification

Nearly the same as ISO, BUT:

- Freedom from holes done differently.
    - Condoms must be washed, powdered and dried.
    - Only electrical test acceptable—no rolling to confirm.

WARNING: This material is only a summary of the standard; do not use this material as a substitute for the complete official standard document.

Overview of ISO 4074:

Natural Latex Rubber Condoms—Requirements and Test Methods

Clauses 1 to 3: Introduction and Definitions

Clause 4: Quality Verification

Clause 5: Design

Clause 6: Inflation Testing

Clause 7: Stability and Shelf Life

Clause 8: Freedom From Holes

Clause 9: Visible Defects

Clause 10: Package Integrity

Clause 11: Packaging and Labeling

Clause 12: Test Reports

Annexes A and B: Sampling

Annexes C to N: Test Methods

ISO 4074 Clause 4: Quality Verification

- Testing done on a sample of each lot
- ISO 2859-1 gives “basic sampling plans”
- Other sampling plans possible
- Purchasers should look at quality system
- Two sampling schemes, depending on whether tests continuing or isolated
- Note handling and storage conditions when sampling
- Lot size is part of manufacturers quality system

ISO 4074 Clause 5: Design

- Integral bead
- Lubrication: method for determination (but no limit)
- Length: > 160 mm
- Width: nominal ±2 mm
- Thickness: method for determination (but no limit)

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ISO 4074 Clause 6: Inflation Testing

- Inflation test for untreated condoms
- Inflation test for oven-treated condoms
- Requirements for extra-strong condoms (almost unused)

Air Inflation Test
- Inflates 150 mm of the condom until burst
- Limits on burst pressure and volume
- AQL for burst properties is 1.5%
- *Test first adopted in Sweden in 1950*

ISO 4074 Clause 7: Shelf Life

- Shelf life data to be available to regulator
- Tests:
  - Minimum stability requirements
  - Real time studies
  - Accelerated studies
- All of these are "type tests"
- Must do real time and minimum stability. If real-time not completed, must do accelerated studies.

ISO 4074 Clause 8: Holes

- Two alternative methods for freedom from holes test
- Maximum allowable hole level 0.25%
- The potential for holes to cause condom failure in use is obvious, but very small holes may pose only very small risk

Water Leakage Test
- Fill with water, examine, close and roll on absorbent paper (ISO)
- Stringent limit on number allowed (AQL 0.25%)
- Small holes not 100% detectable
- Holes hardest to find near closed end
- Boring test requiring concentration
- Currently under review by ISO

Electrical Test
- Fill condom with NaCl solution, dip in NaCl solution, measure the resistance
- Minimum resistance allowed – 1.99 MΩ
- Roll non-compliers to confirm, to avoid false positives
- Stringent limit on number allowed (AQL 0.25%)
- Small holes not 100% detectable
- Currently under review by ISO

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ISO 4074 Clause 9: Visible Defects

- Visible defects to be assessed during holes test
- Only broken beads, missing or severely distorted beads, and permanent creases with adhesion of film are considered

ISO 4074 Clause 10: Package Integrity

- Package integrity test method, to be applied if required
- Pack is immersed in water with vacuum. Endpoints are:
    - bubbles leaking from pack, or
    - water penetrating into pack.

1SO 4074 Clause 11: Packaging and Labeling

- Packaging and labeling requirements for the individual pack and the consumer pack
- Specifications may impose additional requirements

Annexes A and B: Sampling

- Annex A is for continuing sampling
    - Final release testing in a factory
- Annex B is for isolated lots
    - Prequalification sampling
- Both annexes refer specifically to ISO 2859-1

Annex C: Lubricant Testing

- Two choices—ultrasonic or manual
- Weigh the condom and pack, wash off lubricant, dry, and re-weigh
- Method says wash and dry to constant mass
- Need to validate your method
- Then wash using a fixed pattern

Annex D: Length

- Simple principle—must use mandrel
- Things that can go wrong:
    - Not reading the shortest length
    - Wrong size mandrel
    - Stretching, or not smoothing
    - Calibration

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Annex E: Width

- Very simple test—hang over ruler
- Things that can go wrong:
  - Not reading the lowest width
  - Stretching, or not smoothing
  - Calibration

Annex F: Thickness

- Two options:
  - Mass method
  - Dial gauge method
- Mass method is hard to do—need to wash and dry and cut sample
- Dial gauge needs right foot size and pressure
  - Sample must be flat
  - Calibration important

Annex G: Inflation test

- Complex test
- Operator technique very important
- Equipment design also important
- Need to check equipment operation
- Correct calibration essential
- Separate annex on suggested system checks

Annex H: Ovens

- Describes oven-conditioning
- Includes oven specification by reference to ISO 188
- Includes times in oven and cooling time
- Includes temperature tolerance
- The 70C test is likely to be removed in the next revision of the standard
- Annex may be retained to describe 50C testing and maybe shelf life determination

Annex I: Tensile Testing

- Tensile testing applies only to condoms called “extra strong” or similar
- Cut ring sample 20 mm wide across condom
- Put on rotating mounts on tensile tester
- Stretch at 500 mm/min and measure force and elongation at break
- There are very few products claiming extra strength

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Annex J: Real-Time Stability

- How to conduct a real-time stability study
- Store samples at 30C (actually 28 to 35 allowed)
- Must test at least 32 condoms at least once a year
- Observe the trends in mean volume and pressure, and their standard deviations
- Infer when the product will soon be at risk of failing ISO 4074
- Then test a larger sample to verify that product still conforms

Annex K: Accelerated Aging

- Based on the Arrhenius equation
- Two choices:
    - Use ISO 11346
    - Use time-temperature superposition and activation energy of 83 kJ/mole
- As described, these methods don't work well

Annex L: Holes Testing

- Two methods – water leakage and electrical
- Any hole or tear that is visible before the water is added is counted
- Holes found more than 25 mm from the open end after water added are counted
- Water leakage test uses 300 ml of water and requires rolling
- Electrical test uses 200 ml of water and only requires rolling of condoms that conduct

Annex M: Package Seal Test

- Put the samples under water in a vacuum chamber
- Evacuate to 20 kPa
- Look for bubbles
- Cut packs open and look for water inside