Annex 9

WHO/UNFPA guidance on natural rubber latex male condom stability studies

Contents

1. Introduction

Manufacturers of natural rubber latex male condoms are required by regulatory bodies to establish the shelf-life of their products prior to placing them on the market. The methods and data used to establish the shelf-life are assessed as part of the regulatory review processes. The United Nations Population Fund (UNFPA) also requires data supporting shelf-life claims to be submitted as part of the prequalification process for the procurement of natural rubber latex male condoms.

The general procedures for estimating and verifying shelf-life claims are included in International Organization for Standardization (ISO) 4074:2015 (*1*). Requirements relating to shelf-life are specified in Clause 11 and the procedures are specified in Annex K (Determination of shelf life by real-time stability studies) and Annex L (Guidance on conducting and analysing accelerated ageing studies). Annex I (Oven treatment for condoms) specifies requirements for the equipment and procedures used to store condoms at the various temperature conditions required when conducting stability studies.

This document is intended to provide additional guidance to manufacturers on background information relating to natural rubber latex male condom shelf-life and conducting stability studies on these condoms. This information is intended to assist manufacturers in formulating and manufacturing condoms that are stable and can meet the claimed shelf-life specification when stored in adverse climatic conditions.

During the late 1980s, a great deal of attention was focused on the stability of condoms, particularly those intended for distribution in hot climates. A significant number of studies were conducted to try and understand more about how the properties of condoms change when they are stored under different climatic conditions and in different packaging materials. Some of these studies were conducted at universities and research centres. Others were conducted by condom manufacturers. The results of these studies were studied within Working Group (WG) 13 of ISO/TC 157, the ISO technical committee responsible for developing ISO 4074, the international standard for male condoms made from natural rubber latex. As a consequence of these studies, new procedures for determining the shelf-life of condoms were incorporated into the 2002 edition of ISO 4074.

Some of the new procedures were subsequently found to be of limited use for analysing stability data on natural rubber latex male condoms, particularly the methods proposed for analysing results from accelerated stability studies. Following the publication of ISO 4074:2002, the review and analysis of stability data continued within ISO/TC 157 WG 23. This led to substantial simplification and standardization of the methods used to conduct and analyse accelerated

stability studies. These new procedures, along with a number of other changes relating to real-time condom stability studies, were incorporated into the 2014 and 2015 editions of ISO 4074.

2. Storage and ageing conditions

One of the key questions considered by ISO/TC 157 WG 13, when the technical committee started reviewing condom stability, was the environmental conditions condoms might be exposed to, particularly in the hot climatic zones where they were being distributed at the time in HIV/AIDS intervention programmes. Without a full understanding of the expected storage conditions, it is not possible to choose appropriate reference temperatures for conducting stability studies and estimating shelf-life.

The pharmaceutical industry faced exactly the same problem, which led to the development of the concept of mean kinetic temperature. Establishing average temperatures over extended storage periods is relatively simple. This can be done manually by periodically measuring and recording temperatures or automatically using data loggers. However, the rates at which chemical changes occur that can affect the physical properties of products such as condoms do not usually follow a simple linear relationship with temperature. Reaction rates tend to increase exponentially with increasing temperatures. The concept of mean kinetic temperature takes the exponential changes in reaction rates into consideration and provides a method of conducting stability studies at a constant temperature whilst taking into account the impact of the long- and short-term changes in temperature that occur in real-life storage.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)[1] guidelines on pharmaceutical stability studies 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" (2). In other words, if a product is stored at a specified mean kinetic temperature, it will experience the same degree of thermal challenge as a product stored in the equivalent climatic zone, taking into account the normal variations in temperature that will occur over the storage period and the non-linear way in which these temperature changes will affect any chemical reactions occurring within the product.

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[1] Formerly the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, under which name the guidelines were initially published.

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 (*3*) and Wolfgang Grimm in 1986, 1993 and 1998 (*4–6*). The proposal was accepted by the World Health Organization (WHO) Expert Committee on Specification for Pharmaceutical Preparations (ECSPP) in 1996, following extensive consultations (*7*). Table 1 summarizes the world climatic zones as defined in Annex 2, Appendix 1, of the forty-third report of the ECSPP held in Geneva in October 2008 (*8*).

Table 1
Proposed criteria and long-term testing conditions for defined climatic zones

Climatic Zone	Definition	Criteria: mean annual temperature/mean annual partial pressure	Testing conditions
I	Temperate	≤ 15 °C ≤ 11 hPa	(21 ± 2) °C (45 ± 5) % RH
II	Subtropical and Mediterranean	> 15 °C to 22 °C > 11 to 18 hPa	(25 ± 2) °C (60 ± 5) % RH
III	Hot and dry	> 22 °C ≤ 15 hPa	(30 ± 2) °C (35 ± 5) % RH
IVA	Hot and humid	> 22 °C > 15 to 27 hPa	(30 ± 2) °C (65 ± 5) % RH
IVB	Hot and very humid	> 22 °C > 27 hPa	(30 ± 2) °C (75 ± 5) % RH

hPa = hectopascal or millibar; RH = relative humidity.

The mean kinetic temperature of the three most extreme climatic zones – III, IVA and IVB – has been established as 30 °C with a tolerance of ± 2 °C. This temperature has therefore been adopted as the reference temperature for condom stability studies both in ISO 4074:2015 and in the WHO/UNFPA guidance for male latex condoms (*9–11*). The specified lower tolerance limit of −2 °C has also been adopted, but the upper tolerance limit has been 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. The higher temperature limit means that stability studies are likely to be more conservative (that is, the true shelf-life, if anything, is likely to be longer than the estimated shelf-life) and the need for air-conditioning when conducting stability studies is significantly reduced.

Real-time stability studies must therefore be conducted at a temperature of (30^{+5}_{-2}) °C. Maintaining the temperature within this range is very important. Continuous temperature monitoring is strongly recommended and manufacturers conducting stability studies are advised to have contingency plans to cover equipment breakdowns and power cuts. In the event of an oven failure, for example, if the manufacturer can demonstrate that despite a resulting temperature excursion the mean kinetic temperature remained within the specified range of 28 °C to 35 °C, then the results of the study would remain valid.

3. Stability of condoms

The properties of natural rubber latex male condoms can potentially degrade through exposure to a number of environmental factors. These key factors include oxidation, ozone attack, thermal degradation at elevated temperature and exposure to light, particularly ultraviolet (UV) light. Each of these factors is considered below.

3.1   Oxidation

Being an unsaturated hydrocarbon, natural rubber is prone to oxidation if it is not protected by antioxidants and/or oxygen impermeable packaging. The mechanism of oxidation is well established and documented in the scientific literature. It is similar to that for olefins (*12*) but with the additional possibility of formation of cyclic peroxides due to the presence of carbon–carbon double bonds in the rubber (*13*).

 Atmospheric oxygen reacts extremely rapidly with alkyl radicals within the rubber that can be generated by a number of mechanisms, including exposure to light, stress and heat. The resulting peroxy radicals that are formed rapidly abstract hydrogen from methylene groups adjacent to carbon–carbon double bonds in the rubber backbone, forming hydroperoxides. Also generated in this step is another alkyl radical allowing the process to repeat. Substantial repetition can occur, leading to the build-up of large numbers of hydroperoxide groups along the rubber backbone. This process is described as an autocatalytic chain reaction.

The hydroperoxide groups formed along the backbone of the rubber can subsequently decompose, for example, if exposed to heat, breaking the rubber chain (chain scission) and causing a reduction in the strength, integrity and stiffness of the rubber. Radical species generated during the hydroperoxide decomposition process can lead to further oxidation. Depending on conditions, decomposition of the hydroperoxides can also lead to further cross-linking, causing hardening of the rubber.

Since vulcanized natural rubber latex products contain sulfur cross-links, oxidation of these cross-links can also occur either directly by interaction with oxygen or by reaction with the hydroperoxides formed during oxidation of the hydrocarbon rubber backbone. Depending on the length of the sulfur cross-links and the storage conditions, decomposition of the sulfur cross-links can lead to the formation of sulfenic acids. These are powerful antioxidants and are capable of limiting the extent of oxidation that occurs (*14*, *15*).

In practice, condoms are usually hermetically sealed in aluminium foil laminate packages (almost exclusively in the case of condoms intended for public sector distribution). This type of packaging prevents oxygen reaching the condoms, thereby protecting against oxidation. In 1996, Free et al. (*16*) demonstrated, using gas chromatography, that oxygen levels in aluminium foil laminate packages containing condoms dropped to around 1.6% within a few months and the rate of decline in burst pressure was substantially slower at 45 °C than for the same condoms in plastic packaging.

During manufacture prior to packaging, however, the condoms are exposed to atmospheric oxygen and some oxidation is possible. The longer the condoms are stored before packaging the more oxidation can occur, with a build-up of hydroperoxides in the rubber that could shorten the subsequent shelf-life of the product. To minimize the risks from hydroperoxide formation, the WHO/UNFPA specification limits the storage time for bulk condoms prior to packaging to six months.

To protect the condoms against oxidation, manufacturers usually add antioxidants. There are two broad types of antioxidants: those that block the autoxidative chain reaction (sometimes called radical scavengers) and those that safely decompose the resulting hydroperoxides (peroxide decomposers). The most common examples of the former are the hindered phenolic antioxidants such as Irganox 2246 and Wingstay L. These compounds have labile hydrogen atoms that can be easily abstracted by alkoxy radicals, stopping the further propagation of radical species. The resulting free radicals formed are stabilized by delocalization of the free electron and do not react with oxygen.

The other type of antioxidants are peroxide decomposers. These compounds commonly contain sulfur, for example, thioethers and thioesters, and work by safely reducing the hydroperoxides formed by autoxidation. The dithiocarbamate accelerators typically used in latex formulations are very effective peroxide decomposers. Combinations of radical scavengers and peroxide decomposers can be a lot more effective than each type of antioxidant in isolation (synergism) since they work through different mechanisms. The combination of the phenolic antioxidants that are added to the latex compounds during manufacture and the residual dithiocarbamates from vulcanization can produce very powerful antioxidant effects.

Phenolic antioxidants are typically added to latex condom formulations at the rate of 0.5 to 2 parts per hundred of dry rubber (phr). Some are available as premilled dispersions and can simply be added to the latex. If purchased in solid form, antioxidants need to be dispersed in water using suitable dispersing agents and milled to an acceptable particle size. Since residual dithiocarbamate levels vary depending upon the latex formulation, prevulcanization conditions and condom manufacturing and processing conditions, their levels can vary significantly from manufacturer to manufacturer. The extent to which the benefits of synergism between the phenolic antioxidant and any residual accelerators can improve the oxidative stability of condoms is largely unexplored but is likely to be highly variable depending on a range of factors that affect the levels of residual dithiocarbamates in the condom. It is worth noting that Free et al. (*16*) reported very significant differences in the rates of degradation of unpackaged condoms from different manufacturers.

3.2 Ozone

Ozone is an extremely reactive molecule. It is one of the most powerful oxidizing agents known (far stronger than oxygen). Ozone can react extremely quickly with the carbon–carbon double bonds in natural rubber, initially forming ozonides, which, being unstable, can then break down causing chain scission. The rate of reaction depends both on the concentration of ozone and the amount of stress the rubber is under. Typically, ozone attack on rubber causes cracks to appear. The extent and rate of growth of the cracks depends on how stressed the rubber is. Ozone levels tend to be higher in heavily industrialized areas due to air pollution. Certain emissions, such as nitrogen oxides and volatile organic compounds, can interact with sunlight to promote the formation of ozone locally.

Protecting rubber against ozone is usually achieved by adding waxes that "bloom" to the surface, thereby providing a sacrificial coating that "mops up" any ozone present before the rubber is damaged. It is not usual practice to add antiozonant waxes to condom formulations (though they are added to some latex glove formulations). Adequate protection against ozone is usually achieved by keeping bulk condoms covered during storage before packaging. Once lubricated and packed, the condoms are very effectively protected against ozone.

3.3 Light

It is widely acknowledged within the condom industry that exposure of condoms to light, particularly UV light and light from fluorescent tubes, can initiate the degradation of unprotected condoms. It is common practice to store bulk condoms in black plastic bags to minimize exposure to light during manufacturing operations. ISO 4074:2015 specifies that the individual container

or consumer package, or both, shall be opaque to light. If condoms are intended to be supplied only in individual containers, the individual containers shall be opaque (Clause 15.1).

3.4   Thermal stability

Although there is now a reasonable level of understanding about how the physical properties of condoms change over time when stored at different temperatures in anaerobic conditions (that is, in aluminium foil laminate packages), the chemical processes responsible for these changes are still poorly understood. The results of a pilot study investigating changes in cross-link density and cross-link chain length were presented at the Latex and Synthetic Polymer Dispersions Conference, Amsterdam, 2010 (*17*).

The results indicated that statistically significant increases in the density of short-chain monosulfidic and disulfidic cross-links and decreases in the density of long-chain polysulfidic cross-links occurred after 28 days at 70 °C and 120 days at 50 °C. Total cross-link density also decreased when the condoms were stored at 70 °C for 28 days.

Potentially, these changes in cross-link type and density could explain the changes in properties seen in condoms. For example, the decrease in total cross-link density at 70 °C should reduce the stiffness (modulus) of the rubber with a consequential decrease in burst pressure and a small increase in burst volume, as was observed. The changes in cross-link length at relatively constant total cross-link density seen at 50 °C might be expected to lead to a "tighter" network structure, which could explain the reduction in burst volume that was observed at this temperature.

3.5   Continuing vulcanization

Freshly dipped latex condoms may not necessarily be fully vulcanized. There is strong evidence that some condoms continue to vulcanize for quite long periods after manufacture. Evidence for this includes the sharp drop in burst volume and an increase in burst pressure that is sometimes seen when relatively fresh condoms are aged at 70 °C for seven days. These changes can confound the outcome of stability studies, leading to erroneous conclusions about the stability of the condoms concerned. When conducting stability studies, it is therefore advisable to store condoms for a period of at least six weeks from the time of dipping before starting the study. This additional time permits most of the residual vulcanization to be completed and the cross-link network within the rubber to approach equilibrium. Time should also be allowed after packaging to permit the lubricant to migrate into the rolled condom. Typically, this can take a week or two, depending on the lubricant viscosity and dusting powder used.

4. Overview of methods determining the shelf-life of condoms

The methods of assessing the shelf-life of latex condoms have been researched in considerable detail by ISO/TC 157 WG 13. In addition, a number of independent researchers have conducted comparative real-time and accelerated studies. Most notable is the research undertaken by Dr M.C. Bó of the Instituto Nacional de Tecnología, Rio de Janeiro, Brazil (*18*).

All of these studies have involved ageing condoms at different temperatures and comparing how the changes in temperature affect the burst properties over time. The following general trends are usually seen.

- At 70 °C, the burst pressure properties of condoms tend to decline more rapidly than the burst volume properties. Estimates of shelf-life are most likely to be limited by failure of the condoms to meet minimum burst pressure requirements. Burst volume behaviour can vary considerably depending upon the manufacturer but it often remains relatively constant, or even increases initially, before slowly declining. Accelerated stability studies at 70 °C therefore tend to overestimate the decline in burst pressures and underestimate the decline in burst volumes that occur over extended periods of real-time ageing at 30 °C.

- At 30 °C, which is the reference temperature for real-time stability studies, burst volumes tend to decline more rapidly than burst pressures. The shelf-life of the product is more likely to be limited by failure to meet the acceptable quality limit (AQL) requirements for burst volume rather than burst pressure.

- The early phases of stability studies can be misleading, since fresh condoms can undergo changes in burst properties resulting from further vulcanization or maturation of the network structure within the rubber. Often, this can result in an initial fall in burst volume and a rise in burst pressure.

- The Arrhenius relationship, which correlates changes in the rate of chemical reactions with temperature, can often be applied to burst pressure changes occurring at temperatures above 50 °C 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 the methods described in Annex K of ISO 4074:2002 difficult to apply

and potentially unreliable. The Arrhenius relationship may be useful when conducting stability studies on male and female condoms made from synthetic materials but it does not appear to be helpful when it comes to analysing stability data on natural rubber latex male condoms. Because of this method of estimating product, shelf-life based on the Arrhenius relationship, as described for example in ISO 11346 (Rubber, vulcanized or thermoplastic – Estimation of life-time and maximum temperature of use), are not considered in this document.

5. Determination of shelf-life according to ISO 4074:2015

The procedures for determining the shelf-life of a condom are specified in Clause 11 of ISO 4074:2015. The maximum permitted claimed shelf-life is five years from the date of manufacture. The date of manufacture can be the date of dipping or the date of packaging the condoms into their individual sealed containers, depending upon the procedures specified by the manufacturer. The date of manufacture is not permitted to be more than two years from the date of dipping. The WHO/UNFPA specification for male latex condoms, however, limits the maximum storage time for unpackaged condoms to six months from the date of dipping. The date of manufacture permitted by the WHO/UNFPA specification cannot therefore be more than six months from the date of dipping.

The unpackaged condoms must be stored under controlled conditions, as specified by the manufacturer, between dipping and packaging. The procedures for validating the storage conditions and the maximum storage period must be documented. The stored condoms must be protected from exposure to excessive temperature, light, ozone and any other factor that could affect the shelf-life of the packaged condoms.

When conducting stability studies, the condoms used must have been stored for the maximum permitted period between dipping and packaging under the conditions specified in the manufacturer's documentation. Although the WHO/UNFPA specification limits the maximum storage period to six months, manufacturers may use data from studies where the condoms have been stored for longer periods. This is to prevent unnecessary repetition of the stability studies. The six-month maximum storage period, however, still applies to condoms intended for procurement by UNFPA and other public sector agencies, even if the stability studies used to determine the shelf-life of the products concerned were completed using condoms with longer bulk storage periods.

There are essentially three elements to the stability requirement specified in ISO 4074:2015:

i. The manufacturer is required to confirm that the condoms meet the minimum stability requirements of ISO 4074:2015 (Clause 11.2). This requires testing samples of condoms from three lots initially after conditioning for (168 ± 2) hours at (70 ± 2) °C and after conditioning for (90 ± 1) days at (50 ± 2) °C. In all cases, the condoms must comply with the requirements for burst properties specified in Clause 10 of the standard "Freedom from holes and visible defects", as specified in Clauses 12 and 13, and" Package integrity", as specified in Clause 14.

ii. The shelf-life of the product is determined by conducting a real-time stability study according to Clause 11.3 and Annex K of ISO 4074:2015 at a temperature of (30^{+5}_{-2}) °C extending for the fully claimed shelf-life period. The study must confirm that the product conforms with the burst properties specified in Clause 10 of the standard "Freedom from holes and visible defects", as specified in Clauses 12 and 13, and "Package integrity", as specified in Clause 14. Pending completion of the real-time stability study, manufacturers may place the product on the market based on a provisional shelf-life determined in an accelerated stability study completed according to Clause 11.4 of the standard. The real-time shelf-life study must be started before the product can be marketed.

iii. A provisional shelf-life for the product can be determined in an accelerated stability study conducted according to Clause 11.4 and Annex L of the standard. The specified method given in Clause L.2 is much simpler and easier to use than the procedure previously described in the 2002 edition of ISO 4074. It is based on the simple premise that after conditioning the condoms at (50 ± 2) °C, the following provisional shelf-life claims may be made, assuming that the condoms conform to the requirement for burst properties specified in Clause 10 of the standard "Freedom from holes and visible defects", as specified in Clause 12, and "Package integrity", as specified in Clause 14, at the end of each period:

– a shelf-life of two years after a period of 90 days
– a shelf-life of three years after a period of 120 days
– a shelf-life of five years after a period of 180 days.

An alternative procedure is given in Clause L.3 for "Determining the shelf-life of a condom when a control condom is available", which is also included in Annex L. The shelf-life of the control condom must have been confirmed in a real-time study conducted according to Annex K. The alternative procedure is more complicated but does have the advantage that it may be possible to identify

a set of ageing conditions that will permit a provisional shelf-life of five years to be established in less than 180 days.

The Clause L.3 procedure is conducted in two stages. First, the ageing characteristics of samples of the test and control condoms are compared by monitoring the burst properties of the condoms after conditioning for different times at selected temperatures. Based on the outcome of this study, a set of ageing conditions (time and temperature) is selected. The selected conditions must be such that significant changes in the burst properties of the control condoms are observed. A further stability study is conducted on three randomly selected lots of test condoms using the selected set of conditions. If, after the conditioning period, all three lots conform to the requirements for burst properties, freedom from holes and package integrity, then the provisional shelf-life can be assumed to be equal to that for the control condom.

Full details of how to conduct the real-time stability study are included in Annex K of ISO 4074:2015, and details on how to conduct the accelerated study are included in Annex L. These procedures are summarized in Appendix 1 to this guidance document. Additional practical guidance is given in the following section.

6. Practical guidance

As stated above, full details of how to conduct the stability studies are given in ISO 4074:2015. The following guidance provides additional information to supplement the procedures described in the standard.

6.1   Selection of condoms

A minimum of three lots of each type of condom to be tested should be selected from normal production. The lots should be randomly selected from a period of stable production.

All the selected lots must have been stored for the maximum permitted bulk storage time prior to starting the study. UNFPA limits this period to six months but results from lots stored for longer periods are acceptable.

All elements of the stability study (that is, testing for minimum stability), the real-time study and the accelerated study should be done on the same lots. This permits the results to be compared across all of the studies.

6.2   Samples and storage

It is important to calculate the total number of samples required for the study and to include additional condoms as spares. The spares should be sufficient to permit samples to be replaced during testing if required (for example, if it is

determined that a condom has a hole in it during the burst test). There should also be sufficient spares to allow for some of the testing to be repeated (for example, if anomalous results are obtained at one of the time points). The spare condoms shall be subjected to exactly the same treatment as the test condoms.

The condoms should be retested at the start of the study to obtain the initial values for analysis. It is not recommended to rely on the quality control or quality assurance results at the time of manufacture. The properties of the condoms may change between the date of manufacture and the start of the study.

The larger sample sizes specified in Annex B of ISO 4074:2015 are recommended. These sample sizes provide more confidence in the results and are less prone to random sampling errors causing the acceptance numbers to be exceeded when the condoms are, in fact, in compliance. As a minimum, the sample sizes given in Annex A of ISO 4074:2015 must be used, except when otherwise instructed in the relevant annex.

The requirements specified in Annex I of ISO 4074:2015 should be followed for storage conditions. The temperatures should be monitored regularly and recorded. Ideally, monitoring should be done on a continuous basis. The temperatures must remain within the specified tolerances. Adequate space should be left between the samples to maintain good airflow and even temperature distribution. It is strongly recommended that a documented action plan be in place, including such contingencies as a breakdown of the stability ovens or chambers or a power cut.

During the stability study, samples should be tested at regular intervals, as recommended in Annex K, Clause K.2.4 of ISO 4074:2015. This is to provide an early warning should the shelf-life prove to be shorter than the provisional shelf-life estimated from the accelerated stability studies. The intermediate results also provide information about the ageing profile of the condoms over time.

6.3   Testing

After conditioning, the packages shall be kept at (25 ± 5) °C until tested. This allows time for the condoms to come to equilibrium with the test temperature. The condoms shall be tested within 96 hours but not sooner than 12 hours after conditioning.

Before starting testing, it is very important to make sure that certain testing equipment is calibrated and working correctly. The technicians conducting the tests must be properly trained and the training records must be kept up to date.

Full details of testing conditions must be recorded and all results must be correctly captured.

6.4 **Reporting**

Interim reports should be maintained, each being updated as new results become available. Any trends should be monitored as the study progresses, for example, by plotting the results for average burst volumes and pressures over time, together with the standard deviations and number of nonconforming condoms. The reports should include statistical analyses; for example, for burst properties, t-tests or analysis of variance (ANOVA) can be used to compare results between lots and over time to determine if the differences are statistically significant. Fisher exact test or the chi-square test can be used to determine if any changes in the numbers of nonconforming condoms between lots and over time are statistically significant. Linear and non-linear regression analyses can be used to determine trends and extrapolate results to the end of study.

Monitoring the lower one-sided 98.5% limits of the confidence intervals for burst volumes and pressures gives a good indication as to when the numbers of nonconforming condoms are likely to exceed the acceptance numbers. These limits can be calculated from the mean and standard deviations of the burst results using the appropriate t-values for the sample sizes tested. Ideally, the lower 98.5% one-sided limits of the confidence intervals for burst volume should remain above 20 litres and burst pressures above 1.1 kilopascal (kPa) for condoms with mid-body widths in the range 50–56 millimetres. For condoms in different width ranges, the lower 98.5% one-sided limits of the confidence intervals for burst volumes should remain above about 10% of the specified limit in ISO 4074:2015 for the relevant mid-body width of the condoms.

Details about the information to be included in stability reports are given in Clause 16 of ISO 4074:2015 and in the specific annexes referring to stability studies, Annexes K and L. In addition, stability reports, both interim and final, should include full details about the condoms being tested, including lot numbers, date of manufacture (ideally both dipping and packaging), condom type and details about any secondary packaging used in the studies. Full details about the ageing conditions should be included in the report, including any deviations in temperature control. Conclusions about the shelf-life estimates for the products shall be included in the reports, including any methods used to analyse the results and the outcome of any statistical analyses.

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Appendix 1

Summary procedures for conducting stability studies

1. Minimum stability testing

When conducting the minimum stability test, follow the procedure in ISO 4074:2015, Clause 11.2. Condition the 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. Before testing, condition the sample for a minimum of 12 hours but not more than 96 hours at (25 ± 5) °C. Test the condoms for burst properties, freedom from holes and visible defects (including visibly open packaging) and package integrity. In addition, inspect the condoms and packaging for any signs of discoloration and visible defects, and the condoms for odour and ease of unrolling. Finally, confirm whether or not the condoms conform to the relevant requirements specified in ISO 4074:2015.

2. Accelerated stability study

When conducting an accelerated stability study, follow the procedures in ISO 4074:2015, Clause 11.4 and Annex L. Annex L is informative (that is, it does not have to be followed exactly) but deviations should only be made if there is a very good reason to depart from the specified procedures and must be justified. If there is a suitable control condom with a shelf-life already determined by a full real-time stability study, then the procedure described in Clause L.3 can be followed. However, this procedure is more complicated than the simpler procedure described in Clause L.2 when no control condom is available.

Accelerated stability study when no control condom is available (Annex L.2)

Condition the condoms at (50 ± 2) °C using the procedures specified in ISO 4074:2015, Annex I. Remove the samples for testing after specified time periods (90, 120 and 180 days). Before testing, condition the sample for a minimum of 12 hours but not more than 96 hours at (25 ± 5) °C. Test the condoms for burst properties, freedom from holes and visible defects (including visible open seals) and package integrity. In addition, inspect the condoms and packaging for any signs of discoloration, and the condoms for odour and ease of unrolling. Assess conformance with ISO 4074:2015 requirements.

Accelerated stability study with control condom (Annex L.3)

Select the required number of condoms, including spares, from a minimum of three production lots of test condoms and a minimum of two production lots

of control condoms. Test a minimum of 32 condoms per lot, per temperature and conditioning time period. A minimum of two temperatures and five time points at the selected temperatures are recommended. Condition the condoms using the procedures specified in ISO 4074:2015, Annex I. Before testing, condition the sample for a minimum of 12 hours but not more than 96 hours at (25 ± 5) °C. Test the condoms for burst properties. Compare the changes in burst properties for test and control condoms and choose a set of accelerated storage conditions (time and temperature) that results in a significant change in the burst properties of the control condoms.

After determining the set of accelerated storage conditions, select condoms from three production lots and condition them at the selected temperature using the procedures specified in ISO 4074:2015, Annex I. Before testing, condition the sample for a minimum of 12 hours but not more than 96 hours at (25 ± 5) °C. Test the condoms for burst properties, freedom from holes and visible defects (including visible open seals) and package integrity. In addition, inspect the condoms and packaging for any signs of discoloration and visible defects, and the condoms for odour and ease of unrolling. Assess conformance with ISO 4074:2015 requirements.

3. Real-time stability study

Follow the procedures in ISO 4074:2015, Clause 11.3 and Annex K. This annex is normative; the specified procedures should be used as written and should not be changed.

Determine the total numbers of samples required, including spares, allowing for the following:

- testing at the end of the study for burst properties, freedom from holes and visible defects (including visibly open seals) and package integrity, preferably using the sample sizes specified in Annex B of ISO 4074:2015, but at least the sample sizes specified in Annex A;
- monitoring of burst properties during the study (32 or 125 condoms per test).

Condition the condoms at (30^{+5}_{-2}) °C using the procedures specified in ISO 4074:2015, Annex I, or in a controlled environment at (30^{+5}_{-2}) °C. Remove samples for monitoring at regular intervals (one year or less). Before testing, condition the sample for a minimum of 12 hours but not more than 96 hours at (25 ± 5) °C. Test the condoms for burst properties. Assess whether or not it is necessary to terminate the real-time study early. Continue to condition the condoms for the required shelf-life period (maximum of five years) unless the decision is taken to terminate the study early. After the full shelf-life period has been reached, remove the condoms for testing. Before testing, condition the

sample for a minimum of 12 hours but not more than 96 hours at (25 ± 5) °C. Test the condoms for burst properties, freedom from holes and visible defects (including visible open seals) and package integrity. In addition, inspect the condoms and packaging for any signs of discoloration and visible defects, as well as odour and ease of unrolling. Assess conformance with ISO 4074:2015 requirements.