

Annex 7

World Health Organization/United Nations Population Fund guidance on conducting post-market surveillance of condoms

Background

The report of the Fifty-fourth meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSP) in 2019 (1) stated the following:

As agreed at the ECSP meeting in October 2018, the United Nations Population Fund (UNFPA) and WHO have separated out different aspects of the current procedure for contraceptive devices and condoms and are developing seven different documents:

- *prequalification programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices;*
- *technical specifications for male latex condoms;*
- *specifications for plain lubricants;*
- *condom quality assurance;*
- *guidance on testing of male latex condoms;*
- *recommendations for condom storage and shipping temperatures; and*
- *guidance on conducting post-market surveillance of condoms.*

All seven documents were restructured and revised in the first half of 2019, then sent to the Expert Advisory Panel (EAP) and put out for public consultation in July 2019. The comments received were reviewed by a group of specialists in October 2019, prior to being presented to the ECSP. At UNFPA's request, the ECSP focused on the first three documents (on UNFPA's Prequalification Programme guidance, condom quality assurance and specifications for plain lubricants), noting that all comments have been addressed. It suggested some further minor revisions, including recommending changes to clarify that, while the specifications for plain lubricants are principally targeted at procurement agencies, they may also be used by regulators for public procurement. The next steps for the remaining four documents include incorporating comments from the latest consultations and then bringing them back to the ECSP for possible adoption at its next meeting in 2020.

The Expert Committee adopted the following guidelines:

- *World Health Organization/United Nations Population Fund Prequalification Programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices (2);*
- *World Health Organization/United Nations Population Fund technical specifications for male latex condoms (3); and*
- *World Health Organization/United Nations Population Fund specifications for plain lubricants (4).*

The Expert Committee further recommended proceeding with the next steps as discussed.

This is one of four remaining working documents in this series.

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1. Introduction

Good quality condoms conforming to the *World Health Organization (WHO)/United Nations Population Fund (UNFPA) technical specifications for male latex condoms (3)* have excellent storage properties. The combination of individual condom packaging, inner boxes and shipping containers is designed to protect the condoms during shipping and storage. Nevertheless, storage under poor conditions and/or rough handling during shipping might adversely affect the properties of the condoms. Exposure to such adverse conditions is potentially more likely once the condoms have left control of the purchaser and are in the wider distribution chain. For this reason, periodic surveillance testing of product recovered from the field is recommended to confirm that the condoms still conform to the requirements of the *World Health Organization/United Nations Population Fund technical specifications for male latex condoms (3)* and *ISO 4074, Natural rubber latex male condoms – Requirements and test methods (5)*. Surveillance testing may also be conducted to determine if there has been a significant deterioration in condom properties relative to retained samples kept under controlled conditions.

It is recommended that prequalified manufacturers conduct periodic surveillance testing on condoms that are nearing their expiry date and have been stored in hot regions to support the shelf life claims made on the basis of real time and accelerated stability studies. Surveillance testing may have to be undertaken when there are complaints about condoms, particularly if the complaints are clustered and associated with one specific product or even a single lot of product. In such cases, sample sizes can be severely limited and it may be necessary to limit testing to just one property. The selection of sample sizes for such testing can be challenging and the results may be of limited use if only a small number of samples are available.

2. Sampling

In order to conduct post-market surveillance testing on male latex condoms, it might be necessary to recover condoms from any of the following locations:

- warehouses;
- distribution centres;
- wholesalers;
- clinics; and
- retail outlets.

Key issues when recovering samples for surveillance testing are often the sample size and lot integrity. If single lots are being tested, for example, one lot each from a number of manufacturers, then ideally the sampling schemes given in Annex B of *ISO 4074 (5)* should be used. If possible, samples should be taken from at least three lots from each manufacturer to give an indication about lot-to-lot homogeneity. If multiple lots from a single manufacturer are being evaluated, then the sampling schemes of Annex A of *ISO 4074 (5)* are acceptable. If sample sizes are limited then it may be necessary to test only for selected properties.

Sample only for the tests that are needed to check on the parameters in question. Obtaining sufficient samples from warehouses, distribution centres and wholesalers is not usually problematic but sampling from clinics and retail outlets often means that sample sizes have to be restricted. This may limit the types and numbers of tests that can be completed. If an adequate number of samples from one batch is not available at any particular retail outlet or clinic, it may be possible to obtain more samples of the same batch from a nearby retail store or clinic in the region.

If sample sizes are restricted, then they should still be selected from *ISO 2859-1, Sampling procedures for inspection by attributes - Part 1: Sampling schemes indexed by acceptance quality level (AQL) for lot-by-lot inspection - Amendment 1 (6)*. Whenever possible, select sampling schemes that have at least a 95% probability of acceptance if the quality of submitted lots is at the limit of the specified AQL (refer to tables X-A through to X-R of *ISO 2859-1 (6)* for the operating characteristic curves and acceptance probabilities of the sampling schemes). Use sample sizes that are consistent with *ISO 2859-1 (6)*. Sample sizes that fall between the specified sample sizes in the tables should not be used (for example, Table II-A) since it may not be possible to make a statistically valid decision about whether or not the product sampled conforms to the specification. If there are insufficient samples available to use a specified sample size, the next lowest specified sample size, for which there are enough samples and corresponding to that AQL, should be used.

For performance requirements, such as burst properties, freedom from holes and package integrity, avoid zero accept sampling schemes whenever possible (for example, a sample size of 50 for an AQL of 0.25 with an acceptance number of 0). These sampling schemes generally have poor operating characteristic curves which can lead to type I and type II errors (i.e. an incorrect rejection of a true null hypothesis and failure to reject a false null hypothesis respectively, or more simply, false positive and false negative results). If forced to use zero accept sampling schemes, due to a shortage of samples, then be cautious about any conclusions that are reached.

At the time of sampling, full details about the lots being sampled, including the lot numbers, expiry dates and storage conditions, should be noted. Whenever possible, a sampling agency should be used and samples should be taken from lots using procedures to ensure the random selection of condoms from within the lot.

In some cases, it may be necessary to combine samples from more than one lot in order to achieve an adequate sample size for testing. This should be regarded as a last resort situation and is best avoided. Full details of the lots sampled must be recorded and the expiry date noted for each lot sampled. If possible, samples from the different lots that are to be combined should be kept separate throughout the testing process in order to facilitate analysis of the final results. It may be possible, for example, to show that the different lots sampled have very similar properties and so justify using the overall result as an estimate of the quality of all of the lots sampled.

If the test laboratory is located some distance from the location at which the condoms are being sampled, then the transport arrangements needed to deliver the condoms to the laboratory should be considered. It is essential to ensure that the condoms will not be subjected to any adverse conditions in transit that could affect the results of the tests. Sending samples by air freight might, for example, compromise the outcome of any testing for package integrity. The use of data loggers to monitor temperatures during shipment should be used, particularly if the condoms are being shipped from or through countries with hot climates.

3. Testing

The primary focus for testing natural rubber latex male condoms should be the critical performance parameters, i.e. burst properties, freedom from holes and package integrity. Other properties, such as dimensions, are unlikely to change during storage or shipping. Burst properties can be evaluated on a variables basis as well as on an attribute basis (i.e. conformance to the 1.5 AQL for burst properties). Information about average burst volume and pressure, their associated standard deviations and the frequency distributions of the results can be extremely useful in trying to determine if any significant changes have occurred. Comparisons can be made with the original manufacturer's data and the pre-shipment test results. The statistical significance of any changes in properties can be readily assessed by the t-test or analysis of variance (ANOVA). Using such methods may be particularly informative in situations where there are insufficient samples available to make reliable estimates of conformity to the AQLs on an attribute basis.

4. Selection of laboratories

The laboratories used for surveillance testing shall be accredited to *ISO 17025* (7) for the tests being carried out. The laboratories should also participate in an appropriate international inter-laboratory proficiency scheme. Ideally, the same laboratory that did the original pre-shipment testing should be used. This makes the comparison of results much easier and more reliable and permits samples that have been retained under controlled conditions by the test laboratory to be re-tested if necessary.

For more information about the selection of laboratories, please refer to *World Health Organization/United Nations Population Fund Condom quality assurance* (8).

When selecting test laboratories, consideration should also be given to any local customs and import restrictions. Some countries have restrictions on the import of condoms without testing and these rules can even be applied to samples being imported solely for test purposes. One should confirm with the laboratory whether or not there are any rules relating to the import of samples for testing prior to sending the samples.

5. Interpretation of results

Although lot conformity is assessed on an attribute basis, the use of means and standard deviations whenever possible is recommended. This primarily applies to burst testing. Trends in burst properties, particularly when compared to the results from pre-shipment testing, can provide early warning of potential problems.

Reviewing the burst result histograms can reveal very interesting information. Bimodal (or even polymodal) distributions of burst pressure and/or volume are indicators of poor homogeneity within the lot. In some cases, this might indicate that the product is substandard and/or falsified; for example, the lot in question may consist of mixed condoms from different lots or even condoms from different manufacturers. If substandard and falsified medical product is suspected, then forward all of the details to the manufacturer whose name is marked on the pack. The manufacturer should be able to determine the authenticity of the product from the lot number. Producers of substandard and falsified medical products commonly make small mistakes with labelling so return samples of the packaging, and any information received, with the product to the manufacturer for checking. Following confirmation from the manufacturer that the product is falsified, inform the WHO team working on substandard and falsified medical products at rapidalert@who.int.

If regular post-market surveillance testing is being carried out on products from a specific manufacturer, then analysis of trends over time can

provide extremely useful information. Plotting charts, as described in the document *World Health Organization/United Nations Population Fund Condom quality assurance*, Annex 2 (8), for example, is a very powerful method of identifying any concerning trends in product quality. Early identification of an unacceptable trend might, for example, permit a manufacturer to carry out corrective and preventative actions before the product goes out of specification and lots are rejected. Charts can also be used to identify situations where manufacturers may have made changes to the product or production processes and failed to inform the purchaser. Comparing trends for pre-shipment test results with those from surveillance testing might also identify problems relating to the shipping and storage of a product.

References

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