Female Condom:

Generic Specification, Prequalification and Guidelines for Procurement, 2012

World Health Organization

UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS
UNHCR UNICEF WFP UNDP UNFPA UNODC ILO UNESCO WHO WORLD BANK

UNFPA

fhi360

The following organizations support the use of the *WHO/UNFPA Female Condom Generic Specification*:

The Global Fund to Fight AIDS, Tuberculosis and Malaria
FHI360
International Planned Parenthood Federation/CONtraceptive and SRH Marketing LTD (IPPF/ICON)
I + Solutions
Marie Stopes International (MSI)
John Snow, Inc. (JSI)
Joint United Nations Programme on HIV/AIDS (UNAIDS)
PATH
Partners in Population and Development (PPD)
Population Action International
Population Services International (PSI)
Reproductive Health Supplies Coalition (RHSC)
United Nations Population Fund (UNFPA)
World Health Organization, Department of Reproductive Health and Research (WHO/RHR)

Female Condom:

Generic Specification, Prequalification and Guidelines for Procurement, 2012

World Health Organization

UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS
UNHCR UNICEF WFP UNDP UNFPA UNODC ILO UNESCO WHO WORLD BANK

UNFPA

fhi360

Department of
Reproductive Health and Research

WHO/UNFPA Female Condom Generic Specification,
Prequalification and Guidelines for Procurement, 2012

WHO/UNFPA Female Condom Generic Specification, Prequalification and Guidelines for Procurement 2012.

1. Condoms - supply and distribution. 2. Condoms - standards. 3. Quality control. 4. Product packing - standards. 5. Contraceptive devices, Female. 6. Sexually transmitted diseases - prevention and control. 7. HIV infections - prevention and control. I.World Health Organization. II.UNAIDS. III.United Nations Population Fund. IV. FHI360.

Photo credits:
Front cover (left to right): Morten Sorensen/UNFPA; Morten Sorensen/UNFPA; © Win Morgan, Courtesy of Photoshare
Chapter 1: © Win Morgan, Courtesy of Photoshare
Chapters 2-4, 6-9: Morten Sorensen/UNFPA
Chapter 5: © 1999 Sandhya Rao, RPLM, JSI, courtesy of Photoshare
Chapter 10: UNFPA PSB
Annexes: © Center for Communication Programs, Courtesy of Photoshare
Back cover (left to right): Morten Sorensen/UNFPA, Morten Sorensen/UNFPA, © Center for Communication Programs, Courtesy of Photoshare

CONTENTS

ACKNOWLEDGEMENTS 6

INTRODUCTION 8

PART ONE: FEMALE CONDOM – QUALITY ASSURANCE AND WHO/UNFPA SPECIFICATION 11

Chapter 1: Introduction 13

1.1 General 13

1.2 Basis for the *WHO/UNFPA Female Condom Generic Specification* 14

1.3 Clinical Investigation 14

1.3.1 Contraceptive Efficacy Study 15

1.3.2 Functionality study against a equivalent marketed product 15

Table 1 Risk Assessment – Factors to be considered when considering equivalence for assessing clinical evaluation requirements 16

1.4 Setting the Specification for Specific Products 17

1.4.1 Airburst properties 17

1.4.2 Other Requirements 18

1.5 Data sheets 18

1.6 Lot 18

1.7 Lot-by-Lot Pre-shipment compliance testing 19

1.8 Sampling 19

1.9 Acceptable Quality Limit (AQL) 20

1.10 Monitoring Quality 20

1.11 Testing Laboratories 20

1.12 Testing costs 21

1.13 Confirmatory testing 21

Chapter 2: Details of the *WHO/UNFPA Female Condom Generic Specification* 25

2.1 ***Table 2*** General Requirements 25

2.2 ***Table 3*** Performance Requirements 28

2.3 ***Table 4*** Design Requirements 29

2.4 ***Table 5*** Packaging Requirements for Shipment 32

Chapter 3: Summary tables: Prequalification and Lot-by-Lot testing 37

Table 6 Summary of Prequalification Tests 37

Table 7 Summary of Lot-by-Lot Pre-shipment compliance testing and requirements 38

Chapter 4: Workmanship and Visible Defects 41

4.1 Introduction 41

4.2 Types of visible defects in condoms 41

4.2.1 Critical Visible defects 41

Table 8 Critical visible defects—AQL 0.4 41

4.2.2 Non-critical visible defects 42

Table 9 Non-critical visible defects—Recommended AQL 2.5 42

4.2.3 Imperfections 42

Table 10 Imperfections that are not regarded as defects 42

4.3 Packaging defects 43

4.3.1 Individual packages 43

4.3.2 Consumer packs 43

4.3.3 Cartons and Marking 43

Table 11 Packaging defects 43

Chapter 5: Resolution of disputes related to product quality 47

5.1 Introduction 47

5.2 Disputes over laboratory results 47

5.3 Source of disputes arising from laboratory testing 47

5.4 Decisions on re-testing 48

5.5 Re-testing 48
5.5.1 Independent testing laboratory 49
5.5.2 Manufacturer 49

Chapter 6: Bioburden and Microbial Control 53
6.1 Introduction 53
6.2 Bioburden, limits and rationale 53
6.2.1 Bioburden 53
6.2.2 Condom bioburden limits 53
6.2.3 Rationale 53
6.3 Test methods 54
6.3.1 Routine monitoring 54
6.3.1.1 Surface testing 54
6.3.1.2 Powders and liquids 55
6.3.1.3 Air sampling 55
6.3.1.4 Identification of micro-organisms 56
6.3.1.5 Rapid test methods 56
6.4 Guidance for controlling microbial contamination 56
6.4.1 Equipment 56
6.4.2 Environment 56
6.4.3 Personnel 56
6.4.4 Raw materials 56
6.4.4.1 Water 57
6.4.5 Dipping, stripping and drying 57
6.4.6 Slurry treatment 57
6.4.7 Testing, lubrication and packaging 57
References 58

Chapter 7: Test methods 63
7.1 Testing for Bursting Volume and Pressure 63
7.2 Testing for Freedom from Holes and Visible Defects 63
7.3 Testing for Package Seal Integrity 64
7.4 Determining the Width of the Female Condom 64
7.5 Determining the Length of the Female Condom 65
7.6 Determining the Thickness of the Female Condom 65
7.7 Determining the Quantity of Lubricant (Including Powder) 65

Chapter 8: Guidelines on the Assessment of Odour 69

PART TWO: WHO/UNFPA FEMALE CONDOM PREQUALIFICATION SCHEME — FEMALE CONDOM PREQUALIFICATION, TECHNICAL REVIEW PROCESS, PRODUCT DOSSIER (PD) AND SITE MASTER FILE SUMMARY (SMF)

Chapter 9: Female Condom Prequalification 73
9.1 Introduction 74
9.2 Elements of the Prequalification Process 74
9.2.1 Invitation for Expression of Interest 74
9.2.2 Data and information to be submitted 74
9.2.3 Process for submitting documentation 75
9.2.4 The Technical Review Process 75
9.2.5 Submission of Technical Information 76
9.3 Clinical Investigation 76
9.3.1 Contraceptive Efficacy Study 77
9.3.2 Functionality study against an equivalent marketed product 77
9.4 Preparation of a Product Dossier 78
9.4.1 Characteristics of the products 78
9.4.2 Local, country & regional regulatory product approvals 78
9.4.3 Raw materials 78

9.4.4 Supplier(s) 78
Table 12 Primary materials of construction and compounding ingredients (if relevant) 78
9.4.5 Sites of manufacture 79
9.4.6 Risk management of the product 79
9.4.7 Specifications for the finished products 79
9.4.8 Evidence of compliance with WHO/UNFPA's General Requirements 79
9.4.9 Stability data 79
9.4.10 Labelling and additional information 79
9.5 Samples 80
9.6 Preparation of the Site Master File Summary 80
9.6.1 General information 80
9.6.2 Manufacturing certifications 80
9.6.3 Personnel 81
9.6.4 Premises and equipment 81
9.6.5 Documentation 81
9.6.6 Records 81
9.6.7 Production 81
9.6.8 Risk management plan 82
9.6.9 Quality control 82
9.6.10 Distribution, complaints and product recall 82
9.6.11 Self-inspection (internal audits) 82
9.6.12 Corrective and preventative action 82
9.6.13 Design and development 82
9.7 Scope of Manufacturing Site Inspections 82
Table 13 Inspection checklists 83
9.8 Product Testing 86
9.9 Reporting and communication of the results of the site inspection 87
9.10 Decision to prequalify 87
9.11 Listing of prequalified female condom manufacturing sites 88
9.12 Maintenance of prequalification status 88
9.13 Periodic monitoring of the quality of products produced by prequalified manufacturing sites 89
9.14 Reassessment 89

PART THREE: GUIDELINES FOR PROCUREMENT, SPECIFICATION AND PROCUREMENT CHECKLISTS

Chapter 10: Specification and Procurement Checklists 93
10.1 Introduction 93
10.1.1 Comprehensive Condom Programming 93
10.2 Procurement 94
Table 14 Three Phases and 10 steps of Procurement 94
10.2.1 Notes on Country registration 95
Table 15 WHO/UNFPA Specification Checklist 96
Table 16 Procurement Checklist 99
10.3 Condom Storage 104

PART FOUR: ANNEXES

Annex I: Confidentiality Undertaking 107
Annex II: Sample of the letter of application 108
Annex III: Technical Basis for the *WHO/UNFPA Female Condom Generic Specification* 109
Table 17 Comparative 12-month pregnancy rates for barrier contraceptive methods 114
Annex IV: Methods for assessing the quality of suppliers 126
Annex V: Glossary of Terms and Abbreviations 129
Annex VI: Applicable Documents 134
Annex VII: List of Resource Agencies 135

ACKNOWLEDGEMENTS

This manual is a result of a review of the latest available evidence and an extensive consultative consensus-building process with individuals who represent the female condom manufacturing industry, the International Organization for Standardization (ISO), testing laboratories, national regulatory authorities, research institutes, bulk procurement agencies, social marketing companies, international agencies, nongovernmental organizations, consumer groups, and family planning and HIV/AIDS prevention policy-makers and programme managers.

The World Health Organization, Department of Reproductive Health and Research (WHO/RHR), the United Nations Population Fund (UNFPA), the United States Agency for International Development (USAID), the Bill and Melinda Gates Foundation and FHI360 have all supported publication of this manual and would like to gratefully acknowledge the contributions of the following people and organizations:

Co-authors

William Potter, Stapleford Scientific Services Ltd, and John Gerofi, Enersol Laboratories, led the development of this document in close collaboration with Eli Carter, FHI360; Margaret Usher-Patel, Scientist/Secretariat, WHO/ Department of Reproductive Health and Research; Mags Beksinska, MatCH - University of the Witwatersrand; Morten Sorensen, UNFPA; Agnes Chidanyika, UNFPA.

Members of the Female Condom Technical Review Committee and external reviewers:

The co-authors worked closely with other committee members who, in addition to attending the Female Condom Technical Review Committee Meetings, have on their own time participated in ongoing electronic discussions and the extensive external review process.

Members include Erin Balch, USAID; Nathalie Broutet, WHO/RHR; Eli Carter, FHI360; Bidia Deperthes, UNFPA; Tim Farley, WHO/RHR; Els Klinkert, UNAIDS; Francis Ndowa, WHO/ RHR; Twedi Seane, South African Bureau of Standards; K Sivakumar, Independent Technical Advisor; Catherine Richey, WHO/RHR; Anna Ridge, WHO; David Whybrew, Crown Agents; Jakob Srebro, JS International Auditing and Consulting; Markus Steiner, FHI360; Mark Weaver, FHI360; Kevin O'Reilly, WHO; Mags Beksinska, MatCH - University of the Witwatersrand and William Potter, Stapleford Scientific Services Ltd.

WHO and partners would also like to thank other experts and colleagues who so freely contributed their time and expertise during the extensive external review process:

Sophie Logez, The Global Fund to Fight AIDS, Tuberculosis and Malaria; The Chair, Secretariat and members of the International Organization for Standardization Technical Committee 157 (ISO/TC/157) "Non-systemic contraceptives and STI barrier prophylactics"; Tracey Brett, Louise Brooker and Tanya Boler, Marie Stopes International; Harry Jooseery, Partners in Population and Development; Karen Hardee, Population Action International; Nils Gade, Population Services International; Lois Todhunter, Carolyn Hart and Leslie Patykewich, John Snow, Inc. Michael Bartos and Catherine Hankins, Joint United Nations Programme on HIV/AIDS; Jane Hutchings and Lisa Hedman, PATH; Patricia Coffey, PATH; John Skibiak, Steve Kinzett and members of the Reproductive Health Supplies Coalition (RHSC); Jagdish Upadhyay and Kabir Ahmed, United Nations Population Fund; Catherine d'Arcangues, Hendrik Hogerzeil, Helene Moller, Michael Mbizvo and Clive Ondari, World Health Organization; Lorna Wilcox, microbiologist; Catherine Hart, Carol Joanis, Joanis Consulting;

Jeffrey Tremelling, FHI360; Wolfgang Bichmann, KfW Entwicklungsbank—German Development Bank; Lester Chinery, International CONtraceptive & SRH Marketing Ltd.—International Planned Parenthood Federation; Ana Priscilla Herrera García, Ministry of Health, Costa Rica; Dominic Mwakangale, Ministry of Health, Tanzania; Peter Sali, National Drug Authority, Uganda; Keith Neroutsos and Todd Dickens, PATH; Charity Ngaruro, Population Services International; David Whybrew, Crown Agents.; Mark Rilling, USAID; Elizabeth Lule and Sangeeta Raja, World Bank; and Bjorn Fahlgren, WHO.

Benedict Light, UNFPA; Juan Gabriel Wells, Universal Access to Female Condoms Joint Programme (UAFC); Tian Johnson, South Africa Female Condom Lobby; Alexandra Morel, PSI; Raquel Child, Lorenzo Witherspoon and Peter Hall, RHAlliance; Jenny Ji, PATH.

UNFPA support

The success of the Technical Review Committees, the workshops and this guideline would not have been possible without the efficient support provided by Dinna No, Nuria Cardalliaguet Amich and Hayley Traeger (UNFPA, Copenhagen, Denmark).

In addition, UNFPA and WHO would like to thank the representatives of the condom manufacturing industry, national regulatory authorities, testing laboratories, international and bulk procurement agencies, donors and family planning and HIV/AIDS prevention programme managers who attended workshops in December 2010 and January 2012 to introduce and review the specification and prequalification process. Their feedback contributed to the review process and the finalization of this document.

INTRODUCTION

The 2011 Worlds Aids Day Report published by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) states that the number of people living with HIV was estimated at 34 million people at the end of 2010, up 17% from 2001. Women comprise 50% of people living with HIV (1).

Young people between the ages of 15 and 24 account for between 4.3 million to 6.5 million of those living with HIV as of December 2010. Young women are especially vulnerable and they account for a disproportionately 64% of young people living with HIV globally. The 2011 Progress Report on the Global HIV/AIDS Response, published by WHO, UNAIDS and UNICEF states that the mix of components tailored for different populations is the most effective approach to reduce HIV transmission and new data from biomedical studies have expanded the set of available prevention intervention, including preventing sexual transmission by promoting male and female condoms (2).

The World Health Organization estimates that 340 million new cases of curable sexually transmitted infections (STIs), namely syphilis, gonorrhea, chlamydia and trichomoniasis, occur every year throughout the world in men and women ages 15–49 years. In addition, millions of sexually transmitted viral infections occur annually, which causes not only HIV but also genital herpes viruses, human papillomavirus and the hepatitis B virus. Globally, these infections inflict a huge health and economic burden, especially in developing countries (3).

The female condom has the potential to decrease STI statistics as the only female initiated dual protection device that is believed to be effective at preventing STIs and pregnancy (4). Studies have shown that latex and polyurethane, materials commonly used in female condoms, create an effective barrier method against common STIs, including HIV (5,6). Studies also suggest that female condoms could offer similar degrees of protection from STI as male latex condoms although the level of protection has not been quantified for each specific STI (7). For maximum effect, any barrier method for contraception or infection prevention must be used correctly and consistently.

Therefore, it is important for policymakers, programme managers, bulk procurement agencies, social marketing programmes, logistic/procurement officers and national regulatory authorities to know how to apply the essential elements of female condom quality assurance to guarantee that a quality product is purchased, promoted and distributed to the end user. The female condom is an important medical device and needs to be regulated and controlled as such.

Consistent and correct use of condoms is vital to achieve the level of protection required to prevent unintended pregnancy and the transmission of HIV and other STIs. Studies have shown that providing female condoms as part of a comprehensive prevention strategy results in increased levels of protection (8). The female condom is classified by the Every Woman, Every Child effort as one of three reproductive health products that is underutilized (9). Improving access to quality products for HIV prevention and effectiveness of family planning are important factors to consider for universal access to reproductive health.

In many programmes attention tends to be focused on the condom user and the promotion of condoms. Often, inadequate attention is paid to ensuring, as a key component of a comprehensive condom programming strategy, that a quality product is manufactured, purchased, stored, distributed and handled properly.

This publication, *WHO/UNFPA Female Condom: Generic Specification, Prequalification and Guidelines for Procurement, 2012*, provides the essential information required to achieve the procurement and distribution of a quality product.

1.1 Roles of the World Health Organization (WHO), the United Nations Population Fund (UNFPA) and the Joint United Nations Programme on HIV/AIDs (UNAIDs)

UNAIDS recommends condoms in all the interventions it cites to prevent sexually transmitted HIV. It mentions condoms, directly or indirectly, as part of each HIV prevention measure for key audiences (10). The female condom is an important choice for women to protect themselves from HIV/STIs and UNFPA has been intensifying efforts to scale up female condom programming to at least 23 countries through the Global Female Condom initiative by working with key government counterparts and other stakeholders to implement a country driven female condom strategy.

UNFPA is also working with WHO, UNAIDS and many other partners to generate stronger global commitment, increased financing and collective action to support a strategic approach to Comprehensive Condom Programming (CCP) in order to prevent unintended pregnancies and the transmission of STIs including HIV. To help strengthen this approach, UNFPA developed two interrelated tools: the *Comprehensive Condom Programming Framework*, which describes the work areas that need to be addressed in an effective CCP response, and the *Ten-Step Strategic Approach to Scale Up CCP*, which describes a process that country programme managers and their development partners can follow to move CCP from concept to reality (11). Together, they provide national managers with a structural framework and a process to operationalize this vital HIV prevention intervention.

> The purchase of poor-quality condoms will adversely affect every aspect of condom promotion and programming. Not only is it a waste of limited budgetary resources, but also it damages the credibility of the one inexpensive device that has been proven to help prevent the transmission of HIV/STIs and unintended pregnancy.

WHO has worked for more than 15 years in collaboration with UNFPA, UNAIDS and the United States Agency for International Development (USAID) to see that the issue of condom quality assurance is taken very seriously.

WHO has also worked with partners from donor agencies, international and nongovernmental organizations, research institutions, the private sector including the manufacturing community, testing laboratories and consumer groups, and the International Organization for Standardization (ISO) to advocate and support the development of rigorous international standards and the establishment of purchase specifications and a Prequalification Scheme for the production, procurement and distribution of good-quality female condoms.

The manufacturing community has developed improved technologies, and research has generated more awareness of the type of quality assurance systems and laboratory tests needed to ensure that a quality product is manufactured and distributed.

In 2010 the WHO Department of Reproductive Health and Research, in collaboration with FHI360, UNFPA and all key public- and private-sector stakeholders, undertook a technical review process to ensure that the latest available evidence and information were considered prior to publishing this manual.

The technical review process undertaken to prepare this manual is summarized along with a review of the technical basis that underpins the female condom specification detailed here. These activities have led to the publication of this manual, *WHO/UNFPA Female Condom: Generic Specification, Prequalification and Guidelines for Procurement, 2012.*

These guidelines will help policy-makers, procurement officers, logistics and programme managers, national regulatory authorities and testing laboratories make the right decisions to procure, receive, distribute, test and promote a quality product.

1.2 For whom is this document intended?

This document is intended primarily for any policy-maker, manager or procurement officer who has the responsibility for procuring, supplying and promoting female condoms.

Individuals working in reproductive health care programmes, particularly STI/HIV/AIDS prevention and family planning programmes, should also review this document to understand why it is vitally important to establish systems that ensure that a quality product is manufactured, procured and promoted.

Bulk procurement agencies, testing laboratories and national regulatory authorities will also need to study this document in preparation for the manufacture, procurement and supply of female condoms. In addition to these primary users, the document will be useful to manufacturers, social marketing programmes, nongovernmental agencies and policy-makers as they work to improve the acceptability and use of condoms in their target populations.

1.3 Purpose of the document

This document describes a technically sound, systematic process to support the manufacture, prequalification, procurement and distribution of a quality product that can meet the needs of different populations in a broad spectrum of challenging environmental conditions.

UNFPA and WHO/RHR have worked in collaboration with many partners from the private and public sectors to generate the evidence and gain the consensus needed to recommend the procedures detailed in this manual. The importance of using the *WHO/UNFPA Female Condom Generic Specification* and procurement procedures detailed in this manual cannot be overemphasized, as they address issues related to:

- ensuring the procurement of a quality product;
- improving levels of competence in procurement;
- improving levels of confidence in the performance of the product;
- ensuring the health and safety of the end user.

References

1. *How to get to zero: Faster. Smarter. Better.* UNAIDS World AIDS Day Report 2011
2. *Progress report 2011: Global HIV/AIDS response- Epidemic update and health sector progress towards universal access.* WHO, UNICEF, UNAIDS, 2011.
3. *Breaking the chain of transmission, global strategy for the prevention and control of sexually transmitted infections, 2006–2015.* Geneva, World Health Organization, 2007.
4. *PATH, UNFPA. Female Condom: A Powerful Tool for Protection.* Seattle: UNFPA, PATH, 2006. http://www.path.org/publications/files/RH_female_condom.pdf
5. Judoson FN, Ehret JM, Bodin GF, Levin MJ, Rietmeijer CA. *In vitro evaluations of condoms with and without nonoxynol 9 as physical and chemical barriers against Chlamydia trachomatis, herpes simplex virus type 2, and human immunodeficiency virus.* Sexually transmitted diseases 1989;16:51–6.
6. Lytle CD Routson LB, Seaborn, GB, Dixon LG, Bushar HF, Cyr WH.. *An in vitro evaluation of condoms as barriers to a small virus.* Sex Transm Dis 1997;24:161–4.
7. Gallo MF, Kilbourne-Brook M, Coffey PS. *A Review of the Effectiveness and Acceptability of the Female Condom for Dual Protection.* Sexual Health 2012; 9:18-26.
8. Vijayakumar G, Mabude Z, Smit J, Beksinska M, Lurie M. *A review of female condom effectiveness; patterns of use and impact on protected sex acts and STI incidence,* International Journal of STD & AIDS 2006;17:652-9.
9. *Every Woman, Every Child: Female Condom Product Profile.* United Nations Foundation, 2012.
10. *Practical guidelines for intensifying HIV prevention: towards universal access.* Geneva, Joint United Nations Programme on HIV/AIDS, 2007.
11. *Comprehensive Condon Programming Framework.* UNFPA http://www.unfpa.org/webdav/site/global/shared/documents/publications/2011/CCP.pdf

CHAPTER 1

Introduction

PART ONE
CHAPTER 1: INTRODUCTION

1.1 General

This document details the WHO/UNFPA scientific and technical requirements for the prequalification of female condoms for bulk procurement.

The female condom is a relatively new product and, until recently, has only been available from one manufacturer. An international standard developed by the ISO (International Standards Organization) technical committee responsible for developing standards for barrier contraceptives, ISO/TC 157, was published in July 2011. The standard is designated *ISO 25841: 2011*. Since the standard was finalized for publication several new designs of female condoms have been developed. Additionally, more inter-laboratory testing has been undertaken on different types of female condoms and the FC1 condom has been withdrawn from the market. As a consequence, it is now recognized that the standard will need to be revised to accommodate these changes.

ISO 25841: 2011 specifies the essential performance and safety requirements that female condoms are expected to meet and the test methods that are used to assess compliance with these requirements. It is based on extensive research and an ongoing consultation process involving leading experts in all aspects of female condom manufacturing, research, and use from around the world.

The standard has been used as the basis for specifying the requirements in this document. Nevertheless, certain amendments have been made to anticipate expected changes in the standard.

Whereas a standard usually specifies minimum requirements for the key properties that determine the safety and effectiveness of a product, a specification is a statement of the buyer's requirements and covers all the attributes and features of the product. Some of these requirements, such as packaging and labelling, may be unique to the buyer and not fully specified in international and national standards. Each design of female condom will have unique features that also may need to be agreed between the buyer and manufacturer. The buyer's specification must be a detailed and unambiguous statement of the buyer's requirements and describe the means by which those requirements can be measured and assessed. The specification is generally attached to the Bidding Documents and forms part of the supply contract.

It is premature to develop a design-based specification for public sector procurement of female condoms. Many different designs of product are possible, each having its own unique features and specification. Therefore it has been decided to detail the scientific and technical requirements manufacturers must meet in order to be approved for bulk procurement. These requirements incorporate the design and performance requirements of *ISO 25841*. This specification covers the generic requirements for female condoms and is largely performance based. For this reason it is known as the *WHO/UNFPA Female Condom Generic Specification*.

The *WHO/UNFPA Female Condom Generic Specification* has been developed by consensus and is based on available evidence, details of which will be published in a technical basis paper. This generic specification describes the general, design, performance, and packaging requirements for the product and the methods of verification. Female condoms are made and tested in Lots. A Lot is a collection of female condoms of the same design, colour, shape, size and formulation manufactured at essentially the same time using the same process, same specification of raw materials, common equipment, same lubricant and any other additive or dressing and the same packaging materials. Further information about Lots is given in Section 1.6.

The requirements have been divided into four categories as follows:

- **General Requirements** specify the clinical performance requirements of the product, the methods to be used by the manufacturer to set the product specifications for airburst properties, the safety of constituent materials and other characteristics, such as shelf life. These requirements and properties should not vary from Lot to Lot and therefore do not need testing on a regular basis.

- **Performance Requirements** specify the essential performance attributes of the condoms.

These must be tested on a Lot-by-Lot basis since the quality of these attributes may vary due to the manufacturing process. Laboratory tests are carried out to ensure that the condom and the individual packages comply with the specification. Performance requirements detailed in this Specification should not be changed. The Performance Requirements are listed in Section 2.2 of this document.

- **Design Requirements** are mainly concerned with the acceptability of the product to the end user. Some of these properties may be varied within certain limits to meet specific programmatic requirements by agreement with the manufacturer. Unlike the situation with male condoms, however, varying a design requirement might affect the clinical effectiveness of the female condom. Since the performance and acceptability of female condoms are established by clinical investigation the potential impact of any change has to be considered carefully. Such changes are therefore not generally feasible, and users should choose from amongst the approved, available designs. For each design requirement there is a means of verification. These are listed in Section 2.3 of this Specification.

- **Packaging Requirements** are listed in Section 2.4 of this Specification. If appropriate, purchasers may specify specific requirements depending upon the target population. When selecting packaging, manufacturers should consider the needs of disabled users. If consumer packaging is required, it is important to include detailed instructions in the specification and to discuss the design requirements with the manufacturer.

The *WHO/UNFPA Female Condom Generic Specification* and the WHO/UNFPA Prequalification Scheme are designed to ensure that a quality-assured product is purchased and distributed to the end user.

1.2 Basis for the *WHO/UNFPA Female Condom Generic Specification*

Many potential designs of female condom are possible, each with its own set of design parameters and specifications. A wide range of materials can also be used to make female condoms. It is therefore not possible to establish a set of performance requirements for female condoms in the same way as it is for male latex condoms. Certain performance properties, such as burst volume and pressure, will depend upon the materials used and the design of the condom. These properties will therefore vary with condom type and design. Other performance properties, such as acceptance limits for freedom from holes, are independent of the materials and designs used. Specific limits can be set for these requirements. Whenever possible, specific limits have been set in this document.

Female condoms also have a number of essential features that are not found on male condoms. In general terms, female condoms usually have the following components:

1. A sheath that lines the vagina and may extend to cover or partially cover the external genitalia.
2. An external retention feature that prevents the condom from being pushed into the vagina. Commonly this is a ring or frame.
3. An internal retention feature that retains the condom within the vagina and permits safe withdrawal of the penis after use. Examples include rings, foam sponge devices and muco-adhesive tabs.
4. A product insertion feature that facilitates insertion of the condom into the vagina. The internal retention feature may also serve this function.

For the reasons given above, it is not possible to determine the safety, efficacy and acceptability of a specific type of female condom based on its design and the materials used. Instead it is necessary to conduct clinical investigations in humans to confirm the safety, efficacy and acceptability of any new female condom design. These investigations enable an assessment of the overall performance of internal and external retention features, failure modes, safety and effectiveness of female condoms to be made.

1.3 Clinical Investigation

The manufacturer must demonstrate the safety, efficacy and acceptability of a new female condom design in one of the following ways:

1.3.1 Contraceptive Efficacy Study

For novel designs of female condoms that cannot be considered equivalent to an existing marketed product that has an established efficacy rate, a contraceptive efficacy study is required. The study design shall be adequate to allow the 6-month pregnancy rate to be computed using life table methods with at least 100 women years of data (e.g. 200 women completing 6 months). The 12-month pregnancy rate may be extrapolated from the 6-month data providing it is made clear that the value obtained is an estimate and the method of extrapolation is documented. The study should also determine the acceptability of the product and the rates of all failure modes as detailed in Section 1.3.2.

1.3.2 Functionality study against an equivalent marketed product

If the design and specifications of a new female condom are sufficiently similar to those of a marketed device, and that marketed device has an efficacy rate established from a clinical effectiveness study, then the manufacturer may be able to establish the acceptability and clinical effectiveness of the new female condom on the basis of a clinical study comparing the incidence of failures by each of the modes listed later in this section (functionality study). If there is no suitable marketed device available with an established pregnancy rate, then the manufacturer may use a device that has been evaluated directly against a device with an established pregnancy rate and has been shown to be non-inferior to that device, using the definition of non-inferiority given below. To claim exemption, the following requirements shall be met.

- The manufacturer shall conduct a risk analysis using, for example, the procedures described in *ISO 14971* to establish the following:
    - that the new female condom design and specifications are sufficiently similar to those of the marketed female condom, after assessing the impact of each difference in dimension, material, insertion and retention feature or method;
    - that proposed labelling on the incidence of each failure mode described below indicates that the efficacy of the new female condom in preventing pregnancy and STI transmission is expected to be equivalent to the marketed device;
    - that the design of the new female condom does not introduce any new potential failure modes over and above those identified and quantified for the marketed female condom.

Table 1 details the factors and requirements that manufacturers must take into account when conducting the risk assessment.

- The manufacturer shall conduct a randomized controlled clinical investigation comparing the new female condom to the marketed female condom. The number of uses of each type of condom shall be justified by power calculations. A minimum of 5 uses of each condom type by at least 200 women completing the study is recommended.
- The marketed female condom used in the study shall be shown to meet the performance requirements described in Section 2.2 of this document.
- The total clinical failure rate of the new female condom shall be shown to be non-inferior to the total clinical failure rate of the marketed female condom:
    - the upper bound of the one-sided 95% confidence interval for the new female condom total clinical failure rate, minus the marketed female condom total clinical failure rate, shall be less than or equal to 3%
    - the bound shall be calculated using a method that accounts for the unique characteristics of data such as (1) each study participant may contribute data from more than one female condom use and (2) possibly low event rates;
    - to confirm the validity of the study protocol and study population, the total clinical failure rates for the marketed device used in the study shall be equal to or exceed 1%. Based on functionality studies on marketed female condoms, the total clinical failure rate is expected to be at least 1%. Values lower than this are not expected if the study has been completed correctly in a typical population for which the female condom is intended.

Table 1. Risk Assessment – Factors to be considered when considering equivalence for assessing clinical evaluation requirements

Design Element	Property	Equivalence Criteria
Materials	Type	Generic type and subtype (e.g. polyether v polyester, nitrile v natural rubber latex)
	Physical properties	Tensile and elongation Tear test
	Barrier Properties	Barrier to bacteriophage Phi X174 according to ISO 25841
Design/Dimensions	Shape	Shape - sufficiently similar to achieve equivalent functionality (e.g. line the vagina)
	Length	Greater than or equal to 180 mm: within ±10% Less than 180 mm: within ±5%
	Circumference	Greater than or equal to 150 mm: within +/-10% Less than 150 mm: within ± 5%
	Thickness	Greater than or equal to 0.055 mm: within ±10% Less than 0.055 mm: within ±5%
Retention Features	External	Mode of action Material/properties Shape Dimensions
	Internal	Mode of action Material/properties Shape Dimensions
Insertion Feature		Fitness for purpose and safety
Lubrication	Type	
	Volume	
	Location/Distribution	
Physical properties	Burst volume	
	Burst pressure	
	Freedom from holes	

The following are definitions of known female condom failure modes:

a) Nonclinical breakage is defined as breakage noticed before intercourse or occurring after withdrawal of the condom from the vagina. Nonclinical breakage is breakage without potential adverse clinical consequences. The nonclinical breakage rate is calculated by dividing the number of female condoms noted to have broken before intercourse or after withdrawal by the number of female condoms packages opened.

b) Clinical breakage is defined as breakage during sexual intercourse or during withdrawal of the female condom from the vagina. Clinical breakage is breakage with potential adverse clinical consequences. The clinical breakage rate is calculated by dividing the number of female condoms reported to have broken during sexual intercourse or during withdrawal, by the number of female condoms used during sexual intercourse.

Total breakage is defined as the sum of all female condom breakages at any time before, during or after sexual intercourse. It includes both clinical breakages and nonclinical breakages. The total breakage rate is calculated by dividing the total number of female condoms that broke by the number of female condom packages opened.

c) Slippage is defined as an instance when a female condom slips completely out of the vagina during sexual intercourse. The slippage rate is calculated by dividing the number of female condoms that slipped by the number of female condoms used during sexual intercourse.

d) Misdirection is defined as vaginal penetration whereby the penis is inserted between the female

condom and the vaginal wall. The misdirection rate is calculated by dividing the number of reported events of misdirection by the number of female condoms used during sexual intercourse.

e) *Invagination* is defined as an instance when the external retention feature of the female condom is partially or fully pushed into the vagina during sexual intercourse. The invagination rate is calculated by dividing the number of events of invagination by the number of female condoms used during sexual intercourse.

As part of the risk assessment, manufacturers shall determine if any additional failure modes may apply to the specific female condom under consideration because of its design, materials of construction or method of manufacture.

The use of prostate specific antigen (PSA) assays to monitor possible semen leakage into the vagina during functionality studies is encouraged. The additional data provides added reassurance about the effectiveness of the barrier performance of the condom and might mitigate the need for contraceptive efficacy studies in some cases.

1.4 Setting the Specification for Specific Products

As discussed earlier, many performance and design requirements are unique to a specific product. The limits for these requirements cannot be set *a priori* based on knowledge of the product design and the materials used. *It is essential that these limits are established on the basis of the properties of the samples used in the clinical investigation.* Subsequent changes to any of these requirements might impact the clinical effectiveness of the female condom and trigger the requirement for a further clinical investigation.

1.4.1 Airburst properties

The airburst properties of a specific design of female condom are unique to that product and provide an important method of assessing the quality of manufactured incidences. A strict procedure is therefore specified for setting the manufacturer's specification for the minimum bursting volume and pressure for each type of female condom. These limits shall be based on the airburst properties of the Lot or Lots used in the clinical investigation. The procedure is intended to ensure that all future production is of a quality that is equal to or better than the samples used in the clinical investigation to confirm the effectiveness of the product. If the airburst specification is not based on samples from the actual Lot or Lots used in the clinical investigation, then the manufacturers shall fully substantiate that the samples used to set the specification are equivalent to those used in the clinical investigation.

Full information regarding the establishment of the specified airburst requirements shall be included in the Product Dossier submitted for review by WHO/UNFPA. The data submitted shall include the complete set of results used to set the specification.

The following procedure shall be used:

- Determine the airburst properties of the Lot or Lots used in the clinical investigation using a sample size of at least 2,000 female condoms. If more than one Lot was used in the clinical investigation, then the sample shall be drawn across all the Lots, each individual Lot being sampled proportionally to its size.

- Set the minimum airburst limits at 80% of the 1.5 percentile values of the airburst volumes and pressures determined above.

Based on data supplied by manufacturers for both synthetic and natural rubber male latex condoms, an adequate tolerance for the long term Lot-to-Lot variability seen in normal manufacture can be achieved by setting the limits at 80% of the 1.5 percentile values.

For the purposes of this Generic Specification, the relevant percentile x shall be determined by ranking the N data values and taking the value of the n^{th} rank where n = N.x/100 + ½, rounded to the nearest integer; e.g. for N=2,000, the lower 1.5 percentile is the 31^{st} lowest value.

If manufacturers are unable for any reason to test 2,000 female condoms from the Lot or Lots used in the clinical investigation, then they must provide data to confirm that the condoms used to set the specification and those used in the clinical investigation are equivalent.

1.4.2 Other Requirements

In addition to the airburst properties, all critical design requirements shall be the same as the samples used in the clinical investigation. These requirements include:

- the materials used for the sheath and all retention features;
- the method of manufacture of the female condom in including the sheath and the retention features;
- the dimensions of the sheath and retention features;
- the physical properties of the materials used for the sheath and retention features;
- the type and amount of lubricant used.

If any of these critical design requirements are changed for any reason, a full risk assessment must be completed to demonstrate that the safety and effectiveness of the product has not been compromised. A further clinical investigation may be necessary to confirm this.

1.5 Data sheets

The manufacturer shall make available to all interested parties a data sheet that contains the following information:

- full details of materials used for the sheath and the retention features;
- specifications for length, width and thickness of the condom and the retention features. The data sheets shall include sufficient information to allow the properties of the condoms and retention features to be assessed by an independent laboratory, e.g. the location of any measurement and any special procedures or equipment that might be required shall be specified;
- the results of air-burst testing of the clinical investigation Lot(s). This includes the means and standard deviations for the bursting volume and pressure, and the lower limits for bursting volume and pressure as calculated in accordance with the procedures specified in Section 1.4.1 above. Details about the airflow rate, inflation length, mounting equipment and any special preparation procedures required to prepare the condoms for testing shall be provided (including information on whether any of the insertion or retention features need to be removed);
- specifications for amount and type of lubricant and powder used;
- technical drawing(s) showing female condom geometry and correct locations of any retention and insertion features;
- test methods and specifications for the insertion and retention features.

Data sheets shall be clearly labelled to indicate the date that the original specification was established, the revision number and the date the current revision became effective.

1.6 Lot

A Lot is a collection of female condoms of the same design, colour, shape, size and formulation manufactured at essentially the same time using the same process, same specification of raw materials, common equipment, same lubricant and any other additive or dressing and the same packaging materials. All condoms comprising a single Lot will:

- Have components with identical formulations and design;
- Have a sheath component made from the same Lot of primary raw material as far as is practicable. (The use of two primary raw material Lots during the transition period between finished product Lots is permissible as long as full traceability of the raw materials is maintained.);
- Have individual components (e.g. the retaining features) with one, or at most two, Lot numbers per component;
- Be manufactured from components (e.g. the retaining features) made using one, or at most, two Lots of their principal raw materials;
- Have the same design, dimensions, colour, shape and surface texture;

- Be manufactured on the same production line;
- Be vulcanized or welded under identical conditions;
- Be in the same packing;
- Have the same lubricant.

Manufacturers may use different methods of defining a Lot, but whatever method is used it must be consistent with the requirements specified above. During the manufacturing operation, female condoms are often processed in sub-lots, sometimes called bins or baskets, usually on the basis of a fixed time of production on the manufacturing lines. The size of these sub-lots is often determined by the capacity of the intermediate equipment used in the manufacturing operation. Ideally, Lots should be made up of sequential sub-lots made on the same equipment, but this is not always possible.

The maximum size of a Lot is 500,000.

Manufacturers should retain samples from every Lot to assist in the resolution of any disputes relating to quality. It is recommended that the retained samples be kept under controlled temperature conditions consistent with the manufacturer's recommended storage conditions for the duration of the shelf-life of the product.

The date of manufacture (MFD) is the date on which the sheath components of the condoms were fabricated.

1.7 Lot-by-Lot Pre-shipment compliance testing

The manufacture of female condoms is complex and can be influenced by a variety of different manufacturing and raw material factors. The consequences of purchasing and distributing poor-quality condoms in the public sector are severe. For these reasons WHO/UNFPA also recommends that independent Lot-by-Lot Pre-shipment compliance testing of the finished product be undertaken, using an appropriate sampling plan from *ISO 2859–1*, before the condoms are accepted for shipment to the purchaser.

The methods of sampling the condoms for Pre-shipment compliance testing and the relative merits of testing prior to delivery are mentioned in Part 3, Guidelines for Procurement. Either a sampling agency or the testing laboratory should take the samples.

The manufacturer must not select the samples. The selection of suitable test laboratories is discussed in Part 1, Chapter 1, Section 1.12. It is recommended that only one set of Pre-shipment compliance testing be carried out, and this must be done by an accredited laboratory.

Manufacturers must satisfy themselves that individual Lots meet the specification before Lots are submitted for Pre-shipment compliance testing.

1.8 Sampling

The quality of each Lot is estimated by testing a randomly selected sample of condoms from that Lot. The sample sizes are defined in *ISO 25841* using sampling plans specified in *ISO 2859–1 Sampling Procedures for Inspection by Attributes.* These are the most widely used sampling plans for assessing attribute criteria (i.e. whether the product conforms or does not conform to the requirements detailed in the specification).

Sampling for independent testing should be done by either an independent accredited laboratory or by an independent sampling organization and not by the factory producing the condoms. Such sampling is required for prequalification and Pre-shipment compliance testing.

The sampler must verify that each Lot that is sampled complies with the definition of a Lot, as specified in section 1.6.

Samples must be:

- taken in accordance with pre-agreed sampling procedures;
- representative of the Lot of condoms;
- randomly selected (preferably based on random numbers);
- taken by or under the personal full-time supervision of the sampler.

The sample, once taken, must be sealed and dispatched under the sampler's supervision.

At the request of the manufacturer or the procurer, a duplicate sample may be taken for use in case of disputes. The sampling agency must issue a report giving full details of the sampling process. The report shall include the sampling procedures, identification of the cases from which samples are taken and the total number of cases offered for sampling. The sampler should mark the cases from which samples are taken for buyer reference at receipt.

An example of an acceptable sampling procedure is the "Square Root + 1" plan, in which the number of cases from which to take samples is determined by calculating the square root of the total number of cases in the Lot (i.e. SqR of 100 = 10), plus one additional case. The total number of samples required for testing is then randomly selected equally among the cases.

1.9 Acceptable Quality Limit (AQL)

In *ISO 25841* and the *WHO/UNFPA Generic Specification*, the limits for the maximum percentage of defective condoms are specified in terms of Acceptable Quality Limits (AQLs). The technical definition of an AQL is given in the glossary in Annex V. In general terms, it is the highest long-term average percentage of defects that is acceptable.

For important performance properties the AQLs are set as low as practically possible. For example, the limit for freedom from holes is set at 0.25% to ensure that the end user is adequately protected. For properties that are less important and do not affect the performance of the condom, such as non-critical visible defects, slightly higher AQLs are acceptable.

Compliance with the specified AQLs is assessed by testing a sample from each Lot. Testing a sample can only give an estimate of the percentage of defective products in a Lot. The accuracy of this estimate will increase with the size of the sample. The average percentage of defective products—the process average — can be estimated by pooling the results of testing from many Lots. For further details on process average, refer to Annex IV.

As discussed in the previous section, testing is conducted according to sampling plans specified in *ISO 2859–1*. This standard contains sets of tables giving the maximum number of defective products that are allowed in a sample taken from a Lot. The sampling plans are designed to give a high probability (usually greater than 95%) of a Lot being accepted if the process average of defective products is equal to or less than the AQL. In the long run, therefore, the percentage of Lots being rejected should not exceed 5%. If it does, then there is a risk that the manufacturer is not in compliance with the relevant AQL.

1.10 Monitoring quality

As well as reviewing the results of Pre-shipment compliance testing on a Lot-by-Lot basis, it is recommended that purchasers monitor quality on an ongoing basis. This can be done by calculating the process averages or using control charts (e.g. Shewhart charts). Monitoring quality using these methods provides excellent information about trends in product quality and/or early warning of potential problems.

1.11 Testing laboratories

Laboratories may be:

- manufacturers' laboratories;
- independent accredited test laboratories;
- national regulatory laboratories.

Laboratories that test female condoms for regulatory or compliance purposes need to have systems in place to ensure the reliability of their results. ISO has developed a quality management system specifically for laboratories, *ISO 17025*. Laboratories that comply with *ISO 17025* will also operate in accordance with *ISO 9001*. *ISO 17025* covers the essential elements of *ISO 9001* as well as laboratory-specific requirements, such as technical requirements for equipment, calibration, uncertainty management and technical competence of the staff. The laboratory must conduct regular, traceable calibration of its measuring equipment, have an adequate maintenance system, and have systems in place to ensure the technical competence of their staff.

Female condom testing laboratories used for prequalification and Pre-shipment compliance testing should be accredited to *ISO 17025*.

There are a number of international mutual recognition agreements among accreditation bodies, which audit each other for quality. The international umbrella body is:

International Laboratory Accreditation Cooperation (ILAC),
The ILAC Secretariat, P.O. Box 7507,
Silverwater, NSW 2128, Australia.
Telephone: +61 29736 8222;
Fax: +61 2 9745 5311.
http://www.ilac.org.

It is recommended that all laboratories—national, independent and manufacturers—confirm their competence by participation in condom inter-laboratory proficiency trials. In such trials laboratories test samples of condoms supplied by the trial organizers. The results of the tests are returned to the organizers, who analyze them and provide feedback to each participating laboratory. The test results are reported anonymously to all the test laboratories, allowing participants the opportunity to investigate any tests in which their results disagree with those of other participants. Currently, there may be no opportunity for laboratories to participate in trials specifically using female condoms, but the male condom tests are sufficiently similar to be of value.

When assessing a testing laboratory, the following factors should be considered:

- whether the laboratory is accredited by an internationally recognized body;
- whether the laboratory participates in interlaboratory proficiency trials;
- the reputation of the laboratory among large volume purchasers.

1.12 Testing costs

Some buyers question the cost of independent Lot by-Lot Pre-shipment compliance testing when they deal with a supplier with whom they have experience and in whom they have developed confidence.

Some have experimented with "consignment testing" for male condoms, i.e. regarding the whole shipment as a single Lot. The trouble with this method is that it is unlikely that the whole shipment has been manufactured under the same conditions. The shipment is therefore unlikely to meet the definition of a Lot, as described in Section 1.6. Since the homogeneity of the shipment cannot be guaranteed, the statistical principles behind Lot sampling and testing are likely to be compromised. Furthermore, it is difficult to detect problems that may be present in individual Lots. The use of this method increases the risk of a poor Lot being accepted. Buyers who have experimented with it have found that the savings were a false economy.

1.13 Confirmatory testing

In many countries national regulatory authorities confine their role to reviewing the data and conclusions reached by the accredited independent laboratory that has been contracted to undertake the Pre-shipment compliance testing. In some countries, in contrast, the national regulatory authority may require in-country confirmatory testing. Where feasible, the confirmatory testing should be undertaken by the same laboratory that undertook the Pre-shipment compliance testing.

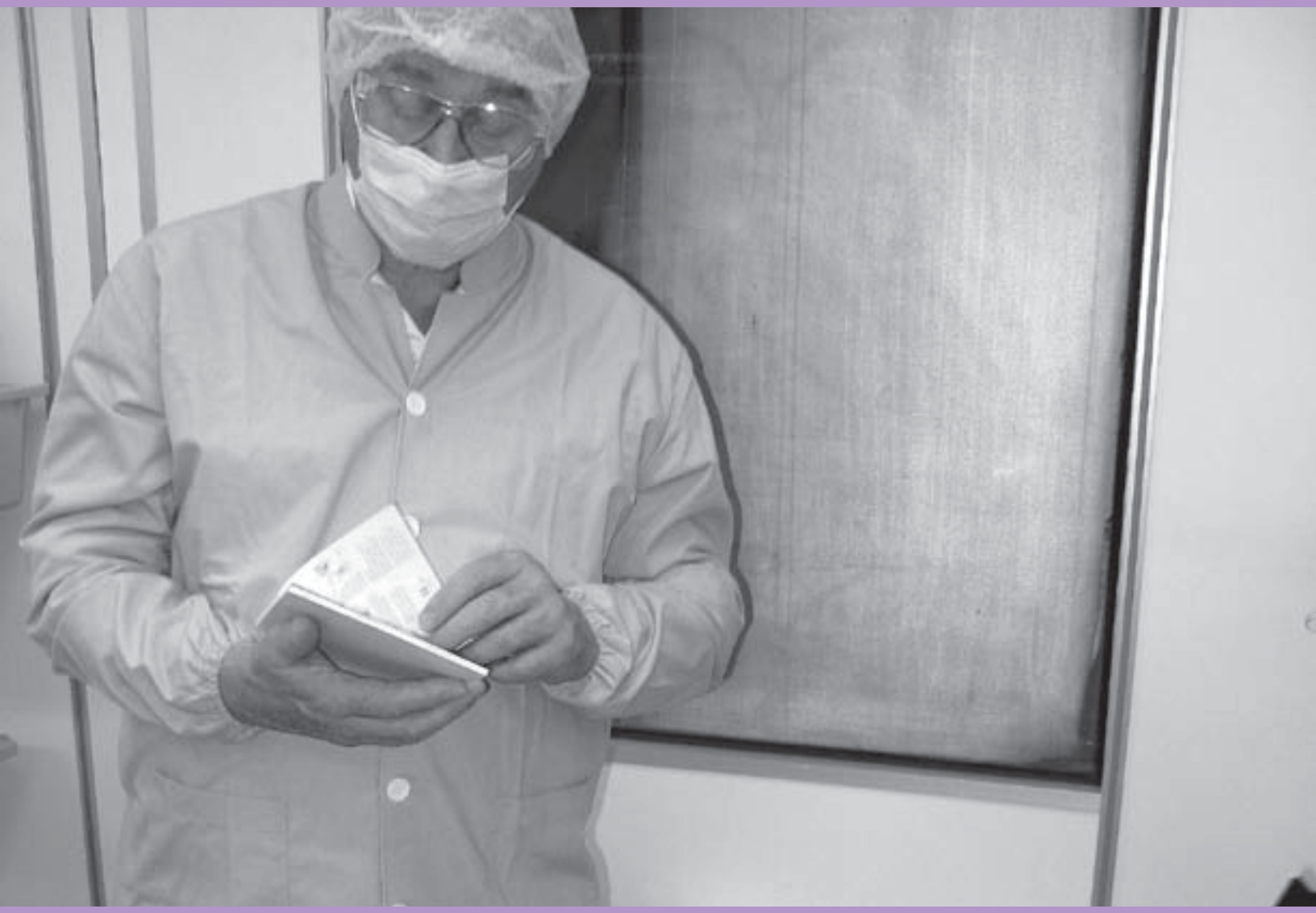
If Lot by Lot confirmatory testing is required, it should replace, rather than repeat, Pre-shipment compliance testing. These requirements should be written into the contractual agreement between the purchaser and the receiving country and/or procuring agency. The testing should be undertaken by a laboratory accredited to *ISO 17025*.

If Pre-shipment compliance testing and confirmatory testing are undertaken by different laboratories, there is a risk of contradictory results.

On occasion the national regulatory authority may have a valid concern regarding possible deterioration of the product during transportation. If this is the case, then confirmatory testing may be undertaken. Local regulatory authorities must take into account the results of Pre-shipment compliance testing before reaching any conclusions about the quality of the product.

Confirmatory testing can be restricted to selected Lots chosen at random from a shipment or consignment. If one or more of the selected Lots fail to comply with the specifications, the remaining Lots should be tested.

It is recommended that, when such testing is undertaken, priority be given to the critical performance parameters of airburst properties and pack integrity. The risk of statistical Lot failures due to sampling error (ie if the sample is not representative of the Lot, due to chance events) should be considered when interpreting such tests. Occasional differences in results between the Pre-shipment compliance tests and the confirmatory tests must be expected.



CHAPTER 2

DETAILS OF THE WHO/UNFPA FEMALE CONDOM GENERIC SPECIFICATION

PART ONE

CHAPTER 2: DETAILS OF THE WHO/UNFPA FEMALE CONDOM GENERIC SPECIFICATION

2.1 General Requirements

General Requirements include the selection and safety of materials used to manufacture the condom and any insertion and retention devices. Manufacturers shall include in their Site Master File and Product Dossier documentary evidence to confirm that the condoms (further explanation on those is given on Chapter 9) comply with the General Requirements listed in the following tables. Verification of conformance to these requirements is assessed during prequalification and in response to any purchaser's doubts about whether the product complies with the *WHO/UNFPA Female Condom Generic Specification.*

Manufacturers are also required to include data in their Product Dossier supporting the shelf-life claims made for the product. Female condoms shall comply with the performance requirements specified in Section 2.2 of this *WHO/UNFPA Female Condom Generic Specification* throughout the stated shelf life of the condom. Manufacturers shall determine the shelf life by real-time studies conducted at (30 -2+5)°C. Pending the outcome of real-time studies, manufacturers may use appropriate accelerated studies to estimate a provisional shelf life. The basis used to estimate the provisional shelf life from the accelerated data must be explained in the Product Dossier and appropriate validation data shall be included.

Table 2. General Requirements (to be included in the Product Dossier and verified during prequalification)	
Clinical investigation reports	Copies of clinical investigation reports shall be made available for review and be included in the product dossier. The reports shall clearly identify the product variant that they relate to. Any changes made to the product since the clinical investigation was completed shall be documented. Where a comparative clinical investigation against a marketed female condom has been conducted, the reports shall clearly identify the marketed female condom including its manufacturer, the date of manufacture, if known, and the expiry date of the samples used in the study. The report shall include the test results for the condoms used in the trial including burst test results.
Specification for Minimum burst pressure and volume	Copies of reports relating to the setting of minimum burst pressure and volume specifications shall be made available and included in the product dossier. Reports shall include the original burst data on the Lot or Lots of condoms used in the clinical investigations and details of how the minimum limits for burst pressure and volume were established. If the burst requirements are not based on the Lot or Lots of condoms used in the clinical investigations, then a full justification is required to establish equivalence between the condom Lot or Lots used to set the specification and those used in the clinical evaluation.
Data Sheets	Copies of the most recent data sheet giving the manufacturer's specification for the product as defined in Section 1.5 shall be included in the product dossier.
Materials	The condoms, retention features and any other components such as insertion features shall be made of suitable materials as specified by the manufacturer. If significant changes are made to the grade or type of materials used, then the manufacturer may be required to repeat one or more of the safety, clinical assessments and stability assessments of the product. Full details of the materials shall be given including, where appropriate, polymer and copolymer compositions. Additional information about the material used for the sheath shall be given including its key physical properties (tensile strength and modulus). For thermoplastic elastomers, the molecular weight and molecular weight distribution shall also be given.
Barrier properties	The barrier properties of the female condom shall be established by viral penetration studies using a suitable surrogate virus, for example bacteriophage Phi-X174. When tested in accordance with the method given in *ISO 25841,* the volume of virus containing medium penetrating the condom shall not exceed twice the limit of detection of the test for at least 80% of the condoms tested. A marketed male latex condom that complies with the requirements of *ISO 4074* may be used as a control in the study.

Table 2. General Requirements (to be included in the Product Dossier and verified during prequalification) (continued)	
Barrier properties (continued)	For condoms made from natural rubber latex with a sheath of minimum thickness 0.055 mm, where the sheath component is made by conventional latex dipping processes, an exception from barrier testing is permissible since the barrier properties of such films to virus are well established. This exemption does not apply if the sheath is made using unusual dipping or vulcanization technology, if the sheath component or the finished condom is subjected to any subsequent treatment process other than washing, or any additive other than the usual vulcanization ingredients and stabilisers are added to the latex.
Bio-compatibility	The condoms shall not liberate toxic or otherwise harmful substances in amounts that can be irritating, sensitizing or otherwise harmful to the user of the condom under normal conditions of use. Biocompatibility assessments shall be conducted in accordance with *ISO 10993–1*. Generally, tests shall be conducted for cytotoxicity according to *ISO 10993–5* and for irritation and sensitization according to ISO *10993–10*. Manufacturers should choose accredited laboratories for these tests, and the results should be interpreted by an accredited toxicologist or other suitably qualified expert. In accordance with *ISO 10993–1*, manufacturers may use existing data on identical materials instead of conducting their own tests. *Expert reports should be available for review.* If there is a likelihood of systemic absorption of any components or residuals, mutagenicity testing shall be performed. The manufacturer shall also obtain, and make available on request from regulatory authorities, toxicity data on all the additives and residual monomers, solvents and known impurities used in the manufacture of the female condom. Suitable Material Safety Data Sheets shall be supplied on request for materials used in the manufacture of the condoms, retention features and lubricant. *Manufacturers and/or the purchasers are advised to confirm local requirements for safety testing with appropriate regulatory authorities in the countries in which the condoms are to be distributed.*
Water-extractable protein levels	***It is recommended*** **that manufacturers of natural rubber latex based female condoms determine the water-extractable levels of proteins in their products.** The recommended levels for soluble protein, as determined by the modified Lowry method, should be less than 200 µg/g. Manufacturers should take steps not to exceed this level and should monitor production periodically. 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. Documentation recording protein levels should be available for review.
Bioburden levels	Condoms are not sterile devices, but nevertheless manufacturers should take steps to minimize the risk of contamination of the products with micro-organisms. Some designs of female condom may increase the risk of microbiological contamination because of the materials used and the additional manipulation required to assemble the finished device. ***It is recommended*** **that bioburden levels on packed condoms be maintained below 100 cfu and not allowed to exceed 500 cfu.** There should be an absence of *Staphylococcus aureus* and *Enterobacteriaceae* including *Escherichia coli*, *Pseudomonas aeruginosa* and all fungi. ***It is recommended*** **that bioburden levels be determined periodically**, e.g. at least quarterly, by extracting the condoms with a neutralizing medium and determining the total viable aerobic count using appropriate test methods. Further information on the rationale for the bioburden limits, methods of determining bioburden levels and general guidelines on controlling bioburden contamination during manufacture is given in Chapter 5 of this document. Confirmation that bioburden levels are below 500 cfu/condom will be assessed for Lots of condoms submitted for prequalification testing.
Nitrosamines	***It is recommended*** **that manufacturers of latex based female condoms take steps to minimize the formation of nitrosamines.** This can be done by ensuring that condoms are adequately leached and washed, by using minimum amounts of accelerators and by choosing accelerators, such as zinc dibutyldithiocarbamate, that have a preferred safety profile[1].

[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.

Table 2. General Requirements (to be included in the Product Dossier and verified during prequalification) (continued)	
Aromatic Amines	Manufacturers using polyurethanes shall take steps to confirm that aromatic amines cannot be leached out of the female condom at levels that could be considered toxic.
Dusting powders	***It is recommended*** **that manufacturers not use excess powder** (maximum recommended is 100 mg per condom). Depending upon the specific nature of the condom, a suitable dusting powder (e.g. cornstarch, magnesium and calcium carbonates) might be required to prevent the condoms from sticking together during manufacture. Manufacturers may use other dusting powders with the agreement of the purchaser. In such cases the purchaser may require the manufacturer to justify the choice of dusting powder. Talc or lycopodium spores shall not be used.
Shelf life	Condoms shall comply with the performance requirements of this *WHO/UNFPA Female Condom Generic Specification* throughout the stated shelf life of the condom. The manufacturer shall determine the shelf life based on the outcome of stability studies and measured from the date of manufacture. *The date of manufacture is the date that the sheath component of the device was manufactured.* *The claimed shelf life shall be not less than three years and not more than seven years subject to confirmation by appropriate stability data.* Shelf life shall be determined on condoms that have been stored for the maximum period of time between sheath manufacture and packaging that is permitted in the Standard Operating Procedures of the manufacturer. Shelf life shall be confirmed by real-time stability studies conducted at (30 -2+5)°C[2] . If the condom or any critical components such as the retention features are made from moisture sensitive materials and a moisture impermeable packaging material is not used, then relative humidity shall be controlled at (75 ± 5)% during real-time stability studies. Manufacturers must commence real time studies before lodging their applications for prequalification. Pending the outcome of the real-time studies, manufacturers may estimate a provisional shelf life using an accelerated ageing study, for example using the procedures described in *ISO 11346 Rubber, vulcanized or thermoplastic - Estimation of life-time and maximum temperature of use*. The procedures used shall be appropriate to the raw materials of the condom. If at any time during the real-time studies the manufacturer becomes aware that the shelf-life estimates made using the accelerated studies are incorrect, the manufacturer must notify UNFPA and the purchasers immediately.
Individual Packaging	The individual packages shall not adversely affect the properties of the female condom. The package shall be sealed and shall provide an adequate level of protection consistent with the materials used to manufacture the condom. The packages shall not allow lubricant to leak. *It is unlikely that biodegradable packaging will provide sufficient product protection for female condoms made from natural rubber latex.* The packages shall have sufficient mechanical strength to protect the condom during shipping and storage. *Purchasers may choose to specify special packaging requirements at the purchase order stage, in which case the requirements must be included in the purchase specification*

[2] That is in the temperature range of 28ºC to 35ºC

2.2 Performance Requirements

The performance requirements specified here are based on the requirements in the current version of *ISO 25841*. These requirements cannot be altered. Verification of compliance with these requirements must be done as part of the prequalification process and the Lot-by-Lot Pre-shipment compliance testing of the product.

For prequalification purposes, i.e. when testing fewer than five Lots, the sampling plans specified in Chapter 3, Table 6 shall be used. For Lot-by-Lot compliance testing, i.e. when testing continuing series of Lots, the sampling plans specified in Chapter 3, Table 7 shall be used.

Table 3. Performance Requirements

Bursting volume and pressure	
Sampling	In accordance with *ISO 2859–1* General Inspection Level I.
Testing	In accordance with the method given in Chapter 7 of this document. Condoms shall comply with the minimum burst volume and pressure requirements specified by the manufacturer as determined according to Section 1.4.
Requirement	The limit for non-conforming condoms is an AQL of 1.5
Freedom from holes and visible defects including critical visible defects in packaging	
Sampling	**ISO 2859–1 General Inspection Level I, but at least Code Letter M shall be used.** For prequalification testing at least Code Letter N shall be used.
Testing	Condoms shall be assessed in accordance with the method given in Chapter 7 of this document. Critical visible defects of the individual packages are also assessed at the same time on the same samples. The list of critical visible defects for the individual packages is given in Section 7.2.
Requirements	The limits for non-conforming condoms are: Freedom from holes: **AQL 0.25** Critical visible defects: **AQL 0.4** Non-critical visible defects: **AQL 2.5** The limit for non-conforming individual packages is an AQL of 0.4 Holes found by the water test but not observed when the condom was inspected prior to filling with water (non-visible holes), that are within 25 mm of the open end, do not count as non-conforming. Descriptions of critical visible defects and non-critical visible defects are given in Section 4. **Exact definitions of critical and non-critical defects should be reviewed and agreed upon during the contractual process.**
Package integrity (seal integrity)	
Sampling	*ISO 2859–1* Inspection Level S-3.
Testing	In accordance with the method given in Section 7.3 of this document.
Requirement	**The limit for non-conforming individual packages is an AQL of 2.5**

2.3 Design Requirements

Since the approval of female condoms is based on a satisfactory outcome from the clinical investigation, any change in the design of the condom or the materials used requires a detailed evaluation to ensure that the safety and effectiveness is not compromised. A full risk assessment using, for example, the procedures described in *ISO 14971* shall be conducted following any significant change to the design, formulation, manufacturing process, equipment used and packaging. As a consequence of the risk assessment, further clinical investigation of the product and/or re-testing may be required. The design of the condom must not be changed from that used in the clinical investigation without consultation and approval from UNFPA.

For the design requirements listed in the Table below, the nominal specified requirements shall be the same as those for the samples of condoms submitted for clinical investigation. All condoms tested in the sample shall fall within the specified tolerances about the specified mean nominal value. Variation of the specified tolerances may be acceptable at the time of prequalification subject to a full justification for the variation and agreement with UNFPA.

Table 4. Design Requirements	
Essential features	
Verify by visual inspection	A female condom will normally have the following essential features: 1. A sheath component that lines the vagina and may extend to cover or partially cover the external genitalia. 2. An external retention feature to prevent the condom from being pushed into the vagina. Commonly this is a ring or frame. 3. An internal retention feature that retains the condom within the vagina and permits safe withdrawal of the penis after intercourse. Examples include rings, foam sponge devices and mucoadhesive tabs. 4. A product insertion feature that facilitates insertion of the condom into the vagina. The internal retention feature may also serve this function.
Sampling	A sample of 13 female condoms shall be taken from each Lot.
Requirement	All condoms in the sample shall have the essential features and components specified by the manufacturer.
Colour	
Pigments	***If any pigment is used to colour the condom, it shall be suitable for use in medical devices.*** Full details of any pigments used shall be supplied along with the relevant Material Safety Data Sheet (MSDS).
Sampling	A sample of 13 female condoms shall be taken from each Lot and inspected visually for colour (colour may be assessed on the same sample of condoms used to assess other design requirements). Reference samples or colour charts may be used to define and assess colour. Exact colour matches may not be possible.
Requirement	All samples shall comply with the specification.
Odour and flavour	
Verify by visual inspection and smell	The condoms shall not give off an unpleasant odour when the package is opened at any time after manufacture and for the shelf life of the product. (Many materials, including natural rubber (NR) latex, have a characteristic odour. Often the odour tends to dissipate quickly once the package is opened. A mild odour that dissipates quickly is acceptable.) It is suggested that appropriate reference samples be retained by the testing laboratory to help resolve disputes over odour. It is recommended that the retained samples be kept for the duration of the shelf life of the condom. Purchasers may, by agreement with the manufacturer, specify the addition of a suitable fragrance and/or flavour. Such fragrances and flavours must be non-toxic, non-irritant and not adversely affect the performance and acceptability of the condom. If a fragrance or flavour is included full details of the fragrance, including an MSDS, shall be supplied.

Table 4. Design Requirements (continued)	
Testing	See Chapter 8 for guidance on odour testing. If a masking agent or fragrance is used, odour testing should become part of the Lot-by- Lot Pre-shipment compliance testing. Odour testing should be included in ageing studies.
Sampling	A sample of 13 female condoms shall be taken from each Lot (odour and flavour may be assessed as described in Chapter 8 on the same sample of condoms used to assess other design requirements).
Requirement	All samples in the Lot shall comply with the specification. Odour evaluation is inherently subjective and a degree of tolerance is required when assessing products for compliance with speciation.
Width	
Sampling	A sample of 13 female condoms shall be tested from each Lot.
Testing	In accordance with the method given in Section 7.4. The width of a female condom is unique to each design. The manufacturer shall specify the nominal width of female condoms at each of the measurement locations given in Section 7.4. The maximum tolerance for width requirements shall be ±2 mm around the nominal specified width.
Requirement	No female condom in the sample tested shall be outside the specified range.
Length	
Sampling	A sample of 13 female condoms shall be tested from each Lot.
Testing	In accordance with the method given in Section 7.5.
Requirement	The length of a female condom is unique to each design. The manufacturer shall specify a nominal length for the female condom consistent with the length of the female condoms used in the clinical investigation described in Section 1.3. The maximum tolerance shall be ±5 mm if the nominal length is 150 mm or less and ±10 mm if the nominal length is greater than 150 mm. No female condom in the sample tested shall be outside the specified range.
Thickness	
Sampling	A sample of 13 female condoms shall be tested from each Lot.
Testing	In accordance with the method given in Section 7.6. The thickness of a female condom is unique to each design. The manufacturer shall specify a nominal thickness of the female condom at each of the measurement locations defined above. The thickness shall be consistent with the thickness of the female condoms used in the clinical investigation described in Section 1.3. The tolerance shall be ±0.01 mm.
Requirement	No female condom in the sample tested shall be outside the specified range.
Quantity of lubricant including powder	
Sampling	A sample of 13 female condoms shall be taken from each Lot.
Testing	In accordance with the method given in Section 7.7. The design of a female condom may include lubrication in any of the following: 1. lubricant pre-applied directly to the female condom during packaging; 2. lubricant supplied in a separate container to be applied to the female condom by the user; 3. lubricant both pre-applied to the female condom and supplied in a separate container. The type and amount of lubricant is unique to each female condom design. The manufacturer shall specify the amount of lubricant, which shall be the same as used in the clinical investigation as described in Section 1.3.

Table 4. Design Requirements (continued)	
Requirement	The manufacturer shall specify the amount of lubricant, which shall be the mean amount of lubricant used in the clinical investigation as described in Section 1.3. All female condoms in the sample tested shall be within ±150 mg of the specified mean. Manufacturers shall identify specifications and test methods as appropriate to verify the design and to ensure the quality and consistency of the lubricant. The specification for the lubricant should include viscosity. If the lubricant is supplied separately from the female condom then manufacturers shall provide full details on how the lubricant should be used. These details shall be consistent with the instruction given with the clinical investigation samples. The quantity of lubricant supplied in the container shall be not less than the amount supplied with the clinical investigation samples. The containers for the lubricant shall not leak. An inspection level of S-3 and an AQL of 1.5 are recommended for assessing lubricant container integrity. Consult the purchase order and specification to determine if additional packaging requirements apply to the lubricant container.
Retention features and other additional components	
Sampling	A sample of 13 female condoms shall be tested from each Lot.
Testing	The dimensions of all retention features and any other ancillary components such as insertion features shall be measured using the methods specified by the manufacturers. Manufacturers are required to specify mechanical properties for the retention features that are relevant to the correct function of the feature. Examples could include stiffness and elastic memory parameters for rings, resilience and recovery times for foams, and adhesion properties for adhesive pads, etc. The specification requirements shall be based on the Lot(s) used in the clinical investigation. Periodically purchasers and other interested parties may assess the physical properties specified for the internal and external retention devices.
Requirement	The dimensions of the retention features and other ancillary components for every condom tested shall comply with those specified by the manufacturer. The specified dimensions for retention features shall be the same as those for the clinical investigation samples within a tolerance of ±5%. The mean mechanical properties of the retention features shall be the same as those used for the clinical investigation samples within a tolerance of ±10%. All samples tested shall comply.
Individual package markings	
Sampling	A sample of 13 individual packages and, if appropriate, 13 consumer packs shall be taken from each Lot.
Testing	The packages are visually inspected to verify the required aspects of package marking.
Requirement	The colour, print design and identification markings, including Pantone references and font sizes, shall be as specified by the buyer and annexed to the specification for the product. All samples shall comply.
Verified by visual inspection	The packages shall not adversely affect the properties of the female condom. The package shall be sealed and shall provide an adequate level of protection consistent with the materials used to manufacture the condom. The packages shall not allow lubricant to leak. The recommended packages shall have sufficient mechanical strength to protect the condom during shipping and storage.

Table 4. Design Requirements (continued)	
Verified by supplier's data or independent test requirement	The Lot numbers on packages should be printed at the time of packaging. If this is not feasible, then manufacturers shall ensure that there are adequate procedures to ensure that the correct Lot number is placed on the packages. The individual package shall have the following markings, which shall be clearly legible under normal and corrected vision: • manufacturer's name or identifier unless specified otherwise by the purchaser; • Lot number or Lot identification code (printed at the time of packaging, not pre-printed); • expiry date: month and year labelled expiry date in language(s) to be specified by the purchaser (printed at the time of packaging, not pre-printed); • clearly legible instructions for use in pictorial form and/or in language(s) to be specified by the purchaser (may be supplied separately if unable to print on pack); • the statement relating to the effectiveness of the condom if required by the purchaser (see information section); • if the condom is made from NR latex, a warning about the risk of allergic reactions to the condom. *Purchasers may specify the use of Braille for specific information including the expiry date.* *If a separate lubricant and condom are supplied in the same package then the expiry date shall be the shorter of the two. The expiry date shall be printed on all packages (i.e. the condom package, the lubricant package and any outer or consumer package).* All inspected packages and, if appropriate, consumer packs shall comply with the packaging requirements.

2.4 Packaging Requirements for Shipment

Inspections or verifications in this section will generally be carried out during prequalification, Lot-by-Lot Pre-shipment compliance testing and periodic inspections.

Information included on all packaging shall be in accordance with the language specified by the purchaser.

Table 5. Packaging Requirements for shipment	
Consumer packaging[3]	No requirements for consumer packs are included in the *WHO/UNFPA Female Condom Generic Specification* If required, the full design of the consumer pack should be specified in accordance with the requirements of the programme.
Information	If, in accordance with local regulations, programme requirements and/or specified by the purchaser, information is to be provided with the condom, then the following instructions should be considered for inclusion in the inner box or the secondary/consumer carton: • to handle the female condom carefully, including removal from the package so as to avoid damage to the condom by fingernails, jewellery, etc.; • how and when to insert the female condom; mention shall be made that the female condom should be inserted into the vagina before any contact occurs between the vagina and the partner's body to assist in the prevention of sexually transmitted infections and pregnancy; • to stop and check if the user feels the female condom slipping into or out of the vagina; • if the lubricant is supplied with the condom but in a separate sachet, then instructions on how to use the lubricant shall be provided along with a description of the lubricant and an expiry date; • a statement informing the user which type of additional lubricant can be used with that specific female condom and how the lubricant should be used; • if the female condom is made with NR latex, a statement instructing the user to avoid use of oil-based lubricants such as petroleum jelly, baby oil, body lotions, massage oils, butter, margarine etc. as these are deleterious to the integrity of the female condom;

[3] Sometimes called wallet packs

Table 5. Packaging Requirements for shipment (continued)

	• a statement instructing the user to consult a doctor or pharmacist about the compatibility of topical medicines and other topical products that might come in contact with the female condom; • advice to seek medical assistance as soon as possible should a female condom fail during use; • advice that, if the individual package is obviously damaged, to discard that female condom and use a new one from an undamaged package; • advice to withdraw the penis soon after ejaculation leaving the female condom in place in the vagina; • instructions for withdrawal and disposal of the female condom; • a statement that the condom is for single use only and that cleaning and reuse can compromise the integrity of the device. ***It is recommended* that the following statement relating to the safety and effectiveness of the condom be included:** **"When used correctly every time you have sex, female condoms reduce the risk of unintended pregnancy, HIV and some other sexually transmitted infections. Use a new condom every time you have sex and follow the instructions carefully".**
Inner boxes	The inner boxes shall be packed into plastic or other waterproof lining bags, which will be placed in three-wall cartons made from weather-resistant corrugated fiberboard with a bursting test strength of not less than 1900 kPa. The inner boxes will be marked in a legible manner to facilitate identification in case of subsequent query. **The following information shall be included in the inner box marking:** • description of contents; • Lot identification number; • month and year of manufacture (including the words *Date of Manufacture, Month, Year*) in language(s) to be specified by the purchaser. The year will be written as a four-digit number and the month, as a two-digit number; • month and year of expiry (including the words *Expiry Date, Month, Year*) in language(s) to be specified by the purchaser. The year will be written as a four-digit number and the month as a two-digit number; • manufacturer's name and registered address; • number of condoms in box; • instructions for storage. **Note: All markings must be legible.** Inner box markings can be specified in accordance with programme requirements.
Exterior shipping cartons	The inner boxes shall be packed into plastic or other waterproof lining bags, which will be placed in three-wall cartons made from weather-resistant corrugated fiberboard with a bursting test strength of not less than 1900 kPa The carton flaps shall be secured with water-resistant adhesive applied to not less than 75% of the area of contact between the flaps, or with water-resistant tape, 75 mm wide, applied to the full length of the centre seams and extending over the ends by not less than 75 mm. The cartons may be secured by plastic strapping at not less than two positions. Alternatively, wire-bound, cleated plywood or nailed wood boxes are acceptable when lined with a waterproof barrier material. The barrier material must be sealed at the edges with waterproof tape or adhesive, and there must be no sharp protrusions inside the boxes. In some countries the three-wall corrugated fibreboard available is not of sufficient strength and rigidity to meet stacking requirements or to resist being cut at the corners when the plastic strapping is applied. In such cases an inner carton of two-walled corrugated fibreboard shall be inserted into the shipping carton before packing the condoms.

Table 5. Packaging Requirements for shipment (continued)	
Exterior shipping cartons	The exterior shipping carton, like the inner box, shall be marked with information about the contents in a clearly legible manner. Information should be printed on two adjacent sides. The information shall include: • a description of the contents; • Lot identification number; • month and year of manufacture (including the words *Date of Manufacture, Month, Year*) in language(s) to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number; • month and year of expiry (including the words *Expiry Date, Month, Year*) in language(s) to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number; • name and address of the manufacturer and/or supplier; • number of female condoms contained in the carton; • the consignee details; • instructions for storage and handling.
Lot traceability	Condom Lots presented for inspection and acceptance must be complete and packed in their exterior shipping cartons. Provision should be made during production for sufficient additional condoms from each Lot to replace those sampled for acceptance testing. Wherever practicable, Lots must be shipped in their entirety and be kept whole during containerization and shipping. The manufacturer should take all reasonable steps to facilitate keeping the shipments as discrete Lots as far as practicable down the distribution chain. These steps may include the use of very large letters for Lot codes, colour coding, and grouping of pallets of the same Lot number.

CHAPTER 3

Summary Tables: Prequalification and Lot-by-Lot testing

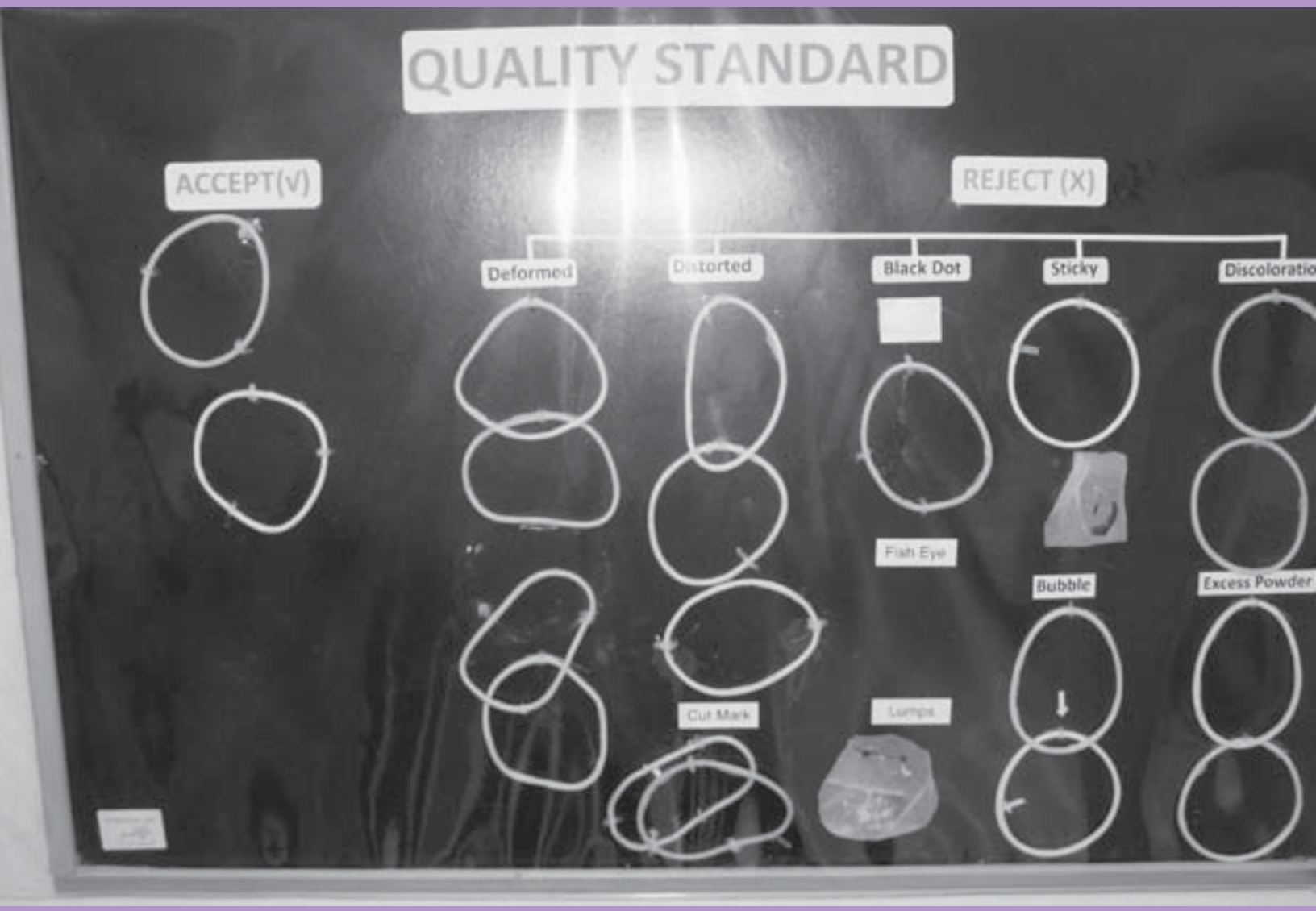
CHAPTER 3: SUMMARY TABLES: PREQUALIFICATION AND LOT-BY-LOT TESTING

The following tables summarize the testing methods and requirements for packaging defects, general requirements, performance requirements and design requirements for prequalification and Lot-by-Lot compliance testing. The requirements shall be assessed against those specified in the manufacturer's Data Sheet for the specific product.

Table 6. Summary of Prequalification Tests (Isolated Lots)

Characteristics	Sampling	Verification	Requirement
Burst volume and pressure	*ISO 2859–1* Level G-I Minimum code letter L (200 samples)	Laboratory testing	Comply with manufacturer's specification AQL 1.5
Freedom from holes	*ISO 2859–1* Level G-I Minimum Code Letter N (500 samples)	Laboratory testing	AQL 0.25
Visible defects	*ISO 2859–1* Level G-I Minimum Code Letter N	Visual inspection	Critical defects: AQL 0.4 Non-critical defects: AQL 2.5
Visible defects individual packages	*ISO 2859–1* Level G-I Minimum Code Letter N	Visual inspection	Critical defects: AQL 0.4
Design	13 Condoms per Lot	Visual inspection and measurement	Comply with manufacturer's specification All samples comply
Package integrity	*ISO 2859–1* Special Inspection Level S-3 Minimum Code Letter H	Laboratory testing	Laboratory testing AQL 2.5
Colour	13 Condoms per Lot	Visual inspection	Comply with manufacturer's specification All samples comply
Scents and flavouring	13 Condoms per Lot	Sensory inspection	Comply with manufacturer's specification All samples comply
Width	13 Condoms per Lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Length	13 Condoms per Lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Thickness	13 Condoms per Lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Odour (if necessary)	13 Condoms per Lot	Sensory inspection	Comply with purchase specification All samples comply
Inner box	*ISO 2859–1* Level S-3	Visual inspection	Comply with purchase specification All samples comply
Exterior shipping cartons	*ISO 2859–1* Level S-2	Visual inspection	Comply with purchase specification All samples comply

Table 7. Summary of Lot-by-Lot Pre-shipment compliance testing and requirements (continuing series of Lots)			
Characteristics	**Sampling**	**Verification**	**Requirement**
Burst volume and pressure	*ISO 2859–1* Level G-I	Laboratory testing	AQL 1.5
Freedom from holes	*ISO 2859–1* Level G-I Minimum Code Letter M	Laboratory testing	AQL 0.25
Visible defects	*ISO 2859–1* Level G-I Minimum Code Letter M	Laboratory testing	Critical defects: AQL 0.4 Non-critical defects: AQL 2.5
Visible defects individual packages	*ISO 2859–1* Level G-I	Visual inspection	Critical defects: AQL 0.4
Package integrity	*ISO 2859–1* Special Inspection Level S-3	Laboratory testing	AQL 2.5
Design	13 Condoms per Lot	Visual inspection	Comply with manufacturer's specification All samples comply
Colour	13 Condoms per Lot	Visual inspection	Comply with purchase specification All samples comply
Scents and flavouring	13 Condoms per Lot	Sensory inspection	Comply with purchase specification All samples comply
Width	13 Condoms per Lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Length	13 Condoms per Lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Thickness	13 Condoms per Lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Lubricant quantity (including powder)	13 Condoms per Lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Odour (if necessary)	13 Condoms per Lot	Sensory inspection	Comply with purchase specification
Packaging and labelling	13 Condoms	Visual inspection	Comply with manufacturer's specification All samples comply
Inner box	*ISO 2859–1* Level S-3	Visual inspection	Comply with purchase specification All samples comply
Exterior shipping cartons	*ISO 2859–1* Level S-2	Visual inspection	Comply with purchase specification All samples comply



CHAPTER 4

Workmanship and Visible Defects

CHAPTER 4: WORKMANSHIP AND VISIBLE DEFECTS

4.1 Introduction

All female condoms in the sample are inspected for workmanship as part of the test for freedom from holes prior to mounting on the test equipment. The number of condoms exhibiting a visible defect is recorded, and defects are classified either according to the type of defect listed below or as specified in the contract.

Visible defects are divided into (a) critical visible defects and (b) non-critical visible defects.

The individual condom packs in the sample also are inspected for critical visual defects before the samples are removed for testing. Critical visible defects in the packaging that could have an adverse effect on the properties of the condom are listed in Section 7.2.

4.2 Types of visible defects in condoms

It is not possible to define all critical and non-critical visible defects, and it may be necessary to exercise some judgement about whether a particular visible defect is critical.

If the visible defect may affect the performance of the female condom, the defect is considered critical. If a defect not listed below is considered critical by any party, then the purchaser, test laboratory and manufacturer must consult with each other to agree on the classification of the defect concerned.

4.2.1 Critical visible defects

Critical visible defects may adversely affect the performance of the condom. Condoms having critical visible defects are therefore non-conforming.

The most common critical visible defects are covered by *ISO 25841*. Some of the more common critical visible defects are described in Table 8.

They are evaluated by visual inspection as part of the procedure for testing for freedom from holes. An AQL of 0.4 is applied to these defects.

Other types of critical visual defects are occasionally seen, and they should be assessed for their potential effect on the performance and acceptability of the condom. If a

Table 8. Critical visible defects—AQL 0.4

Defect	Description
Blister/bubble	An obvious circular or teardrop-shaped thin area with a well-defined border in the film. (Such defects may break under pressure.)
Coagulum (large)	For female condoms made out of NR or synthetic latex, rubber particles with any dimension greater than 1 mm. These may cause the condom to fail in use.
Embedded and surface particles	Any particle with any dimension of 1 mm or greater. These may be dirt, hair, insects, etc.
Retention features	Broken, cracked, missing, damaged or severely distorted retention features (as in *ISO 25841:2011*). Incomplete attachment of the sheath to the external retaining feature. Disintegrating sponge internal retention features. Presence of sharp edges on retention features that could cause discomfort or damage to the vagina or penis.
Crack marks	Lines that penetrate the surface of the film, formed by shrinkage of the latex during drying. These do not include flow lines or marks from the mould.
Delamination	For female condoms made out of NR or synthetic latex, areas where the individual layers of latex separate (if the condom is formed by two or more dips in the latex).
Thin areas	Small areas of the condom that are visibly thin. These can show up as bulges with well-defined edges on the freedom-from-holes test. Condoms that look asymmetrical when filled with water are not necessarily in this category (see Table 10).
Seams	For female condoms made by welding, poorly welded or creased seams that could fail in use or cause discomfort. Large lumps of material within the seam that could potentially cause discomfort or damage to the vaginal mucosa.
Insertion feature (if applicable)	Any sharp edge, crack, or distortion that may damage the condom, cause the device to fail, or damage the vaginal mucosa. Additional critical visible defects may need to be identified depending upon the design of the insertion feature.
General	Any defect that can reasonably be seen to adversely affect the performance or safety of the product.

defect can reasonably be expected to affect the performance, safety or acceptability of the condom then it should be classified as a critical defect.

4.2.2 Non-critical visible defects

Non-critical visible defects are considered minor defects, as they may not cause the female condom to fail specification. Nevertheless, they are undesirable from the user's standpoint. If non-critical visible defects are specified in a purchase specification, then an AQL of 2.5 is recommended. Inspection for non-critical visible defects is conducted on the samples used for freedom from holes testing.

Depending upon the requirements of the specific user population, the purchaser may wish to include in the specification specific non-critical visible defects, including the most common ones, as listed in Table 9. Detailed descriptions of the non-critical visible defects should be discussed with the manufacturer and included in the contract.

Other types of non-critical defects should be assessed to determine if they will affect the acceptability of the product.

Table 9. Non-critical visible defects—Recommended AQL 2.5

Defect	Description
Pleat/crease	The film sticks to itself, and the pleat/crease cannot be removed by gentle stretching of the adjacent film.
Faulty retention features (minor)	Uneven, partially distorted or otherwise minor defects in the internal and external retention features.

4.2.3 Imperfections

Occasionally, imperfections can be seen in female condoms that do not affect the performance or acceptability of the condom. A list of the more common imperfections that fall into this category is given in Table 6. No action should be taken when these imperfections are seen.

Table 10. Imperfections that are not regarded as defects

Phenomenon	Description
Micro-coagulum	For female condoms made out of NR or synthetic latex, particles of rubber with dimensions less than 1 mm.
Flow lines	Lines of denser material in the film.
Concave spot at end of condom	For female condoms made out of NR or synthetic latex, an apparent indentation caused during the withdrawal of the former (dipping mould) from the latex.
Distortion due to rolling	Apparent variations in condom width due to stretching during rolling.
Bulges	Large bulges or distortion of the female condom during the freedom-from-holes test that are due to minor differences in thickness or product design. (These may or may not have well-defined edges.)
Uneven lubricant	A portion of the sheath part of the female condom may appear dry. This can be regarded as an imperfection if it does not interfere with the insertion of the condom into the vagina.
Seam imperfections	Minor creases close to the seams that have no impact on the airburst properties of the condom
Uneven colour	Minor streaking of the sheath or retention features and uneven colour or discoloration.

Note: Any visible hole anywhere in the female condom, including close to the external retention feature, is not acceptable. These defects are counted as holes if they can be seen before water is added to the condom, even if they are within 25 mm of the open end.

4.3 Packaging defects

The main packaging defects are listed in Table 11. Additional defects are sometimes detected only after shipment.

4.3.1 Individual packages

The requirements for individual packages are specified in Section 2.3.

4.3.2 Consumer packs

There are no requirements for consumer packs included in the *WHO/UNFPA Female Condom Generic Specification*. Purchasers should fully specify requirements in accordance with programme needs. Compliance should be assessed by visual inspection, using a sampling plan in accordance with *ISO 2859–1* Inspection Level S-3. It is recommended that an AQL of 2.5 be applied to consumer pack requirements.

4.3.3 Cartons and marking

Purchasers should fully specify requirements in accordance with programme needs. Compliance should be assessed by visual inspection, using a sampling plan in accordance with *ISO 2859–1* Inspection Level S-3. It is recommended that an AQL of 4.0 be applied to carton requirements.

Table 11. Packaging Defects

Consumer packs	
Empty or partially empty packs Discolouration Delamination	Illegible printing Missing manufacturer's name Incorrect/missing Lot number Incorrect/missing date of manufacture Incorrect/missing expiry date
Cartons and markings	
Non permanent markings Empty cartons or cartons not filled to order Damaged cartons that may affect the integrity or the quality of the condoms inside Number of condoms not as specified. Packages or strips not as specified. Packaging/packing materials not as specified, missing, damaged or non-serviceable.	Illegible printing Missing manufacturer's name Incorrect/missing Lot number Incorrect/missing date of manufacture Incorrect/missing expiry date Shipping cartons inadequately closed and secured Poor application of internal packaging and packing material Distorted intermediate packages.

CHAPTER 5

Resolution of Disputes Related to Product Quality

CHAPTER 5: RESOLUTION OF DISPUTES RELATED TO PRODUCT QUALITY

5.1 Introduction

There are a number of possible causes of disputes relating to quality during a contract to supply female condoms. These may involve:

- interpretation of the contract;
- payment schedules;
- delays in delivery schedules;
- completion schedules;
- independent laboratory test results;
- design issues;
- condition of the female condoms on arrival in-country or at some time after delivery.

It is essential that the procurement contract specify a process for the resolution of any disputes that might arise over contract or product quality issues. This chapter deals only with disputes related to results of product testing.

5.2 Disputes over laboratory results

Disputes over product acceptance most often arise when independent testing determines that the product is not in compliance with the required specification or standard. It is also possible for a manufacturer to dispute a decision made by the sampling agency regarding product packaging or appearance.

In most cases manufacturers accept the results of independent laboratories and replace Lots that have been rejected. When they question the results, they usually present their own test results or other evidence to suggest that the independent tests are incorrect and do not accurately represent the quality of the product tested.

5.3 Sources of disputes arising from laboratory testing

Laboratory testing is always done on a sample from the production Lot. There are generally two main sources of uncertainty in test results:

- **The uncertainty arising due to sampling errors.** There is uncertainty in estimating the properties of any population This is due to the fact that the sample may not be fully representative of the population and has nothing to do with the uncertainties associated with the actual tests used or errors or mistakes made by laboratory staff. This uncertainty decreases as the sample size is increased. The sampling plans specified in *ISO 25841* generally provide a 95% to 99% probability that a Lot that is just within specification will be accepted. (For sampling plans with acceptance number zero, the probability of acceptance can be as low as 90%.) There is, therefore, a small risk that Lots of acceptable quality will be occasionally rejected.

- **Testing or reporting mistakes due to operator error, equipment malfunction, drifts in calibration, transcription errors and other causes.** These types of mistakes are, in principle, preventable and should be minimized by application of the quality management system and procedures outlined in *ISO 17025.* In addition, there is also the normal uncertainty associated with measurement.

There are a number of important consequences that have to be considered because of the inherent limitations in the sampling plans. These are:

- In any shipment of female condoms there is always a risk that some Lots will be rejected even though they are in compliance with the relevant AQLs. Manufacturers can minimise this risk by ensuring that the process averages are maintained well below the AQL. For example, by operating with process averages that are half of the relevant AQLs, manufacturers can cut the risk of rejecting Lots that are actually in compliance to less than 1%.

- Manufacturers and purchasing agencies should plan on the assumption that some Lots, possibly up to 5%, will be rejected. Estimates of volume requirements and pricing should take into account the impact of Lot failures. Again, manufacturers can keep down the percentage of Lots rejected by maintaining process averages well below the relevant AQLs.

- Lots with defect levels slightly above the AQL have a significant chance of being accepted.

As a general rule, when the level of Lot failures exceeds 5% over a large number of Lots, i.e. 50 or more, then doubts can be raised about the quality of the manufacturer's production. Similarly, if the percentage of Lots rejected exceeds 10% in the short term (e.g. between 5 and 50 Lots), then again doubts can be raised about the quality of the products.

Finally, if any two Lots in a sequence of five Lots are rejected, there is a significant risk that the process average may exceed the AQL; further investigations of quality should be undertaken according to the techniques described in Annex IV.

It is because of these issues that WHO/UNFPA recommends only one accredited laboratory undertake the pre-shipment compliance testing.

5.4 Decisions on re-testing

Re-testing should be undertaken only when:

1. There is considerable evidence that the laboratory has made a mistake.

2. There is considerable evidence that the test result is not representative of the population from which the Lot is taken.

Because of the operating characteristics of the sampling plans specified in *ISO 25841*, which are primarily intended for the routine testing of a continuing series of Lots, there can be a significant probability that a rejected Lot will be accepted on re-test even if the Lot is not in compliance with the relevant AQLs. This means that, in many cases, re-testing will lead to conflicting results.

Therefore, re-testing should be undertaken only when there is strong evidence that an error has been made. More information on the statistical issues associated with sampling is given in Annex IV.

Before a re-test is considered, all available data should be reviewed and discussed with the independent laboratory. If a manufacturer disputes a test result, the following issues should be considered in deciding whether to allow a re-test:

- What is the margin by which the product has failed to comply?

- Is the manufacturer's history of production for the client a good one?

- What is the nature of the difference between the manufacturer's and the laboratory's test results?

The amount of information available for review depends on the type of test. With inflation testing, for example, data on the number of non-compliers will be available as well as the individual volumes and pressures. In this case a detailed comparison of the data from the manufacturer and the test laboratory can be conducted, and it may be possible to identify the cause of disagreement. If, however, the dispute relates to freedom from holes, then the manufacturer must provide detailed and credible pre-release in-process test results to support the claim for a re-test. The independent laboratory should be able to provide the condoms with holes found during test.

If there is a dispute over a Lot or shipment of female condoms, then the laboratory should keep non-conforming condoms until the dispute is resolved.

When the Lot concerned is part of an ongoing order and there is historical or concurrent data on at least 10 Lots, the process average can be estimated by one or more of the techniques given in Annex IV. If this process average is within the AQL, a re-test may be allowed.

5.5 Re-testing

Where re-testing is done, the second test should give additional confidence about the result, compared with the first test. Re-testing may be done using the next higher inspection level defined in *ISO 2859* than the one used for the first sample (e.g. G-II instead of G-I).

Where possible the re-tested sample should be taken from the laboratory's retained sample or the duplicate taken at the time of sampling. If this is insufficient, or if the sample is suspect, a new sample will need to be taken.

If a result is disputed, the laboratory and the manufacturer should be asked to verify basic issues, including:

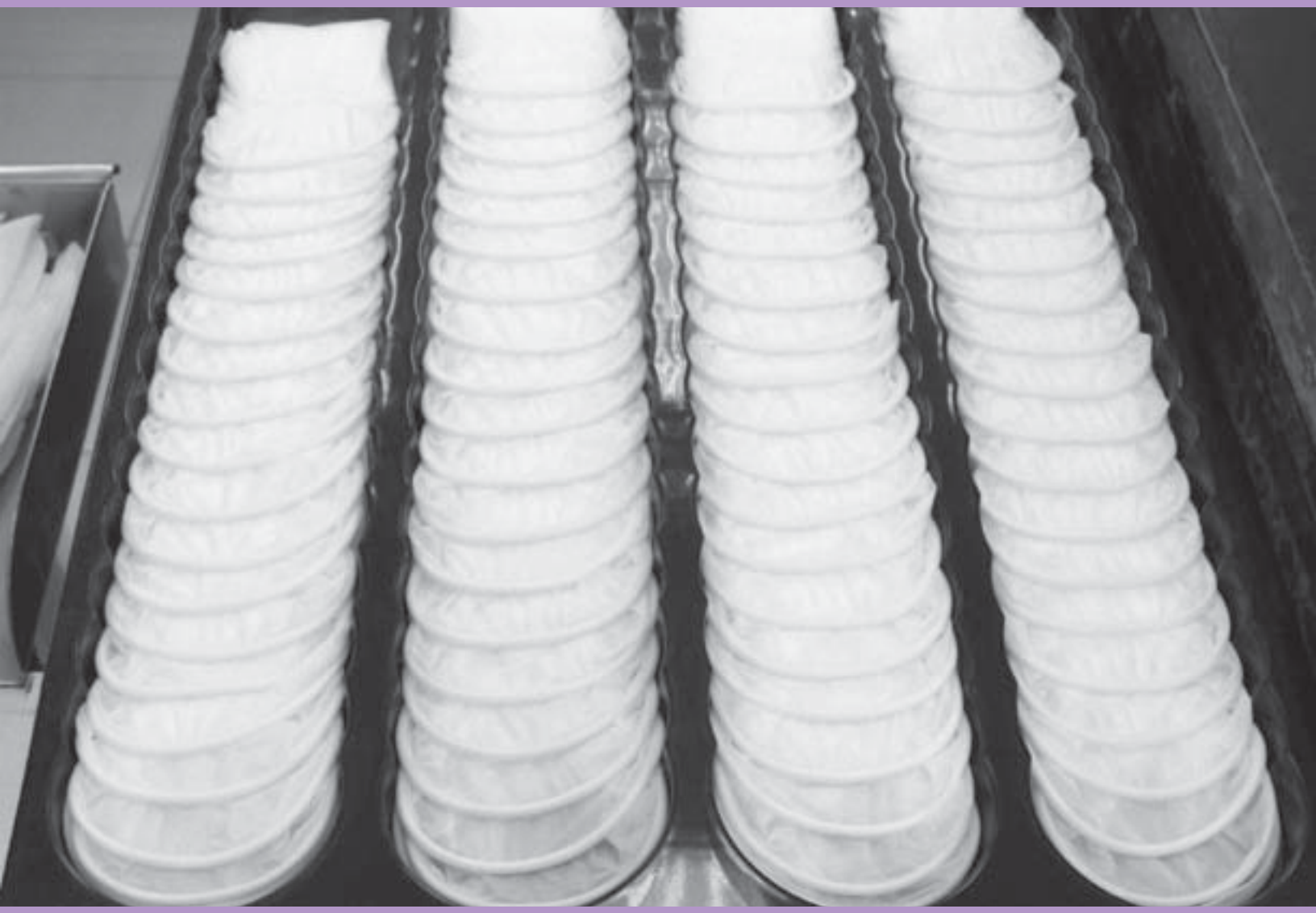
5.5.1 Independent testing laboratory

- verify that testing was performed as prescribed in the test method applicable to the order concerned;
- verify that test equipment was in proper working order and in calibration at the time of testing;
- check on staff performance by looking at the relevant tester's results on other products tested at about the same time;
- verify the identity of the test samples and that the normal precautions were taken not to damage the samples prior to testing;
- verify the uncertainty estimates being applied to the measurements.

If the laboratory has any doubts about any of these issues, it should re-test the products free of charge.

5.5.2 Manufacturer

- review manufacturing and test documents for completeness and for anomalies that may indicate problems;
- review all the items above that the independent testing laboratory is required to verify.



CHAPTER 6

Bioburden and Microbial Control

PART ONE

CHAPTER 6: BIOBURDEN AND MICROBIAL CONTROL[4]

6.1 Introduction

This section was originally prepared to provide an accurate explanation regarding bioburden and microbial control for male latex condoms for national regulatory authorities, programme managers, procurement bodies and other interested parties.

It has been adopted to provide information for bioburden control in female condom manufacturing. Recommendations are made for bioburden limits for packaged products and guidance is given for controlling and monitoring bioburden during production.

6.2 Bioburden, limits and rationale

6.2.1 Bioburden

Control of microbial contamination on medical devices is essential to ensure the consistency and safety of the product. The total population of viable aerobic micro-organisms on the product and inner individual packaging is termed the bioburden. Micro-organisms normally associated with contamination during manufacturing are bacteria, yeasts and fungi. Although some viruses can survive for varying times, they cannot multiply outside the body and are therefore not normally included in bioburden counts.

A number of sources, such as raw materials, process water, manufacturing equipment, packaging materials, personnel and the environment, can contribute to the total bioburden count of a final packaged product. In order to control and minimize bioburden, regular monitoring of these sources should be maintained.

Because bioburden control is a requirement of good manufacturing practice (commonly called GMP) (1–3) of medical device manufacture, this monitoring may also be used as part of the quality control system to ensure adequate environmental control, efficacy of cleaning procedures, and adherence to GMP.

It is recommended that bioburden levels be determined periodically—for example, at quarterly or, ideally, weekly intervals. The frequency of testing depends to a large extent on the manufacturing process, the materials being used and the past record of the factory.

Standard Operating Procedures (SOPs) for bioburden monitoring should include limits for each stage of the manufacturing process and should include equipment and the environment.

6.2.2 Condom bioburden limits

Searches of the scientific literature have failed to identify any reports of genito-urinary infections linked to use of condoms that may have been contaminated during manufacture. Nevertheless, limits for bioburden levels on final packed product are recommended in order to ensure product quality and user safety.

Final packed product should have a bioburden maintained at less than 100 colony forming units (cfu) per item. Occasional excursion above this recommended limit may occur but, if so, should not be allowed to exceed 500 cfu per item. If the higher end of the limit is exceeded, immediate action should be taken to reduce the bioburden, for example, by undertaking cleaning and sanitizing procedures.

There should be an absence of all pathogenic organisms and in particular of *Staphylococcus aureus, Pseudomonas aeruginosa* and *Enterobacteriaceae,* including *Escherichia coli.* There should also be no growth of fungi and yeasts.

Routine testing of condoms may be conducted using the Total Viable Count (TVC) methods (4–6) and the Specified Organism Test (7, 8).

6.2.3 Rationale

Staphylococcus aureus organisms, which are carried by 25% to 32% of the general population (9,10), may be pathogenic and can cause severe infections of skin, wounds, respiratory tract, and the urinary tract as well as septicaemia (11–13). Some specific *Staphylococci* produce an enterotoxin (14,15) that, if ingested, causes gastric upset and food poisoning.

Staphylococci may also produce a toxin (TSST) (16) that causes toxic shock syndrome (17). This has never been implicated in condom use, however. It was classically associated with prolonged insertion of highly absorbent tampons, but it is now known that other medical conditions are related to the syndrome (18).

[4] Author: Lorna M. Willcox, FIBMS (January 2009).

Poor GMP may facilitate cross-contamination with *Staphylococci* from manufacturing operators to the product.

Pseudomonas species are opportunistic pathogens that are often resistant to many of the commonly used antibiotics. They may cause a range of infections, particularly in people whose immune systems are compromised. They have been known to cause lung, ear, eye, and urinary tract infection and septicaemia (19–21). This organism is frequently found in water supplies. Therefore, strict contamination control of all process water is required.

Enterobacteriaceae including *Escherichia coli,* may cause infections of many sites including the genital and urinary tracts, brain, blood and gastro-intestinal tract (22, 23). Specific *Escherichia coli* strains produce an enterotoxin that causes food poisoning and may lead to kidney and liver failure (24). Poor personal hygiene, especially inadequate hand-washing after using the toilet, will cause cross-infection with *Escherichia coli* by transfer between people touching surfaces, materials and products.

Some fungal species have been shown to cause slow deterioration of latex products and should therefore be absent from the final packed product (25–27). Yeast species may cause infections of skin, mouth and genital areas. Therefore, these also should be absent from final packaged product (28, 29).

6.3 Test methods

Bioburden testing should be conducted at regular intervals—for example, quarterly, but preferably weekly. It is recommended that results are regularly monitored so that bioburden trends may be analysed in order to validate microbiological control measures and to monitor environment and product for significant changes. Regular monitoring of results will also enable any necessary remedial actions to be completed as soon as possible.

Bioburden testing should be conducted in accordance with written procedures. The methods used must be adequate to extract bioburden from the test sample, including surfaces, and must maintain the viability of the organisms extracted. The culture media used must support growth of the extracted bioburden. To allow comparisons over time, sampling systems should be consistent.

Some of the samples tested may contain materials that might inhibit growth of micro-organisms. It is recommended that culture media used contain additives that will neutralize these antimicrobial effects (30–32).

When tests are conducted, care must be taken to avoid contamination of samples, culture media and test equipment. Careful control and good aseptic technique will ensure that there is no inadvertent external contamination.

All methods utilized must be validated in order to ensure that test requirements are met. Dilution factors and recovery factors will be calculated from these validation studies and must be incorporated into the test calculations (33).

It may be possible to utilize rapid methods both for routine monitoring of the environment, equipment and materials and for testing of condoms. There will be interference, however, from chemicals and powder used in the manufacturing process. Therefore, an extensive validation programme will be required, particularly if used for condom Total Viable Counts.

When micro-organisms are isolated, some additional testing must be completed to ensure that the isolates are none of the prohibited organisms.

6.3.1 Routine monitoring

Routine monitoring procedures for the manufacturing environment and equipment may involve the following methods:

6.3.1.1 Surface testing

Testing of surfaces may be carried out using swabs, contact plates, contact slides or the rapid bioluminescence test.

Contact plates and slides are designed so that the surface of the solid media may be directly applied to the test surface and then incubated. Such tests are quick and easy to use, and results are directly related to the contact area. The disadvantage is that possibly not all

organisms will adhere to the media, and the plates or slides can be used only on flat surfaces (34, 35).

Determining bioburden by use of swabs is particularly useful for monitoring irregularly shaped equipment and difficult-to-access surfaces. Swabs are normally moistened in a liquid medium and then rubbed across a predetermined area. The swab may be directly applied to agar medium, or the swab may be immersed in liquid media, agitated to remove organisms and the TVC completed as for liquid testing. Direct application of the swab to the agar may not remove all organisms from the swab, whereas using an intermediate liquid stage will improve recovery of the organisms (34).

Bioluminescence testing (36, 37) is especially helpful for examining surface bioburden because results are rapidly obtained and will confirm whether cleaning procedures have been carried out correctly. This will enable a quick response to any problem areas identified, thereby preventing product contamination. The test method utilizes the reaction that occurs between bacterial adenosine tri-phosphate (ATP) and firefly luciferin/luciferase, resulting in emission of light.

6.3.1.2 Powders and liquids

Microbiological testing of powders and liquids can be achieved utilizing pour plates, spiral plating/spread plates, membrane filtration or the dilution droplet technique of Miles and Misra. In the case of water testing, the Most Probable Number (MPN) method can also be considered (30, 39–41).

A measured amount of powder can be dissolved in either a suitable solvent or in liquid culture media. Testing then proceeds as for liquid samples. Solvents and powder samples may have an inhibitory effect, however. Therefore, suitable dilutions or neutralizing agents should be used.

For the pour plate method samples of liquid are added to cooled molten agar and mixed, and plates are poured. When set, plates are incubated at appropriate temperatures and times, and colonies are counted.

Alternatively, a liquid sample may be directly applied to the agar surface, spread and then incubated. A smaller sample may be required in order to ensure that discrete colonies are cultured and so enable accurate counting. Samples may be delivered and spread using spiral plating equipment. The number of colonies can be related to the volume of suspension delivered, and the total count calculated.

For the Miles and Misra method, a series of dilutions are made from the samples. Then measured drops are placed on the agar surface. A minimum of five separated drops from each dilution is required. Plates are allowed to dry and are incubated, and counts are made.

When large sample volumes are available, particularly as in the case of water testing, the MPN method may be used. A range of dilutions is made in liquid growth medium. The range must be selected so that that the lowest dilutions do not show microbial growth. Tables have been produced, such as those by DeMan, using statistical assessments to determine the MPNs of organisms present in the initial sample.

In tests of chlorinated water, any residual antimicrobial effect of the chlorine may be neutralized with sodium thiosulphate.

The membrane filtration technique utilizes a membrane with a sub-micron pore size, large enough to enable large volumes to pass under pressure, but small enough to retain bacteria. The membrane is then placed onto an agar plate and incubated, and colonies are counted. This technique is particularly useful when there are low numbers of microbes or when there may be interfering substances in the liquid sample being tested.

6.3.1.3 Air sampling

Microbiological testing of air samples may be achieved by using settle plates or by active air sampling (42–44) during normal production. Agar plates are left exposed for a defined period of time in the area under test. They are then incubated and colonies are counted. Whyte has established that, for a bioburden of 100 cfu per m^3, a 90 mm diameter plate exposed for an hour will show 10 or 11 cfu (42).

Active sampling systems are also available (45, 46). Air is drawn into a device for a measured period of time. The micro-organisms are deposited onto agar, which is then incubated. Types of active air samplers available are slit

samplers, centrifugal samplers and impaction samplers. The cost of equipment and consumables may be high.

Membrane filtration may also be used. Air samples are passed through a sub-micron membrane filter pad for a designated time. The membrane is subsequently placed on an agar surface and then cultured to determine bacterial numbers present in the air sample.

In the case of all air sampling techniques, loss of viability may occur due to desiccation of the organisms. Hence, prolonged sampling times should be avoided.

6.3.1.4 Identification of micro-organisms

On completion of the primary testing, additional tests may be required to identify any organisms isolated, in order to confirm that none of the prohibited organisms are present. A gram stain, coagulase test and oxidase test will indicate whether species identification is required. Biochemical profiles may be used to identify organisms to species level.

6.3.1.5 Rapid test methods

There are rapid test methods available that may be considered for testing materials and product and for environmental testing. Rapid test technology obtains bioburden measurement by utilizing turbidity, bioluminescence, conductance or impedance (35, 36, 47, 48).

The advantage of using rapid methods for routine monitoring is that any increase in bioburden will be detected early, thus allowing action to be taken quickly to prevent continuing contamination of product.

The disadvantage of using rapid methods is that there may be interference from some samples that could nullify the use of these techniques. There must be extensive validation programmes, and initial outlay for equipment will be high. Dependant on the particular rapid test method used, ongoing supplies of consumables may also be expensive.

6.4 Guidance for controlling microbial contamination

Cleaning and sanitizing procedures and bioburden limits should be established for all manufacturing procedures and for environmental monitoring. A period of preliminary testing will determine baseline counts to enable routine test limits to be established.

When defined, the recommended limits must be at a level that will ensure product safety. After bioburden limits have been established, routine testing programmes can be installed for all stages of the manufacturing process.

6.4.1 Equipment

All manufacturing equipment, including tote bins, should be cleaned and sanitized at regular intervals to a written schedule. Cleaning should be microbiologically validated using surface test methods to ensure the efficacy of the cleaning procedures and to ensure that there is no cross-contamination onto product.

6.4.2 Environment

The manufacturing environment should be controlled to minimize microbial contamination and to ensure that pests such as rodents, birds and insects do not gain access to any manufacturing areas. This is especially important in the manufacturing stages after final drying. It is recommended that air sampling be regularly conducted, particularly in areas where the condoms are most vulnerable to microbial contamination, until product has been packaged.

6.4.3 Personnel

Microbial contamination may also arise from personnel. When standing still, a person will normally shed 100,000 particles per minute. Moving may increase this to more than one million particles per minute. These particles will contain microbes normally present on skin. Coughing, sneezing and touching product or equipment will also greatly add to the bioburden. Suitable protective clothing and gloved hands will give a measure of protection against this contamination. GMP training will help to enforce correct handling procedures to ensure that contact and cross-contamination between personnel and product are minimized.

6.4.4 Raw materials

All raw materials, including water and packaging materials, should be tested at regular intervals. Some

materials may have an inherent antimicrobial effect. If this has been confirmed, then monitoring may continue at a much reduced rate on these particular materials.

6.4.4.1 Water

Water is a major material that may be used during manufacturing, and so it must be controlled microbiologically and chemically.

Some incoming water supplies may contain extremely high bioburden levels, particularly in adverse local weather conditions such as very heavy rainfall or drought, and must be treated before storage. Treatment methods may include filtration, reverse osmosis (RO) (49, 50), ultraviolet irradiation (UV) or chemical treatment. It should be noted that chemical treatment may interfere with production processes and, depending on the chemicals used, may also cause adverse reactions in personnel.

After initial treatment the stored water should be kept under controlled conditions to minimize any further contamination or growth of micro-organisms.

Additional treatment of water may be necessary to produce deionised (DI) or softened water. Many micro-organisms find favourable conditions for growth on the DI resin beds and on RO membranes. It is essential, therefore, that the servicing protocols be followed rigorously to prevent colonization of the equipment with microbes.

If UV irradiation is used, monitoring of the system to confirm correct UV emission is essential in order to ensure that the UV lamps have not become partially obscured and therefore ineffective.

6.4.5 Dipping, stripping and drying

For some types of female condoms the sheath component is made by latex dipping processes similar to those used for male condoms. Dipping lines utilize large volumes of process water, which is sometimes recirculated at certain points of the process. It is recommended that there is no recirculation, but, if recirculation is necessary, it should be kept to a minimum and only recirculated for short periods of time or for a single re-use. Microbiological testing will confirm whether bioburden is being properly controlled under these circumstances.

All equipment should be regularly monitored, using surface testing methods that will confirm the efficacy of cleaning.

Handling of condoms should always be carried out with gloved hands. Whenever necessary, gloves should be either sanitized with antimicrobial wipes or else replaced. Any antimicrobial materials used for sanitizing must not interfere with process or product or adversely affect personnel.

It is recognized that heat and drying will inactivate many micro-organisms. Nevertheless, there are species that can survive such treatment, and, therefore, dryers should be cleaned and sanitized at intervals and included in the monitoring programme.

6.4.6 Slurry treatment

Where the sheath component is made by dipping it is usual practice to wash sheath in a slurry containing a powder, both to remove residual chemicals from the sheath and to leave a light coating of powder on the sheaths to prevent them sticking together during drying and subsequent storage. The slurry is a rich medium normally stored at a temperature that is optimal for microbial growth. Therefore, great care must be taken firstly in the cleaning and sanitizing of the mixing vessels, the reservoir tanks and the processors, and secondly in the choice of materials used to make the slurry. The water quality used in this process is particularly important. Ideally, slurry should not be recycled. Bioburden should be regularly monitored using TVC tests for liquids.

If necessary, consideration may be given to antimicrobial treatment of the slurry. Depending on the biocide used, it is possible that this may interfere with processing, cause skin reactions in operators and users and possibly be ineffective at the pH of the slurry. If a biocide is used, a full risk assessment must be completed.

6.4.7 Testing, lubrication and packaging

After drying, condoms will be subjected to 100% testing for freedom from holes. Depending upon the design of the condom different methods may be used. These include electronic (wet or dry), vacuum and gas leakage methods. After testing, the condoms are ready for lubrication and packaging. Bioburden of the

liquids, the water in the testing baths in the case of wet testing and the lubricant and the lubricating and packaging equipment should be frequently monitored.

These processes should be maintained in a controlled environment. Personnel in these manufacturing areas should wear protective clothing and gloves and maintain a high standard of GMP.

All lots of packaging material should be microbiologically tested before release for use.

Once the condoms are sealed in their individual containers, they are protected from contamination, and any further operations do not necessarily have to be carried out in controlled environments. If any further operations are carried out where un-packed condoms are stored, however, appropriate controls remain necessary.

References

1. The Council of the European Communities. *Council Directive 93/42/EEC of 14 June 1993 concerning medical devices***.** (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31993L0042:EN:HTML).
2. U.S. Department of Health and Human Services, Food and Drug Administration. Good manufacturing practice for medical devices. 21 CFR 820. 1 April 2009.
3. *ISO 13485:2003, 6.4, 7.5,2,1* Medical devices—quality management systems.
4. See Appendix 1, following, Method 1.
5. See Appendix 1, following, Method 2.
6. *German Pharmacopoeia* (DAB), 1996: V2.1.8.1 and V2.1.8.2.
7. *United States Pharmacopeia*, 31 (2008) Specified organisms test <62>.
8. *British Pharmacopoeia*, 2010 Volume IV, Appendix XVI, B1 and B2.
9. Arch G et al. Nasal carriage of *Staphylococcus aureus* and MRSA in the USA 2001–2002. *Annals of Family Medicine*, 2006, 4(2):132–137.
10. Chambers HF. The changing epidemiology of *Staphylococcus aureus. CDC Emerging Infectious Diseases*, 2001, 7(2):178–182.
11. Matsukawa M. *Staphylococcus aureus bacteriuria* and surgical site infection by MRSA. *International Journal of Antimicrobial Agents*, 2001, 17(4):327–330.
12. Muder RR et al. Isolation of *Staphylococcus* from the urinary tract. *Clinical Investigation of Disease*, 2006, 42(1):46–50.
13. Plourd D, McGregor J. Practical guide to diagnosing and treating vaginitis. *Medscape General Medicine*, 1999, 1(2). (http://www.virtual.unal.edu.co/cursos/medicina/2005100/archivos/Diagnosing%20and%20Treating%20Vaginitis.htm).
14. Genigeorgis CA. Present state of knowledge on staphylococcal intoxication. *International Journal of Food Microbiology*, 1989, 9(4):327–360.
15. Bennett RW. Staphylococcal enterotoxin and its rapid identification. *Journal of Food Protection*, 2005, 68(6):1264–1270.
16. Epidemiologic notes and reports: toxic-shock syndrome. *Morbidity and Mortality Weekly Report,* 1997 (June 6), 46(22):492–495.
17. Garbe PL et al. *Staphylococcus aureus* isolates from patients with non-menstrual toxic shock syndrome. *Journal of the American Medical Association*, 1985, 253(17):2538–2542.
18. Herzer CM. Toxic shock classically associated with prolonged tampon use; now other conditions have been related to this syndrome. *Journal of the American Board of Family Practitioners*, 2001, 14(2):131–136.
19. Bowler P. The anaerobic and aerobic microbiology of wounds. *Wounds*, 1998, 10(6):170–178.
20. Chen S et al. *Pseudomonas* infection. *eMedicine* (updated October 2009). (http://emedicine.medscape.com/article/970904-overview).
21. Blair KA. Evidence based management of UTI across the lifespan: current update. *Journal of Nurse Practitioners*, 2007, 3(9):629–632.
22. Urinary tract infections: contemporary management. *Urology Nurse*, 2008, 28(5):333–341.
23. Baerheim A. Generalised symptoms in adult women with acute uncomplicated lower urinary tract infection: an observational study. *Medscape General Medicine*, 2003, 5(3).
24. Centers for Disease Control and Prevention. *Escherichia coli* 0157:H7 infections in children. *Morbidity and Mortality Weekly Report*, 2008 (Jun 13), 57(23):625–628.
25. Rook J. Microbiological deterioration of vulcanised rubber. *Applied Environmental Microbiology*, 1955, 3(5):302–309.
26. Borel M et al. Degradation of natural rubber by *Fungi imperfecti. Agricultural Biology and Chemistry*, 1982; 46(4):877–881.
27. Lugauskas A et al. Physical and chemical aspects of long-term biodeterioration of some polymers. *Environmental Toxicology*, 2004, 19(4):318–28.
28. Fan SR et al. Clinical characteristics of vulvovaginal Candidiasis. *Journal of Obstetric and Gynaecological Research*, 2008, 3(4):561–566.
29. Reid G, Bruce A. Treating and preventing urogenital infections: yeast vaginitis. *Medscape General Medicine*, 2001, 3(4).
30. United States Pharmacopeia, 31 Microbiological tests <61>. May 2009
31. Tests for Microbial Enumeration, *British Pharmacopoeia,* 2010, Appendix XVI B2, Common neutralising agents for interfering substances, Table 2.6.12.3.
32. *ISO 14698–1* Cleanrooms and associated controlled environments—Biocontamination control—Part 1: General principles and methods.
33. Bioburden recovery validation. *Journal of Parenteral Science & Technology*, 1990, 44:324–331.
34. Favero MS. Microbiological sampling of surfaces. *Journal of Applied Bacteriology*, 1968, 31:336–343.
35. Whyte W. Methods for the efficiency of bacterial surface sampling. *Journal of Hospital Infection*, 1989, 13:33–41.

36. Venkateswaren K et al. ATP as a marker of viable micro-organisms in clean-room facilities. *Journal of Microbial Methods*, 2003, 52(3):367–377.
37. Hawronsky JH. Review: ATP—a universal hygiene monitor. *Trends in Food Science and Technology*, 1997, 6(3):79–84.
38. *ISO 11737–1* Sterilization of medical devices - Microbiological Methods. Determination of a population of micro-organisms on products. Annex B. Guidance on methods of determining bioburden.
39. Tests for Microbial Enumeration, *British Pharmacopoeia,* 2010, Appedix XVI B2, Most probable number method, Table 2.6.12-2.
40. Tests for Microbial Enumeration, *European Pharmacopoeia,* 2002, Suppl. 4.2: 133-612.
41. DeMan JC. Most Probable Number (MPN) tables. *European Journal for Applied Microbiology*, 1983, 17:301–305. (See also *British Pharmacopoeia* 2010, IV (Appendix XVIB):418.)
42. Whyte W et al. Airborne bacteria sampling. *Journal of Parenteral Science & Technology*, 1986, 40(5):182–187.
43. Andon BM. Active air versus passive air (settle plate) monitoring in routine environment monitoring programmes. *Journal of Pharmaceutical Science and Technology*, 2006, 60(6):350–355.
44. Whyte W. In support of settle plates. *Journal of Pharmaceutical Science and Technology*, 1996, 50(4):201–204.
45. Temprano G et al. Comparative study of airborne particles: assessment methods in microbiological environmental monitoring. *Journal of Pharmaceutical Science and Technology*, 2004, 58(4):215–221.
46. *BS EN 13098:2001*, Workplace atmosphere—guidelines for measurement of airborne micro-organisms and endotoxin.
47. Waweria M et al. Impedance microbiology: applications in food hygiene. *Journal of Food Protection*, 1999, 62(2):1488–1469.
48. Edmondson AS. New approaches to bioburden estimation. *Conference Proceedings. Bioburden in Medical Device and Surgical Dressing Manufacture*, March 1992:127–139.
49. Treating the water we drink. *Water Review Technical Brief*, 1994, 9(4) (http://www.wqa.org/sitelogic.cfm?ID=475).
50. Wright S et al. Microbial fouling of a reverse osmosis membrane municipal water treatment system. *Water Environment Research*, 2008, 80(8):703–707.

CHAPTER 7

Test Methods

CHAPTER 7: TEST METHODS

The test methods specified here are based on those published in *ISO 25841: 2011* but have been updated to include expected changes that will appear in future editions of the standard. The need to amend the test methods has arisen because of new products becoming available.

7.1 Testing for Bursting Volume and Pressure

Prior to testing, the condoms shall be preconditioned under controlled conditions at a temperature of (25±5)°C and a relative humidity of (55±15)% for (24±2) hours. Humidity control is not required for condoms with a sheath made from NR latex.

Any readily detachable internal retention feature shall be removed together with any insertion device, if appropriate. The external retention feature shall not be removed or adjusted unless this is essential to conduct the test, in which case it shall be removed by carefully cutting the sheath as close as possible to the retention feature.

The equipment used to conduct the test shall have a rod or mandrel with a smooth spherical or hemispherical head of 20 mm diameter to ensure that the condom is correctly mounted at the correct inflation length. The inflation length shall be specified by the manufacturer and be as far as is reasonably practicable at least 90% of the nominal length of the condom. The equipment shall also be fitted with a clamping device that is free from sharp edges and protrusions to secure the condom, and a means of measuring the volume of air within a maximum uncertainty of ±3% and the pressure with a maximum uncertainty of ±0.05 kPa. The clamping device should clamp the sheath close to the external retention feature. Alternatively, if the design of the condom permits, the external retention feature may be clamped directly. The clamping device shall be of sufficient diameter to prevent creasing and rucking of the condom. A minimum diameter of 50 mm is recommended.

Inflate the condoms with air at a flow rate of 24 to 30 litres/minute and record the inflation volume and pressure at burst. The test shall be conducted under controlled conditions [temperature (25±5)°C]. If a manufacturer specifies a different air flow rate, then full justification of the rate shall be given.

If a female condom exhibits any obvious leak before reaching the minimum bursting volume and/or pressure limits then discontinue the test, record the condom as leaking and treat it as a non-complier.

Measure and record the bursting volume, in litres rounded to the nearest 0.1 litre if the minimum burst volume limit is below 15 litres, and to the nearest 0.5 litre if the minimum burst volume limit is 15 litres or above. The bursting pressure, in kilopascals, shall be rounded to the nearest 0.05 kPa. Record as non-compliers all condoms bursting below the minimum bursting pressure and volume. If a condom is observed to leak after reaching the minimum bursting pressure and/or volume it should be counted as complying.

7.2 Testing for Freedom from Holes and Visible Defects

Use the testing apparatus described in *ISO 25841: 2011*. The equipment shall consist of a suitable rack or carousel with individual removable mounts for the condoms and a means of sealing the mounts to prevent water loss when they are removed from the rack or carousel. The mounts shall have a suitable diameter to prevent creasing and rucking of the condom. A diameter of 50 mm is recommended. A clamping ring might be required to retain the condom on the mount.

Inspect the individual packages for critical visible defects. The specified critical visible defects for the individual packages are:

- There shall be no empty packages.
- There shall be no evidence of lubricant leakage.
- The outside surface of the package shall be clean.
- There shall be no separation of the layers of laminate if laminated packaging materials are used.
- The package shall have a clearly visible notch or other device to enable easy opening without damaging the condom. Tearing from the notch shall not make

any important information printed on the package, including Lot number, Expiry Date or instruction for use, illegible.

Remove the female condoms from the individual package and inspect the condom for any visible defects. Remove any detachable internal retention feature and, if appropriate, insertion feature. Do not remove or adjust the external retention feature. Inspect the entire condom for visible defects and visible holes. If any visible hole or tear is noticed the condom shall be deemed non-complying and further testing of that condom shall be discontinued.

Calculate the maximum fill volume for the condom using the following equation:

$$MFV = 1.9lw^2/1000\pi$$

Where l is the nominal length of the condom in mm, w is the average nominal width of the condom and MFV is the maximum fill volume in cm^3.

The average nominal width is the average of the widths specified at 25%, 50% and 75% along the length of the condom from the closed end. See "determination of width" in Section 7.4 for further information.

Mount the condom on the test equipment. Add water (temperature between 10°C to 40°C) to the female condom until either the maximum fill volume is reached or the condom is full, whichever is less. With automated equipment, the fill volume may be determined and set in advance using a trial condom.

Allow the female condom to hang for a minimum of one minute and inspect for signs of leakage. Count any condoms exhibiting leakage as non-compliers.

Remove the condom and holder from the rack or carousel and seal the mount to prevent water loss. If no holes have been detected during hanging, roll the condom on coloured absorbent paper. Suspend the mount over the edge of the test table to maximize contact between the condom and paper. Use even and firm hand pressure. Complete at least one whole rotation in each direction. Examine the paper for signs of leakage. If wet patches appear on the paper, locate the source of the leak. Continue the rolling until the leak has been found or it is determined that the initial wet patch was introduced by a means other than a leak from the condom. Twist the female condom just below the midway position to create two sections and press the distal end onto the paper to ensure all surfaces are tested. Examine the paper for signs of leakage. Record all results and mark the location of any leaks found on the condom.

7.3 Testing for Package Seal Integrity

Given the wide range of packaging options that are possible for female condoms, it is not possible to specify a test method that is suitable for all package types. The following test method is based on that used for male latex condoms and is recommended as the method that should be used by default. It may be necessary to modify the pressure to adapt the tests for some packaging types. If the method is changed or another method is used, then manufacturers shall provide full details of the test method. The test method shall provide assurance that the pack seal is adequate to protect the condom and prevent leakage of any lubricant.

Submerge the individual packages in water contained in a suitable vessel to allow a vacuum to be applied above the surface of the water. The uppermost surface of the packages shall be covered by not less than 25 mm of water. A dye may be added to the water to make leakage of water into the packages easier to detect. Two or more packages may be tested at the same time, provided that they are placed in such a manner that all parts of every package under test can be observed for leakage during the test. Evacuate the chamber to an absolute pressure of (20±5)° kPa. Observe the packages for leakage in the form of a steady stream of bubbles. Isolated bubbles caused by entrapped air are not considered to be leaks. Hold the vacuum for 1 minute. Release the vacuum, open each package and examine the packages for the presence of water inside. Packages exhibiting a continuing stream of bubbles or found to contain water when opened after testing are non-compliant.

7.4 Determining the Width of the Female Condom

Remove any detachable internal retention device and, if appropriate, insertion device from the condom. If necessary, the external retention feature may be

removed to facilitate measurement and the lubricant may be removed using a suitable method such as wiping. Lay the condom flat over the edge of a calibrated steel ruler with a scale divided into millimetres. Ensure that the ruler is perpendicular to the female condom's axis, allowing it to hang freely over the ruler.

Measure the width of the condom to the nearest 1.0 mm at points located 25%, 50% and 75% along the length of the condom measured from the closed end. Use the nominal length of the condom to determine the measuring points. Female condoms subjected to this test may also be used for determination of length.

The average of all three nominal width requirements shall be used to calculate the maximum fill volume for freedom from holes testing.

7.5 Determining the Length of the Female Condom

Remove any detachable internal retention device and, if appropriate, insertion device from the condom. The external retention feature shall not be removed or adjusted. To facilitate measurement the lubricant may be removed using a suitable method such as wiping.

Place the condom over a suitable mandrel with a spherical or hemispherical head of diameter 25 mm and let it hang freely, stretched only by its own weight. The mandrel shall have a scale divided into millimetres. The length scale on the mandrel shall begin with zero at the tip of the closed end of the female condom. Measure, to the nearest 1 mm, the length of the condom on the scale at the open end. If the measurement varies along the circumference, use the shortest measurement. Female condoms subjected to this test may also be used for determination of width.

7.6 Determining the Thickness of the Female Condom

Remove any internal retention feature from the female condom and, if appropriate, any insertion feature. Cut the condom open longitudinally using scissors or a suitable blade and if necessary remove the external retention feature. Remove lubricants either by washing with a suitable solvent, such as propan-2-ol or by wiping. Powders should not be added since these could affect the thickness measurement.

Measure the thickness of the condom at points located 25%, 50% and 75% along the length of the condom from the closed end, using a flat foot micrometer (dial or digital type) with graduations not larger than 0.001mm having a foot pressure (22±5) kPa. Use the nominal length of the condom to determine the measuring locations. At each location make three measurements of the thickness at equidistant points around the circumference of the condom.

7.7 Determining the Quantity of Lubricant (Including Powder)

The lubricant mass is determined by the difference between the mass of the female condom (and any insertion and retention features) and individual packages before and after washing off the lubricant using a solvent. If a sponge internal retention feature is used, this could affect the accuracy and reliability of the test method. Manufacturers using sponge internal retention features should be aware of this potential issue when specifying the lubricant quantity. A balance accurate to 1 mg shall be used. Propan-2-ol (laboratory reagent grade) is the preferred solvent but manufacturers may specify alternative solvents if necessary, subject to satisfactory validation studies. An ultrasonic bath may be used to facilitate washing the condom, in which case the immersion time in the solvent shall be between 2 and 10 minutes. Any insertion and retention features should be removed if possible and washed separately. After washing the condom, individual packages and any insertion and retention features shall be dried at a temperature not exceeding 50°C to constant mass (±10 mg). Washing and drying shall be repeated until a constant mass (±10 mg) is achieved.

CHAPTER 8

Guidelines on the Assessment of Odour

CHAPTER 8: GUIDELINES ON THE ASSESSMENT OF ODOUR

Odour can be assessed by a panel. There are certain guidelines that apply when assessing the odour of condoms. Following these guidelines should help provide a more consistent level of odour assessment. Recommendations include:

- The panel should consist of between 6 and 10 individuals.
- Panellists should not wear perfume, smoke or be exposed to strong odours on assessment days.
- Panellists should be trained and may be required to undergo periodic assessments using appropriate reference odours and samples.
- Odour assessments should not be carried out in a factory or other environments where strong background odours may be present.
- Odour assessments should be done blind and in a random order, without the panellists being aware of the source of the samples.
- Adequate time should be allowed between samples for the panellists' olfactory sense to recover.
- To prevent fatigue, the number of samples evaluated in one session should be limited.
- An appropriate grading system should be developed to quantify the intensity, acceptability and type of odour. For example, odour intensity can be rated on a balanced scale from 0 (no perceptible odour) to 6 (extremely strong odour).
- Control samples should be included to allow comparisons to be made between different panels and different sessions.
- The time delay between opening a condom pack and smelling the condom can be critical. This time should be standardized.

It is recommended that manufacturers retain samples for reference purposes and to help resolve disputes. Retained samples should be kept for the duration of the shelf life of the product.

PART TWO
WHO/UNFPA FEMALE CONDOM PREQUALIFICATION SCHEME: FEMALE CONDOM PREQUALIFICATION, TECHNICAL REVIEW PROCESS, PRODUCT DOSSIER (PD) AND SITE MASTER FILE SUMMARY (SMF)

CHAPTER 9

Female Condom Prequalification

PART TWO

CHAPTER 9: FEMALE CONDOM PREQUALIFICATION

9.1 Introduction

This chapter sets out UNFPA and WHO's requirements regarding prequalification, specifications and quality of female condoms.

UNFPA is committed to purchasing products from factories which have been pre-qualified according to its prequalification scheme. The scheme is intended for products that are either already on the market or are ready for market approval. In order to be granted prequalification, a manufacturer must:

1. Apply to UNFPA for prequalification, in response to invitations that are published annually

2. Supply adequate information in the format required, in particular information about the product in the Product Dossier and the clinical data, and information about the factory in the Site Master File Summary.

3. Satisfy WHO and UNFPA, through the technical review process, that the product and the production process are adequately documented, and that the safety and efficacy of the product have been demonstrated.

4. Be approved on the basis of a factory inspection by UNFPA-appointed inspectors. Associated with this inspection is an independent test of the factory's product.

5. Have a product which complies with the *WHO/UNFPA Female Condom Generic Specification*

6. Have a factory capable of producing product in commercial quantities, which is certified to comply with *ISO 13485*. (Manufacturers who are in the process of obtaining certification may apply, but final prequalification will be subject to *ISO 13485* certification)

The manufacturers on the list of prequalified female condom manufacturing sites offer products that, as part of the WHO/UNFPA Prequalification Scheme, have been found to be acceptable, in principle, for procurement by United Nations agencies.

The aim of the WHO/UNFPA Prequalification Scheme is to determine whether the applicant/manufacturer meets the minimum requirements detailed in the relevant ISO standards and the *WHO/UNFPA Female Condom Generic Specification* in respect of product quality and safety, production and quality management, regulatory approvals and capacity of production.

Each female condom is a unique product, and the prequalification process therefore involves a detailed technical review of the product design, safety and efficacy.

WHO/RHR and UNFPA have agreed to integrate the Female Condom Prequalification and Technical Review Processes. This means that for each product, when the Technical Review Process has been successfully completed and manufacturing sites have been successfully inspected, the female condom manufacturing site will be fully prequalified.

The manufacturer will not need to go through a prequalification process for another three years unless there are major changes in the manufacturing process and/or problems associated with quality assurance of the product.

Continuation of the prequalification at the end of the period will depend on a satisfactory resubmissions of documentation and a re-inspection of the factory, but the technical review process will not be repeated unless there are changes to the design, or important new clinical information becomes available.

The WHO/UNFPA Prequalification Scheme and Female Condom Technical Review Process involve the following key activities:

- publication of the invitation to submit an EOI;
- submission of an EOI by the applicant;
- evaluation of documents submitted in response to the EOI;
- manufacturing site inspection;
- product testing;

- review of the clinical investigation for the safety and efficacy of the product;
- review of testing and inspection reports to assess the acceptability of each applicant;
- publication and periodic updating of a list of prequalified products and manufacturing sites on WHO and UNFPA web sites.

The steps in the prequalification process are described below.

9.2 Elements of the Prequalification Process

9.2.1 Invitation for Expression of Interest

Invitations to interested parties to submit an Expression of Interest (EOI) are published at regular intervals on the web sites of the United Nations Global Market Place (UNGM) (http://www.ungm.org), UNFPA (http://www.unfpa.org/public/) and WHO (http://www.who.int/prequal/) and possibly through other media, such as the international press.

Each invitation will be open and transparent, inviting all relevant parties to submit EOIs for the product listed. The applicant/manufacturer will be given a specified period to submit the responses from the time of publication of the advertisement.

In situations of high public health concern, as determined by WHO, UNFPA may also directly invite relevant parties to submit their product for assessment by UNFPA under this procedure without publication of an invitation for EOIs.

Manufacturers/applicants should submit their EOIs to the UNFPA focal point with the relevant information requested in the invitation. UNFPA will receive and record the EOI from each manufacturer and issue an acknowledgement of receipt.

The official language of the Prequalification Scheme is English. All documents submitted as part of an application for prequalification will be in English. If the original of any required document is not in English, the manufacturer must submit a copy of the original plus a certified copy of the translation into English. A manufacturer/applicant must also provide an electronic version of this material. The electronic must be in addition to, and not in place of, the hard copy of the documentation.

All correspondence between UNFPA and the applicant will be in English. All reports on the inspections issued by the inspectors and by UNFPA will be in English.

The Prequalification Scheme does not apply to agents, distributors or suppliers engaged only with testing, lubricating and packaging.

9.2.2 Data and information to be submitted

Interested applicants must submit to the UNFPA focal person the following documentation in hard copy:

- covering letter expressing interest in participating in the UNFPA prequalification procedure and confirming that the information submitted in the Product Dossier and Site Master File Summary is complete and correct;
- Product Dossier, in the format specified in the WHO/UNFPA guidance documents for submitting product data and information;
- clinical information to support the safety and efficacy of the device, or to establish substantial equivalence to an existing device;
- product samples as examples of products produced;
- a Site Master File Summary for each manufacturing site listed in the Product Dossier, in the format specified in the WHO/UNFPA guidance documents for submitting a Site Master File Summary;
- copies of all current certifications/accreditations, all manufacturing licences/registrations held, and a copy of the company registration;
- copies of certificates and relevant documentation as applicable in the country where the site is located, such as: the certificate stating the principal place of incorporation (for applicants that are corporations), specific certification/licences required in the country for manufacturing or exporting, and other legal documents such as Trading Certificates;

- contact information of bankers, including all appropriate banking account references and codes.

9.2.3 Process for submitting documentation

- Hard copies and electronic versions of all documents must be submitted with the letter of application.
- Documentation, in English, should be submitted by courier or registered mail.
- The letter of application must clearly state: **"Request for prequalification for female condoms"**.
- Applications for prequalification with supporting documents should be submitted in sealed envelopes not later than the date specified in the invitation for EOIs, clearly marked

  "Application to prequalify for female condoms"
  and delivered to:
  Attention: *[insert name of UNFPA representative]*
  United Nations Population Fund
  Midtermolen 3, P.O. Box 2530
  DK 2100 Copenhagen 0, Denmark
  Tel: +45 35 46 7162, Fax: +45 35 46 7018

- The back of the envelope should display the information shown in the box below.

Invitation for Expression of Interest

Managed by: UNFPA Procurement Services Branch
Copenhagen Denmark

Invitation for Prequalification
UNFPA Procurement Services Branch
Midtermolen 3, PO BOX 2530
DK 2100, Copenhagen 0
Denmark

UNFPA will receive and record the EOI from each applicant/manufacturer and issue an acknowledgement of receipt.

UNFPA reserves the right to accept or reject late applications.

9.2.4 The Technical Review Process

The Technical Review Process will follow specific criteria formulated by the Female Condom Technical Review Committee, taking into account the international standard for female condoms, *ISO 25841:2011* and the requirements specified in the *WHO/UNFPA Female Condom Generic Specification*. The review will cover issues related to:

- Design - risk assessment
- Product specification
- Manufacturing and packaging process validation
- Product and process validation
- Clinical investigation for safety and efficacy.

It is understood that completing this process may take time depending on whether or not a manufacturer has any ongoing clinical investigation studies. The duration of the study and expected time frame to review and review the report will be factored into the review process.

At the end of this initial Technical Review Process each manufacturer will be issued with a confidential report that summarizes the conclusions and recommendations of the experts. If there is any remedial action required by the manufacturer in response to issues raised by the technical experts, the manufacturer will be expected to respond within a specified timeframe. If no response is received then the review process will be discontinued.

Once the review of the manufacturing process and product quality, safety and effectiveness have been satisfactorily completed, UNFPA will schedule a factory assessment.

Please note that a product cannot be prequalified unless it has satisfactorily completed each component of the Technical Review Process including:

- Satisfactory review of the Product Dossier and Site Master File
- Satisfactory review of the clinical investigation of the safety and efficacy of the product

- Satisfactory factory site inspection
- Satisfactory independent tests of product samples.

It is therefore essential that manufacturers review the following guidelines to ensure they provide, to the fullest extent possible, the information requested by the Female Condom Technical Review Committee.

Members of the Female Condom Technical Review Committee are selected based on their technical expertise and experience in the fields of manufacturing, product process validation and quality assurance, product quality testing and testing procedures, and clinical research and analysis.

Each member of the team will have to declare and sign a Conflict of Interest Form and be subject to the Confidentiality Agreement as detailed in Annex 1 of this paper.

It should be noted that the aim of the WHO/UNFPA Prequalification Scheme is to determine whether the applicant/manufacturer meets the minimum requirements detailed in the relevant ISO standards[5] and the *WHO/UNFPA Female Condom Technical Review Process* in respect of product quality and safety, production and quality management, regulatory approvals and capacity of production.

Periodic reassessment of the prequalification status of the product and manufacturing site will be undertaken at intervals of every three years or less.

9.2.5 Submission of Technical Information

This section is intended to provide guidance on the format and content of a prequalification application for female condoms and their manufacturing sites.

The text is intended to be explanatory and illustrative only. The content of the following sections includes relevant information described in existing guidelines of WHO and the ISO.

[5] ISO documents are available from: International Organization for Standardization, ISO Secretariat, 1, ch. de la Voie-Creuse, CP 56, 1211 Geneva 20, Switzerland; http://www.standardsinfo.net/

Each section, including attachments, should be clearly referenced in the table of contents and in the documents. The table of contents should list the sections, sub-sections and titles in numerical order with the corresponding page numbers. All pages should be consecutively numbered throughout the documents.

During the review, particular attention will be focused on the manufacturer's specification for the products and the justification used by the manufacturer to set the specification requirements, particularly in respect of the minimum values for bursting pressure and volume. Manufacturers are requested to provide full supporting data to justify the specification, including copies of the original test results where appropriate.

The technical information must include the following documents:

1. Full details of the clinical investigations carried out on the device (which should be included in the Product Dossier)
2. The Product Dossier
3. The Site Master File Summary

These documents are described below.

9.3 Clinical Investigation (to be included in the Product Dossier)

The manufacturer must demonstrate the acceptability, safety and efficacy of a new female condom design by conducting appropriate clinical investigations. A full report of the studies, including participant selection and characteristics, study protocol, drop-out rate with reasons, the acceptability of the product, the rates of all failure modes and a statistical analysis of the results must be submitted with the application. Depending on the level of similarity of the product to existing, pre-qualified products, the study may be a functionality study or a contraceptive efficacy study (see below). Prostrate-specific antigen (PSA) is being investigated as a marker for semen exposure in condoms studies and may provide an alternative method of assessing condom efficacy. In the case of a contraceptive efficacy study, details about when each pregnancy was diagnosed must be included in the report.

All clinical studies must have been designed and supervised by people with appropriate qualifications in medicine and biostatistics. The study protocol must have been reviewed and approved by an ethics committee acceptable to UNFPA/WHO. Studies must also comply with local regulatory and legal requirements. The CV of the principal investigator must be submitted with the study report.

Where a manufacturer can demonstrate that both the design and materials of a new female condom are essentially identical to one which has previously been prequalified by WHO/UNFPA, the requirements for a functionality study may be waived. In this case, the manufacturer must submit detailed material and design specifications for both the new product and the marketed product against which equivalence is being claimed.

Depending upon the design of the female condom, acceptability, safety and efficacy can be demonstrated clinically in one of the following ways:

9.3.1 Contraceptive Efficacy Study

For novel designs of female condoms that cannot be considered equivalent to an existing marketed product that has an established efficacy rate, a contraceptive efficacy study is required. The study design shall be adequate to allow the 6-month pregnancy rate to be computed using life table methods with at least 100 women years of data (e.g. 200 women completing 6 months). The 12-month pregnancy rate may be extrapolated from the 6-month data, providing it is made clear that the value obtained is an estimate and the method of extrapolation is documented. The study should also determine the acceptability of the product and the rates of all failure modes as detailed in Section 1.3.2.

9.3.2 Functionality study against an equivalent marketed product

If the design and specifications of a new female condom are sufficiently similar to those of a marketed device, and that marketed device has an efficacy rate established from a clinical effectiveness study, then the manufacturer may be able to establish the acceptability and clinical effectiveness of the new female condom on the basis of a functionality study, comparing the frequency of failures. Known female condom failure modes are described in the *Generic Specification*. If there is no suitable marketed device available with an established pregnancy rate, then the manufacturer may use a device that has been evaluated directly against a device with an established pregnancy rate and has been shown to be non-inferior to that device, using the definition of non-inferiority given below. To claim exemption the following requirements shall be met.

The manufacturer shall conduct a risk analysis using, for example, the procedures described in *ISO 14971* to establish the following:

1. that the new female condom design and specifications are sufficiently similar to those of the marketed female condom to lead to the expectation that the clinical efficacy of the two devices will be similar. When conducting the risk analysis, the following issues shall be included in the assessment: the differences in dimensions, materials, insertion and retention features or methods, and proposed labelling;

2. that the design of the new female condom does not introduce any potentially new failure modes over and above those identified and quantified for the marketed female condom.

The manufacturer shall conduct a randomized controlled clinical investigation comparing the new female condom to the marketed female condom. The marketed female condom used in the study shall be shown to meet the performance requirements described in Section 2.2 of the *Generic Specification*, i.e;

1. the total clinical failure rate of the new female condom shall be shown to be non-inferior to the total clinical failure rate of the marketed female condom;

2. the upper bound of the one-sided 95% confidence interval for the new female condom total clinical failure rate, minus the marketed female condom total clinical failure rate, shall be less than or equal to 3%

3. the bound shall be calculated using a method that accounts for the unique characteristics of data, such as (1) potential clustering of failures within certain couples (2) possibly low event rates.

To confirm the validity of the study protocol and study population, the total clinical failure rates for the

marketed device used in the study shall be equal to or exceed 1%. Based on functionality studies on marketed female condoms, the total clinical failure rate is expected to be at least 1%. Values lower than this are not expected if the study has been completed correctly in a typical population for which the female condom is intended.

9.4 Preparation of a Product Dossier

This document is intended to provide guidance on the format and content of a prequalification application for a specific female condom design manufactured at specific manufacturing sites.

The text in this section is intended to be explanatory and illustrative only.

Each section, including attachments, should be clearly referenced in the table of contents and in the product file. The table of contents should list the sections, sub-sections and titles in numerical order with the corresponding page numbers. All pages should be consecutively numbered throughout the document.

9.4.1 Characteristics of the products

Provide the following information on the design of each female condom produced at this manufacturing site:

- A sketch of the assembled product;
- Dimensioned, labelled, drawings of each component, including length, widths at relevant points;
- Descriptions of surface textures and any colour, flavour, finishing powders and lubricants used.

9.4.2 Local, country & regional regulatory product approvals

Provide copies of relevant certificates related to the product including local product/marketing approvals, CE marking, etc.

List the countries in which:

- the products have been registered and granted a marketing authorization;
- an application for marketing authorization is currently pending;
- any marketing approvals that have been revoked within the last five years.

9.4.3 Raw materials

List all raw materials, including lubricants. Use the following table as an example.

Add additional explanatory information if required and modify the table as necessary.

9.4.4 Supplier(s)

State the name, street address and country of each facility where the primary raw material for constructing the sheath component of the device is obtained.

State the name and address of the supplier of all other significant components.

Table 12. Primary materials of construction and compounding ingredients (if relevant). Include materials used for the insertion and retention features.

Chemical name	Brand name	Manufacturer	Function
Other			
Chemical name	**Brand name**	**Manufacturer**	**Function**

9.4.5 Sites of manufacture

State the name and street address of each facility where any aspect of manufacture occurs, including production, packaging and quality control. Indicate the activity performed at each site.

Include the names and addresses of any off-site contractors that undertake the manufacture of any key primary components of the female condom, including the sheath, film materials for the sheath and the external and internal retention features and, if appropriate, insertion device.

Provide telephone number(s), fax number(s) and e-mail address(es) for each manufacturing site associated with condom production.

9.4.6 Risk management of the product

Provide the Risk Management Plan for the product according to *ISO 14971* and *ISO 13485*.

9.4.7 Specifications for the finished products

Provide a full specification for the finished product. The specification should be consistent with the requirements specified in the *WHO/UNFPA Female Condom Generic Specification*. Include a copy of the data sheet referred to in Section 1.5 of the *WHO/UNFPA Female Condom Generic Specification.*

Answer the following questions:

- Do the female condoms that you currently manufacture meet the requirements of *ISO 25841* and/or *WHO/UNFPA Female Condom Generic Specifications*?
- If not, describe the differences between the condoms you currently manufacture and condoms that will be produced to meet the *ISO 25841* and/or *WHO/UNFPA Female Condom Generic Specification*

9.4.8 Evidence of compliance with WHO/UNFPA's General Requirements

Provide the following information:

- verification that a clinical assessment has been carried out in accordance with *ISO- 25841* and/or *WHO/UNFPA Female Condom Generic Specification* (If the clinical assessment is included in the Product Dossier, that assessment provides the verification.);
- verification that appropriate viral barrier studies have been completed;
- summary reports of biocompatibility evaluations in accordance with *ISO 10993* Sections 1, 5 and 10, including, if available, toxicologists' reports;
- if the product is made from NR latex, confirmation whether or not, protein levels on finished products are periodically monitored; if so, provide summary data as appropriate;
- confirmation whether or not bioburden levels on finished products are periodically monitored; if so, provide summary data. If bioburden levels are not monitored, state whether or not you are prepared to do so.

9.4.9 Stability data

Data supporting the stated shelf life of the product shall be presented. This should include real-time data from stability studies conducted at 30°C (range 28°C to 35°C).

If results from real-time studies are not available, manufacturers must initiate the studies immediately.

Pending the outcome of the real-time studies, manufacturers may provide data on validated accelerated stability studies at elevated temperatures together with the method validation report in full. Nonetheless, a real-time study must be in progress by the time the application for prequalification is lodged with UNFPA.

9.4.10 Labelling and additional information

Provide examples of the labelling that will be used for the:

- individual packages;
- inner boxes;
- exterior shipping cartons.

Provide an example of the labelling and additional information that will be supplied with the condoms, including the instructions for use. All labelling and additional information, including the instructions for use, shall comply with the requirements specified in the *ISO/ 25841* and/or the *WHO/UNFPA Female Condom Generic Specification.* Manufacturers that do not provide labelling and additional information in accordance with the above requirements at the time of prequalification may supply draft copy or print proofs for review. Actual examples of printed individual packaging, if necessary for current products, should be supplied to allow assessment of the quality of the print used for Lot number, manufacturing date and expiry date.

Manufacturers should note that requirements for labelling and additional information may be subject to specific contractual requirements, depending upon the requirements of the purchaser.

9.5 Samples

Provide samples of the condoms (at least 10 packaged condoms of each design) produced at this manufacturing site.

9.6 Preparation of a Site Master File Summary

A separate Site Master File (SMF) Summary for each manufacturing site must be prepared and sent with the letter of application.

An SMF Summary should be succinct and, as far as possible, not exceed 25 A4-sized pages.

An SMF Summary is a document prepared by the manufacturer from the documented quality management system. It should include the following:

- specific factual information about the manufacturing operations;
- quality assurance procedures carried out at the named site;
- description of any closely integrated operations at adjacent or nearby buildings.

If only part of a manufacturing operation is carried out on the site, the SMF Summary needs to describe only the operations carried out at that site.

A Site Master File must be presented for the site manufacturing the sheath component and the site assembling and testing the final products, if these operations are done in different locations.

The layout of the SMF Summary should include a title page and table of contents.

Clauses 5.1 through 5.13, which follow, describe the required contents of the SMF Summary.

9.6.1 General information

1. Name and exact address of the site, including fax number, e-mail, and 24-hour telephone numbers;
2. brief information about the corporate structure, including information about holding or parent company, affiliates, subsidiaries and partners;
3. total manufacturing capacity of the site, including:
   - primary manufacturing capacity
   - electronic (or equivalent) testing capacity
   - packaging capacity;
4. length of time manufacturing female and, if appropriate, male condoms at this manufacturing site. Length of time manufacturing condoms at other sites;
5. what other, if any, manufacturing activities take place at this site;
6. summary of type of condoms manufactured at this site (include details of any male condoms manufactured).

9.6.2 Manufacturing certifications

A list and copies of all relevant certifications, including *ISO 13485* and, if applicable, *ISO 9000* series.

9.6.3 Personnel

1. total number of persons employed in female condom manufacturing;

2. numbers employed, divided into the following categories: senior management, production management, quality assurance, quality control, maintenance, and administration;

3. an organization chart showing all management and supervisory positions, including the arrangements for quality assurance and quality control;

4. the qualifications, experience and responsibilities of key personnel, senior managers, and directors, quality assurance supervisors, production manager/directors and laboratory manager/director, if appropriate;

5. a summary of policy and procedure for health requirements for personnel engaged in production;

6. a brief description of the staff training scheme and the structure and maintenance of training records;

7. a brief summary of personnel hygiene and safety requirements, including protective clothing;

8. confirmation that there is a written health and safety policy and a summary of the key components of this policy;

9. information on the use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis.

9.6.4 Premises and equipment

1. a simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings not required);

2. the nature of construction of the building and finishes of floors, ceilings and walls;

3. a brief description of ventilation systems, including steps taken to prevent product contamination and excessive exposure of staff to ammonia and dust (if appropriate);

4. a brief description of the areas for handling compounding ingredients (if appropriate);

5. a brief description of procedures and arrangements for storing quarantined materials, work in progress and finished products;

6. a description of water systems, including sanitation and effluent treatment; schematic drawings of the systems are desirable;

7. a summary of planned preventive maintenance programmes for manufacturing and testing equipment;

8. a brief description of major equipment used in production and control laboratories, including major computer systems used for production and quality control (a full list of equipment is not required);

9. qualification and calibration arrangements, including the recording system, for computerized systems validation, and external calibration laboratory accreditations for those laboratories providing traceable calibrations;

10. availability of written specifications and procedures for cleaning manufacturing areas and equipment;

11. a brief summary of the procedures for monitoring and controlling microbiological contamination in production areas and of the product and procedures for controlling the purity of the air and water.

9.6.5 Documentation

Arrangements for the preparation, revision and distribution of all necessary management system documentation.

9.6.6 Records

Arrangements for safe storage, access and retrieval of records.

9.6.7 Production

1. A brief description of production operations, using, wherever possible, flow sheets and charts and specifying important parameters; include brief details of the scale of production; identify equipment by type (e.g. dipping machines, extruders, welding

machines, electronic (or equivalent) testing machines); and state working capacity where relevant;

2. summary of the procedures for the handling of starting materials, work in progress, packaging materials and finished products, including product release and storage;

3. a brief description of the general policy for process validation and a summary of the validation plan.

9.6.8 Risk management plan

Provide a summary of the risk management assessment undertaken in accordance with *ISO 14971* of the manufacturing process.

9.6.9 Quality control

1. brief details of the quality control system and of the activities of the quality control department;

2. brief details of the sampling and testing requirements for any bought-in components including, if applicable, the retention features and any insertion device;

3. brief details of the sampling and testing procedures for in-process testing and final product release, including pass/fail criteria.

9.6.10 Distribution, complaints and product recall

1. a brief description of procedures and arrangements for Lot traceability;

2. a brief description of the arrangements for managing and recording complaints and product recalls.

9.6.11 Self-inspection (internal audits)

A short description of the self-inspection (internal audit) system.

9.6.12 Corrective and preventative action

A brief description of procedures and arrangements for identifying the need for and implementation of corrective and preventative action.

9.6.13 Design and development

A brief description of procedures used to control design and development.

9.7 Scope of manufacturing site inspections

The objective of the manufacturing site inspection is to:

- determine if female condoms are competently and consistently manufactured to the required specifications;

- verify whether the production processes occur as described in the Product Dossier and Site Master File Summary.

UNFPA will plan and coordinate inspections at manufacturing sites to assess the manufacturing process, the product and the quality management systems for compliance with requirements specified in the *WHO/UNFPA Female Condom Generic Specification* and relevant current editions of international standards including:

- *ISO 25841. Female Condoms— Requirements and Test Methods*.

- *ISO 13485. Medical Devices—Quality Management Systems: Requirements for Regulatory Purposes*.

- *ISO 14971. Medical Devices—Application of Risk Management to Medical Devices*.

- *ISO 10993–1. Biological Evaluation of Medical Devices. Part 1. Evaluation and Testing*.

- *ISO 10993–5. Biological Evaluation of Medical Devices. Part 5: Tests for in vitro Cytotoxicity*.

- *ISO 10993–10. Biological Evaluation of Medical Devices. Part 10: Tests for Irritation and Sensitization*.

- *ISO/IEC 17025. General Requirements for the Competence of Testing and Calibration Laboratories*.

The inspection will be performed by a team of inspectors, consisting of experts appointed by UNFPA. The inspectors must have documented qualifications; expertise in condom manufacturing, auditing and quality management systems; and specific experience with inspecting condom manufacturing sites. The inspectors must comply with the confidentiality and conflict-of-interest rules of UNFPA.

The following checklist is an indicative guide for the manufacturing sites inspection and details the key areas to be reviewed during the inspection. Condom manufacturing sites vary widely in size, scale, manufacturing equipment and processes employed.

Inspectors will use their expertise and knowledge of condom manufacturing to tailor the inspection checklist to the specific situation presented at each inspection site.

Table 13. Inspection checklist	
Areas under inspection	**Comments**
1. General company detail	
Address and contact detail	
Condom designs manufactured	
Independent certifications of systems and products, including regulatory approvals	
Markets served	
Operating hours and shifts	
2. Management team and key staff	
Detail of management and key staff, including authority and responsibilities	
Organizational chart	
Out-of-office hours, responsibilities and authority	
3. Human resources	
Staff numbers and areas of deployment	
Staff selection, induction and training systems	
Records	
4. Production capacities throughout the operation	
Number and type of machines	
Quoted output and yields	
Actual sales for past three years	
5. Raw materials	
Raw materials selection, storage and quality	
Vendor evaluation/validation	
Security of material supplies	
Quality assurance and storage procedures	
Status indication, labelling and documentation	
Environment	
6. Preparation of dispersions and compounds (where applicable)	
Process	
Adequacy of equipment	
Adequacy of staff	
Testing and controls	
Documentation and labelling	
Environment	

Table 13. Inspection checklist (continued)	
Areas under inspection	**Comments**
7. Latex pre-vulcanization and maturation process and controls (where applicable)	
Process	
Adequacy of equipment	
Adequacy of staff	
Testing and controls	
Documentation and labelling	
Equipment and process validation	
Environment	
8. Manufacturing of sheath (including assembly if applicable)	
Materials used	
Process	
Adequacy of equipment	
Adequacy of staff	
Testing and controls	
Documentation and labelling	
Equipment and process validation	
Environment	
9. Testing	
Process	
Adequacy of equipment	
Adequacy of staff	
Testing and controls	
Documentation and labelling	
Equipment and process validation	
Environment	
10. Packaging (including assembly if applicable)	
Materials used	
Process	
Adequacy of equipment	
Adequacy of staff	
Testing and controls	
Documentation and labelling	
Lot coding	
Equipment and process validation	
Environment	
11. Consumer/customer packing	
Materials used	
Process	
Adequacy of equipment	
Adequacy of staff	
Testing and controls	

Table 13. Inspection checklist (continued)	
Areas under inspection	**Comments**
Documentation and labelling	
Understanding of Lot coding	
Environment	
12. Warehousing	
Adequacy	
Segregation	
Labelling	
Stock control/rotation	
Presence of aged or non-conforming goods	
13. Distribution procedures	
Agreements	
Records	
14. Quality control plan	
Detail of product testing throughout each stage of the manufacturing process, including Lot release	
Process yields throughout each stage of manufacture	
15. Provisions for storage and control of work in progress	
Segregation	
Labelling	
Status identification	
Environment	
Security	
16. Outgoing product quality	
Review of process averages	
Verification of complying product and process capabilities	
17. Quality system and documentation	
Quality policy and objectives	
Quality manual	
Documentation and structure	
SOPs and work instructions	
Documented versus actual practices	
Document control	
Process approach	
Records	
Contract review	
Risk review assessment and management	
Complaints, recall, vigilance and advisory notices	
Post-market surveillance	
Internal audit	
Control of non-conforming product (corrective and preventive action)	
Lot traceability	

Table 13. Inspection checklist (continued)	
Areas under inspection	**Comments**
Statistical analysis of collected data	
Product Dossier	
Site Master File Summary	
Management review and improvement	
18. Maintenance	
Documented programme, including schedule	
Detail of maintenance for key areas	
Records of maintenance	
Adequacy of maintenance programme	
19. Laboratory facilities, competence and calibration	
Routine activities of each lab	
Equipment and methods	
Reporting of results	
Documentation	
Calibration system	
Certifications	
Participation in inter-laboratory trials	
Research and development activities	
Understanding and competence	
20. Shelf-life stability	
Detail of studies conducted	
Programme for retention of samples	
Building, grounds and services	
Overall fabrication and condition of premises	
Pest and rodent control	
Compressed air	
Process water quality	
Effluent treatment	
Electricity	

9.8 Product testing

Products will be sampled for testing, either prior to or after the inspection by an independent sampler, or by the inspectors during the site inspection. The sample size is taken in accordance with the current international standard for female condoms, *ISO 25841* Annex B. The range of tests to be conducted will be in accordance with the *WHO/UNFPA Female Condom Generic Specification.* All product testing will be undertaken by independent test laboratories, selected by UNFPA, of defined and documented competence and experience, as demonstrated by accreditation to the current *ISO 17025* standard. The sample will be packed and sealed by the inspectors or the independent sampler, as appropriate. The inspectors may take the sample with them or arrange for the manufacturer to have the sealed box sent to the selected laboratory by courier (at UNFPA's expense). ***The manufacturer will receive a copy of the test report.***

9.9 Reporting and communication of the results of the site inspection

At the conclusion of the inspection, the inspectors will prepare a brief written summary report outlining the key findings and observations discussed with the manufacturer during the site inspection. This report will be provided to UNFPA, with a copy to the manufacturer. In addition, the inspection team will finalize its main report according to the established UNFPA SOP and format, describing the findings, evidence and recommendations. The report will be submitted to UNFPA. The inspection report will be communicated by UNFPA to the applicant and/or manufacturer. If any additional information is required, or corrective action has to be taken by the applicant/manufacturer(s), UNFPA will postpone its decision on the acceptability of the site(s) involved until such information has been evaluated or the corrective action has been taken and found satisfactory in accordance with the time frame and recommendations made by the UNFPA inspectors.

UNFPA reserves the right to terminate the procedure of quality assessment of a specific manufacturing site/product if the applicant/manufacturer is either not able to provide the required information or not able to implement the corrective actions within a specified time period, or if the information supplied is inadequate to complete the quality assessment process.

In the event of any disagreement between an applicant and UNFPA, an SOP established by UNFPA for the handling of appeals and complaints will be followed to discuss and resolve the issue. The ownership of any of the reports produced in the course of, or as the result of, the assessment of documentation, product testing and inspection of the manufacturing site lies with UNFPA. Thus, UNFPA shall be entitled to use and publish such reports and/or a summary of a report, subject to the protection of any commercially confidential information of the applicant and/or manufacturer. Confidential information may include:

- confidential intellectual property, "know-how" and trade secrets (e.g. formulas, programmes, process or information contained or embodied in a product, unpublished aspects of trademarks, patents);

- commercial confidences (e.g. structures and development plans of a company).

Provisions of confidentiality will be contained in the exchange of letters, to be concluded before the assessment of the Product Dossier or inspection of the manufacturing site(s), between UNFPA and each applicant/manufacturer.

Notwithstanding the foregoing, UNFPA and WHO reserve the right to share a summary and/or the full evaluation and inspection reports with the relevant authorities of any interested Member State of UNFPA and/or WHO.

9.10 Decision to prequalify

It is UNFPA's responsibility to compile the information submitted in response to the invitation for EOI, the assessment report, the inspection report and the test report. A UNFPA staff member with appropriate experience and training will assess the information about each applicant/manufacturer and, in consultation with the assessors and inspectors, will make a final decision about the outcome of the prequalification process.

Based on this assessment, UNFPA will either:

- Prequalify female condoms manufactured at a specific site without conditions. This will only be the case when no evidence that corrective action should be taken is submitted to UNFPA.

or

- Require the manufacturer, where deemed necessary, to undertake specified corrective action(s). The inspectors may also recommend further inspection and/or product testing once the corrective actions have been completed. The manufacturer must carry out the corrective action within an agreed time period and provide UNFPA with evidence, where required, showing that the corrective action has been taken. If UNFPA is satisfied with this additional information, the manufacturing site will be added to the list of prequalified condom manufacturers.

or

- Determine that a manufacturing site is ineligible for prequalification (without any requirement for

corrective action being offered). This will not, however, preclude the applicant/manufacturer from resubmitting an application in response to future invitations for EOIs.

Where the inspectors recommend corrective action requiring a subsequent inspection, the manufacturer must advise UNFPA within an agreed period of time that corrective action has been completed and provide the relevant evidence, if required. The recommendation for corrective action may include further independent product testing. After review of the evidence, UNFPA will decide whether or not to schedule a further inspection.

If a further inspection is deemed necessary, the inspection process and assessment will be implemented in accordance with the procedure detailed in Clauses 9.7, 9.8 of this chapter. Any re-inspection may be at the expense of the manufacturer. UNFPA reserves the right to terminate the procedure of quality assessment of a specific product if the applicant/manufacturer is:

- not able to provide the required information;

and/or

- unable to implement the corrective actions within a specified time period; and/or if the information supplied is inadequate to complete the quality assessment process.

The findings of the inspection may include non-mandatory observations aimed at highlighting potential for improved manufacturing and quality management practices.

If evidence supporting mandatory improvement actions or additional information is required, or other corrective actions have to be taken by the manufacturer, UNFPA will postpone its final decision until such information has been evaluated or the corrective action has been taken and found satisfactory in light of the specified international standards, as detailed in the list of relevant standards on page 82 of this chapter.

If the applicant/manufacturer has not submitted a satisfactory response within 12 months of submission of the report from UNFPA, the application will lapse, and the applicant will need to reapply in response to a future invitation for an EOI. Each applicant will receive a letter from UNFPA informing it of the outcome of the quality assessment process. UNFPA aims to inform the manufacturer formally of the results of the process within 30 days of receipt of all final reports.

9.11 Listing of prequalified female condom manufacturing sites

Once UNFPA is satisfied that the quality assessment process is complete and where the Product Dossier and corresponding manufacturing site have been found to meet the prequalification requirements, the product produced at the specified manufacturing site(s) will be listed on the WHO and UNFPA web sites.

The list of prequalified female condoms and corresponding manufacturing sites will be compiled and updated in accordance with an SOP established by UNFPA for this purpose.

9.12 Maintenance of prequalification status

Once the product is included in the list of prequalified female condoms and corresponding manufacturing sites, the applicant/manufacturer is required to advise UNFPA, within four weeks, of any matter that affects the information on which the approval was based. This includes but is not limited to:

- change of premises;
- change in production and testing equipment;
- change in senior management;
- product recalls;
- change in certifications or licenses held by the manufacturer;
- reports of adverse events;
- change in condom design;
- change in suppliers not previously listed in the Site Master File summary;

- change in specification of raw materials;
- change in packaging;
- new information about shelf-life.

It is the applicant's responsibility to provide UNFPA with the appropriate documentation (referring to relevant parts of the Dossier) to prove that the implementation of any intended variation will not have an adverse impact on the quality of the product that has been prequalified. UNFPA will undertake an evaluation of variations according to established UNFPA guidelines and SOPs and communicate the outcome to the applicant. Compliance with the requirement to report changes will be checked during the inspections carried out by UNFPA.

9.13 Periodic monitoring of the quality of products produced by prequalified manufacturing sites

At periodic intervals UNFPA may, through an independent sampler, take random samples of female condoms produced by listed manufacturers. Samples will be taken from intact LOTS stored in the manufacturer's or distributor's warehouse. The sample size will be in accordance with the current international standard for female condoms ISO 25841 Annex B.

The range of tests to be conducted will be in accordance with LOT-by-LOT Pre-shipment compliance testing as detailed in the Female Condom: Generic Specification, Prequalification and Guidelines for Procurement, 2012.

All product testing will be undertaken by an independent test laboratory, selected by UNFPA, of defined and documented accreditation to the current ISO 17025 international standard. In the event of failure to meet the established requirements for testing, UNFPA will investigate the problem and communicate this to the manufacturer and/or applicant, if different from the manufacturer. UNFPA may request reports from consumer or regulatory authorities or from other procurement agencies relating to the quality and supply of the prequalified female condoms. Complaints communicated to UNFPA concerning female condoms procured through this Prequalification Scheme will be investigated in accordance with an SOP established by UNFPA for that purpose. After investigation, UNFPA will provide a written report of the complaint investigations, including recommendations for action, to the applicant/manufacturer. UNFPA will require evidence of effective action taken, where relevant.

UNFPA will make the report available to the appropriate authorities of the country where the manufacturing site is located, subject always to considerations of commercially confidential information. UNFPA reserves the right to make such reports public, if it considers this to be of public health importance. In addition, UNFPA reserves the right to share the full report and/or summary report and/or recommendations for action with WHO and relevant authorities of interested Member States of WHO.

9.14 Reassessment

UNFPA aims to undertake a reassessment of female condoms manufactured at a specific site at intervals of no more than three years. Such reassessments will consist of a comprehensive evaluation of documentation, site inspection and product testing similar to the initial prequalification assessment. Reassessment may also be required in the following situations:

- if the female condoms supplied by the manufacturer are considered by UNFPA or by one or more of the other United Nations agencies not to be in compliance with the agreed WHO/UNFPA Specification and Pre-shipment compliance testing requirements, as detailed in Female Condom: Generic Specification, Prequalification and Guidelines for Procurement, 2012.
- if a complaint considered serious in nature has been received by UNFPA or one or more of the other United Nations agencies or organizations
- if there is a significant change in the manufacturing process in respect to one or more of the items listed in Clause 9.12, above.

All relevant information including the reassessment of submitted documentation and site inspection reports, together with monitoring information, will be

considered by the designated UNFPA official, and a decision will be made to either:

- maintain the female condom and its manufacturing site on the list of prequalified products without need for corrective actions;

or

- maintain the prequalification status of the female condom and its manufacturing site with a requirement for corrective actions and, where agreed to by UNFPA, further product testing and/or a site inspection;

or

- suspend prequalified status.

UNFPA aims to advise the applicant/manufacturer of the result of the reassessment and make any necessary amendments to the list of prequalified manufacturing sites and products within 30 days of receipt of the data on the basis of which the decision is made.

The updated list will be published on the WHO and UNFPA prequalification web sites.

UNFPA will de-list any prequalified product and manufacturing site if the submitted information is subsequently found to be incorrect or fraudulent.

CHAPTER 10

Specification and Procurement Checklists

PART THREE

CHAPTER 10: GUIDELINES FOR PROCUREMENT AND PROCUREMENT CHECKLISTS

10.1 Introduction

An effective supply chain ensures that the right quality product, in the right quantities, and in the right condition is delivered to the right place at the right time, for a reasonable cost. To accomplish this purpose, the customary supply cycle has four major components: product selection, product procurement, product distribution and product use. Part 3 of this manual addresses the procurement component of the supply chain cycle, identifying the key procurement steps used to enable reproductive health care programmes to receive and store good-quality female condoms that meet the needs of their clients.

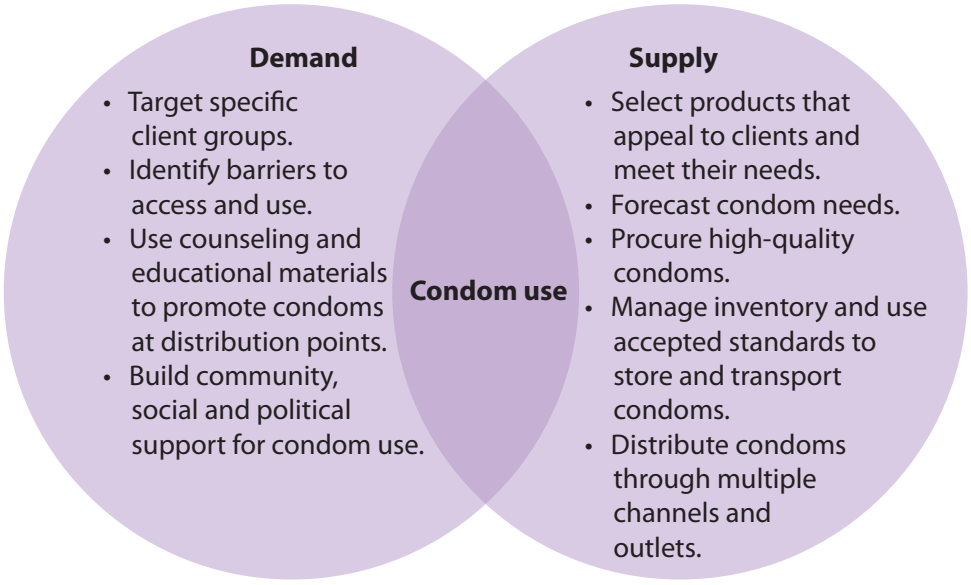
Before addressing the details of the procurement process, however, it is important to understand the broad context and ultimate objective of effectively procuring quality female condoms, which is to support a country's efforts to achieve its goal of Comprehensive Condom Programming.

The goal of Comprehensive Condom Programming is to develop strategies and programmes through which every sexually active person at risk of unintended pregnancy, HIV and other sexually transmitted infections, regardless of age, culture, economic situation, gender, marital status, religion or sexual orientation, has access to good-quality female and male condoms when and where she or he needs them, is motivated to use female or male condoms as appropriate, and has the information and knowledge to use them consistently and correctly. The overall aim is to decrease the number of sex acts that go unprotected, thereby reducing the incidence of unwanted pregnancy and sexually transmitted infections, including HIV.

10.1.1 Comprehensive Condom Programming

Comprehensive Condom Programming links and integrates a number of activities, including leadership and coordination, male and female condom promotion, communication for behaviour change, market research, segmentation of messages, optimized use of entry points (in both reproductive health clinics and HIV prevention/management venues), advocacy and coordinated management of procurement, distribution and supply[6]. Figure 1 illustrates the key demand and supply elements that must be addressed in condom programming.

Figure 1. Elements of condom programming



Source: *Condom programming for HIV prevention —an operations manual for programme managers.* UNFPA, PATH, WHO 2006

[6] Condoms and HIV prevention: position statement by UNAIDS, UNFPA and WHO. March 2009.

Effective procurement processes must be part of a strategic and co-coordinated effort to improve access to and the use of male and female condoms to prevent unwanted pregnancy and the transmission of sexually transmitted infections including HIV. For further information on Comprehensive Condom Programming, refer to: http://www.unfpa.org/hiv/programming.htm.

10.2 Procurement

This section identifies the fundamental steps in the procurement process that enable country programmes to receive good-quality condoms in the right quantities, in the right condition, delivered to the right place, at the right time, for a reasonable cost.

Detailed methodologies for conducting the public-sector procurement process and managing the supply chain have been developed by a number of international agencies working in the field of contraceptive procurement and logistics management.

To ensure that the procurement steps identified in this manual are harmonized with the latest guidance on Comprehensive Condom Programming, two key manuals have been used as reference documents:

- *Condom Programming for HIV Prevention—An Operations Manual for Programme Managers.* UNFPA, PATH, WHO, 2006;
- *Procurement Capacity Toolkit: Tools and Resources for Procurement of Reproductive Health Supplies.* PATH, 2009.

The 10-step approach to procurement identified in this part is based on the *Procurement Capacity Toolkit: Tools and Resources for Procurement of Reproductive Health Supplies* (PATH, 2009). This toolkit synthesizes the public-sector supply process for reproductive health commodities into three phases: programme planning, procurement process, and performance. Within these three phases 10 required steps are identified that are designed to support the purchaser in obtaining a good-quality product at a reasonable cost at the needed time.

The three phases and 10 steps of public-sector health care procurement are identified in Table 14.

It should be noted that:

a) The steps outlined in this manual define effective practice, but the actual procurement process that a purchaser follows will vary slightly, depending on such factors as government procurement regulations, source of funding, whether qualified manufacturers exist in-country, country registration requirements and the purchaser's own procurement procedures and requirements. See additional notes below on country registration requirements.

Table 14. Three Phases and 10 steps of Procurement

Phases	**Ten steps of procurement**
1 Programme planning	1. Defining supply requirements
	2. Customize the specification
	3. Assessment of procurement options
	4. Budget, funding and procurement requisition
Critical link: funded procurement requisition	
2. Procurement processs	5. Procurement planning
	6. Developing Bidding Documents and inviting offers
	7. Selecting suppliers (see notes on regulatory approval)
	8. Contract negotiation/award
Critical link: signed contract and payment guarantee	
3. Performance	9. Contract performance and monitoring
	10. Delivery of goods

b) Although the procurement steps have been presented in a sequential format, it is often necessary to implement several steps at the same time.

c) Procurement steps may vary from country to country, but, to be undertaken effectively, each step requires: leadership; adequate human and financial resources; willingness to collaborate and coordinate with the different parties involved in each step of the procurement process; timely decision-making.

10.2.1 Notes on Country registration

National regulatory approval is an important component of contraceptive quality assurance), but it can also work against timely delivery and low prices if the procuring entity does not understand national regulatory practices or fails to act on that understanding.

Female condoms are considered medical devices in most countries and registration requirements for medical devices vary greatly from one country to the next.[7] Unregistered products can be refused entry into the country and quarantined, returned, or destroyed. Regardless of their disposition, they are not available to the RH program for distribution.

The time required for national regulatory approval and registration can be significant, but if a procuring entity limits eligibility for bidding to only products that have been registered by the country's national regulatory authority, it can limit competition — which can lead to higher product prices being offered. If a procuring entity opens competition to products that have not been registered in the country, prices offered may be lower, but the contract may be delayed while the regulatory registration process unfolds; which can result in later delivery.

The additional time for product registration should be considered in the procurement planning process. Product registration can take from 3 to 12 months, sometimes longer. It depends on the product itself, the capabilities and capacity of the national regulatory authority, and how the national regulatory authority intends to approach the approval process.

Purchasers who are aware of national regulatory processes are the more likely to be successful at satisfying program needs for safe, effective products; low prices; and specified delivery dates.

[7] Adapted from *Procurement Capacity Toolkit: Tools and Resources for Procurement of Reproductive Health Supplies. PATH, 2009.*

WHO/UNFPA Specification Checklists

The following checklists are designed as useful tools to ensure that every step in the preparation of a specification and in the procurement process has been effectively addressed. Procurers are encouraged to photocopy the checklists and follow the steps outlined.

Table 15. WHO/UNFPA Specification Checklist
Refer to Part 1, Chapter 1 for the Generic Specifications.

Step	Checklist	Action	Comments
1	**Are the condoms for:** • Social marketing programmes • Public sector • Both		
2	**Target population:** • Family planning programmes • STI/HIV/AIDS prevention programmes • Specific population groups		
3	**What are the regulatory requirements?** (Refer to Procurement Checklist)		
	What steps are required to register the product in the country? • Time required to register • Information required • Costs and fees registration		
	What are the customs clearance requirements? • Clearance • Exemptions/waivers • Documentation required		
	What are the programmatic requirements?		
4	**Where are stocks of condoms held?**		
	How long will existing stocks last?		
	Are high-priority areas or populations identified?		
	What is the delivery schedule?		
	What quantity is needed over what period?		
	What is the storage capacity—where and what quantity?		
	Is a distribution system in place?		

Table 15. WHO/UNFPA Specification Checklist (continued)			
Step	**Checklist**	**Action**	**Comments**
5	**Sampling agency and testing laboratory selected**		
	Prequalified suppliers reviewed		
	Testing regimes for Pre-shipment compliance testing—testing laboratories selected		
	Is confirmatory testing required?		
6	**Prepare specification**		
	General Requirements specified as detailed in the *WHO/UNFPA Female Condom Generic Specification*		
	Performance Requirements specified as detailed in the *WHO/UNFPA Female Condom Generic Specification*		

	Check Design Requirements:
	• Essential features: retention features and other additional components
	• Colour: Indicate pigment and discuss with manufacturer
	• Scent and flavouring: If fragrance is required, add to specification and discuss with manufacturer
	• Shape and texture:
	  ◦ State width
	  ◦ State length
	• Thickness as recommended in the *WHO/UNFPA Specification*
	• Lubricant as recommended in the *WHO/UNFPA Specification*		

	Check Packaging Requirements:
	• Individual packaging and packaging markings according to the *WHO/UNFPA Specification*
	• Language agreed to by manufacturer
	• Individual packaging foil markings:
	  ◦ Manufacturer's name and address
	  ◦ Expiry date and date of manufacture
	  ◦ Lot number
	• Other references required by regulatory authority
	• Shelf life (not less than 3 years and not more than 7 years)		

Table 15. WHO/UNFPA Specification Checklist (continued)			
Step	**Checklist**	**Action**	**Comments**
6 (cont.)	What additional individual packaging markings are required? • AIDS Help-Line • License number • "Not for sale" • Instructions for use and disposal		
7	**Specify packaging**		
	Check packaging design: • Colour (Pantone number) • Font • Logo • Style • individual packaging colour • individual packaging shape Individual packaging approval: What procedure to follow?		
8	**Check Packaging Requirements:**		
	• Inner boxes and outer cartons according to the *WHO/UNFPA Specification* • Markings of inner boxes and cartons according to the *WHO/UNFPA Specification* • Inner pack quantity—any additional requirements: • Logo? • Address of procuring agency? • Donor logo?		
9	**Consumer packs specified by purchaser:** • Wallet size and design • Number per strip		

Table 16. Procurement Checklist
Check the cycle of procurement, as it can take between 12 and 18 months to procure condoms.

Step and Checklist	Yes	Date Completed	Comments/Notes
Step 1: Define programme context			
Which donor agencies, nongovernmental agencies, social marketing agencies, commercial enterprises and different public-sector ministries are involved in the procurement, distribution and promotion of condoms?			
What are the sources of funding?			
What sources of supply are used?			
History of condom procurement over the last three years			
1.2 Forecast programme requirements			
Research population's current needs and unmet needs			
History of previous shipments?			
Trends in condom use and procurement?			
What is the desired buffer stock level?			
Is there a Logistic Management Information System in place that captures stock level and distribution?			
What are the requirements of National Regulatory Authorities regarding procurement and importation?			
How are condoms imported into the country?			
Problems encountered in past procurement of condoms?			
Length of previous procurement cycles?			
Current stock levels and where condoms are stored? What is the annual consumption? How many months will current supplies last? Any products that may not be distributed before expiry date?			
Projected time-scale for distribution?			
Projected requirements?			
Time-scale for delivery?			
Storage and distribution system in place?			
Step 2: Customize the Specification			
Refer to WHO/UNFPA Specification			
General Requirements should not be modified			
Performance Requirements should not be modified			
Design Requirements can be modified			
Packaging Requirements should not be modified			
Consumer pack designed and approved			
Specification of consumer pack prepared for discussion with manufacturer			
Other issues			
Step 3: Assessment of procurement options			
Select one method: i) Procure directly from a manufacturer through competitive bidding process			

Table 16. Procurement Checklist (continued)			
Step and Checklist	**Yes**	**Date Completed**	**Comments/Notes**
ii) Source from a procurement agency			
iii) Source from an international procurement agency/ organization			
iv) Buy from a social marketing organization			
Step 4: Budget, funding and procurement requisition			
Estimate procurement costs to determine budget: • unit price; • freight cost and insurance; • sampling and testing; • import/customs clearance costs; • post-shipment confirmatory testing; • taxes.			
Also consider: • warehouse and storage costs; • distribution costs; • promotion costs.			
Funding: Identify and secure funding			
Identify key challenges and how you are going to deal with them			
Step 5: Procurement Planning			
Obtain authorization to contract and commit funds			
Confirm budget allocations and timing for availability of funds			
Review technical specifications to ensure that they are complete and in a format consistent with international standards			
Confirm the date, delivery location and mode of transport			
Visit customs authorities and discuss procedures			
Review regulations covering national regulatory procedures, importation and distribution of condoms			
Confirm specific country requirements and national regulatory procedures: • Is there a mandatory national quality standard? • How are the standards applied? • Is there a requirement to test every Lot of condoms before it is shipped to the country? • Is there a competent accredited laboratory in-country? If not, is there an accredited regional laboratory? • What other entry requirements are there? • Is there a registration requirement prior to importation?			
Visit National Regulatory Authority and review and understand procedures			

Table 16. Procurement Checklist (continued)			
Step and Checklist	**Yes**	**Date Completed**	**Comments/Notes**
Step 6: Developing Bidding Documents and inviting offers			
Identify information required for Bidding Documents: • instructions, rules, and procedures for bidding; • information about where and when bids will be opened; • information about how bids will be evaluated and how the purchaser will select the winning bid; • information about any factors in addition to price that the purchaser will consider; • technical specifications and compliance requirements; • quantity, delivery schedule and delay clauses (requirements); • national regulatory requirements; • terms and conditions for the future contract between the purchaser and the winning bidder;. • request for documentary evidence of manufacturing quality assurance measures; • procedure for resolution of disputes; • procedures for Pre-shipment compliance testing and, if required by national bodies, confirmatory testing procedures; • shipping arrangements; • payment arrangements; • sample forms containing necessary wording for the bidder to use.			
Any other issues?			
Use WHO/UNFPA prequalified suppliers: • verify manufacturing capacity; • seek information on potential suppliers; • select an independent testing laboratory; • select an independent sampling agency. • general conditions of contract;			
Prepare Bidding Document package: • general instructions to bidders; • special instructions to bidders; • eligible/ineligible countries and suppliers; • special conditions of contract; • technical specifications; • schedule of requirements and delivery dates; • evaluation criteria; • qualification criteria; • bid and contract forms, which include: ◦ price schedule			

Table 16. Procurement Checklist (continued)			
Step and Checklist	**Yes**	**Date Completed**	**Comments/Notes**
• bid security form • performance security form • contract agreement form.			
Invitation to bid: Media for advertising bid invitation known?			
Receiving and managing bids: • Bids must be held unopened until the stated day and time of bid opening. • Bid envelopes should stamped with the date and time received.			
Step 7: Selecting suppliers			
Agree on criteria for evaluating bids			
Is assistance required to review and interpret documentary evidence supplied by manufacturers?			
Check to see if the suppliers have confirmed that they: • are capable of providing the quantities required within the desired time frame; • have a proven record of manufacturing products that conform to the WHO/UNFPA Specification, the purchaser's specification, or similar requirements; • are WHO/UNFPA prequalified suppliers, if that qualification has been identified in the Bidding Documents as a requirement for bidding; • will permit a sampling agency to perform random sampling of condoms at the site of the manufacturing facility; • will accept Pre-shipment compliance testing and, if required, confirmatory testing; • will accept the test results of an independent laboratory agreed to by both parties; • will accept the procedure for the resolution of disputes; • will accept the general and specific conditions of the contract.			
Eliminate non-specialized procurement agents and importers from the list of potential suppliers.			
Step 8: Contract negotiation/award			
Is the supplier chosen on the basis of: • WHO/UNFPA prequalified supplier; • quality of the product; • capacity to supply; • price; • ability to meet the requirements of the contract.			
Payment guarantee in place?			

Table 16. Procurement Checklist (continued)			
Step and Checklist	**Yes**	**Date Completed**	**Comments/Notes**
Step 9: Contract Performance and Monitoring			
System to proactively manage contract in place?			
Lot-by-Lot Pre-shipment compliance testing organized?			
Step 10: Delivery of Goods			
Are procedures for customs clearance known and implemented?			
Is storage organized?			
Are arrangements made for every Lot manufactured to be sampled and tested for compliance with the specification prior to shipping?			
Are regulatory requirements met?			
Is assistance to interpret the results of the laboratory tests required? (Discuss with laboratory or contact Help-Line.)			
Is there an established procedure for the resolution of disputes?			
Do you know the delivery schedule?			
Do you know the customs clearance procedures? Do you have all the appropriate information and forms required for customs clearance?			
Does the regulatory authority require confirmatory testing? If yes, have sampling procedures and testing regime been agreed upon?			
Is the regulatory authority familiar with the process for resolving disputes?			
Has the delivery schedule been reconfirmed?			
Is the customs clearance procedure known?			
Has all of the customs documentation been received?			
Do you need to deal with any factors that could delay receipt of the shipment?			
Are storage facilities ready and prepared to receive the shipment of condoms?			
Has transportation been organized?			
Storage			
Clean, dry, well-ventilated environment?			
No contact with oil, petrol, water, ultraviolet light?			
In original packaging with manufacturing markings?			
Stored on the basis of first in-first expiry out?			

10.3 Condom Storage

Factories prequalified by UNFPA to supply female condoms will have provided evidence to verify the claimed shelf-life of the product. The shelf-life is determined by a real-time study, conducted at a specific temperature (30(+5 -2) C) because this is the mean kinetic temperature of the most extreme climate in climatic zones III and IV. Female condoms from prequalified manufacturers can therefore be stored at average temperatures in tropical climates for the stated shelf life period without risk of deterioration. More information about the rationale for choosing (30 -2+5)°C as the storage temperature for stability studies is given in the Technical Basis Paper in Annex 3.

Since the shelf-life of the condoms will have been determined at (30 -2+5)°C, air-conditioned storage is not necessary, but it would be an advantage in hot climates if available. In hot climates it is important that condoms are stored in a well-ventilated environment away from direct sunlight and other sources of heat in order to minimize the exposure of the condoms to high temperatures. Similar precautions should be taken during transportation and delivery. Condoms stored outdoors in shipping containers are particularly vulnerable, as the temperatures inside containers can be substantially above ambient temperatures, resulting in faster deterioration. Storage time in containers should be minimized.

The condoms are sealed in individual packages, which are themselves packed in cardboard. The cardboard storage containers are vulnerable to moisture and should be stored in a dry storeroom away from walls and placed on pallets to protect against moisture from warehouse floors. Cartons should be stored at least 10 cm off the floor, 30 cm away from the walls and stacked no more than 2.4 metres high. Condoms are fully protected by the individual package. However, cosmetic damage to the individual package and damage to the outer packaging can make the product appear damaged and therefore less acceptable to the user. Contaminants of any sort (e.g. powders or liquids) should be avoided.

Condoms should be left in their original cartons and inner boxes until needed for end use distribution. The cartons should be positioned so that the Lot number and expiry date are visible. The cartons should be identified and their locations recorded to ensure that specific Lots can be located. To minimize the chance of product expiration the lots should be released on a *first expiry—first out basis* (FIFO).

Damaged or expired condoms should be kept separately and disposed of in accordance with local procedures for the disposal of damaged medical devices.

For additional information in chart format on condom storage, refer to: http://deliver.jsi.com/dlvr_content/resources/allpubs/guidelines/GuidPropStor_Char.pdf.

For detailed information on the in-country management of storage and distribution, refer to the UNFPA-published *Condom Programming for HIV Prevention—An Operations Manual for Programme Managers* and PATH's *Procurement Capacity Toolkit: Tools and Resources for Procurement of Reproductive Health Supplies.*

PART FOUR

Annexes

ANNEX I
CONFIDENTIALITY UNDERTAKING

The assessors and inspectors will treat all information to which they gain access during the evaluations and inspections or otherwise, in connection with the discharge of their responsibilities regarding the above-mentioned project, as confidential and proprietary to UNFPA and parties collaborating with UNFPA in accordance with the terms set out below.

Assessors and inspectors will take all reasonable measures to ensure that:

- confidential information is not used for any other purpose than the evaluation/inspection activities described in this document; and

- confidential information is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Assessors and inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they can clearly demonstrate that any part of the confidential information:

- was known to them prior to any disclosure by or on behalf of UNFPA (including disclosure by manufacturers); or

- was in the public domain at the time of disclosure by or on behalf of UNFPA (including by manufacturers); or

- has become part of the public domain through no fault of theirs; or

- has become available to them from a third party not in breach of any legal obligations of confidentiality.

Conflict of interest

Before undertaking the work, each assessor and inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest.

If, based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the evaluator or inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to UNFPA. In this connection each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify UNFPA of any change in this information.

All inspectors furthermore agree that, at the manufacturer's request, UNFPA will advise the manufacturer in advance of the composition of the team performing the site inspection and the identity of each inspector and will provide their curricula vitae. The manufacturer then has the opportunity to express possible concerns regarding any of the inspectors to UNFPA prior to the visit. If such concerns cannot be resolved in consultation with UNFPA, the manufacturer may object to a team member's participation in the site visit.

The manufacturer must make such an objection known to UNFPA within 10 days of receipt of the proposed team composition from UNFPA. In the event of such an objection, UNFPA reserves the right to cancel all or part of its agreement with, and the activities to be undertaken by, that inspector.

ANNEX II
SAMPLE OF THE LETTER OF APPLICATION

PREQUALIFICATION OF FEMALE CONDOM PRODUCTS AND MANUFACTURING SITES

Date _____

To: United Nations Population Fund
Midtermolen 3, P.O. Box 2530
DK 2100 Copenhagen 0, Denmark

Dear Sir/Madam,

Being duly authorized to represent and act on behalf of *[insert name of manufacturer]* (hereinafter referred to as the "Applicant"), and having reviewed and fully understood all the prequalification information provided, the undersigned hereby applies to be prequalified by UNFPA as potential suppliers of female condoms.

Attached to this letter are copies of original documents defining:

- The Applicant's legal status
- Product Dossier
- Clinical Evaluation (including CV of principal investigator)
- Site Master File Summary;
- Sample products.
- Current quality certificates and registrations

UNFPA and its authorized representatives are hereby authorized to conduct any enquiries or investigations to verify the statements, documents, and information submitted in connection with this application, and to seek clarification from our bankers and clients regarding any financial and technical aspects.

This Letter of Application will also serve as authorization to any individual or authorized representative of any institution referred to in the supporting information to provide any information deemed necessary and requested by UNFPA to verify statements and information provided in this application or with regard to the resources, experience, and competence of the Applicant.

The Applicant declares that all the information provided with the application is valid.

Name of Applicant *[insert name of manufacturer]* _____

Name of Responsible Officer _____

Signature _____

Position/Title _____

ANNEX III

TECHNICAL BASIS FOR THE WHO/UNFPA FEMALE CONDOM GENERIC SPECIFICATION

1. Background

Although the female condom only became widely available commercially in the 1990s, the concept of an internal sheath that can be inserted into the vagina prior to intercourse to protect against pregnancy and sexual transmitted infections is certainly not new. According to legend Minos, the mythical king of Crete, used a female sheath made from a goats bladder to protect a women while he cast off his serpent bearing semen (1). In 1907 Graham filed US patent 899,251 for a bag that could be inserted into the vagina of an animal prior to coitus to collect semen for artificial insemination purposes. The bag is described as being made from a flexible material such a soft rubber and having a flexible frame or binding at its open end that rests against the vulva and so prevents the bag from being pushed all the way into the vagina. The patent also describes the bag as having a band of less yielding material at an intermediate position along its length, the band being approximately ovoid in section so as to retain its shape *in situ* and prevents the walls of the vagina from collapsing the bag. The device described by Graham has all of the features considered essential in a modern female condom.

During the US Food and Drug Administration (FDA) panel meeting on March 7, 1989, which was held to review the classification of the Wisconsin Pharmacal Company female condom, reference was made to a device, the Gee Bee Ring, which was distributed in the 1930s as a female condom (2). Bounds et al (3) reported that female condoms were also available in the UK, the Capote Blanco in the 1920s and the Capote Anglaise or Ladies Own Sheath in the 1960s. None of these products, however, appear to have been widely used or to have achieved commercial success.

Other early examples of female condoms appear in the patent literature. A US patent, 3,536,066 filed in 1967, by Ludwig describes a device consisting essentially of a panty or bikini bottom containing a "cul-de-sac proboscis with bellow like circular folds" in the crotch region of the bikini. The device is worn by the woman. During intercourse the man pushes the "cul-de-sac proboscis" into the vagina. In this patent, Ludwig essentially described what is known today as the panty or bikini condom. Freimark in 1975 filed US patent 4,004,591for a "contraceptive device to be worn internally by women..." The patent describes a tubular member made of a compliant material designed to fit snugly within the vagina and having two flaps extending outwardly at the open end intended to cover the labia majora of the wearer and the adjacent epidermal area. Despite many attempts to develop a commercially viable female condom, it is only in the last 20 years that any degree of success has been achieved.

In the late 1980s a design for a female condom was developed by Hessel, a Danish physician. The product was widely patented around the world (e.g. US patents 4,735,621 and 4,976,273). Hessel sold the rights to the product to Chartex Resources Limited, a private British company which in turn selected Wisconsin Pharmacal Company as the U.S. licensee for product. In 1996 Wisconsin Pharmacal changed its name to The Female Health Company (FHC), a US public company. FHC then purchased Chartex and now owns worldwide rights to the Female Condom. The product was originally launched in a number of European countries including Switzerland, France, the UK, Italy and Austria in 1992. FDA premarket authorization was obtained in 1994, clearing the way for the condom to be sold in the US. The product has been distributed under a number of names, depending upon the market and distribution route. Names include: Reality, Femidon, Dominque, Femy, Myfemi, Protectiv' and Care.

In 2003 FHC began the development of a second generation female condom with the primary intent of reducing the cost of the product. The new version, known as FC2, is manufactured from a synthetic latex by a dipping operation, a process similar to that used in the manufacture of male latex condoms. FC2 received European marketing authorization (CE Mark) in 2005 and FDA premarket approval in 2009. Following the successful development of FC2, FHC has stopped manufacturing the original condom, which is now designated FC1.

With FC1 and FC2, FHC effectively opened the market for female condoms. A number of other manufacturers have developed or are in the process of developing new types of female condoms. Examples include:

The VA w.o.w® (worn of women) Condom Feminine® or L'amour made by Medtech Products Ltd, Chennai, India. This product is often called the Reddy female condom after the name of its designer.

The Woman's Condom developed by PATH (Program for Appropriate Technology in Health) in the US and now under manufacturing scale-up in China at Shanghai Dahua, Medical Apparatus Co., Ltd.

The Cupid Female Condom manufactured by Cupid Ltd, Mumbai, India.

The Phoenurse Female Condom produced and distributed in China by Condombao Medical Polyurethane Co. Ltd, Shanghai, China.

Additionally there are a number of panty or bikini condoms in limited distribution. These products consist of a panty that is worn by the woman that has a means of attaching a sheath. The panty serves the function of preventing the sheath being pushed completely inside the vagina.

2 Female Condom Design

Female condoms are designed to be inserted into the vagina before penetration by the male. In principle a female condom can be inserted some time before intercourse and this is often seen as one of the potential advantages of the device. It is both under the control of the woman and, if previously inserted, does not interfere with sexual intercourse. Depending upon the specific design, the device might also provide some protection to the external genitalia, another potential advantage over male condoms.

There are many possible different designs of female condoms, but all of those in current distribution or development have the following features:

- *A sheath that lines the vagina.* The sheath is made from polymer and is usually elastic. Common materials include polyurethane (FC1, Woman's Condoms, Phoenurse), synthetic rubber latex (FC2) and natural rubber latex (Reddy and Cupid).

- *An external component* that prevents the condom from being pushed into the vagina during intercourse. This may be a ring (FC1, FC2, and PATH Woman's Condom) or a semi-rigid frame (Reddy and Cupid). The external component may be integral with the sheath, as is common in those devices that use a ring, or may be attached to the sheath as is commonly the case when a frame is used.

- *An internal retention feature* that keeps the condom inside the vagina. Commonly used features include elastic rings (FC1, FC2, and Phoenurse) and sponges (Reddy and Cupid). The Woman's condom, developed by PATH, is unique in including a number of hydrophilic polyurethane foam pads towards the closed end of the condom that adhere gently to the vaginal wall.

- *A means of inserting the condom into the vagina*. The internal retention feature may be used for this purpose, particularly in the case of those condoms that have an internal ring or there may be a separate applicator that can be discarded after insertion. The PATH Woman's condom is unique in having an insertion device made from polyvinyl alcohol that dissolves once within the vagina and so releases the condom.

Female condoms are usually pre-lubricated but some are supplied with a sachet of lubricant to be applied immediately before use. Silicone fluids and water based lubricants are used. Depending upon the materials used to manufacture the condom, it may have greater tolerance to a wider range of personal lubricants than is the case for male latex condoms. As with male condoms, the products are distributed in individual packages designed to protect the condom during transit and storage. One or more individual packages may be packed in a consumer pack, particularly in the case of products intended for retail distribution. Some materials used in female condom manufacture, for example polyurethanes and synthetic rubber latex, have excellent oxidation resistance allowing for a wider choice of film materials for the individual package.

3 Regulatory

Male and female condoms are regulated around the world as medical devices. The precise definition of a medical device varies depending upon regulatory authority, but all are based on the same general principle that a medical device is an instrument, apparatus,

implement, appliance, etc. used for the treatment, diagnosis, monitoring or alleviation of a disease, injury or other similar condition where the primary intended purpose of the device is not achieved by chemical, pharmacological, immunological or metabolic means.

There are two dominant regulatory systems for medical devices — the US scheme operated by the FDA and the European CE Mark scheme operated within Europe. Both are legally binding schemes enforced by Federal Law in the US and European Directives in Europe. These schemes are often used as the basis of many other local national schemes. In fact, many national regulatory bodies with take market authorizations under the FDA and CE Mark procedures as evidence that a product has been adequately tested for safety and effectiveness. Within the public sector condom distribution system, many agencies require FDA and/or CE Mark market authorization for male condoms, and it is expected that similar requirements will apply to female condoms.

The classification of medical devices within the FDA and European schemes follows different procedures but in both systems the category into which a product is assigned depends upon the level of risk associated with that product. Devices that carry high levels of risk because of their mode of action, their method of use, the nature of the condition they are treating, or the level and nature of exposure to the device, are subject to more stringent requirements for demonstrating their safety and effectiveness. Under FDA procedures devices are assessed and classified into three categories based on expert panel reviews. Approximately 1,700 different generic classes of medical device have been classified this way. The FDA determined, based originally on a panel review held in 1989, that female condoms are Class III (premarket approval) (4) devices, the most stringent class for medical devices. Under European procedures devices are classified according to a set of rules listed in the Medical Device Directive (93/42/EEC). Applying these rules to the female condom results in the device being allocated to Class IIb. This classification is a little less demanding than that determined by the FDA.

Irrespective of the classification, female condoms, as relatively new medical devices, should be subject to clinical studies to verify their effectiveness and safety. For well established devices, such as male latex condoms, compliance with an appropriate national, European or international standard is often accepted by regulatory authorities as evidence of an acceptable level of effectiveness. The FDA, for example, will accept compliance with *ISO 4074*, the international standard for male latex condoms, and/or ASTM D3492 08, the American standard for male rubber condoms, as sufficient evidence of a satisfactory clinical performance in a 510(k) premarket notification. Similarly, Notified Bodies within Europe, the organizations responsible for assessing medical devices, will accept compliance with *EN ISO 4074* (the European designation for the international standard for male latex condoms) as sufficient evidence that the condoms comply with the essential requirements of the Medical Device Directive 93/42/EEC (MDD). Male latex condoms are therefore considered to be well established products and clinical trails are no longer required as long as they are equivalent in design, manufacture and materials to existing products.

The FDA specifies that female condoms must be approved through the premarket approval process (PMA), which requires the submission of a dossier detailing many aspects of the product in including manufacturing information, non-clinical data, safety data and clinical effectiveness data. When reviewing FC1, the FDA required, as part of the PMA process, clinical evidence supporting the contraceptive effectiveness of the product. The pivotal study involved the recruitment of 375 subjects in a prospective, multi-centre, single-arm international trial. More details on this study are given later in this paper. FC2 was granted premarket approval on the basis, inter alia, of a pivotal prospective randomized, cross-over clinical trial comparing the failure rates of FC1 and FC2 in which 276 subjects were enrolled. The FDA and the Obstetrics and Gynaecology Devices Advisory Panel, which recommended granting the PMA, accepted that FC2 was broadly equivalent to FC1 on the basis of non-clinical data and functionality data and therefore agreed that a full contraceptive efficacy study on FC2 was not necessary. The FDA's position on the need for contraceptive efficacy studies for new types of female condoms will therefore depend to some extent on the degree of equivalence between the new designs and FC1/FC2.

A number of manufacturers of new designs of female condoms have been able to obtain approval for CE Marking of the products within Europe without significant clinical data. The exact basis of these

marketing authorizations is not clear, but since there is no harmonised standard within Europe for female condoms, there is an underlying presumption that evidence of satisfactory compliance with the essential requirements of the MDD would require clinical investigations. It remains to be seen if recent amendments to the MDD by Directive 2007/47/EC which, inter alia, place greater emphasis on the need for clinical data for all devices regardless of classification will impact on the European approval process. The amendments came into force on 21 March 2010.

4 Standards

International and national standards have been developed for many medical devices. Standards often play a key role in the regulatory process for medical devices. It is common practice for regulatory bodies to insist that products meet local and/or international standards as a condition for regulatory clearance. Within Europe, compliance with a harmonised European standard is one method of demonstrating that a product meets the essential requirements of the MDA (93/43/EEC), facilitating clearance for CE Marking. In the US, the FDA generally requires that a medical device complies with the appropriate US (ASTM) and/or international (ISO) standards.

International standards are developed and published by ISO, the International Organization for Standardization. ISO is a network of the national standards institutes of 163 countries. It is based on the principle of one member body per country. The Central Secretariat of ISO is based in Geneva, Switzerland.

ISO standards are developed by technical committees comprising experts from a wide background representing manufacturers, vendors, users, consumer groups, testing laboratories, private and public sector bodies, procurement agencies, regulatory bodies, governments, research organizations, etc. The standards are consensus driven, industry-wide and voluntary. The approval process consists of a series of international reviews and ballots with a majority of at least two thirds of participating national member bodies approving the standard.

Within ISO, Technical Committee 157, designated *ISO/TC 157* Non-systemic contraceptives and STI barrier prophylactics, is responsible for developing standards for barrier contraceptives including male and female condoms. Working Group 18 of *ISO/TC 157* has been developing the ISO standard for female condoms for several years. The standard is now at the FDIS (final draft international standard) stage, the final stage before publication, and has been circulated for voting. It was recognised, however, that some minor but important changes were required to the standard prior to publication but these were not incorporated into the draft that was circulated for voting. The outcome of voting is therefore uncertain. If approved, immediate revision may be required. When published, the standard for female condoms will be designated *ISO 25841*.

Also within *ISO/TC 157*, Working Group 20 is developing a standard providing guidance on conducting clinical evaluations of female condoms. This standard is being developed in parallel with an equivalent standard for clinical investigations on synthetic male condoms. Work on the standard for female condoms is still at an early stage (working draft). When published, this standard will be designated *ISO 29943-2*.

ISO standards usually specify requirements and test methods for the specific products concerned. In the case of female condoms, which can be made to a variety of designs and from a wide range of materials, specifying certain performance requirements such as minimum air inflation limits is therefore not possible. There are similar issues when specifying certain design requirements such as dimensions. Instead, the approach adopted in the current draft of the female condom standard *(ISO/FDIS 25841.2)* is to rely upon a clinical evaluation to establish the acceptability and effectiveness of the device, and to specify how the manufacturer should set the specification for the product. The draft standard does specify the test methods that must be used and the properties that must be specified. More details about these requirements are given later in the paper.

5 Clinical Studies on Female Condoms

As the first female condom to be widely marketed, FC1 has been subject to a significant number of clinical studies, details of which have been published. The same is true of FC2 but being a newer product the number of published studies is still relatively few.

There are very few published papers on other types of female condoms, and what published work there is tends to be restricted at present to user acceptability studies.

5.1 Contraceptive Efficacy

An early, prospective study to determine the contraceptive efficacy of FC1 was conducted in the UK by Bounds et al (3) in 1992. Based on 106 self-selected women that were included in the analysis, the estimated typical use 12-month life-table rate pregnancy rate was 15% (95% CI 3.5 to 26). For those subjects that used the device consistently, the 12-month life-table method failure rate was reported as 5% (95% CI 0 to 11). It was originally planned to recruit 200 women into the study but recruitment had to be cut short because of administrative difficulties importing the device into the UK from the USA. Of the women recruited into the study, 56% dropped out because they found aspects of intercourse using the method unsatisfactory. Of the women dropping out, 33% did so in the first month.

The pivotal study (Farr et al (5)) on FC1 that was used for the basis of FDA PMA was conducted by FHI360 and the Contraceptive Research and Development Program (CONRAD) with funding from the United States Agency for International Development (USAID). The trial was conducted in nine centres (6 US, 2 Mexico, 1 Dominican Republic). Eligible participants aged 18 to 40 in mutually monogamous relationships used FC1 as their only means of contraception for a period of six months in an open label non-comparative trial with follow up at one, three and six months, during which a pelvic examination was performed, the coital log and product use history were recorded, and additional supplies of the product were distributed. At six months, or earlier in the case of discontinuation, a Pap smear and a urine pregnancy test were completed and subjects were asked to complete an open-ended questionnaire to assess product acceptability. There was a further follow up two weeks later for a final urine test for pregnancy. In total 377 subjects were enrolled in the study with 328 contributing to the final analysis for contraceptive efficacy.

The 6-month life-table probabilities of pregnancy in typical use were 12.4% (standard error [SE] 2.6%) for the US subgroup and 22.2% (SE 5.3%) for the Latin American subgroup. Over the whole group the 6-month life-table pregnancy rate was 15.1% (SE 2.3%). The difference between the two subgroups was not statistically significant (two-sided z-test for life-table probabilities, significance level 0.05 Trussell et al (6) "Typical use" means that the female condom was not always used correctly or with every act of intercourse. Comparative rates where the subjects reported using the condom correctly and with every act of intercourse (perfect use leading to the lowest expected pregnancy rate) were 2.6% (SE 2.7%) for the US subgroup, 9.5% (SE 6.7%) for the Latin American subgroup and 4.3% (SE 1.8%) over the total group.

Six-month life-table discontinuation rates in the efficacy population were 34.5% (SE 3.2%) for the US subgroup and 56.2% (SE 4.5%) for the Latin American subgroup. The main reasons for discontinuation in the efficacy population were personal reasons (22.3% of the total group) and accidental pregnancy (11.9% of the total group). Personal reasons included the subject relocating, dislike of the device and loss of partner. Although these discontinuation rates appear high, they are not dissimilar to rates recorded in other studies on female barrier methods of contraception including the sponge (46.4%) diaphragm (43.7% to 48.5%) and cervical cap (46.9%).

By convention it is usual to cite 12-month contraceptive failure rates in published studies rather than 6-month rates as in this study. Given the high discontinuation rates usually seen in studies on barrier contraceptive methods, recruiting sufficient numbers to provide 12 month data is difficult and very costly. Trussell et al (6) estimated the 12-month pregnancy rates for the US subgroup in the study by using comparative data from efficacy studies on other female barrier methods, including the sponge, diaphragms and the cervical cap to estimate the ratio of pregnancy rates in the first and second 6-month periods. They concluded that for the US subgroup the 12-month typical use pregnancy rate should be in the order of 21.1% (c.f. 12.4% for the 6-month rate) and the perfect use 12-month rate 5.1% (c.f. 2.6% for the 6-month rate).

Typical comparative 12-month pregnancy rates for other barrier contraceptive methods are given in Table 17.

Table 17. Comparative 12-month pregnancy rates for barrier contraceptive methods (7)

Method	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year
	Typical Use	Perfect Use	
No method	85	85	-
Spermicide	29	18	42
Sponge (Parous)	32	20	46
Sponge (Nulliparpous)	16	9	57
Diaphragm	16	6	57
FC1	21	5	49
Male condom	15	2	53

In a smaller study (8) conducted in 10 centres in Japan in which 195 subjects were involved, of which 190 contributed data on contraceptive efficacy, the 6-month life-table pregnancy rate was 3.2% (95% CI 0.7-5.7%) for typical use and 0.8% (95% CI 0.0-2.3%) for perfect use. The author speculated that the much reduced pregnancy rate in this study might be due to the lower frequency of intercourse (coital rates were 59% lower than in the US study reported above).

5.2 STI Reduction

A number of studies have investigated the role of FC1 in STI reduction strategies. Some of these have focused on the acceptability of frequency of use of the device, for example Macaluso (9) and Musaba (10), and have not looked at the effectiveness of the device in preventing disease transmission. Even in those studies where an assessment of the device in preventing disease transmission has been undertaken, it is often not possible to make a reliable estimate of the reduction in STI transmission compared to either the male condom or unprotected intercourse, either because of study design or study size. In a number of studies, trends to reduced STI infection were seen when the female condom was introduced, but no case in the studies summarised below was statistical significance at the 95% level achieved. In a review of published papers on the female condom, Vijayakumar et al (11) concluded that there is limited but convincing evidence that FC1 is effective in increasing protected sex and decreasing STI incidence among women. The review included 137 articles and abstracts related to various aspects of the female condom as well as a closer analysis of five randomized controlled trials on effectiveness. It should be noted that because of the ethical issues associated with the exposure of control groups to risk of infection, questionable compliance of study participants and the reliance on self reporting of condom usage, determining the efficacy of any type of condom against STI infection is difficult and the results are often open to challenge.

Macaluso et al (12) showed that the rate of re-infection in a group of 920 women attending public STI clinics over a period of 6 months was reduced by 70% (relative rate= 0.3, 95% confidence interval: 0.1-0.6) when they used either male or female condoms consistently and correctly, compared to inconsistent users. STI incidence was lower among consistent users who mixed condom types than among exclusive male condom users. The authors concluded that consistent condom use reduces STI risk, but incorrect use and condom failure may greatly reduce effectiveness. They also concluded that the female condom appears to be at least as effective as the male condom as a barrier to STI, but it is not possible to determine the relative effectiveness of male and female condoms from this study.

French et al (13) followed 1442 women attending an STI clinic who were randomly assigned to receive either female or male condoms. During follow-up the women were tested for gonorrhoea, chlamydia, early syphilis, and trichomoniasis. The incidence rates for the first new post-intervention STI per 100 women-months of observation were 6.8 in the female condom group and 8.5 in the male condom group (rate ratio = 0.79, CI: 0.59-1.06). The authors conclude that women counselled on, and provided with, female condoms fared no worse and experienced a non-significant reduction in STIs compared to the male condom group. A potential confounding factor in the study is that women in the female condom arm had continued access to male condoms from sources outside of the clinic, with male condoms accounting for 1/3 of condom protected sex acts in this study arm. Women in the male condom arm had little access to female condoms and therefore rarely used them.

Soper et al (14) compared the rates of re-infection after 45 days with trichomoniasis in a group women follow-

ing treatment for the disease. The women were assigned to use the female condom in a control group on the basis of their response to a demonstration of the product. Of 104 women completing the study satisfactorily, 50 were in the control group and 54 in the female condom user group, but of the 54 in the user group only 20 reported using the female condom consistently. Re-infection rates were 7/50 (14%) in the control group, 5/34 (14.7% in the noncompliant female condom user group and 0/20 (0%) in the consistent female condom user group. Although there were no infections in the consistent user group, the reduction was not statistically significant compared to the control group ($p = 0.08$) or the noncompliant group ($p = 0.09$). This study suggests that using the female condom consistently reduces the risk of trichomoniasis infection, but it was too small, and therefore underpowered, to demonstrate that the reduction was statistically significant.

Hoke et al (15) followed 1,000 sex workers in Madagascar for 18 months to assess whether distributing both female and male condoms led to increased protection levels and decreased STIs. For the first six months participants had access to male condoms only, whereas for the final 12 months they had access to both male and female condoms. The researchers interviewed participants about condom use every two months and tested for chlamydia, gonorrhoea and trichomoniasis every six months. For the six months of male condom distribution only, participants used protection in 78% of sex acts with clients. Following female condom introduction, protection at months 12 and 18 rose to 83% and 88%, respectively. Aggregate STI prevalence declined from 52% at baseline to 50% at month six. With the female condom added, STI prevalence dropped to 41% and 40% at months 12 and 18, respectively. The authors concluded female condom introduction is associated with increased use of protection to levels that reduce STI risk.

Fontanet et al (16) estimated that additional protection against STIs would be offered to sex workers in Thailand by giving them the option of using the female condom when clients refused to use a male condom. The women were assigned to two groups, one in which they were instructed to use male condoms consistently (male condom group) and the other in which they had the option of using the female condom if clients refused or were not able to use male condoms (male/female condom group). Assignment was done by establishment to prevent women in the male condom group having access the female condoms. The proportion of unprotected sexual acts (defined as sexual acts in which condoms were not used, torn, or slipped in or out) and incidence rate of gonorrhoea, chlamydia, trichomoniasis and genital ulcer disease were measured over a 24-week period and compared between the two study groups. Condom use was very high in both groups (97.9 and 97.3 % of all sexual acts, respectively, $P > 0.05$). Male condom use was lower in the male/female condom group when compared with the male condom group (88.2 and 97.5%, respectively, $P < 0.001$), but this was counterbalanced by the use of female condoms in 12.0% of all sexual acts in the male/female condom group, contributing to a 17% reduction in the proportion of unprotected sexual acts in this group when compared to the male condom group (5.9 versus 7.1%, respectively, $P = 0.16$). There was also a 24% reduction in the weighted geometric mean incidence rate of STIs in the sex establishments of the male/female condom group compared to the male condom group (2.81 versus 3.69 per 100 person-weeks, $P = 0.18$). These are promising trends but the reductions in proportion of unprotected sex acts and STI infection in the male/female condom group were not statistically significant.

Feldblum et al (17) assessed the impact on STI prevalence of a female condom introduction and risk-reduction program at Kenyan agricultural sites in a cluster-randomized trial to determine whether a replicable, community-level intervention would reduce STI prevalence. Six matched intervention sites received an information/motivation program with free distribution of female and male condoms, and six control sites received only male condoms and related information. Participants were tested for cervical gonorrhoea, chlamydia and vaginal trichomoniasis at baseline and then at six and 12 months. Consistent male condom use was more than 20% at 12 months in both arms. Consistent female condom use was reported by 11% and 7% of intervention site women at six and 12 months. Unadjusted prevalence was 16.5% and 17.4% at the intervention and control sites respectively at six months and 18.3% and 18.5% at 12 months. Logistic regression models confirmed the null effect of the female condom intervention. The investigators concluded that the female condom introduction did not enhance STI prevention at these sites.

5.3 Functionality Studies

Given the problems and very high costs associated with conducting contraceptive efficacy studies on condoms, it is common to rely upon functionality studies of failure rates including slippage and breakage when assessing the effectiveness of condoms. The rationale behind these studies is that if a condom is made out of a barrier material that does not allow the passage of sperm or the microorganisms that are responsible for STIs, if the condom completely covers the penis or lines the vagina, and if during use the condom does not break or slip off, then it should be effective as both a contraceptive and for STI prophylaxis. Functionality studies are generally simpler and much less expensive to run than contraceptive and STI studies, and often raise fewer ethical issues. FC2 received FDA premarket clearance on the basis of a pivotal clinical study demonstrating that failure rates were non-inferior to those of FC1, rather than on the basis of a contraceptive efficacy study.

As more functionality studies have been completed on female condoms, there has been a convergence of opinion on the major failure modes associated with these devices. The failure mode definitions have been reviewed by ISO/TC 157 WG 18 and by the WHO Female Condom Technical Review Committee. The agreed definitions were published by Beksinska et al.(18) They are summarised below:

Nonclinical breakage is defined as breakage noticed before intercourse or occurring after withdrawal of the condom from the vagina. Nonclinical breakage is breakage without potential adverse clinical consequences. The nonclinical breakage rate is calculated by dividing the number of female condoms noted to have broken before intercourse or after withdrawal by the number of female condom packages opened.

Clinical breakage is defined as breakage during sexual intercourse or during withdrawal of the female condom from the vagina. Clinical breakage is breakage with potential adverse clinical consequences. The clinical breakage rate is calculated by dividing the number of female condoms reported to have broken during sexual intercourse or during withdrawal by the number of female condoms used during sexual intercourse.

Total breakage is defined as the sum of all female condom breakages at any time before, during or after sexual intercourse. It includes both clinical breakages and non-clinical breakages. The total breakage rate is calculated by dividing the total number of female condoms that broke by the number of female condom packages opened.

Slippage is defined as an instance when a female condom slips completely out of the vagina during sexual intercourse. The slippage rate is calculated by dividing the number of female condoms that slipped by the number of female condoms used during sexual intercourse.

Misdirection is defined as vaginal penetration whereby the penis is inserted between the female condom and the vaginal wall. The misdirection rate is calculated by dividing the number of reported events of misdirection by the number of female condoms used during sexual intercourse.

Invagination is defined as an instance when the external retention feature of the female condom is partially or fully pushed into the vagina during sexual intercourse. The invagination rate is calculated by dividing the number of events of invagination by the number of female condoms used during sexual intercourse.

As part of the risk assessment, manufacturers should determine if, because of the design, materials of construction or method of manufacture, any additional failure modes may apply to the specific female condom under consideration.

In a 6-month prospective functionality study in 869 women attending two clinics in Alabama, Valappil et al (19) compared the failure rates of FC1 and male condoms in a 6-month prospective functionality study in 869 women attending two STI clinics. The brand or brands of male condom used was not specified in the paper (it is not stated clearly if single or multiple brands were used). Based of a total of 20,148 acts of intercourse, the breakage rate of female condoms was determined to be 0.1% (95% CI 0.05 to 0.21) compared to 3.1% (95% CI 2.8 to 3.4) for male condoms. Slippage rates were determined as 5.6% (95% CI 5.1 to 6.1) for the FC1 and 1.1% (95% CI 0.9 to 1.3) for male condoms. The definitions of slippage used in this study differ from those specified for male condoms by Steiner et al and for female

condoms by Beksinska et al (ibid). The male condom slippage definition did not differentiate between complete slippage off the penis (which is classified as a clinically significant failure since it could lead to pregnancy) and partial slippage (which is not classed as a clinically significant failure). The definition of female condom slippage included both the condom slipping out of the vagina and the condom being pushed into the vagina. The latter failure mode is now classified separately as invagination. No mention was made of the rates of misdirection, i.e. the penis being inserted to the side of the female condom in direct contact with the vaginal wall.

The pivotal clinical study that was used to support the FDA PMA review was conducted by Beksinska et al (20) (2006) in South Africa. It was a multicentre, randomized, prospective, crossover study comparing the failure rates of FC1 and FC2. A total of 276 women were enrolled, with 201 completing the study (73%). All women were using hormonal contraceptives, an IUD or were sterilized (tubal ligation). The study included women recruited from both urban and rural areas with a wide range of backgrounds, including commercial sex workers, students and attendees at family planning and STI clinics. Participants reported condom failure rates through coital logs and follow-up visits. Vulval inspection and macroscopic examination of the vaginal epithelium were conducted at each follow-up visit. In total, 1920 FC1 and 1881 FC2 condoms were used.

Clinical breakage rates during intercourse were 0.47% for FC1 and 0.43% for FC2 (95% CI for the difference -0.62 to 0.53). Misdirection was 1.26% for FC1 and 0.64% for FC2 (95% CI for the difference -1.33 to 0.09). Invagination (outer ring pushed completely or partially into the vagina) was 3.14% for FC1 and 2.98% for FC2 (95% CI for the difference -1.24 to 0.91). Complete slippage of the condom out of the vagina was low, 0.21% for FC1 and 0.11% for FC2 (95% CI for the difference -0.39 to 0.19). Overall, the total clinical failure rate was 5.24% for FC1 and 4.3% for FC2. The upper 95% limit for the difference in total clinical failure rates between FC2 and FC1 was approximately 1%. On the basis of these results the FDA concluded that FC2 was non-inferior to FC1 with respect to failure rates.

5.4 Prostate Specific Antigen (PSA)

Functionality studies rely very heavily on self reporting of condom failures and the assumption that semen does not leak into the vagina unless one or more of the defined types of failures occurs. Self reporting of failures is not necessarily reliable for a number of reasons, including poor recording and recall of events by the subjects and failure to even notice that the condom has failed. There have been some instances in studies on male condoms where reportedly failed condoms have been found to be intact when examined post coitally in the laboratory. For this reason researchers have investigated other biological markers that can be used to indicate the entry of semen into the vagina. Of these markers, the most widely researched is prostate specific antigen (PSA), a glycoprotein produced by cells of the prostate gland.

PSA is a protease that is present in the seminal fluid at high concentrations, its function being to break down the high molecular weight protein responsible for the seminal coagulum into smaller polypeptides, resulting in liquefaction of the coagulum (21). Because serum PSA levels can be elevated in men with prostate cancer, as well as with some benign prostate conditions, measuring serum PSA has become a standard screening test, both for detecting prostate cancer as well as for monitoring men with the disease. For this reason a number of quantitative and semi-quantitative assays have been developed for PSA. The availability of routine, validated assays and the high concentrations of PSA found in semen make it an excellent marker for detecting leakage into the vagina in barrier contraceptive studies.

Hobbs et al (22) evaluated a rapid PSA test against a quantitative assay to identify semen in vaginal swab specimens taken from 492 women participating in two separate research studies in Bangladesh and Zimbabwe. They found that the rapid test (ABAcard p30 from Abacus Diagnostics) was 100% sensitive (95% CI 98%-100%) and 96% specific (95% CI 93%-97%) compared with the quantitative assay (IMx from Abbott Laboratories) in detecting >1.0 ng PSA/ml vaginal swab eluate. The rapid PSA results were semi-quantitative and correlated well with PSA concentrations.

Since the late 1990s a number of researchers have published papers on the use of PSA assays on post coital vaginal swabs to monitor leakage of semen in

studies on both male and female condoms. Lawson et al (23) compared three potential semen biomarkers, acid phosphatase (AP) activity, PSA, and the human seminal plasma antigen (MHS-5), by vaginal swabbing after women were inoculated intra-vaginally with six measured, increasingly larger doses of their partners' semen. Pre-inoculation levels for PSA were low (0.00-1.25 ng/ml), levels for AP were variable (0-350 U/l), and levels for MHS-5 were all negative. All post-inoculation samples were positive for PSA, whereas for AP, 64 of 117 (55%) were positive and 14 of 120 (12%) were positive. The authors concluded that PSA immunoassay was the best semen biomarker under the sampling and testing conditions used.

Macaluso et al (24) reported a study in which 40 women were exposed to different volumes of their partners' semen (10 µl, 100 µl, and 1 ml). Vaginal fluid samples were taken before and immediately after exposure, and then after 1, 24 and 48 hours. PSA was measured using an enzyme-linked immunoassay. Average PSA level pre-exposure ranged between 0.43 and 0.88 ng/ml. Immediately after exposure, average PSA levels were 193 ng/ml when exposed to10 µl of semen, 472 ng/ml when exposed to 100 µl of semen and 19,098 ng/ml when exposed to 1 ml semen. The PSA levels declined within one hour and returned to background at 48 hours. Bahamondes et al (25) also showed increasing vaginal PSA detection rates with increasing exposure to semen. They reported that PSA levels were lower for nurse-collected samples compared to self-collected samples, and attributed this to the delay in sampling associated with nurse collection.

In studies on male condoms, Walsh et al (26) compared pre-coital and post-coital vaginal PSA levels after unprotected intercourse and intercourse with intact deliberately punctured condoms. PSA was detected in 100% (24/24) of vaginal samples collected immediately after unprotected intercourse and in none of the vaginal samples collected more than 24 hours after intercourse (0/90). Excluding uses where the condom failed during intercourse, PSA was detected in 2% (1/47) of the post-coital vaginal samples collected after use of intact condoms and in 41% (14/34) of the samples collected after use of punctured condoms (1-mm holes).

In a further study by Walsh et al (27), 830 couples enrolled in a condom efficacy study were asked to collect a baseline sample of ejaculate from the inside of the first condom they used and to collect a post-coital vaginal sample whenever a study condom broke or slipped off during intercourse. For those couples (68) who subsequently experienced a condom failure, the PSA levels inside of the first condom used averaged 13.4 µg per swab compared to post-coital vaginal levels after condom breakage of 5.7 µg per swab (data from 79 couples). For those couples experiencing condom slippage off the penis, the average post-coital vaginal PSA level was 2.5 µg PSA per swab. These results suggest that even when a condom fails there is still some degree of protection.

Several studies have been undertaken on female condoms where PSA has been monitored, usually in addition to the failure modes reported above. Macaluso et al (28) (2002) assessed the frequency of female condom failure in women recruited in Birmingham, Alabama by monitoring pre- and post-coital PSA levels in vaginal fluid. A total of 175 women used 2,232 female condoms (FC1). Semen exposure was assessed using two different criteria based on the differences between pre- and post PSA levels. One criterion was more sensitive to semen exposure than the other but more likely to be affected by false positives. The second criterion was less sensitive to false positives but might miss exposure to small quantities of semen. Semen exposure was detected in 7% to 21% cases of condom use depending on which exposure criterion was used. Higher rates of exposure were reported when condoms broke (67% to 73%), slipped in (invagination - 55% to 74%), leaked (44% to 57%) or were bypassed (misdirection - 52% to 57%). Based on logistic regression analyses for repeated measurements, user-reported problems accounted for less than 59% of the instances of semen exposure. The authors concluded that exposure was associated with user-reported problems but also occurred in their absence. Reported problems and semen exposure decreased with user experience.

The failure rates of male and female condoms were compared in two randomized trials, one in the US and the other in Brazil(29) (Chen et al 2007). In both trials self reporting of failures by questionnaire and PSA monitoring of pre- and post-coital vaginal PSA levels were used to assess failure rates. Failure rates by self reporting were significantly higher in the US study compared to the Brazil study for both female and male

condoms. Total reported problems for female condoms were 29% in the US versus 5% in Brazil. Equivalent results for male condoms were 8% in the US versus 3% in Brazil.

Assessment of the PSA data was done by stratification into four categories: non-exposed (≤1 ng/ml); low (>1 ng/ml ≤22 ng/ml), moderate (22–99 ng/ml) and high ≥100 ng/ml). Based on the distribution of PSA levels it was concluded that there were no statistically significant differences between semen exposure levels in the case of male condoms between the US and Brazil. In the case of female condoms, post-coital vaginal PSA levels in Brazil were higher than in America, a result that is in marked contrast to the self-reported failure rates. The authors concluded on the basis of these results that self reporting may be less reliable than using PSI to assess condom failure. Other studies, for example Minnis et al (30), have reported similar conclusions.

Galvão et al (31) reported that semen exposure (post-coital vaginal PSA > 1 ng/ml) in the Brazil study occurred more frequently with female condoms (22% of uses) than with male condoms (15%), although the difference was small and not statistically significant at higher PSA levels (≥ 150 ng/ml).

6 Manufacture

Female condoms are made by a number of different manufacturing techniques and generally include additional steps over and above those used in male condom manufacture. The sheath component can be made by welding together pre-formed sheets of material or by dipping. As is the norm for male condoms, the sheath components are subjected to 100% testing to screen out defecting sheaths containing holes or tears than could lead to leakage. Electrical conductivity testing, gas leakage and vacuum retention tests are or have been used. Depending upon the design of the condom, it may be necessary to conduct this testing before final assembly of the condom, e.g. insertion of the internal retention feature or mounting the sheath on the external retention frame. Final packing and lubrication follows the same general principles used for male latex condoms, but the equipment and procedures may differ.

Given the more complex design of female condoms and the possible need for specialised, automated equipment, the establishment and validation of manufacturing facilities is generally more expensive and demanding than for male latex condoms. Early manufacturing may well be completed on pilot scale equipment, often with quite a high degree of manual operation. Initial production capacity may therefore be severely limited because of this and Lot (batch) sizes may be unusually small when compared to those employed in male latex condom manufacture. These limitations can place particular demands on quality control and quality assurance operations. High levels of testing may be required and statistical controls may need to be introduced to ensure adequate levels of Lot-to-Lot reproducibility. The selection and characterization of product for clinical evaluation and other important studies such as stability testing can therefore be highly demanding. It is essential that manufacturers can demonstrate that the products selected are typical of normal production and comply with the specification established for the product.

Given that for many product designs initial manufacture will be on the pilot scale and it is during this period that clinical and other critical evaluations will have been carried out, the subsequent scale-up of manufacturing operations places special demands on the manufacturers. If, as a consequence of scaling up, the manufacturing process any of the key design or performance properties of the condom change significantly, then further clinical and other evaluations may be necessary in order to confirm that the safety and effectiveness of the product has not been compromised. Manufacturers, auditors and inspectors need to pay special attention to any changes in the scale of manufacture, the type of equipment used or the automation of any of the process steps to ensure that the product is not significantly affected by the changes.

7 Testing

Testing procedures and requirements for female condoms are defined in the draft international standard, ISO/FDIS 25841.2. Essentially the test methods are derived from those used for male condoms. On a routine Lot-by-Lot basis the following key requirements are assessed:

- Design
- Dimensions

- Bursting pressure and volume
- Freedom from holes and visible defects
- Packaging and labelling requirements including pack integrity

Additionally, further testing is required during the design and development phase of the product or following a significant change in the design, materials of construction or manufacturing procedures for the condom:

- Barrier properties (lack of permeability to viruses, etc)
- Biocompatibility
- Clinical evaluation
- Stability/shelf life assessment

Some regulatory bodies may request more information. For example, the FDA typically requires extensive characterization of the polymeric materials used in the construction of the device, including monomer composition, molecular weights, molecular weight distributions, residual monomer and catalyst composition, etc. The FDA may also request information about the physical properties of the retention features and thermal characterisation of the polymeric materials by DSC. To a significant extent the nature of the information requested will depend upon the materials used. Although this might appear excessive, the better the materials and the properties of the condom and critical components are characterized, the less likely are any unexpected outcomes from the clinical evaluation and the easier it will be to implement essential material and process changes later.

Many of the routine tests follow the procedures used for male latex condoms, although some changes in the test equipment may be necessary. For example, new or modified mandrels will probably be required for determining the lengths of the condoms and for conducting the air inflation test. Special mountings with sealing plugs are required for the freedom from holes test. Modifications may also be necessary to the pressure transducers and flow meters in the inflation test equipment to accommodate the differences in bursting pressures and volumes between male and female condoms. Modifications may be necessary for the pack integrity test, given the different dimensions and materials of construction that are used for female condom packs.

Full details of the test methods and equipment are given in the relevant annexes of ISO/FDIS 25841.2 and, although this standard has not yet been published, it is unlikely that significant changes will be made to these tests. Additionally, manufacturers are required to specify any further information that is required for testing, such as the dimensions of the mandrels used to measure length and conduct the inflation test. Failure by independent test laboratories to follow the manufacturers' recommendations might result in conflicting or incorrect results.

Specific issues relating to the various test methods are summarized in the following sections.

Freedom-from-Holes Testing

Only the water leakage test is specified in ISO/FDIS 25841.2. With the possibility of many different designs and materials, the reliability of the electrical conductivity test is questionable. The fill volume for the test is not specified; this will depend to large extent on the dimensions of the condom and the modulus (stiffness) of the material used for the sheath component. Instead of defining a fill volume, as is the case with male latex condoms, the instruction is to fill the condom with water to the top of the fill plug. With many materials this will be satisfactory, but there may be issues with condoms made from low modulus materials. In such cases the manufacture will have to specify the fill volume in order to prevent overfilling of the condom, which could lead to excessive stretching and eventual bursting of the condom. For all female condoms an AQL of 0.25 is specified for freedom from holes, the same requirement as for male condoms.

Bursting Volume and Pressure

Testing for airburst properties is a requirement for all types of female condoms. It is seen as a critical performance test and is used to control both the quality and strength of the product. The same AQL, 1.5, is specified as for male condoms, but unlike male latex condoms it is not possible to specify minimum bursting

pressures and volumes since these will vary depending upon the design of the condoms and the materials used. ISO/FIDS 25841.2 specifies that manufacturers set the minimum limits for bursting pressure and volume based on the properties of the Lot or Lots of condoms used in the clinical investigation(s) undertaken to demonstrate the effectiveness of the products. The logic is that any future Lot should be no worse in terms of bursting properties than the Lot or Lots used in the clinical studies. Procedures for setting these limits are given in the draft standard.

This requirement makes it essential that manufacturers characterize the airburst properties of the condoms used in the clinical studies. A sample size of at least 2,000 condoms is recommended to ensure that an adequate representation of the distribution of burst properties is obtained, particularly around the 1.5 percentile region which is used as the basis for setting the specification. If manufacturers find it necessary to combine small Lots or sub-Lots in order to make sufficient samples for the clinical studies, then precautions should be taken to ensure that the Lots or sub-Lots are of consistent quality. Various statistical techniques can be used for this; the use of control charts, for example, is one method that can be used to establish requirements for Lot-to-Lot or sub-Lot to sub-Lot consistency.

Manufacturers need to be aware of the implications of setting the specification in this way. Any future material or manufacturing process change that affects the properties of the condoms such that a revision in the specification is required might invalidate the outcome of the clinical evaluation. Further clinical studies may be required to confirm that the effectiveness of the product has not been compromised. The need for such clinical studies is assessed by conducting a risk assessment according to *ISO 14971*. Regulatory bodies will generally want to review the risk assessment and may or may not accept the conclusions reached by the manufacturer.

Clinical Investigations

A key principle underlying ISO/FDIS 25841.2 is that the clinical performance and effectiveness of a condom cannot be determined solely from the design specification and a knowledge of the materials used. It is generally necessary to demonstrate that a new or modified condom design has an acceptable level of clinical effectiveness by conducting a clinical investigation. The type of clinical investigation required depends upon how closely the product matches existing female condoms in the market place.

If the manufacturer can demonstrate that the new product is sufficiently similar to a design that is already approved and marketed, then they may be able to demonstrate that the product has an acceptable level of effectiveness in a functionality study designed to determine the failure rates for each of the possible failure modes identified for the product. If not, then the manufacturer may need to complete a full contraceptive efficacy study. In order to determine the type of trial required, manufacturers are required to conduct a risk assessment in accordance with *ISO 14971*. There are no guidelines in ISO 25841.2 on what constitutes equivalence to a marketed product. This is left to the discretion of the manufacturers and the regulatory bodies that will review any regulatory submission. Manufacturers are strongly advised to undertake discussions with the relevant regulatory bodies and agree on the nature of any clinical investigations that will be required prior to commencing any clinical work.

Ideally manufacturers should undertake a contraceptive efficacy study to determine the pregnancy rate for the condom. ISO/FDIS 25841.2 currently specifies that the 12-month pregnancy rate should be determined, but for various reasons this is probably impractical and instead it is now proposed that the 6-month rate would be acceptable (this change has still be to be confirmed). The standard provides only limited guidance at present on conducting contraceptive efficacy studies. If such studies are necessary then it is essential that manufacturers use research organizations and advisers with the appropriate knowledge and expertise to undertake such studies.

Reasonably detailed requirements for the outcome of functionality studies to determine the failure rates are given in *ISO 25841.2* for those cases where the manufacturer can make a sufficiently strong case of equivalence to a marketed product. The marketed product should have a known pregnancy rate determined from a contraceptive efficacy study (or have been evaluated directly against such a product). The upper bound of the one-sided 95% confidence

interval for the combined clinical failure rates of the new or modified product shall not exceed that for the control (marketed) product by more than 3%. A draft standard for conducting such clinical investigations is under development by ISO/TC 157 WG20 (currently designated document WD 29942-2) based on recommendations developed on behalf of WHO.

Biocompatibility

Requirements for biocompatibility testing of female condoms are essentially the same as for male condoms. The finished product and its components together with any lubricant, additive, dressing material, or powder applied to it, as well as all retention or insertion devices, have to be evaluated. The testing specified in *ISO 10993-1*, taking into account the nature and duration of exposure to the product, includes cytotoxicity according to *ISO 10993-5* and irritation and sensitization according to *ISO 10993-10*. Some regulatory bodies may request additional testing such as subacute and subchronic toxicity according to *ISO 10993-11*. Accredited laboratories should be used for all biocompatibility testing, and the outcome should be assessed by suitably qualified personnel such as toxicologists.

Barrier Properties

Since a wide range of materials could be used in the manufacture of female condoms and some of the materials may be placed under permanent stress, such as when stretched over an external frame that forms part of the external retention feature, it is a requirement in ISO/FDIS 25841.2 that the barrier properties of any new or modified design of female condom shall be established by viral penetration studies. The recommended organism is bacteriophage Phi-X174. Full details of the test method, which was originally developed by the US FDA, are given in the draft standard. Essentially a titre of bacteriophage (the challenge medium) is placed inside the condom and any leakage through the film is detected by collecting and culturing a medium placed outside the condom. The use of an appropriate control condom, such as a male condom, meeting the requirement of *ISO 4074* is specified.

Interpretation of the test results can be problematic. In most cases no significant migration of virus across the condom is usually seen, demonstrating that the condom film is an effective barrier, but with a few individual condoms it is common to see minor leakage equivalent to a few micro litres of challenge medium. Rarely, significant leakage is seen with an individual condom due to the presence of a hole. The low level leakage, which can be seen with both latex and synthetic materials, is probably due to the presence in some condoms of tiny holes that are too small to be of any clinical significance, or to be detected by any of the standard freedom-from-holes test. It is for this reason that the use of a control is strongly recommended and care is required when interpreting the results.

Stability Studies and Shelf-Life Determination

Manufacturers are required to determine the shelf life of the female condom by real time studies at $(30\ ^{+5}_{-2})$°C. The justification for this temperature range for real time studies is exactly the same as for male latex condoms; 30°C is the mean kinetic temperature of the most extreme climatic zones III, IVa and IVb as classified by WHO (32). The normal temperature tolerance range of ±2°C has been extended to +5°C to simplify studies in hot climates where daytime temperatures indoors can exceed 32°C. Manufacturers electing to use moisture permeable packing for female condoms should also control the humidity during real time studies to (75 ± 5)% to meet the requirements for climatic zone IVb.

Pending the outcome of real time studies manufacturers may designate a provisional shelf life for a product on the basis of accelerated studies. In recent years significant progress has been made on simplifying accelerated stability studies on male latex condoms, largely because substantial data have now been generated allowing the real-time studies at $(30\ ^{+5}_{-2})$°C to be correlated with those from accelerated studies. This has allowed new proposals to be adopted in the 2010 WHO/UNFPA Specification for Male Latex Condoms whereby specified periods of accelerated ageing at 50°C can be deemed to be equivalent to specific shelf-life periods at $(30\ ^{+5}_{-2})$°C.

There is currently insufficient evidence to adopt the same approach for female condoms made from natural rubber latex, and the approach certainly cannot be used for female condoms made from synthetic materials. *ISO/FDIS 25841.2* provides guidance on conducting and analysing accelerated studies. The methods of analysis are primarily based on using the Arrhenius relationship, which relates changes in the rates of

chemical reactions to changes in temperature. There is insufficient data available at present to determine how well these methods work.

8 Patents

Given the limited availability of female condoms currently and their relatively recent introduction to the market, there are perhaps a surprising number of published patents covering the product category. Many of these are relatively recent and therefore still in force. Usually a patent provides a period of protection to the inventor, assignee or licensee for a period of 20 years. A quick search of the international patent literature indicates that the number of patents covering either female condom designs or specific aspects of their manufacture probably runs to several hundred.

The primary purpose of the patent is to provide a period of exclusivity during which time the inventor, assignee or licensee is protected from competition by another party copying the specific patented features of the product. Should another party infringe the patent claims by selling a product with the same features that are covered by the patent's claims, then the patent holder can bring an action in the civil courts to claim damages for past infringement and obtain an injunction to prevent future sales. In cases of blatant infringement punitive damages may be awarded in some countries such as the US but usually damages are based on loss of sale and/or licensing fees.

A patent is not a right to practice or use the invention. It is quite possible that a patent holder may still infringe an earlier patent even though the patent they hold is perfectly valid. This is common with patents that cover improvements to products and processes. In order to ensure that a patent holder can sell a product without fear of infringing an earlier patent, particularly in a crowded patent area, it is essential to conduct a freedom-to-operate review. Such a review considers the claims in prior published patents and determines if there is any risk of infringement. When conducting such a review, it is necessary to be aware of the doctrine of equivalents, which is part of the patent law in many countries. This covers the situation where minor changes are made so that product does not fall within the literal claims of an existing patent but nevertheless has essentially the same features or adopts the same solutions. The way in which the rule is applied varies depending upon country, but it does mean that making minor changes to a product to avoid an existing patent does not guarantee non-infringement. A professional right to practice review not only reduces the risk of accidentally infringing an existing prior art patent, it also reduces the risk of punitive damages being awarded if there does turn out to be an infringement. In such cases a manufacturer can claim that they took due care to prevent infringing existing patents.

The cost of a freedom-to-operate review varies significantly depending upon the nature of the product and the number of patents that have to be taken into consideration. Given the number of patents in the female condom sector, the cost is likely to be in the order of £5,000 to £15,000.

Finally, it is important to recognize that it is not necessary to patent a new product in order to develop and sell it. Many designs are simply not patentable over the prior art. To be patentable a new product or process has to have an inventive aspect that is not obvious to those "skilled in the art" for that particular product or process category. Nor is the possession of a published patent a guarantee that the patent is valid. A published patent can be declared invalid for a number of reasons, one of them being obviousness over existing prior art. The Graham patent from 1907, for example, discloses several features of female condoms that can be found in current designs. This prior art could, in principle, provide grounds for rejecting some claims in modern patents covering these design features.

9 Key Issues

There are a number of key issues that need to be addressed when considering the requirements, specification, and prequalification of female condoms for public sector distribution. Each type of female condom will be of unique design, will have its own specification and will have been subjected to some level of clinical evaluation. Additionally, it is necessary to confirm that adequate pre-clinical testing has been conducted to ensure that the product is safe and that adequate manufacturing development and validation have been completed to ensure that the product can be made to a consistent standard. Given that in many cases the products could

be relatively new, manufacturing equipment, processes and procedure may still be undergoing development, scale-up and optimisation. Some of the issues that need to be addressed during the review process are summarised below:

1. ***Pre-clinical testing**:* It is essential to confirm that all necessary pre-clinical testing has been carried out to ensure the safety of the product. Unlike with male condoms, consideration has to be given to any ancillary devices on female condoms, such as the retention features and insertion devices. Consideration also has to be given to the extended time period that some female condom designs may be left within the vagina and the wider range of materials that may be used.

2. ***Product specification:*** The specification will have been set by the manufacturer. It is essential to assess whether the specification is adequate in terms of scope and requirements to ensure that the product is manufactured to a consistent standard. Unlike male condoms, consideration has to be given to the adequacy of specification of the ancillary components of female condoms, such as the retention features, insertion devices, lubricant, packaging, etc. Further, it is necessary to confirm that the specification has been correctly based on the characteristics of the products used in the clinical evaluations.

3. ***Test methods:*** Special test equipment will be probably be required for each type of female condom, at least as far as mounting mandrels and clamping arrangements for airburst testing and mounts for freedom-from-hole testing are concerned. Manufacturers will have to supply additional information on test methods and equipment to allow independent laboratories to test the products correctly. Consideration must be given to need and desirability of removing ancillary components, in particular the retention features, in order to facilitate testing. Specific test methods for the ancillary components may also be required. The number of laboratories appropriately equipped to test female condoms in general, and specific product types in particular, may be restricted. There may be significant restrictions on the number of laboratories for which the scope of *ISO 17025* accreditation extends to female condoms. Again it is necessary to consider the ancillary components and determine whether test methods are available and adequate to characterise these.

4. ***Manufacturing and quality management:*** As with male condoms consideration has to be given to the quality management system and processes used in the manufacture of the product. With some designs of female condom manufacturing, operations could still be in the transition phase between pilot and full operation. Consideration may have to be given to the equivalence of products manufactured on different scales and possible use of different equipment.

5. ***Clinical evaluation:*** Consideration will have to be given to the types and results of clinical investigations undertaken to confirm the acceptability and effectiveness of the products. As part of this assessment the equivalence of the design and function of the device relative to marketed products will need to be considered.

6. ***Shelf life and stability:*** Given the wide range of materials that could be used for the construction of female condoms, the number of packaging options and the unique design of each individual product, very limited guidelines can be given on the methods used to justify shelf-life claims. The requirements for shelf-life verification of ancillary components, such as the retention features, also need to be taken into consideration. Data from real-time studies may be limited, given that some products may have only recently been developed or modified.

1 Youssef, H. The history of the condom, J R Soc Med, 1993; 84(4) 226 – 228

2 *Federal Register* Vol. 64, No. 111 Thursday, June 10, 1999 / Proposed Rules.

3 Bounds et al, Female condom (Femidom). A clinical study of its use-effectiveness and patient acceptability. *The British Journal of Family Planning,* 1992; 18: 36-41.

4 Code of Federal Regulations 21CFR844.5330 revised April 1, 2009.

5 Farr et al, Contraceptive Efficacy and Acceptability of the Female Condom. *American Journal of Public Health*, 1994; 84(12) 554-558.

6 Trussell et al, Comparative Contraception Efficacy of the Female Condom and Other Barrier methods. *Family Planning Perspectives*, 1994; 26: 66-72.

7 Trussell et al, *Contraceptive Technology*, 19th edition. New York NY: Ardent Media, 2007.

8 Trussell, Contraceptive Efficacy of the Reality Female Condom. *Contraception*, 1998; 58: 147-148.

9 Macaluso et al, Female Condom Use Among Women at High Risk of Sexually transmitted Disease. *Family Planning Perspectives,* 2000; 32 (3): 606-612.

10 Musaba et al, Long-term use of the female condom among couples at high risk of human immunodeficiency virus infection in Zambia. *Sex Transm Dis.* 1998; 25(5): 260-4

11 Vijayakumar et al, A review of female-condom effectiveness; patterns of use and impact on protected sex acts and STI incidence. *Int J STD AIDS*. 2006 Oct;17(10):652-9.

12 Macaluso et al, His Condom or Her Condom? A Comparative Efficacy Study Among Women at High STD Risk. Draft Manuscript. Final Report NIH Contract N01-HD-1-3135.

13 French et al, Use-effectiveness of the female condom versus male condom in preventing sexually transmitted disease in women. *Sex Transm Dis.* 2004; 30(5): 433-439.

14 Soper et al, Prevention of vaginal trichomoniasis by compliant use of the female condom. *Sex Transm Dis*, 1993; 20(3): 137-139.

15 Hoke et al, Temporal trends in sexually transmitted infection prevalence and condom use following introduction of the female condom. *Sex Transm Dis*, 2007; 18(7): 461-466.

16 Fontanet et al, Protection against sexually transmitted diseases by granting sex workers in Thailand the choice of using the male or female condoms; results from a randomized controlled trial. *AIDS*, 1998: 12(14): 1851-9.

17 Feldblum et al, Female condom introduction and sexually transmitted infection prevalence: results of a community intervention trial in Kenya. *AIDS*. 2001 May 25;15(8): 1037-44.

18 Beksinska et al, Standardized definitions of failure modes for female condoms. *Contraception* 2007;75: 251–5 [Epub 2007 Feb 7].

19 Valappil, et al, Female condom and male condom failure among women at high risk of sexually transmitted disease. *Sex Transm Dis*, 2005: 32(1); 35-43.

20 Beksinska et al, Performance of the Reality Polyurethane Female Condom and a Synthetic Latex prototype; A Randomized Cross-Over Trial among South African Women. *Contraception*, 2006: 73; 386-393.

21 Oesterling JE, Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. *J Urol*, 1991; 145 (5): 907-230.

22 Hobbs et al, Good performance of rapid prostate-specific antigen test for detection of semen exposure in women: implications for qualitative research. *Sex Transm Dis*, 2009; 36(8): 501-6.

23 Lawson et al, Objective markers of condom failure. *Sex Transm Dis*, 1998: 25(8): 427-32.

24 Macaluso et al, Prostate-specific antigen in vaginal fluid as a biologic marker of condom failure, *Contraception*, 1999: 59(3): 195-201.

25 Bahamondes et al, Prostate-specific antigen in vaginal fluid after exposure to known amounts of semen and after condom use: comparison of self-collected and nurse-collected samples. *Hum Reprod*, 2008: 23(11); 2444-51.

26 Walsh et al, Evaluation of prostate-specific antigen as a quantifiable indicator of condom failure in clinical trials. *Contraception,* 1999: 60(5); 289-98.

27 Walsh et al, Use of prostate-specific antigen (PSA) to measure semen exposure resulting from male condom failures: implications for contraceptive efficacy and the prevention of sexually transmitted disease. *Contraception*, 2003: 67(2): 139-50.

28 Macaluso et al, Efficacy of the female condom as a barrier to semen during intercourse. *Am J Epidemiol*, 2003: 157(4): 289-97.

29 Chen et al, Self-reported mechanical problems during condom use and semen exposure. Comparison of two randomized trials in the United States of America and Brazil. *Sex Transm Dis*, 2007: 34(8): 557-62.

30 Minnis et al, Biomarker validation of reports of recent sexual activity: results of a randomized controlled study in Zimbabwe. *Am J Epidemiol*. 2009: 170(7): 918-24. Epub 2009 Sep 9.

31 Galvão et al, Effectiveness of female and male condoms in preventing exposure to semen during vaginal intercourse: a randomized trial. *Contraception*, 2005: 71(2): 130-6.

32 World Health Organization, Expert Committee for Pharmaceutical Preparations, 40th Report, *Technical Report Series*, No 937, 2006.

ANNEX IV
METHODS FOR ASSESSING THE QUALITY OF SUPPLIERS

There are a number of methods for assessing the quality of manufacturers. Because of the inherent uncertainty in estimating the quality of a single Lot by testing a sample as described in Chapter 1, it is only by monitoring quality across many Lots that a reliable picture can be established about the quality of a specific manufacturer. Decisions based on information from a small number of Lots—for example, in the case of short-term or small-volume contracts—can be misleading when considered in isolation.

In general, it is most important to monitor the quality and consistency related to the Performance Requirements.

Unless there is specific concern about an established supplier's ability to comply with the design-related requirements, it is probably not worth monitoring these properties.

At the present stage of development of female condoms, there are few experienced manufacturers, and several companies seeking to enter the market with new products.

For a new manufacturer, it is not possible to get historical data, and it is not likely that such manufacturers will be able to produce several Lots of product to produce a track record, unless the products can be sold.

Those manufacturers which have at least several months of experience of continuous manufacture on a full-size plant can be assessed using the techniques applied to male condoms, as listed below:

1.1 Process average

The process average is the percentage of condoms that are non-conforming over a defined time period or quantity of production. It is calculated for each requirement detailed in the *WHO/UNFPA Specification* by dividing the number of non-conforming condoms by the total number of condoms tested. Ideally, the process average for a specific attribute should be not greater than half the specified AQL.

1.2 Control charts

Control charts provide a very convenient and simple way of monitoring quality over time and observing trends in process averages. They can provide early warning of any change in quality, alerting both manufacturers and purchasers to potential problems. They can be used retrospectively to assess how stable a process is. They provide a means of correlating changes in process average with process operating conditions or change in raw material batch. Their use is strongly recommended to confirm that a manufacturer has production under control and is capable of achieving the quality levels specified.

To construct a control chart, the percentage defects for each Lot is plotted against Lot number or any other appropriate parameter such as date of manufacture. Control charts can also be constructed for variable data, such as average burst volumes and burst pressures, and for standard deviations. Warning and control limits are usually added to the control chart to allow changes in quality to be assessed quickly. Typically, warning limits are set at the overall mean ±2 standard errors of the means. If the warning limits are approached, it implies that changes are occurring that could lead to problems with product quality, and action should be taken to restore the process to normal operation.

Action limits are set at the overall mean ±3 standard errors of the means. If the action limits are approached, then it is most probable that a statistically significant change to product quality has occurred, and immediate action must be taken to address the problem.

The standard error of the means is determined by calculating the standard deviation of a sequence of Lot means when the process is considered to be operating in statistical control. It is recommended that data from between 20 and 30 individual Lots be used when computing the standard error of the means.

Typically, for male latex condom production the standard error of the means, expressed as a percentage of the overall means, for burst volume and burst pressure data is in the region of 6%. Any shift in the average burst pressure or volume of a Lot or Lots by more than 18% to 20% almost certainly signals that there has been a highly statistically significant change in the manufacturing process and/or the materials used. There is currently insufficient public data available on female condoms to assess whether the standard errors are of similar magnitude but shifts in the order of 20% or

more might signal a need for further investigation and tighter monitoring of the manufacturer.

Monitoring changes in average burst volumes and pressures using control charts is an excellent method of detecting significant changes in the quality of production. This procedure can be implemented as an alternative to testing oven-conditioned condoms for bursting volume and pressure on a Lot-by-Lot basis.

Cumulative sum (cusum) control charts can also be used. In these charts the cumulative difference between the actual result and the target or expected result is plotted in place of the process average. Cusum charts have the advantage of being able to detect changes in underlying quality more rapidly than standard charts based on the process average, but they are more complex to construct and not quite so intuitive to understand.

Refer to a standard textbook on quality control procedures or statistics for more information on control charts. Procedures for producing these charts are also given in a series of ISO standards: *ISO 7870* is a general guide and introduction to control charts; *ISO 8245* describes Shewhart charts and includes techniques for charting attribute data; and *ISO 7966* describes acceptance charts. Cusum charts are described in parts 1–4 of *BS 5703*.

1.3 Aggregate analysis

On occasion it might be useful to determine whether a shipment consisting of a number of Lots is in compliance based on an aggregate assessment of the results taken across all the Lots tested. In order to do this, the acceptance number for the total sample size may be calculated using the table below. The acceptance numbers (D) can be calculated from the following equations for any specific AQL and aggregated sample size (N).

AQL 0.25: $D = 0.01(0.25N + 8N^{0.55})$
AQL 1.0: $D = 0.01(1.0N + 17N^{0.55})$
AQL 1.5: $D = 0.01(1.5N + 22N^{0.55})$
AQL 2.5: $D = 0.01(2.5N + 30N^{0.55})$
AQL 4.0: $D = 0.01(4.0N + 36N^{0.55})$

These formulae provide similar acceptance criteria to those in *ISO 2859-1*, but they can be used for much larger sample sizes.

For additional advice on calculating and using these acceptance numbers, please contact the Help-Line.

When using the aggregate analysis method, it is also necessary to take into account the results for individual Lots and the process average before reaching a decision about the capability of the manufacturer.

1.4 Number of Lots rejected

Another approach is to review the number of Lots rejected over the long term. If this number significantly exceeds 5%, there is a high probability that the manufacturer's process average is greater than the stipulated AQL. A problem with this approach is that the number of Lots that may fail in the short run will vary considerably and may exceed 5% because of the same type of sampling errors that apply to individual Lots. Therefore, this rule can only be applied to large numbers of Lots.

The sampling plans given in *ISO 2859–1* do, however, contain a useful guide that can be used to identify potential problems with quality in the short term. These plans are primarily intended to be used with the switching rules, which alter the probability of acceptance of Lots on the basis of history. The switching rules are not generally used in the condom sector, but the rule for switching to tightened inspection is a very useful indicator of potential problems. This switch is triggered whenever there are two Lot rejections in any continuous sequence of five or fewer Lots. If this occurs, the quality of all further Lots from the manufacturer should be closely monitored, and the procedures described in this annex should be used to determine the process average. Discontinuation of supply may be appropriate if this investigation confirms a serious quality problem.

1.5 New Manufacturers

For new manufacturers, very little historical data is available, and the techniques listed above may not be applicable. At least 10 and preferably 30 full-size commercial Lots are needed to get meaningful results from methods 1.1 and 1.2. Method 1.3 will indicate whether the total production is likely to be within the AQL, while 1.4 is difficult to apply to small numbers of Lots unless the product is very bad.

Where insufficient Lots have been produced, it may be possible to assess performance by comparison with the condom manufacturer's specification, as used for the clinical trial of the product. Approval of the product will have been based on the results of this trial.

In some cases, the product used for the clinical trial will have been made on a pilot plant, and the product characteristics could change significantly when full production begins,

The parameters available for analysis are very similar to those for experienced manufacturers, but the approach taken may need to be slightly different. The following criteria can be considered, by looking at the results for all Lots produced:

1. Does every Lot of product produced so far comply with the *ISO 25841* requirement for freedom from holes?

2. Does every Lot of product comply with the manufacturer's limits for burst volume and pressure?

3. Is the trend in mean values of burst volume and pressure steady or increasing, over time? How do the results compare with the clinical trial Lot?

3. Is the trend of standard deviations of the burst properties steady or decreasing, over time? How do the results compare with the clinical trial Lot?

4. If there are seams, is the strength of these steady or increasing, over time? How do the results compare with the clinical trial Lot?

5. If there are seams, is the strength of these steady or increasing, over time? How do the results compare with the clinical trial Lot?

6. Do all the design characteristics comply with the manufacturer's specifications?

7. Do all the Lots comply with the package seal requirements of *ISO 25841?*

Any indication that performance parameters (eg burst volume and pressure, seam strength) are decreasing, or that their standard deviations are increasing should be a trigger for further investigation. Non-compliance with *ISO 25841* requirements should be treated similarly.

Contact the Help-Line for further information: HELPLINEcondomquality@fhi.org.

ANNEX V
GLOSSARY OF TERMS AND ABBREVIATIONS

Acceptance number	The highest number of non-compliers (failures) allowed in a specific test from a selected sample.
AFRO	WHO Regional Office for Africa.
Aggregate analysis	A retrospective method of assessing whether the total number of defective condoms found in a series of Lots is within the normal statistical bounds of the specific sampling plans being used. It helps determine accept/reject numbers for the total sample size obtained by aggregating the results from a number of Lots for any specific AQL and aggregated sample size (N).
AQL	Acceptable Quality Limit. The quality level that is the worst tolerable process average when a continuing series of Lots is submitted for acceptance sampling (*ISO 2859–1*). *N.B.: Manufacturers should be consistently achieving a process average that is better than the AQL.*
Aseptic technique	Precautionary measures taken to prevent external contamination of materials, samples, and culture media, employed during testing.
Batch	Sometimes used in place of "Lot" (see definition of Lot). (WHO recommends that "Lot" be used when referring to condoms.) Can also refer to a homogenous quantity of latex that has been compounded and is ready for dipping, from which several Lots will be made. Or, to describe a quantity of individual raw materials.
Bead	The thickened ring formed at the open end of the condom.
Bid security	A guarantee from a bank that the bidder will perform its obligations in regard to the bid.
Bioburden	The population of micro-organisms on a raw material, component, product, packaging or equipment.
Bioluminescence	When bacterial adenosine triphosphate (ATP) reacts with firefly luciferin and luciferase, light is emitted. Bioluminescence tests are designed to measure the amount of light produced, which will be related to the number of micro-organisms present in the sample.
CCP	Comprehensive Condom Programming.
CDC	U.S. Centers for Disease Control and Prevention.
CE mark	On condom packaging, a mark certifying that the product conforms to the essential requirements of the European medical device directive 93/42/EEC.
cfu	Colony forming units—an estimate of the number of viable micro-organisms per unit measured.
C/L	Commercial letter of credit.
Compliance testing	A regime of testing to verify that a Lot complies with the specification.
Condom procurement cycle	The time taken from making the initial forecast to the completion of the final shipment.

Comprehensive Condom Programming	A strategic approach to create the demand for and ensure the supply of good-quality male and female condoms
Confirmatory testing	Testing carried out on receipt of a product in a country.
Consumer pack	A wallet or carton into which one or more individual packages are inserted for marketing purposes.
DFID	U.K. Department for International Development.
Design Requirements	Characteristics of the condom that are specified according to the buyer's requirements.
DI	Deionised water
DRA	Drug regulatory authority.
EOI	Expression of Interest.
Expiry date	The date at which the product is no longer considered acceptable for use.
Exterior shipping carton	The container into which a number of inner boxes are packed.
FIFO	First in, first out.
FHI360	Family Health International 360
Forecast	An assessment of the future requirements of a programme, based on historical trends, research, or feedback from field workers on current needs.
General Requirements	The general quality characteristics of condoms that are verified before supply commences and that are not expected to vary from Lot to Lot.
GMP	Good manufacturing practice. A code of practice aimed at ensuring the product is consistently manufactured to the required standard.
GTZ	Deutsche Gesellschaft für Technische Zusammenarbeit.
HIV	Human immunodeficiency virus.
ICH	International Conference on Harmonization.
INCOTERMS	Defines when the ownership, responsibility and liability for a shipment is transferred from the supplier to the client and/or receiving country.
Inner box	A box used to contain a convenient number of condoms in packages or consumer packs. Inner boxes typically contain 100–200 condoms; where a gross (144 condoms) is used as the unit of purchase, inner boxes are usually specified to contain one gross.
Inspection level	The degree of examination of the Lot, as specified in *ISO 2859–1*. The higher the inspection level, the more samples will be tested and, hence, the lower the risk of faulty products reaching the end user.
IPPF	International Planned Parenthood Federation.

IPPF/ICON	International Planned Parenthood Federation, International Contraceptives Sexual and Reproductive Health.
IUD	Intrauterine device.
ISO	International Organization for Standardization.
ISO/TC 157	International Organization for Standardization, Technical Committee 157 for Non-Systemic Contraceptives and STI Barrier Prophylactics.
JSI	John Snow, Inc.
Length	The length of the condom measured from the open end to the tip, excluding any reservoir.
Lot	A quantity of condoms of a single grade, class, size and composition, manufactured under essentially the same conditions. With certain exceptions, all the condoms comprising a Lot will have identical formulation; the same dimension, colour, shape, and surface texture; be manufactured on the same production line; and be vulcanized under the same conditions.
Lot number or code	A unique identifying alphanumeric code assigned to a Lot.
Lowry method (modified)	A method for determining the water-extractable protein levels in latex products.
MFD	Manufacturing date. Date on which the sheath components of the condoms were fabricated.
MFV	Maximum fill volume for water testing for freedom from holes
MPN	Most Probable Number.
MSDS	Material Safety Data Sheet.
MSH	Management Sciences for Health.
NR	Natural rubber
National Regulatory Authority	A regulatory body with authority in a specific country to control the importation and distribution of medical products. See also Regulatory Authority.
Opportunistic pathogen	An organism that does not normally cause disease but becomes pathogenic under certain circumstances.
PATH	Program for Appropriate Technology in Health.
Performance Requirements	The critical tests of quality that all Lots must pass in order to provide adequate consumer protection.
Prequalification	The steps taken by the buyer to verify a manufacturer's suitability to provide condoms of the required quality. The WHO/UNFPA Prequalification Scheme includes periodic assessment of manufacturing dossiers, testing of samples and factory inspection. UNFPA is committed to only purchasing female condoms from factories that have been pre-qualified according to the WHO/UNFPA Prequalification Scheme

Pre-shipment compliance testing	A regimen of compliance tests carried out before a shipment leaves the supplier's factory.
Process average	The long-term average percentage of non-complying condoms calculated separately for each attribute. [Ideally, the process average for a specific attribute should be less than half the specified AQL].
PSA	Prostate specific antigen
PSI	Population Services International.
Random sample	A sample of condoms drawn randomly from a Lot for testing purposes.
Regulatory authority	A national or international body set up to oversee the safety, efficacy and quality of medical devices, including condoms, imported and distributed within a country or region.
Rejection number	The minimum number of non-compliers (failures) in a test sample that will cause a Lot to be rejected.
RHSC	Reproductive Health Supplies Coalition.
Reservoir	A narrow portion of the condom at the closed end, designed to contain ejaculate. The reservoir is sometimes called the teat.
RO	Reverse Osmosis. A process used to provide pure water by removing unwanted salts and microorganisms by applying pressure in the opposite direction of natural osmotic flow across a semi-permeable membrane.
Sampling plan	A specific plan that indicates the number of units (condoms) from each Lot that are to be inspected (sample size) and the associated criteria for determining the acceptability of the Lot (acceptance and rejection numbers).
SDA	Sabourauds Dextrose Agar.
SMF	Site Master File Summary.
Shelf-life	The period of time after manufacture that the product is considered acceptable for use.
SOP	Standard operating procedure.
Specification	A detailed statement of a product's requirements as established by the buyer. Usually, a specification is based on an established standard.
Standard	A detailed statement of the minimum acceptance requirements, as established by a national or international regulatory authority.
STIs	Sexually transmitted infections.
SWAp	Sector-wide approach.
TSST	Toxic shock syndrome toxin
TVC	Total Viable Count. The number of living micro-organisms in a given sample.

UN	United Nations.
UNAIDS	Joint United Nations Programme on HIV/AIDS.
UNFPA	United Nations Population Fund.
UNICEF	United Nations Children's Fund.
USAID	United States Agency for International Development.
USFDA	United States Food and Drug Administration.
UV	Ultraviolet irradiation. Normally emitted at a wavelength of 254 nm; may be used to diminish or eliminate bioburden in process water.
Viscosity	The resistance to flow of a fluid.
WHO	World Health Organization.
WHO/RHR	World Health Organization, Department of Reproductive Health and Research.

ANNEX VI
APPLICABLE DOCUMENTS

Various external documents form part of the *WHO/UNFPA Specification*, and the buyer may wish to mention them in any Invitation to Bid or order sent to the supplier. In every case the edition of the document is the one in force on the date of the Invitation to Bid.

These are standards published by the International Organization for Standardization (ISO).
Copies can be obtained from the national standardization organization in the buyer's country or from:

International Organization for Standardization ISO Central Secretariat
1, ch. de la Voie-Creuse CP 56
1211 Geneva 20, Switzerland
Telephone: +41 22 749 0111
E-mail: central@iso.org
Web site: http://www.iso.org

Latex condoms

ISO 4074:2002	Natural Latex Rubber Condoms Requirements and Test Methods
Cor 1:2003	
Cor 2:2008	
ISO 25841:2011	Female Condoms Requirements and test methods

Testing methods[8]

ISO 25841:2011	Female Condoms Requirements and test methods
ISO 25841:2011Annex A	Sampling Plans Intended for Assessing Compliance of a Continuing Series of Lots of Sufficient Number to Allow the Switching Rules to Be Applied
ISO 25841:2011Annex B	Sampling Plans Intended for Assessing Compliance of Isolated Lots
ISO 25841:2011Annex C	Determination of Total Lubricant in Condoms in Individual Female Condom Containers
ISO 25841:2011 Annex D	Determination of Female Condom Length
ISO 25841:2011 Annex E	Determination of Female Condom Width
ISO 25841:2011 Annex F	Determination of Female Condom Thickness
ISO 25841:2011 Annex G	Testing for Female Condom Package Integrity
ISO 25841:2011 Annex H	Determination of Barrier Properties Using the Bacteriophage Method
ISO 25841:2011 Annex I	Determination of Bursting Volume and Bursting Pressure
ISO 25841:2011 Annex J	Testing for Holes
ISO 25841:2011 Annex K	Determination of Shelf-Life by Real-Time Stability Studies
ISO 25841:2011 Annex L	Guidance on Conducting and Analysing Accelerated Aging Studies
ISO 4074:2002	
ISO 12243:2003	Medical Gloves Made from Natural Rubber Latex Determination of Water-Extractable Protein Using the Modified Lowry Method
ISO 2859–1	Sampling Procedures and Tables for Inspection by Attributes

[8] Please note that date of publication of standards are accurate at the time of publication of this document. With international standards always check the date of the latest edition.

ANNEX VII
LIST OF RESOURCE AGENCIES

Centers for Disease Control and Prevention Programme Services and Evaluation Division of Reproductive Health
1600 Clifton Road N.E. (Mailstop K-22)
Atlanta, Georgia 30030, USA
http://www.cdc.gov/health/diseases.htm

Crown Agents Services, Ltd.
St. Nicholas House, St. Nicholas Road
Sutton, Surrey SM1 1EL, UK
http://www.crownagents.com/
enquiries@crownagents.co.uk

FHI360
P.O. Box 13950
Research Triangle Park, NC 27709, USA
http://www.fhi360.org
publications@fhi.org

International Laboratory Accreditation Cooperation (ILAC)
NATA 7 Leeds Street
Rhodes, NSW, Australia
http://www.nata.asn.au

International Organization for Standardization (ISO)
ISO Central Secretariat
1, ch. de la Voie-Creuse
CP 56
1211 Geneva 20, Switzerland
http://www.iso.org
central@iso.org

John Snow, Inc.
1616 North Fort Myer Drive
Arlington, Virginia 22209, USA
http://deliver.jsi.com/dhome

Maternal, Adolescent and Child Health -MatCH University of the Witwatersrand
155 Juniper Road
Overport, 4091
Durban, South Africa
http://www.match.org.za
info@match.org.za

Partners in Population and Development
P.O. Box 6020
Gulshan 1, Dhaka 1212
Bangladesh
http://www.partners-popdev.org/abtppd/abtppd_secretariat_contact.asp

Population Action International
1300 19th Street N.W., Second Floor
Washington, DC 20036, USA
http://www.populationaction.org
pai@popact.org

Population Services International Procurement and Logistics
1120 19th Street N.W., Suite 600
Washington, DC 20036, USA
http://www.psi.org
publications@psi.org

Program for Appropriate Technology in Health (PATH) Publications
P.O. Box 900922
Seattle, WA 98109, USA
http://www.path.org
publications@path.org

Reproductive Health Supplies Coalition Secretariat
Rue Marie-Thérèse 21
1000 Brussels, Belgium
http://www.rhsupplies.org/
secretariat@rhsupplies.org

UNAIDS
20 Avenue Appia
CH-1211 Geneva 27, Switzerland
http://www.unaids.org
unaids@unaids.org

UNFPA Technical and Evaluation Division, Reproductive Health Branch
605 Third Avenue
New York, New York 10158, USA.
http://www.unfpa.org/procurement
http://www.unfpa.org/publications

World Bank Publications
1818 H Street N.W.
Washington, DC 20433, USA
books@worldbank.org
pic@worldbank.org

World Health Organization
Documentation Centre, Department of Reproductive Health and Research
20 Avenue Appia
CH-1211 Geneva 27, Switzerland
http://www.who.int/reproductive-health

This document has been prepared in consultation with representatives from:

U.S. Agency for International Development (USAID) • Department for International Development (DFID) • World Bank • U.S. Centers for Disease Control and Prevention • Crown Agents • International Standardization Organization (ISO) Technical Committee 157 • John Snow, Inc. (JSI) • Program for Appropriate Technology in Health (PATH) • Population Services International (PSI) • Population Action International (PAI)