



## **SECTION FOUR**

### **Annexes**



## ANNEX I

### TECHNICAL BASIS FOR THE WHO/UNFPA SPECIFICATION, 2003–2010

#### 1 Review of the technical process to publish the Male Latex Condom: Specification and Guidelines for Procurement (WHO, 2004)

The *Male Latex Condom: Specification and Guidelines for Condom Procurement* was updated and published by the World Health Organization (WHO) in January 2004. Included in that document was the *Model Specification for Male Latex Condoms*. The 2004 publication was based on an extensive review and technical consultative process to ensure that it reflected the latest available information. WHO, in collaboration with Family Health International, UNFPA and UNAIDS, undertook the following activities:

- Supported the preparation of a technical background paper for the meeting by Dr William Potter, reviewing the evidence base for the *Specification and Guidelines for Condom Procurement*.
- Supported the preparation of a technical background paper by Dr John Gerofi, reviewing the available information on whether two sizes of condoms meet the needs of all potential users.
- Supported the preparation of a review of the literature to collate the latest available evidence on the efficacy and effectiveness of the male latex condom to prevent the transmission of STIs/HIV.
- Convened an Informal Technical Consultation, held in Johannesburg, South Africa, in May 2002, in collaboration with the WHO Africa Regional Office (WHO/AFRO); the Reproductive Health Research Unit, Department of Obstetrics and Gynaecology, University of the Witwatersrand; and Chris Hani Baragwanath Hospital in Soweto, South Africa. This meeting involved 32 participants, including representatives from bulk procurement agencies; international organizations and nongovernmental agencies; manufacturers; testing laboratories and programme managers from China, Ghana, Nigeria, South Africa, Thailand and Zimbabwe; and the national bureaus of standards of South Africa and Tanzania. The purpose of the meeting was to review the 1998 WHO publication *Specification and Guidelines for Condom Procurement* against the latest available information, programmatic experience and the newly published *ISO 4074:2002* standard.

A report of the meeting is available from the documentation centre of WHO, Department of Reproductive Health and Research (WHO/RHR) by e-mail (rhrpublication@who.int). It will also be published on the WHO/RHR web site (<http://www.WHO.int/reproductivehealth>).

- Convened a meeting with delegates to the International Organization for Standardization Technical Committee 157 (ISO/TC 157), which is responsible for the revision and publication of *ISO 4074 Natural Latex Rubber Condoms*. This meeting took place during the 19th annual meeting of the delegates to ISO/TC 157, with support from the Malaysia Department of Standards and the Secretariat to ISO. The meeting was held on 12 July 2002 in Kuala Lumpur, Malaysia, and involved 67 delegates representing manufacturers, testing laboratories, scientists and consumer groups from 19 countries. The purpose of this meeting was to review and receive comments on the revised *Model Specification* for the male latex condom in order to foster consensus and commitment to support the use of the *Model Specification* and recommended procurement procedures.
- Conducted an external review of the revised *Male Latex Condom: Specification and Guidelines for Condom Procurement* between January and March 2003. The document was sent to 120 reviewers who represented the interests of bulk procurement agencies, international organizations and nongovernmental agencies, manufacturers, testing laboratories and programme managers. The response rate was 60%. Comments were collated and reviewed by a small team of technical experts prior to the final revision of this document.
- Reviewed the *Model Specification* in June 2003 against the conclusions and recommendations made at the 20th annual meeting, in Denver, Colorado, USA, of delegates to ISO/TC 157, who were responsible for the revision and publication of *ISO 4074 Natural Latex Rubber Condoms*.

All papers and consultations were used as a basis for formulating the WHO/UNFPA/UNAIDS/FHI publication, *Male Latex Condom: Specification and Guidelines for Condom Procurement* (WHO 2004).

References from these papers have been included in the bibliography of this annex.

## 2 WHO/UNFPA Prequalification Scheme for Male Latex Condoms

In 2001 WHO established a Prequalification Scheme as a service to facilitate access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis. From the outset, the Prequalification Scheme was supported by UNAIDS, UNICEF, UNFPA and the World Bank as a concrete contribution to the United Nations priority goal of addressing widespread diseases in countries with limited access to quality medicines. Prequalification was originally intended to give United Nations procurement agencies, such as UNICEF, the choice of a range of quality medicines. With time, the growing list of products that have been found to meet the set requirements has come to be seen as a useful tool for anyone bulk-purchasing medicines, including countries themselves and other organizations.

Since 2002 the prequalification of manufacturers of male latex condoms has been recommended by WHO and incorporated into the guidelines for procurement in the *Male Latex Condom: Specification and Guidelines for Procurement* (WHO, 2004). UNFPA and other agencies independently implemented Prequalification Schemes based on these recommendations.

In 2006 it was agreed that WHO would work with UNFPA to formulate a Prequalification Scheme for male latex condoms and intrauterine devices (IUDs) that would be harmonized with the WHO Prequalification Scheme for Essential Medicines. The Prequalification Scheme would support a rigorous process of assessment, and all manufacturers successfully completing this process would be listed on the WHO and UNFPA web sites as prequalified suppliers. This list would then be available to all bulk procurement agencies and national authorities that wish to purchase these medical devices.

In order to achieve this objective, WHO set up a series of meetings engaging a team of technical experts and has published Prequalification Schemes for male latex condoms and the TCu-380A IUD. These schemes are

harmonized with the WHO Prequalification Scheme for Essential Medicines, recognizing of course that both the condom and the IUD are classified as medical devices rather than medicines. The schemes were presented to and approved by the 42nd WHO Expert Committee on Specifications for Pharmaceutical Preparations, October 2007, and approved for publication subject to external review.

The Prequalification Scheme for male latex condoms was then reviewed by programme managers and representatives from the condom manufacturing industry, regulatory authorities and national testing laboratories at three prequalification workshops—held in Beijing, China; Delhi, India; and Bangkok, Thailand—in January and February 2008. The Prequalification Scheme was revised based on feedback received and published by WHO/UNFPA in May 2008<sup>1</sup>. As a result of feedback from the participants in these workshops, a guidance document on how to implement the Prequalification Scheme was prepared and has since been reviewed by participants in prequalification workshops undertaken in Botswana, Indonesia, South Africa, and Viet Nam, from January to March 2009. Both the Prequalification Scheme and the Prequalification Operational Guidance document have been included in Section 2 of this manual.

## 3 Technical basis for updating the WHO/UNFPA Specification, 2008–2009

In 2008 ISO published a second technical corrigendum to *ISO 4074* and, as of late 2009, following a periodic review, ISO is updating the standard. A committee draft of the proposed revised standard was published for review in 2008 by national standards organizations and other agencies represented at the international standard committee for non-systemic contraceptives and STI-barrier prophylactics, *ISO/TC 157*. The date of publication of the revised *ISO 4074* standard is difficult to estimate since the timing depends upon achieving consensus, but it is unlikely to be before 2011.

1 *Forty-second report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, WHO, May 2008 (WHO Technical Report Series, No. 948).

Since the publication of the 2003 Model Specification, manufacturers, laboratories, agencies and other bodies have gained considerable experience with applying the procedures for determining the shelf-life of condoms. As a consequence, it has now been recognized that some of the procedures and requirements for shelf-life determination that are specified in *ISO 4074:2002* and cross-referenced in the 2003 Model Specification are inappropriate and required review.

With the introduction of the WHO/UNFPA Prequalification Scheme, the publication of the second technical corrigendum to *ISO 4074* and the pending revision of *ISO 4074*, it was recognized that the 2003 publication needed updating. A technical basis paper for the revision of the Model Specification was developed by Dr William Potter, reviewing the implications of the publication of the second technical corrigendum to *ISO 4074*, the proposed changes to *ISO 4074* and feedback from the prequalification workshops.

WHO, UNFPA and FHI convened a meeting of the Male Condom Technical Review Committee on 14–18 July 2008 to update the specification and procurement guidelines, taking into account the recommendations and information in the technical basis paper. Experts from a broad range of interested parties, including donors, international agencies, bulk procurement agencies, non-governmental agencies, national regulatory authorities and testing laboratories, were invited along with independent experts to participate in the technical review process. The recommendations from this meeting formed the basis for a core team of technical experts to revise the specification and procurement guidelines for male latex condoms. The revised specification was reviewed by all members of ISO/TC 157 during the 25th annual meeting, hosted by WHO/UNFPA/FHI/PATH, 13–18 October 2008, in Montreux, Switzerland, and again at the 26th annual meeting in October 2009 in Shanghai, China.

Reports of the Male Condom Technical Review Committee meetings are available from the WHO Department of Reproductive Health and Research.

This annex is designed to explain the technical basis for the updated *WHO/UNFPA Specification*. It includes, where appropriate, the rationale for changes that have been made to the *WHO/UNFPA Specification*.

### **3.1 Requirements**

#### ***3.1.1 General Requirements***

General Requirements are those properties of the condom that are not expected to change from LOT to LOT. Manufacturers are expected to include evidence that the products comply with the General Requirements in their Product Dossiers and Site Master File summaries.

#### ***3.1.2 Materials***

Many of the materials used in latex formulations are irritating and sensitizing if used in excess. Manufacturers are required to demonstrate that their products are safe, using the appropriate sections of *ISO 10993 Biological Evaluation of Medical Devices*. In response to feedback from manufacturers, more details about the type of biological evaluations required and the specified parts of *ISO 10993* that apply to condoms are given in the *WHO/UNFPA Specification*. The safety assessment must include any dusting powder, colourant, lubricant and any other material that is added to the condom as well as any biocides added to the slurry, leach or washing solutions. A dossier containing the safety assessment, including expert reports interpreting the outcome of the studies, shall be made available to prospective purchasers. Summary reports must be included in the Product Dossier.

Manufacturers may rely upon regulatory clearance from internationally recognized regulatory authorities to substantiate the safety of their products. Examples of acceptable approvals include a 510(k) premarket clearance to market the product from the U.S. Food and Drug Administration (USFDA) and approval for CE marking from a European Notified Body. When reliance upon such regulatory documentation is made, the manufacturer shall be required to supply all supporting documentation used in making the submission.

#### ***Allergic reaction***

Two types of potential allergic reaction to latex condoms are possible. The first, more common potential risk is of a Type IV reaction. This type of reaction, also known as delayed hypersensitivity, most usually causes a skin rash (contact dermatitis). It is caused primarily by accelerator residues remaining in the condom. Manufacturers are encouraged to minimize accelerator residues by using the minimum amount of these chemicals in their formulations, effectively leaching and washing the condoms

and choosing accelerators with a good safety profile such as zinc dibutyldithiocarbamate (1).

The second type of allergic reaction is a Type I hypersensitivity to some of the naturally occurring water-soluble proteins found in latex. This type of allergic reaction to condoms is extremely rare. One report cites the incidence of latex protein allergy amongst condom users as 0.08% (2). Type I allergic reactions tends to affect the respiratory system and can, in extreme circumstances, lead to anaphylaxis.

#### *Protein levels*

Manufacturers shall take every precaution through effective leaching and washing of the product to maintain low levels of residual extractable proteins and shall periodically determine the residual protein levels to confirm the effectiveness of the washing and leaching procedures.

Feedback from manufacturers indicated that guidance on maximum permissible protein levels in condoms would be useful. Accordingly, a guideline limit of not more than 200 µg of water-soluble protein, as determined by the modified Lowry method, per gram of condom is recommended. There is no specific standard for determining the protein levels in condoms; the methods described in *ISO 12243*, *EN 455-3* and *ASTM D5172* for determining the protein levels in medical gloves can be modified for condoms.

#### *Nitrosamines*

Chemicals known as nitrosamines can be formed in condoms in very small quantities, typically below 500 µg/kg, by the interaction of accelerator residues in the condom with nitrogen oxides from the air. These chemicals are potentially carcinogenic. The levels of nitrosamines typically found in condoms constitute only a small proportion of normal nitrosamine exposure (3). Nevertheless, manufacturers should try to minimize the amounts of nitrosamines formed by using minimum amounts of accelerator, choosing accelerators, such as zinc dibutyldithiocarbamate, that have a preferred safety profile and ensuring that the condom is well leached.

#### *Bioburden level*

Condoms are not sterile products and, given their mode of use, there is no need for them to be sterile.

Nevertheless, manufacturers are required to minimize the risks of microbial contamination during manufacture and packaging. In response to requests from the manufacturers, recommendations for the maximum recommended microbial bioburden on condoms prior to packaging are now included in the *WHO/UNFPA Specification*. The technical basis for recommending these limits has been reviewed and is given in Annex II.

#### **3.1.3 Shelf-life**

Manufacturers are required to verify the shelf-life of their products using real-time stability studies. Critical to conducting these studies is the choice of a reference temperature appropriate to the expected storage conditions for the condoms in the destination countries.

The International Conference on Harmonization (ICH) guidelines on pharmaceutical stability studies<sup>2</sup> define the concept of mean kinetic temperature as “a single derived temperature which if maintained over a defined period would afford the same thermal challenge to a pharmaceutical product as would have been experienced over a range of both higher and lower temperatures for an equivalent defined period”. In other words, the mean kinetic temperature is a single temperature that will result in the same degree of thermal challenge to a product as storage in a particular climatic zone, taking into account the normal variation in temperature over the storage period. It also takes into account the changes in rates of chemical reactions that occur as the temperature increases.

The concept of dividing the world into four climatic zones to facilitate the stability testing of pharmaceutical products was proposed by Paul Schumacher in 1972 (4) and Wolfgang Grimm in 1986 (5), 1993 (6) and 1998 (7). The proposal was accepted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1996, following extensive consultations (8). The mean kinetic temperature of the two most extreme climatic zones, Zone III (hot/dry) and Zone IV

2 *Guidance on stability testing: stability testing of new drug substances and products*. (CPMP/ICH/2736/99). Geneva, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 2003 (<http://www.emea.europa.eu/pdfs/human/ich/273699en.pdf>).



(hot/humid), was established as 30 °C. Proposals are at an advanced stage to divide Zone IV further on the basis of humidity, but this will not affect the choice of 30 °C as the mean kinetic temperature.

Given that the mean kinetic temperature for the two most extreme climatic zones is 30 °C, this temperature is specified as the reference temperature for condom stability studies. A tolerance of -2 °C has been allowed, based on conventional practice. The upper tolerance was increased to +5 °C to simplify temperature control requirements when conducting real-time stability studies in countries where ambient temperatures may periodically exceed 32 °C. Real-time studies shall therefore be conducted at a temperature of  $(30 \pm 2)$  °C.

Methods of assessing the shelf-life of latex condoms have been researched in considerable detail by a working group, ISO/TC 157 WG 13, a subcommittee of ISO/TC 157. Since the publication of *ISO 4074:2002*, manufacturers have been required to complete both accelerated and real-time studies to determine the shelf-lives of their condoms. In addition, a number of independent researchers have undertaken comparative real-time and accelerated studies, most notably Dr M.C. Bo of the Instituto Nacional de Tecnologia, Rio de Janeiro, Brazil (9). Much, but not necessarily all, of this information has been made available to ISO/TC 157 WG 13. In the data supplied, the following general trends are usually seen in the way in which the burst properties of condoms change under accelerated and real-time storage conditions:

1. At higher temperatures, i.e. above approximately 50 °C, the burst pressure properties of the condom tend to decline more rapidly than the burst volume. Estimates of shelf-life are most likely to be limited by failure of the condoms to achieve the minimum AQL requirements for burst pressure. Burst volume behaviour can vary considerably depending upon manufacturer, but often the burst volume remains relatively constant or even increases initially before slowly declining.
2. At lower temperatures, particularly at 30 °C, which is the reference temperature for real-time stability studies, burst volumes tend to decline more rapidly than burst pressure. The shelf-life

of the product is more likely to be constrained by failing to achieve the AQL requirements for burst volume than for pressure.

3. The early phases of stability studies can be misleading since fresh condoms can undergo changes in burst properties resulting from maturation of the network structure within the latex film. Often, this can result in an initial fall in burst volume and a rise in burst pressure.
4. The Arrhenius relationship, which correlates changes in the rate of chemical reactions with temperature, can often be applied to burst pressure changes but not necessarily to burst volume changes. Even when the Arrhenius relationship is found to apply to burst volume data, the activation energy differs from that determined using burst pressure data. These factors, coupled with the different behaviour patterns observed in burst property trends at low and high temperatures, make application of the methods described in Annex K of *ISO 4074:2002* difficult and potentially unreliable.

Given this new information, ISO/TC 157 WG 13 agreed to recommend to ISO/TC 157 a number of changes to the procedures and requirements for determining the shelf-life of the condoms by accelerated studies. These changes are being considered for inclusion in the next edition of *ISO 4074*. They apply only to accelerated studies. The requirement to confirm the shelf-life of the product through real-time studies at  $(30 \pm 2)$  °C will remain unaltered in the next edition of *ISO 4074*. The proposed changes are:

1. To retain the requirement to conduct a minimum stability assessment on any new or modified condom as described in the relevant clause of *ISO 4074*. This requires the manufacturer to demonstrate that condoms remain in compliance with the minimum airburst requirements of the relevant clause after conditioning for  $(168 \pm 2)$  hours at  $(70 \pm 2)$  °C and  $(90 \pm 1)$  days at  $(50 \pm 2)$  °C. A provisional shelf-life of two years may be assigned to products that meet this requirement.
2. To amend Annex K, which describes procedures for conducting accelerated studies, to allow a provisional shelf-life of three years to be assigned

to a product if it remains in compliance with the airburst requirements of the relevant clause of *ISO 4074* for a period of 120 days at  $(50 \pm 2)$  °C or a provisional shelf-life of five years if it remains in compliance after 180 days at  $(50 \pm 2)$  °C. An alternative procedure is also being proposed that would allow a new or modified product to be compared with a control product in a parallel stability study, providing the shelf-life of the control product has already been validated by a real-time study.

After considering the proposals made by ISO/TC 157 WG 13, the experts present at the WHO/UNFPA/FHI Technical Review Committee Meeting, in July 2008, agreed to adopt the following requirements for shelf-life in the *WHO/UNFPA Specification*:

1. Manufacturers shall confirm, using real-time studies at  $(30 \pm 2)$  °C, that the condoms comply with the performance requirements of the *WHO/UNFPA Specification* throughout the stated shelf-life. Manufacturers shall stipulate a shelf-life based on the outcome of stability studies and measured from the date of manufacture, which for the purposes of the *WHO/UNFPA Specification* is defined as the date of dipping. The stated shelf-life shall be not less than three years and not more than five years from the date of manufacture.
2. Pending the outcome of real-time studies, manufacturers may claim a provisional shelf-life based on demonstrating compliance with the performance requirements of this *WHO/UNFPA Specification* on the basis of accelerated studies conducted at  $(50 \pm 2)$  °C.
  - a. A provisional shelf-life of three years may be claimed after an ageing period of 120 days.
  - b. A provisional shelf-life of five years may be claimed after a period of 180 days.

It is emphasized that manufacturers are required to demonstrate that the condoms comply with all the performance requirements of the *WHO/UNFPA Specification* throughout the shelf-life of the product. This means that, as part of any stability study, changes in burst properties, freedom from holes and pack integrity will have to be monitored.

### **3.1.4 Minimum stability requirements**

ISO/TC 157 has determined that all condoms shall meet minimum stability requirements before being placed on the market. This allows manufacturers and purchasers to assess the stability of a product relatively quickly. Additionally, it has been agreed that products meeting these requirements may be assigned a provisional shelf-life of two years. These requirements are specified in Clause 7.2 of *ISO 4074:2002* and will most probably be retained in the next edition of the standard.

The test for minimum stability includes accelerated conditioning regimens at  $(50 \pm 2)$  °C for 90 days and  $(70 \pm 2)$  °C for 7 days. The temperatures and times have been selected on the basis of practical experience with stability studies on condoms. Meeting these requirements does not imply that the condoms will have any specific shelf-life. In practice, it is anticipated that manufacturers will continue the study at  $(50 \pm 2)$  °C for 120 and/or 180 days to estimate a provisional shelf-life for the product.

The minimum stability test can be commenced as part of the prequalification stage of the procurement procedure and must be completed before any contract is confirmed.

## **3.2 Performance requirements**

### **3.2.1 Bursting volume and pressure**

The inflation test was adopted by ISO for condom testing in 1990 and has always been a part of the WHO specifications. The condom is inflated with air until it bursts. The test challenges a large part of the surface area of the condom, and flaws in the latex film will reduce the burst volume and pressure of the condom. The 2003 *Model Specification* requires that samples from every LOT of condoms are inflation-tested without oven treatment and with oven treatment at  $(70 \pm 2)$  °C for  $(168 \pm 2)$  hours.

Two corrigenda to *ISO 4074* have been published. The first, published in December 2002, corrected a number of errors in the original text of *ISO 4074:2002* and increased the upper limit of the temperature tolerance for conducting real-time stability studies to 35 °C from 32 °C. Relevant amendments to *ISO 4074:2002* resulting from Corrigendum 1 were incorporated into the 2003 *Model Specification and Procurement Guidelines*.



The second corrigendum, published in April 2008, eliminated the requirement specified in Clause 6.2 and other related parts of *ISO 4074:2002* for LOT testing of oven-treated condoms. Clause 6.2 specified that condoms conditioned for  $(168 \pm 2)$  hours at  $(70 \pm 2)$  °C shall meet the minimum airburst requirements specified in clause 6.1. It is expected that the next edition of *ISO 4074* will not include requirements for LOT testing of oven-treated condoms.

The implications of eliminating the need for inflation testing after oven treatment were reviewed at the WHO/UNFPA/FHI Male Condom Technical Review Committee meeting. There was some reluctance to drop the requirement to test oven-treated condoms completely from the *WHO/UNFPA Specification* since the test can, on occasions, provide potential warning of shelf-life problems when condoms are stored in hot climates. It was originally agreed to retain the test on an intermittent sampling basis and recommend that samples be drawn from every fifth LOT for inflation testing after oven treatment.

Following an external review, consensus could not be reached on the need for this requirement. As an interim measure, pending the production of definitive evidence supporting the benefits of testing oven-conditioned condoms on a LOT-by-LOT basis, this requirement has been made optional in the *WHO/UNFPA Specification*. Purchasers may wish to include this requirement in specific contracts depending upon their level of confidence in the supplier.

It is recommended as an alternative that purchasers develop systems to monitor the variability in LOT-to-LOT average burst pressures and volumes for untreated condoms. Individual LOT average values should not vary by more than  $\pm 20\%$  of the overall average across all LOTS tested. Any LOT exhibiting a shift from the overall mean that is larger than 20% should be quarantined until further investigations are carried out, and any long-term shift in the LOT average should be investigated. Monitoring is best achieved by using a control chart. Further information on methods of monitoring quality using control charts is given in Annex IV.

The test methods and minimum burst volume and pressure requirements in this section are identical to those in

*ISO 4074*. The pass/fail criterion is based on constraining the number of condoms bursting below the limits stated. ISO/TC 157 is currently considering introducing requirements for humidity control during burst testing. The proposed limits are  $(55 \pm 15)\%$  relative humidity. If humidity control is adopted and incorporated into a future edition of *ISO 4074*, then by reference to this standard the same limits will apply to the test method specified in the *WHO/UNFPA Specification*.

The relevance of inflation testing to the performance of the condom in use has been explored in many articles (10–14). Inflation testing is currently regarded as a reliable and effective method of assessing the strength and consistency of condoms.

### **3.2.2 Freedom from holes and visible defects**

A condom with a hole in it is clearly defective. The methods for testing for freedom from holes in the *WHO/UNFPA Specification* are identical to those in *ISO 4074*, as are the requirements. These test methods have been used for condoms for many years.

There are two alternative tests. The first is a visual test, in which the condom is filled with water and inspected for leakage. The second is a conductivity test, in which the condom is filled with a salt solution and immersed in a tank containing salt solution. An electrical voltage is applied across the film. If there is a hole in the condom, it is detected by a flow of current. Any holes detected by the electrical conductivity test are confirmed by the water test. The equivalence of the two tests has been verified by a study funded by the European Commission (15).

Some modifications to the electrical test for freedom from holes are being considered by ISO/TC 157 based on recommendations from working group ISO/TC 157 WG 19. The proposed changes are intended to address possible issues with the sensitivity of the electrical test with certain types of condoms. The proposed changes include increasing the amount of electrolyte to 300 ml, filling the condoms with electrolyte before immersing them in the electrolyte bath, and applying the voltage between the condom and the electrolyte bath before the start of immersion. If these changes are adopted and incorporated into a future edition of *ISO 4074*, then by reference to this standard the same

changes will also apply to the test method specified in the *WHO/UNFPA Specification*.

Several studies have investigated the viral barrier properties of condoms that pass the tests for freedom from holes (16–20). These studies have demonstrated that intact condoms are, for all practical purposes, an effective barrier to the smallest viruses.

*ISO 4074* also requires that, at the time that testing for freedom from holes is being done, the condoms are examined visually for specified visible defects that may render the condom likely to fail in use. Such defects include a broken, missing or severely distorted bead or permanent creases with adhesion of the film (see Section 1, Chapter 3, Workmanship and Visible Defects).

### **3.2.3 Package seal integrity**

The purpose of the package is to protect the condom from mechanical damage, oxygen, ozone and light and to prevent lubricant from leaking. Exposure to oxygen, ozone and ultraviolet and visible light increases the risk of degradation of the condom.

The test adopted is identical to that in *ISO 4074*. It involves putting the packs under water in a transparent container and then drawing a vacuum on the container. The packs are observed for signs of rising bubbles while under vacuum. The vacuum is then removed and the packs are opened for evidence of ingress of any water. The presence of rising bubbles while under vacuum or the ingress of water into the pack after removing the vacuum indicates a leaking pack.

## **3.3 Design requirements**

The recommended design features are specified, but they may be modified by the purchaser to suit local conditions and preferences. They are modified in the appropriate clause by mutual agreement among the purchaser, manufacturer and recipients. It is recommended that only well-established commercial designs be used.

The differences in manufacturing costs for established designs are generally marginal, but it is expensive for a manufacturer to change a design or introduce a new one.

### **3.3.1 Shape and texture**

The conventional parallel-sided (cylindrical) condom shape has been in the WHO specification since it was

first published. In the commercial sector a variety of other shapes are available. There are few studies on the relative acceptability and efficacy of condom shapes. Two of these studies (21, 22) indicate that approximately equal proportions of people preferred each of the variants covered in the trials.

The design details of shaped condoms are specific to particular manufacturers who have the appropriate formers and testing mandrels. Selecting a particular non-parallel profile may thus reduce the range of possible suppliers.

Textured condoms can be more difficult to manufacture. Depending upon the type and location of the texturing, it may be difficult to measure the thickness of textured condoms. Members of the Male Latex Condom Technical Review Committee agreed to make this version of the *WHO/UNFPA Specification* more flexible regarding the shape and texture of condoms that could be ordered for bulk procurement.

### **3.3.2 Integral bead**

The integral bead (or rim) is a ring of rubber at the open end of the condom.

### **3.3.3 Colour**

Pigments may be added to the latex formulation. They need to be selected so that they are not harmful to the users as demonstrated by biocompatibility studies conducted according to *ISO 10993*.

Some pigments may affect the physical properties of the rubber and increase the incidence of holes. Such pigments should not be used.

Appropriate methods of defining the colours shall be agreed upon between the manufacturer and purchaser. The use of Pantone colour charts may be useful. Strips that mix different coloured condoms are not recommended because they require the mixing of condoms from different LOTS. This complicates sampling for quality assurance as well as the tracing of defects.

### **3.3.4 Odour and flavouring**

Rubber products generally have some odour. Inadequate washing of the product during manufacture and excess of some chemicals may cause a smell that is stronger than normal. Only subjective assessments of smell are practical at this stage.

It is possible to mask the smell of rubber or provide a pleasant smell using some flavours or fragrances. It is, however, preferable to eliminate the odour as far as possible by selection of formulation and processing conditions. Condoms often smell most strongly when the pack is first opened. Odours can disperse relatively quickly.

Flavouring can be used on condoms, especially if they may be used for oral sex. It is usual to add flavouring and fragrances to the lubricant.

Fragrance and flavouring must be discussed and agreed on by the manufacturer and purchaser. They need to be selected so that they are not harmful to the users as demonstrated by biocompatibility studies conducted according to *ISO 10993*.

More details on assessing odour using a panel of testers are given in Annex III.

### **3.3.5 Width**

Condom width is defined as the width when the condom is laid flat; it is half the circumference.

The relative circumferences of the condom and penis determine how well the condom fits. Excessively large or small condoms relative to penis size appear to increase the risk of failure. It appears from the limited information available that three widths of condoms will meet the needs of most of the population<sup>3</sup>. Condoms of a width of 49 mm are readily available from many manufacturers, and this is therefore the preferred size for a narrower condom. The standard width for condoms is usually 52 to 53 mm (WHO/UNFPA specify 53 mm ± 2 mm). There is no recognized size for larger condoms. Some manufacturers produce condoms of 56 mm width or more.

### **3.3.6 Length**

Based on the information available in the literature and anecdotally, there is a weak correlation between mean penis circumference and mean penis length. As far as it is possible to ascertain from the limited data available at the country level, the narrower condoms

should be shorter. Therefore, it is recommended that the minimum length of the condom depend upon the chosen width.

### **3.3.7 Thickness**

The thickness range has been chosen to avoid both very thin and very thick condoms. The very thin products are likely to fail inflation requirements, while the very thick ones appear to offer no added efficacy (23) and are likely to be less acceptable to users. The normal thickness range for condoms is between 0.060 and 0.080 mm. Condoms thinner than 0.060 mm are normally classified as thin, and those thicker than 0.080 mm are normally classified as thick.

The method of determining thickness follows *ISO 4074* and involves weighing a known area of the condom, then dividing by the density. Alternatively, the thickness may be determined using a micrometre with a foot diameter of (5 ± 2) mm and a foot pressure of (22 ± 4) kPa. It is expected that more details of the micrometre method will be included in the next edition of *ISO 4074*. The micrometre method can give different results than the weight method because of partial compression of the film during the micrometre test. Therefore, care should be taken in a contract to specify the referee method to be used. It is expected that the weight method will remain the preferred method in the next edition of *ISO 4074*.

The Male Latex Condom Technical Review Committee agreed to retain measuring at the three specified locations along the condom length irrespective of the decision to be made by ISO/TC 157. *ISO 4074* currently specifies that the thickness shall be measured at three points along the length of the condom—at 30 mm from the open end, at the midpoint and at 30 mm from the closed end.

### **3.3.8 Extra strong condoms**

There is currently no published evidence to verify claims that extra strong condoms, which tend to be thicker than standard condoms, break less often in use. There is evidence, however, that using an additional lubricant, supplied separately and applied to the condom at the time of use, can reduce the rate of breakage during anal intercourse (23).

3 Review paper prepared by J Gerofi, to be published on the WHO/RHR web site.

### 3.3.9 Lubricant

Silicone fluid is the most commonly used lubricant for condoms and is therefore recommended. It is inert and has minimal effect on the properties of the latex film. The quantity used has been selected to provide as high a level of lubrication as practical without creating package sealing problems in the factory.

Other lubricants, especially glycols and water-based lubricants, can be used. If the lubricant used is water-based, preservatives may be needed to prevent microbial growth.

Powders are added to condoms to facilitate manufacturing and allow them to unroll easily. Acceptable powders include starch and calcium carbonate. Talc and mica should not be used. Manufacturers may use other powders by agreement with the purchaser. In such cases the choice of powder may need to be justified.

Some manufacturers add biocides to the powder slurry to prevent bacterial growth. The choice of biocide and the amount used require careful consideration to achieve an acceptable level of bacterial control without increasing the risk of irritation or sensitization to end users and manufacturing personnel. A full risk assessment is required to justify the use of any biocide.

Lubricant quantity is measured by weighing the condom and pack before and after washing and drying. The difference between these values is taken as the quantity of lubricant and powder added.

Additional lubricants, supplied separately and applied to the condom at the time of use, are sometimes used to improve lubrication and comfort. Research suggests that this is particularly important for anal intercourse (23), where breakage rates might be reduced by using additional lubricants.

Any additional lubricant that is used must not have a deleterious effect on the properties of the condoms, such that the risk of breakage is increased. Methods of testing additional lubricants for compatibility with condoms are being developed by working group ISO/TC 157 WG 15, but poor inter-laboratory reproducibility has delayed the development of a widely acceptable procedure. Usually, these additional lubricants are water-based, but

glycol-based lubricants are becoming more common. Household products are also sometimes used as sexual lubricants. Some have a highly damaging effect on latex and should not be used with condoms (see box).

### 3.3.10 Spermicidal additives

Spermicidal additives to the lubricant have been used in some commercial products. Recent summaries of research findings suggest that these spermicides (predominantly nonoxynol-9) have significant irritant effects, and, overall, their use is not recommended (24).

### 3.3.11 Addition of medicinal substances to condom lubricants

In the commercial sector there is increasing availability of condoms containing medicinal substances. Many manufacturers incorporate the medicinal substance into a viscous gel or paste to localize it within the closed end of the condom. This is done to ensure that only the male partner is exposed to the active ingredients. If a medicinal substance is added to a condom, it is recommended that it is not added directly to the lubricant, as both partners will then be exposed to it. The most common example of a medicinal substance added to a condom is a local anaesthetic such as benzocaine.

Condoms containing medicinal substances are subject to local regulatory requirements for medicines, and there may be legal issues with their distribution. **The inclusion of such products in bulk procurement programmes is therefore not recommended in this WHO/UNFPA Specification.** It is suggested that individual bulk procurement agencies should consider all the issues before procuring this type of condom.

#### Household products that should not be used with condoms:

- Baby oil
- Burn ointments
- Cooking oil
- Dairy butter
- Fish oil
- Haemorrhoid ointment
- Insect repellent
- Mineral oils
- Palm oil
- Petroleum jelly
- Rubbing alcohol
- Suntan oil

#### 4 Individual package materials and labelling

Aluminium foil laminates are the most commonly used packaging material. It is important that the packaging protect the condom from oxygen, ozone and ultraviolet and visible light; be easy to open; and not leak lubricant.

There are requirements for labelling individual packs to provide the minimum essential information for the end user. The labelling also helps to track the storage, supply and distribution of the condoms and can be used to locate LOTS if there are ever any questions about the quality of the product.

In addition, it is a requirement of *ISO 4074* to include essential information for the condom user, which includes instructions for use, advice on disposal of the product after use, a statement that the condom is for single use only and the number of the international standard, *ISO 4074*. The Male Latex Condom Technical Review Committee recommended that, in addition, the *WHO/UNFPA Specification* include a requirement for a statement about the effectiveness of the condom.

#### References

- 1 Tinkler J et al. Risk assessment of dithiocarbamate accelerator residues in latex-based medical devices: genotoxicity considerations. *Journal of Food Chemistry and Toxicology*, 1998, 36(9–10): 849–866.
- 2 Liss G, Sussman G. Latex sensitization: occupational versus general population prevalence rates. *American Journal of Industrial Medicine*, 1999, 35:196–200.
- 3 Proksch E. Toxicological evaluation of nitrosamines in condoms. *International Journal of Hygiene and Environmental Health*, 2001, 204(2–3):103–110.
- 4 Schumacher P. Über eine für die haltbarkeit von arzneimitteln maßgebliche klimaeinteilung [The impact of climate classification on the stability of medicines]. *Pharmazeutische Industrie*, 1972, 34:481–483.
- 5 Grimm W. Storage conditions for stability testing (Part 2). *Drugs Made in Germany*, 1986, 29:39.
- 6 Grimm W. Storage conditions for stability testing in the EC, Japan and USA, the most important market for drug products. *Drug Development and Industrial Pharmacy*, 1993, 19(20):2795–2830.
- 7 Grimm W. Extension of the International Conference on Harmonization tripartite guideline for stability testing of new drug substances and products to countries of climate zones III and IV. *Drug Development and Industrial Pharmacy*, 1998, 24(4):313–325.
- 8 WHO Expert Committee on Specifications for Pharmaceutical Preparations. 34th Report. Geneva, World Health Organization, 1996 (WHO Technical Reports Series, No. 863 Annex B).
- 9 Bo MC et al. Prediction of shelf-life of natural rubber male condoms—a necessity. *Polymer Testing*, 2007, 26(3):306–314.
- 10 Free MJ, Skiens EW, Morrow MM. Relationship between condom strength and failure during use. *Contraception*, 1980, 22:31–37.
- 11 Free MJ et al. An assessment of burst strength distribution data for monitoring quality of condom stocks in developing countries. *Contraception*, 1986, 33(3):285–299.
- 12 Steiner M et al. Study to determine the correlation between condom breakage in human use and laboratory test results. *Contraception*, 1992, 46(3):279–288.
- 13 Benton KWK et al. An actual use comparison of condoms meeting Australian and Swiss standards: results of a double-blind crossover study. *International Journal of STDs & AIDS*, 1997, 8:427–431.
- 14 Gerofi JP, Shelley GA. Condom inflation testing: strain distribution during test. *Journal of Testing and Evaluation*, 1991, 19(3):244–249.
- 15 White N, coordinator. Assessment of methods for finding holes in condoms. *EC Contract MAT1-CT 940050* (<http://www.durex.com/scientific/abstracts/white2.html>).
- 16 Van de Perre P, Jacobs D, Sprecher-Goldberger S. The latex condom, an efficient barrier against sexual transmission of AIDS-related viruses. *AIDS*, 1987, 1(1):49–52.
- 17 Minuk GY et al. Efficacy of commercial condoms in the prevention of hepatitis B virus infection. *Gastroenterology*, 1987, 93(4):710–714.
- 18 Retta SM et al. Test method for evaluating the permeability of intact prophylactics to viral-size microspheres under simulated physiologic conditions. *Sexually Transmitted Diseases*, 1991, 18(2):111–118.
- 19 Lytle CD, Routson LB, Cyr WH. A simple method to test condoms for penetration by viruses. *Applied Environmental Microbiology*, 1992, 58(9):3180–3182.
- 20 Voeller B, Nelson J, Day C. Viral leakage risk differences in latex condoms. *AIDS Research and Human Retroviruses*, 1994, 10(6):701–710.
- 21 Garside R. Condom shape: a neglected factor influencing use and acceptability? UK Family Planning Research Network. *International Journal of STDs & AIDS*, 1999, 10(12):785–790.
- 22 Macaluso M et al. Safety and acceptability of a baggy latex condom. *Contraception*, 2000, 61(3):217–223.
- 23 Golombok R, Harding R, Sheldon J. An evaluation of a thicker versus a standard condom with gay men. *AIDS*, 2001, 15:245–250.
- 24 WHO/CONRAD Technical Consultation on Nonoxynol-9. World Health Organization, Geneva, October 2001. ([http://www.global-campaign.org/clientfiles/N9\\_meeting\\_report.pdf](http://www.global-campaign.org/clientfiles/N9_meeting_report.pdf)).