BIOTOOLS B&M LABS.S.A.

Manufactured by:

BIOTOOLS B&M Labs, S.A.
Valle de Tobalina - 52 - Nave 39
28021 Madrid
Spain

Tel. (34) 91 710 00 74
Fax (34) 91 505 31 18
e-mail: info@biotools.eu
www.biotools.eu

BIOPAP Kit

Kit for Papillomavirus (HPV) DNA detection in human clinical samples

Instructions for Use

Ref. 90.013

PLEASE READ THE INSTRUCTIONS FOR USE THOROUGHLY BEFORE USING THE KIT, ESPECIALLY IF YOU ARE NOT FAMILIAR WITH THE PROTOCOL.

BIOPAP Kit

For research use only (RUO)
Not for use in diagnostic procedures
Test results may be used for preliminary analysis only

Some of the applications which may be performed with this product may be covered by applicable patents in certain countries. The purchase of this product does not include or provide a license to perform patented applications. Users may be required to obtain a license depending on the country and/or application. Biotools does not encourage the unlicensed use of patented applications.

PLEASE CHECK KIT AND REAGENTS INTEGRITY BEFORE USE. USE OF DETERIORATED KITS MAY CAUSE LACK OF RESULTS AND/OR EQUIVOCAL RESULTS.

INTENDED USE

The BIOPAP Kit is a method for the determination, in a qualitative form, of human papillomavirus (HPV) by DNA amplification. The test detects thirty-two (32) HPV genotypes (6, 11, 13, 16, 18, 30, 31, 32, 33, 34, 35, 39, 40, 42, 43, 44, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 62, 64, 66, 67, 68 and 69) in cervix samples. The BIOPAP Kit can differentiate between two HPV groups: generic HPV genotypes (6, 11, 13, 16, 18, 30, 31, 32, 33, 34, 35, 39, 40, 42, 43, 44, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 62, 64, 66, 67, 68 and 69), and oncogenic HPV genotypes (16, 18, 31, 33, 35, 52, 58 and 67).

The BIOPAP Kit is to be used with the following cervix samples:

- Samples taken with validated sterile cotton swabs. Use conservation solutions which do not contain denaturing substances or that may interfere with DNA polymerase activity[1].
- Standard cytological samples or after-colposcopy cytological samples, but before adding iodide or acetic acid. Use conservation solutions which do not contain denaturing substances or that may interfere with DNA polymerase activity.
- Samples taken with brush-type specific devices, such as Cervical Sampler™.

SUMMARY AND EXPLANATION OF THE TEST

Human Papilloma Virus (HPV) is a virus affecting mainly to cutaneous and anogenital tissues, and with average prevalence values around 15 %, but with a high degree of variation depending on age and other demographical values[2]. HPV is a DNA virus, with a genome of approximately 8,000 nucleotides. Diseases caused by infection by HPV vary from condiloma to neoplasic transformations in cervix, vagina and vulva, as well as carcinoma. Some genotypes, of more than 100 genotypes described up to date, are associated to neoplasic transformation in cervix[3]. Neoplasic transformation is associated to the expression of E6 and E7 genes. Traditionally, presence of genotypes 16 and 18 is associated with high risk of neoplasic development[4]. Assignation of risk for other HPV genotypes is based on phylogenetic and/or epidemiological criteria. Thus, types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 and 82 are classified as high risk based on both classification criteria[5]. Regarding HPV 67, which has been classified as high risk upon the phylogenetic point of view by some authors[6], a cervix cancer cell line has been isolated, which presents integrated sequences from this type of HPV[7]. Also, types 26, 53 and 66, classified as high risk upon phylogenetic criteria, are now considered as probably carcinogenic based upon epidemiological criteria (see Muñoz *et al.*). Finally, types HPV 70 and 73 are of variable classification depending on the applied criteria (see Muñoz *et al.*).

HPV cannot be cultured *in vitro*, and there are no immunological techniques for its detection. Traditional techniques for indirect detection of HPV include physical examination to observe cellular changes associated with viral replication, followed by Papanicolau staining. Alternatively, hybridisation on biopsies can be performed for detection of the presence of viral DNA.

Viral DNA, in contrast to whole viral particles, is present in all epitelial layers. Presence of oncogenic HPV genotypes is directly associated with cervix cancer, and therefore, an early and trustworthy diagnosis is vital for correct patient management.

[1] Use of solutions similar to PreservCyt® may cause a decrease in the yield of amplification reactions.
[2] Parkin *et al*., 1999. CA Cancer J Clin, 49: 33-64.
[3] Schwartz *et al.*, 2001. J Clin Oncol, 19: 1906-15.
[4] Jacobs *et al.*, 1995. J Clin Microbiol, 33: 901-5.
[5] Muñoz *et al.*, 2003. New Engl J Med, 348: 518-27.
[6] Chan *et al.*, 1995. J Virol, 69: 3074-83.
[7] Koopman *et al.*, 1999. Cancer Res, 59: 5615-24.

The BIOPAP Kit is an amplification test for the qualitative detection of HPV DNA, as well as for differentiation between oncogenic and generic genotypes, and has been developed for use with cervix samples.

PRINCIPLES OF THE PROCEDURE

BIOPAP Kit is a test for qualitative analysis, using a DNA amplification technique for direct detection of DNA through agarose electrophoresis and ethidium bromide staining. Viral DNA present in positive samples is specifically amplified by using specific primers, which hybridise in homologous sequences in the viral genome.

The kit consists of a multiplex amplification reaction, using two pair of primers. One pair of primers (Pair 1 – GEN1 and GEN2) hybridises with sequences common to all tested HPV genotypes (L1 and L2 genes), and therefore, indicates HPV presence. The second pair of primers (Pair 2 – ONC1 and ONC2) hybridises with specific sequences for oncogenic HPV genotypes (E6 and E7 genes).

The first pair of primers renders a band of approximately 450 bp, while Pair 2 renders a product of approximately 250 bp. For band analysis, agarose electrophoresis must be performed, followed by ethidium bromide staining.

The detection process using BIOPAP Kit consists of three main steps: sample preparation, viral DNA amplification and detection by agarose electrophoresis and ethidium bromide staining.

Sample Preparation

The BIOPAP Kit is used with DNA purified from cervix samples.

NOTE

For viral DNA purification, use of SPEEDTOOLS TISSUE DNA EXTRACTION KIT (Ref. 21.135, 21.136, 21.137) is recommended. Use of other methods is also possible. However, the user must confirm that the purified DNA can be used with the BIOPAP Kit (concentration 50-100 ng/µl, $A_{260/280}$=1.8 – 2.0, absence of inhibitors that may affect the amplification, etc.). It is recommended to check the quality and suitability of the purified DNA for amplification reactions, for example, by performing control amplifications in parallel. For further information, please contact our Technical Dpt. (info@biotools.eu).

Amplification and Detection

Target selection

Selection of the target HPV sequences has been based on the study of highly conserved regions in the HPV genome for tested generic genotypes (GEN1 and GEN2 primers), and of minimally variable regions for tested oncogenic HPV genotypes (ONC1 and ONC2). Selected regions have a high degree of conservation between the tested genotypes. Pair 1 (GEN1 and GEN2) defines a segment of approximately 400 bp, while Pair 2 (ONC1 and ONC2) defines a sequence of approximately 250 bp in oncogenic HPV genotypes.

Amplification

DNA amplification is performed with a thermostable DNA polymerase from *Thermus*. In the presence of magnesium, and with the suitable salt and ionic strenght conditions, the enzyme shows DNA polymerisation activity using as anchor a primer and a DNA molecule as template.

DNA purified from the sample to be analysed is added to the reaction mix in the corresponding amplification vial. The amplification vial contains all necessary reagents to perform the amplification reaction, and only DNA and sterile bidistilled water must be added. Reaction mixture, already containing DNA, is incubated at different temperatures, in order to allow the hybridisation of the primer pairs to the DNA from the sample. Once hybridisation of primer pairs has taken place, and in the presence of triphosphate deoxynucleotides, the DNA polymerase extends the primer and forms a DNA strand complementary to the template DNA. Cyclic repetition of this process results in exponential amplification of the sequences originally present in the sample included between the primer pairs.

Detection

Detection of amplified products is performed by agarose gel electrophoresis followed by ethidium bromide staining.

NOTE

Ethidium bromide is a highly mutagenic intercalating agent. We recommend use of gloves and the maximum caution in handling.

HPV presence is indicated by a band of approximately 450 bp. If oncogenic HPV genotypes are present in the sample, an additional band of 250 bp will also appear.

REAGENTS

BIOPAP Kit contains amplification reagents in liquid format for performance of 96 amplification reactions (Ref. 90.013). Thaw and handle reagents on ice. Do not freeze/thaw Kit vials repeatedly. In case of frequent use, we recommend the aliquoting of the vial contents.

Store all Kit vials at **-15±8ºC**.

- **HPV Mixture:** Two vials: 2 x 1980 µl
  A Tris-HCl solution, containing <10 % glycerol, KCl, <0.001 % dATP, dCTP, dGTP, dTTP and primers. HPV reaction mixture includes all the amplification reagents for the HPVs detection and differentiation of oncogenic and generic genotypes, except $MgCl_2$ and DNA polymerase, in the optimal proportions to allow an effective amplification of the *HPVs DNA*.

- **50 mM $MgCl_2$ Solution:** Vial: 1.8 ml
  Mix well before use.

- **Biotools DNA polymerase (1 U/µl):** Vial: 105 µl
  Add to reaction mixtures shortly before introduction of vials in thermal cycler.

- **Positive Control:** Vial: 300 µl
  The positive control vial contains DNA sequences of both generic HPV (2x 10^6 copies/µl) and oncogenic HPV (10^6 copies/µl), in a Tris-HCl EDTA solution. The positive control included in the kit is non-infective, and can be used as intra-tube control.

MATERIALS REQUIRED BUT NOT PROVIDED

NOTE

For all equipments, regular maintenance and calibration is necessary. Follow manufacturer's instructions, and check working parameters regularly, specially for thermal cyclers and pipettes. Maintenance and calibration of instruments allows its correct functioning, and helps detecting problems that may render an incorrect analysis result.

Pre-amplification area

- Equipment, reagents and disposable material necessary for DNA purification (depending on the method, follow manufacturer's instructions)
- Timer
- Automatic pipettes[8] (10, 20 and 200 µl), filter or positive displacement tips, RNase-free[9]
- Disposable examination gloves, powder-free
- Sterile bidistilled water
- Screw cap polypropylene tubes, 1.5 ml capacity, non siliconised, conical, sterile, RNase-free. It is recommended to use screw cap tubes, in order to avoid the potential contamination of samples and controls.
- Racks for 1.5 ml vials
- Containers for disposal of potentially-infectious material
- Disposable filter paper for working surface, cleaning paper for accidental spills
- Termi-DNA-Tor[10] or equivalent, in order to remove DNA from working surfaces

[8] Precision of automatic pipettes must be in the range of 3 % of the indicated volume. If necessary, calibrate and check regularly, following manufacturer's instructions. It is recommended to use RNase-free filter tips and positive displacement tips, in order to avoid cross contamination between samples and amplicons.
[9] It is recommended to use different sets of pipettes for each reaction step (pre-amplification, amplification, post-amplification), in order to avoid contaminations that may render false positive results.
[10] Available in Biotools' catalogue (Ref. 40.201).

Amplification area

- Thermal cycler: Eppendorf MasterCycler™ Personal, MJ Research MiniCycler™ or Applied Biosystems GeneAmp™ 2700. Use of this kit in other equipments has not been tested. For further information, contact our Technical Dpt. (info@biotools.eu).
- Laminar flow cabinet
- Racks for reaction vials
- Amplification vials (0.2 ml, thin-walled).
- Sterile bidistilled water (Ref. 20.033 or equivalent)
- Automatic pipettes (10, 20 and 200 µl), filter or positive displacement tips, RNase-free
- Disposable examination gloves, powder-free
- Containers for disposal of potentially-infectious material
- Disposable filter paper for working surface, cleaning paper for accidental spills
- Termi-DNA-Tor or equivalent, in order to remove DNA from working surfaces

Post-amplification area

- Electrophoresis power supplies and tanks
- Gel Documentation system
- UV transilluminator
- Ethidium bromide
- Low EEO agarose (Ref. 20.011) or equivalent
- TAE or TBE
- DNA Ladder ranging between 150 to 700 bp (Ref. 31.006) or equivalent
- Electrophoresis loading buffer
- Automatic pipettes (10, 20 and 200 µl), filter or positive displacement tips, RNase-free
- Disposable examination gloves, powder-free
- Protective mask / googles for UV
- Microwave

WARNINGS AND PRECAUTIONS

Following is a list of warning and precautions. For a complete information, we recommend to read the Material Safety Data Sheet (MSDS), available in our webpage (www.biotools.eu), or by request to our Technical Dpt. (info@biotools.eu).

A. Research Use Only.
B. This test must be used with cervix samples collected, handled and stored as indicated in the corresponding chapter. Efficiency of the test in other samples has not been tested.
C. The kit detects the following genotypes: 6, 11, 13, 16, 18, 30, 31, 32, 33, 34, 35, 39, 40, 42, 43, 44, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 62, 64, 66, 67, 68 and 69. Detection of other genotypes (including those that may be considered as oncogenic now or in the future) has not been tested. The kit only detects the indicated genotypes, and classifies them as generic HPV genotypes (6, 11, 13, 16, 18, 30, 31, 32, 33, 34, 35, 39, 40, 42, 43, 44, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 62, 64, 66, 67, 68 and 69), and oncogenic HPV genotypes (16, 18, 31, 33, 35, 52, 58 and 67). This classification is based on current knowledge on HPV genotypes, but genotypes now considered as generic may be considered as oncogenic now or in the future, or depending on the clinical case considered. Oncogenic genotypes are those detected by the kit, which does not mean that other genotypes not detected by the kit are or may be oncogenic.
D. Handle all samples and discarded material as infectious or potentially infectious.
E. Use powder-free examination gloves while handling reagents or samples, as well as lab coat. Wash hands thoroughly after performing the test.
F. Open and close reagent vials carefully. Observe temperature and light exposure instructions. After use, close vials and store at indicated temperatures.
G. All materials used with the kit, including reagents and samples, must be discarded as to inactivate all possible infectious agents
    1. **Solids**: autoclave
    2. **Liquids**: add sodium hypochloride[11] at a final concentration of 1 %, and incubate 30 minutes at room temperature before discarding any material.
H. Spills: wash spills with a 5 % solution of sodium hypochloride. Cover surface with absorbent material, saturated with a 5 % solution of sodium hypochloride. Let at least for 10 minutes. In order to avoid fume exposure, a plastic or glass cover can be used. All materials used for washing spills must be treated as infectious or potentially infectious material.

[11] Commercial bleach usually contains sodium hypochloride at a concentration of 5 %. Bleach can be used, after performing the necessary calculations in order to achieve the indicated concentration.

I. Do not use product after expiry or best before date.
J. Kit components have been tested as a whole. **Do not interchange components** with other kits, or components from different lots.
K. Nucleic acids are very sensitive to degradation by nucleases. Nucleases are present in human skin and surfaces that have been in contact with humans. Wash with Termi-DNA-Tor and cover working surfaces with suitable paper. Use powder-free examination gloves throughout the whole process.
L. Extreme care must be taken when aliquoting the different volumes in each reaction step. Mix well after addition of each reagent, unless otherwise noted. Read instructions for use of automatic pipettes.
M. Do not pipette by mouth.
N. Packaging material included with the kit is resistant to the indicated storage conditions. Storage at different conditions can cause breakage of the material, and possible contamination of kit contents.
O. Plastic material included with the kit is resistant in the normal conditions of use. Use of plastic material in extreme conditions may cause its breakage, and therefore, impossibility to use the kit.
P. Kit reagents, once used, must be discarded. Reagents cannot be reused once they have been used for the analysis of clinical samples, as this may cause false positive or false negative results.
Q. Laboratory workflow must be unidirectional, from pre-amplification area to amplification area. Specific equipment for each working area must be used, in order to avoid cross contaminations. Equipment used for amplification must remain in this area at all times.

STORAGE AND HANDLING INSTRUCTIONS

1. After reception, store the different reagents at the indicated temperatures (at -15±8ºC). Use non frost-free freezers. Also, for frequent use (more than 1 time a week), aliquot the contents of the vials in different tubes, in order to avoid repeated freeze/thaw cycles.

2. Do not use the kit after expiry date. The closed kit is stable until the indicated date, if storage instructions are correctly followed. Do not mix reagents from other kits and/or other lots. If trace amounts of reagents remain, they must be discarded.

SAMPLE COLLECTION, TRANSPORT AND STORAGE

The different cervix samples recommended for use with the BIOPAP Kit are indicated at the beginning of this Manual. Samples taken with other methods or transported according to different specifications have not been tested for use with the kit. Cervix samples must be collected before applying acetic acid or iodide if colposcopical examination is to be performed.

Cervical brushes and swabs

Samples may be stored up to three days at room temperature (maximum 25 ºC), and shipped without refrigeration to the clinical analysis laboratory. For prolonged storages, we recommend temperatures of -15±8 ºC. Once in the laboratory, they can be stored at 2-8 ºC if analysis is to be performed in 48 hours. If the analysis is to be performed later, store samples at -15±8 ºC. Samples must be kept away from heat sources and preserved of environmental humidity. Bacterial growth must be avoided and DNA integrity must be kept.

Cervical biopsies

Fresh biopsies of up to 5 mm must be used. Biopsy must be immediately placed in a preservative medium and stored at -15±8 ºC. Biopsies can be shipped by express courier (24 hours maximum) at a maximum temperature of 25 ºC, and stored at -15±8 ºC in the laboratory until performance of the test. Biopsies with a diametre under 2 mm must not be used.

In order to avoid accidents or accidental opening of the sample container, it is recommended to seal its closure with Parafilm® or equivalent before freezing.

Sample shipment must comply with local, national and international regulations for transport of etiological agents.

INSTRUCTIONS FOR USE

NOTE

Thaw all reagents on ice. Keep on ice while in use.

Amplification must be started in the next 10 minutes after adding the purified DNA and controls to the amplification mix.

Check thermal cycler regularly. Non-existent or poor calibration of the equipment may render equivocal results.

1.- Final reaction volume is 50 µl. Calculate the necessary volume of **HPV Mixture, $MgCl_2$**, **Biotools DNA Polymerase** and **Positive Control** for the analysis of samples and controls. It is recommended to include one Positive Control and one Negative Control in each round of analysis (this must be taken into account when calculating necessary volume for performance of all reactions).

2.- Mix the necessary volume of **HPV Mixture, $MgCl_2$** and **Biotools DNA Polymerase** for the number of reactions to perform in a 1.5 ml vial. **Perform this process in a laminar flow cabinet**. Keep the reaction mixture (reaction mixture = HPV Mixture + $MgCl_2$ + Biotools DNA Polymerase) on ice:

Reagent	For 3 reactions	For 10 reactions	For n reactions
HPV Mixture	112.5 µl	375 µl	37.5 * n µl
50 mM $MgCl_2$ Solution	4.5 µl	15 µl	1.5 * n µl
Biotoools DNA Polymerase (1U/µl)	3 µl	10 µl	1 * n µl

3.- Aliquot 40 µl of the reaction mixture in each amplification vial, **in the laminar flow cabinet.**

4.- Remove vials from laminar flow cabinet. Add 50-100 ng from DNA from the purified samples and/or controls to each amplification vial. Complete up to 50 µl final volume with sterile bidestilled water.

NOTE

For Positive Controls use 5 µl of Positive Control vial. For Negative Controls use 5 µl of sterile bidistilled water.

Clinical samples, depending on their nature and viraemia levels, may have different DNA concentrations, and therefore, amount of template to be added to the amplification reaction is expressed in ng rather than indicating sample volume. Quantity and purity of template must be calculated, e.g. by measuring $A_{260/280}$ values.

5.- Close amplification vials. Place them in thermal cycler. Store remaining of Kit reagents at -15±8ºC.

Perform the amplification according to the following program:

94 ºC	5 min	
94 ºC	30 sec	35 cycles
55 ºC	1 min	
72 ºC	1 min	
72 ºC	10 min	
4 ºC	∞	

NOTE

This protocol has been adapted for Eppendorf, MJ Research and Applied Biosystems GeneAmp™ thermal cyclers. For other thermal cyclers, optimisation of reaction parameters may be necessary. For any question, please contact our Technical Dpt. (info@biotools.eu).

INTERPRETATION OF RESULTS

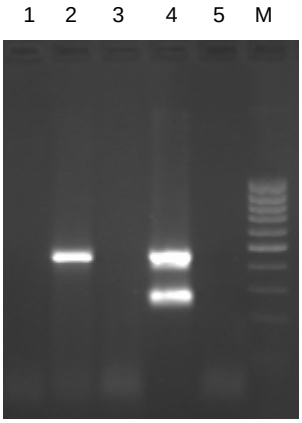
The analysis of amplification products is performed by horizontal electrophoresis in low EEO-agarose gels (e.g. MB Agarose, Ref. 20.011). Band visualisation is improved in 1.5-2 % gels using TAE 1X or TBE 0.5X as running buffers. It is recommended to add ethidium bromide in the agarose gel for a better resolution and visualisation.

NOTE

Ethidium bromide is a highly mutagenic intercalating agent. Use of gloves and maximum caution is recommended on handling this reagent.

Samples containing generic HPV sequences will render a band of approximately 450 bp, while samples containing oncogenic HPV genotypes will also render a band of approximately 250 bp (see Figure 1). In some cases, for oncogenic genotypes, only the 250 bp band will appear, with no 450 bp band. This does not interfere in the result. Nevertheless, should this occur, annealing temperature is to be decreased at 47 ºC for obtaining of the 450 bp band.

Figure 1: *Detection of HPV with BIOPAP Kit. Lane 1 and Lane 3: samples from healthy patients; Lane 2: patient infected with a generic HPV; Lane 4: patient infected with an oncogenic HPV; Lane 5: negative control; M: 100 bp Ladder (Ref. 31.006)*



QUALITY CONTROL

It is recommended that at least one (1) Positive Control and one (1) Negative Control be run each time the test is performed. As with any new laboratory procedure, novel users should consider performing additional controls (both positive and negative) until a high degree of confidence is reached.

The amplification vials containing the positive control must render two amplification bands (450 bp and 250 bp). Vials containing the negative control (sterile bidistilled water) must render no bands. Any analysis not fulfilling any of these results must be completely invalidated and discarded. It is necessary to repeat the process from its beginning, including DNA purification, processing other aliquot of the original sample. A failure of instruments during the test, indicated by error messages, also means that the test has not been valid. Repeat all the procedure for each sample from the amplification step.

For laboratories requiring an external control, this must contain a defined number of copies of the target sequence for HPV, and the viraemia levels in this control must be a multiply of the limit value of the testing procedure.

PROCEDURAL PRECAUTIONS

1. Laboratory workflow must be unidirectional, from pre-amplification area to post-amplification area. Pre-amplification tasks must be initiated with the preparation of the reagents and sample purification. Equipments, materials and reagents must be dedicated and they must not be used for other activities or be transferred from one to another area. Gloves must be worn in each area, and must be discarded before proceeding to the next area. Equipments and materials used for setting-up of reactions must not be used for other activities, or for pipetting or processing amplified DNA or other DNA sources.

2. As with any analytical procedure, it is fundamental to use a good laboratory practice to obtain good results with this technique. Due to the high analytical sensitivity of the test, extreme care must be taken in order to keep the purity of all kit reagents and all reaction mixes. All reagents must be carefully checked in order to ascertain their purity. Discard all suspect reagents.

PROCEDURAL LIMITATIONS

1. Research Use Only.
2. Instructions must be followed in order to obtain correct results. Should the user have any questions, please contact our Technical Dpt. (info@biotools.eu).
3. This test has been validated for use with the reagents provided by the kit. The use of other amplification methods, or the use of equipment not fulfilling the specifications, may render equivocal results. User is responsible for validating the modifications for this test, in any of the indicated parameters.
4. This test has been validated with samples collected and shipped as per the “Sample Collection” chapter. Any modification has not been validated, and therefore, obtained results may not be correct.
5. Detection of HPV DNA depends on the number of viral particles present in the sample, and can be affected by sample collection methods, patient-related factors (e.g. age, symptoms), or for infection stage and sample size.
6. False negative results may be obtained due to polymerase inhibition. It is recommended to perform control reactions to distinguish between inhibition and true negatives.
7. Cross contamination between samples and exogenous DNA can only be avoided by following good laboratory practice. Instructions in this document must be strictly followed.
8. Use of this product is limited to qualified professional personnel, experienced in DNA purification and DNA amplification techniques.
9. It is important to pipette the indicated amounts, and mix well after each reagent addition. Check pipettes regularly.

WARRANTY

Products are guaranteed to conform to the quality and content indicated on each vial and external labels during their shelf life. BIOTOOLS obligation and purchaser’s rights under this warranty are limited to the replacement by BIOTOOLS of any product that is shown defective in fabrication, and that must be returned to BIOTOOLS, freight prepaid, or at BIOTOOLS’ option, replacement of the purchasing price.

Any complaint on damaged goods during transport must be directed to the handling or transport agent.

Product for Research Use Only. This product must be used by qualified professionals only. It is the responsibility of the user to ascertain that a given product is adequate for a given application. Any product not fulfilling the specifications included in the product sheet will be replaced. This warranty limits our responsibility to the replacement of the product. No other warranties, of any kind, express or implied, including, without limitation, implicit warranties of commercialisation ability or adequacy for a given purpose, are provided by BIOTOOLS. BIOTOOLS will not be held responsible for any direct, indirect, consequential or incidental damage resulting of the use, misuses, results of the use or inability to use any product.

Manufactured by:

BIOTOOLS, Biotechnological & Medical Laboratories, S.A. has been evaluated and certified to accomplish ISO 9001:2008 requirements for the following activities: Research and development of biotechnology products and manufacture of biotechnology and in vitro products.
Valle de Tobalina – 52 – Nave 39, 28021 Madrid – Spain

BIOTOOLS
BIOTOOLS B&M LABS.S.A.