



Technical file:

Lab-On-Time™ Strep A Rapid Diagnostic Test (RDT) Device

(Throat Swab)


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1 GENERAL ASPECTS:

1.1 Product name

Lab-On-Time™ Strep A Rapid Diagnostic Test Device

1.2 Manufacturer's name and address

BMT Biomarketing, Ltd.

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Office: 14 Ha'ilan St. Or-Akiva, 3060000 Israel

Mailing address: PO Box 420, Zichron Ya'akov 3095203 Israel

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1.3 EC Authorized representative

MedNet GmbH, Borkstrasse 10, D-48163 Münster, Germany; Tel. 49-251-32266-0; Fax: 49-251-32266-22. CE assessment route chosen: Directive 98/79/EC concerning in-vitro diagnostic medical devices: Conformity assessment was performed according to Annex III of the Directive with Annex I rules.

1.4 Notified Body

Not required

1.5 Classification of the product category

1.5.1 Non-list A and B of Annex II

1.5.2 GIVD classification number : 15-70-01-03

1.6 Quality system certifications

BMT BioMarketing Ltd - ISO 13485:2003; ISO 9001:2008

2 LAB-ON-TIME DEVICE PRINCIPLE AND COMPONENTS

2.1 Product category

in-vitro diagnostic medical device.

2.2 Product name and Cat. No.

Lab-On-Time™ Strep A Rapid Diagnostic Test Device; Cat. Numbers: 51083, 51084

2.3 Product GIVD classification

15-70-01-03

2.4 General description

Streptococcus pyogenes is non-motile gram-positive bacteria, characterized by the Group A Streptococcus (GAS) antigen and a leading cause of pharyngitis, spreading through contact with droplets from an infected person's cough or sneeze. More than 10 million non-invasive GAS infections (primarily throat and superficial skin infections) are detected annually in the USA, accounting for 15-30% of sore throats in children¹. Most GAS infections cause relatively mild (noninvasive) illnesses such as strep throat, scarlet fever, and impetigo (a skin infection).

Occasionally, these bacteria may cause severe and even life-threatening invasive diseases, such as endocarditis, meningitis, puerperal sepsis, and arthritis. Left untreated, these infections can lead to serious complications, including rheumatic fever and peritonsillar abscess. Approximately 9,000-11,500 cases of invasive disease (3.2 to 3.9/100,000 population) occur each year in the United States alone, resulting with death in 10%-15% of all invasive cases¹. Globally, GAS infection has been estimated to cause more than 500,000 deaths annually, making it one of the world's leading pathogens².

Traditional identification procedures for Group A Streptococci infection involve the isolation and identification of viable organisms using techniques that require 24 to 48 hours or longer. The Lab-On-Time™ Strep A Rapid Test Device is a rapid test to qualitatively detect the presence of Strep A antigens in throat swab specimens, providing results within 5 minutes. The test utilizes antibodies raised against Lancefield Group A Streptococcus (GAS) antigen that selectively detect this antigen following nitrous acid extraction of throat swab specimens.

2.5 Intended use

The Lab-On-Time™ Strep A Rapid Test is an integrated device for the simultaneous collection of a throat swab sample and the performance of a rapid diagnostic test for the direct detection of Strep A in throat swab specimens.

2.6 Device components and sourcing

The Lab-On-Time™ Strep A Rapid Test device is comprised of five components:

- I. Lateral flow diagnostic test strip for Strep A detection
- II. Treated swab tip for throat sample collection
- III. Device Cover - holding the swab tip in a specific position
- IV. Device Base - holding the lateral flow diagnostic test strip in a specific position
- V. Device Cap - serving to protect the device's swab tip

A plastic tube containing bacterial extraction Reagent A is an additional kit component.

The following table (1) describes the sourcing of all device components:

Table 1: Lab-On-Time™ RDT Device Components and Reagents Sourcing

Item	Description	Authorized Supplier	Supplier Cat #	BMT Cat #
Diagnostic test strip	Strep A - specific Lateral flow test strip	BMT	N/A	51065; 51067
Swab tip	Flocked fiber swabs	Puritan Medical Products	25-3206-H	N/A
Device Cover	Injection molded plastic (ABS) cover	Rimoni Industries	P2950001	P2950001
Device Base	Injection molded plastic (ABS) base	Rimoni Industries	P2950002	P2950002
Device Cap	Injection molded plastic (ABS) cap	Rimoni Industries	P2950003	P2950003
Capped Reagent A tube	Polypropylene tube with cap	Romical	411-117041 (tube) 411-118133 (cap)	N/A
Sodium nitrite	Extra pure, >98%	DAEJUNG	7601-4405	N/A
Citric acid monohydrate	Analytical grade >99.5%	DAEJUNG	2562-4400	N/A
Ethanol	Absolute, anhydrous, extra pure for analysis, >99.9%	CARLO ERBA Reagents, SAS	Cat no. 4146052	N/A

2.7 Specific Device and Kit Components

2.7.1 Lateral flow diagnostic test strip for Strep A detection:

2.7.1.1 Test principle:

The Lab-On-Time™ Strep A Rapid Test Device comprises a lateral flow diagnostic test strip for the performance of a qualitative, solid phase, two-site sandwich immunoassay for the detection of Strep A in throat swab specimens. The strip membrane is pre-coated with anti-Strep A antibodies at the test line region of the strip. During test performance the solubilized throat swab specimen reacts with anti-Strep A antibodies labeled by colored

colloid particles. The antibody-bound antigens migrate chromatographically by capillary flow on the membrane to react with anti-Strep A antibodies immobilized on the membrane's Test line to generate a colored line. The presence of this colored line in the test region indicates a positive result, while its absence indicates a negative result. To serve as a procedural control, a colored line will appear in the Control line region indicating that proper volume of specimen has been added and membrane wicking has occurred.

As shown in Figure 1 below, the specimen applied to the sample pad (A) migrates via capillary forces along the membrane to react with the colored conjugate in the conjugate pad (B). Strep A present in the specimen binds to the conjugate, forming a colored antibody-antigen complex. The Rabbit anti-Strep A and Streptavidin-IgG immobilized in the test zone of the membrane captures the test region (C). The formation of a visible colored line in the test region indicates a positive result (C). The absence of a colored line in the test zones suggests a negative result. In the control zone of the membrane, immobilized reagents capture colored conjugate regardless of test specimen composition. The resulting visible colored band (D) confirms control line.

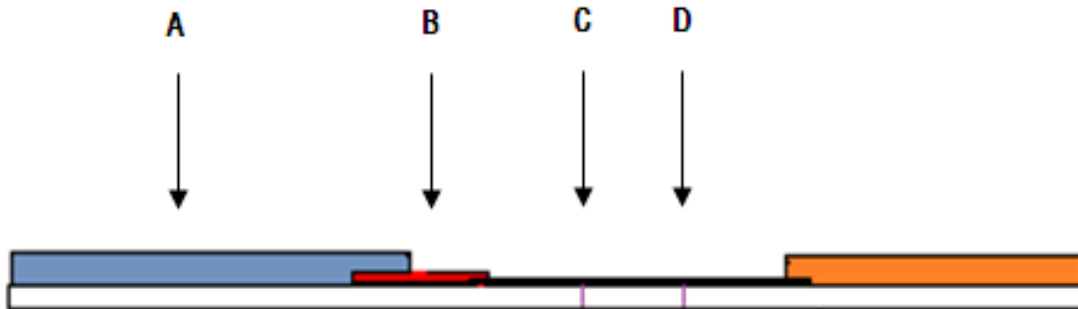


Figure 1: Test Principle

2.7.1.2 Test strip composition:

- | | |
|--|-----------------------------|
| A) Rabbit anti-Strep A | B) Streptavidin Rabbit IgG |
| C) Biotin-BSA | D) Adhesive plastic backing |
| E) Membrane | F) Label pad |
| G) Absorbent pad | H) Sample pad |
| I) Plastic device | J) Strip label |
| K) Desiccant | L) Extraction Reagent |
| M) Swab tip with edible acidic reagent | N) Strep A positive control |
| O) Strep A negative control | P) Extraction Tube |
| Q) Tube dropper in package | R) Package insert |

2.7.1.3 Test strip manufacturing process:

- a) Coat the latex conjugated recombinant Rabbit anti-Strep A on the label pad.
- b) Use the sprayer to dispense recombinant Streptavidin-rabbit IgG and Rabbit anti-Strep A onto the membrane.
- c) Assemble the membrane, label pad, absorbent pad and sample pad on the plastic backing.
- d) Use the cutter to cut the plastic backing into strips of selected size.
- e) Test the assembled device according to the QC procedure and release the finished product.

2.7.2 Treated swab tip for throat sample collection:

Group A Strep (GAS) antigen serves as the basis for most commercial rapid diagnostic tests for Strep A infection. The classical protocol for GAS antigen extraction from bacteria hasn't changed much since it was first described by Lancefield in 1933³ and consists of interacting the bacteria with nitrous acid solution, formed *in-situ* by reacting sodium nitrite (NaNO₂) with a mild acid (usually acetic or citric acids).

One of the hallmarks of the Lab-On-Time™ Strep A diagnostic device and the core of our patent-pending technology is the incorporation of the acidic reagent in the swab tip that is used for bacterial collection from patient's throats. Once the acidified swab tip carrying the collected bacterial sample is interacted with a sodium nitrite solution (supplied in a separate tube) the acidic reagent dissolves in and acidifies the sodium nitrite solution resulting in nitrous acid formation, which in-turn effectively extracts the GAS antigen from bacteria carried by the swab tip. Typically, citric acid - a Generally Regarded As Safe (GRAS) reagent - is incorporated into the swab tip by means of solvent evaporation, followed by swab tip excision to the right size (around 24mm) required for its integration into the Strep A Lab-On-Time™ device.

This entire process of swab treatment, resizing and assembly starts with sterile flocked fiber (or other) swabs purchased from leading manufacturers, followed by dip-coating with citric acid solution, drying, excision and assembly - all performed in a clean room (ISO5) controlled environment essential to minimize sporadic contamination of the swab tip by bacteria and other microorganisms.

2.7.3 Device Cover:

The device cover serves to hold the swab tip in a specific position and mechanically secure it to prevent its dislocation from the device under normal operating conditions. Figure 2 displays a schematic side-view of the Cover.

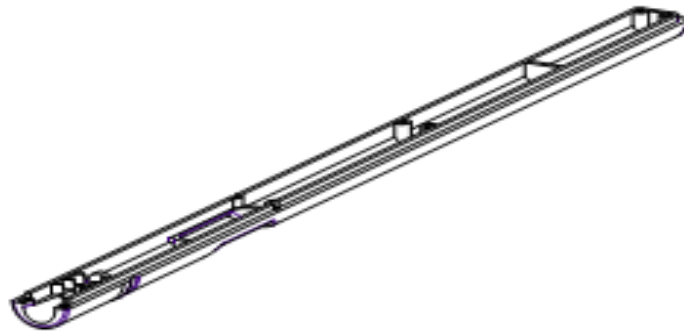


Figure 2: Lab-On-Time™ Device Cover

All plastic device parts are injected from medical grade ABS that has been sterilized by gamma irradiation (see additional detail below) prior to device assembly.

The left side of the device cover shown in Fig. 2 incorporates a groove equipped with several plastic protrusions that serve to lock the swab tip stem into the cover following the use a pneumatic piston for inserting the swab tip stem into this groove.

2.7.4 Device Base:

The device base has a groove that serves to hold the test strip in place so that it is correctly juxtaposed vis-a-vis the swab tip held by the device cover. Fig. 3 below displays a schematic side-view of the device Base.

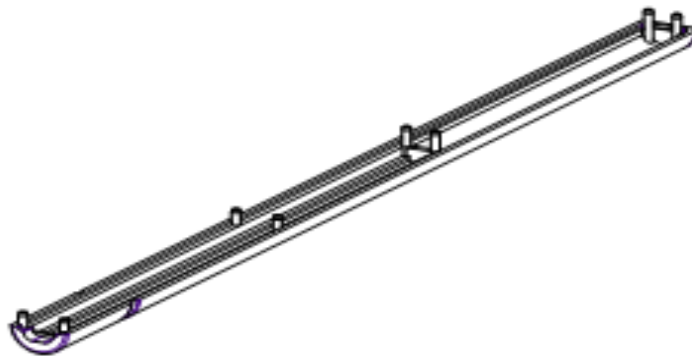


Figure 3: Lab-On-Time™ Device Base

2.7.5 Device Cap:

The device cap serves to protect the device swab tip from mechanical damage and contamination.

2.7.6 Reagent tube containing bacterial extraction Reagent A:

In order to effectively extract the GAS antigen from bacterial wall, the bacteria are solubilized by a nitrous acid extraction solution, formed by reaction between the citric acid incorporated into the swab tip and a nitrite salt solution. The nitrite salt solution (Reagent A) is comprised of 250ul 1.19M NaNO₂ in ultrapure water. The citric acid incorporated into the swab tip is solubilized by swirling the swab tip carrying the biological sample several times in Reagent A that is pre-aliquoted into a securely capped polypropylene tube. This affects both - the acidification of Reagent A to form nitrous acid and the efficient *in-situ* extraction of the bacteria carried by the swab tip.

3 DEVICE ASSEMBLY

The Lab-On-Time™ Strep A diagnostic device is assembled according to BMT SOP 107, as described briefly also below:

- a) Insert treated swab tip into plastic cover of the device by means of pneumatic insertion. The swab tip assembled in the device cover groove and the protrusions holding it in place.
- b) Insert the diagnostic test strip into the plastic base of the device. Correct positioning of the test strip in the device base is required for effective capillary fluid flow from the flocked fiber of the swab tip to the sample pad of the diagnostic test strip to achieve diagnostic test performance.
- c) Assemble device base and cover by means of manual placement and application of pneumatic pressure to force the two parts together.
- d) Apply device cap to the swab tip end of the device.
- e) Pack the assembled device together with a desiccant packet into a laminated aluminum pouch and heat-seal the pouch.

Fig. 4 below shows a schematic representation of the device assembly process:

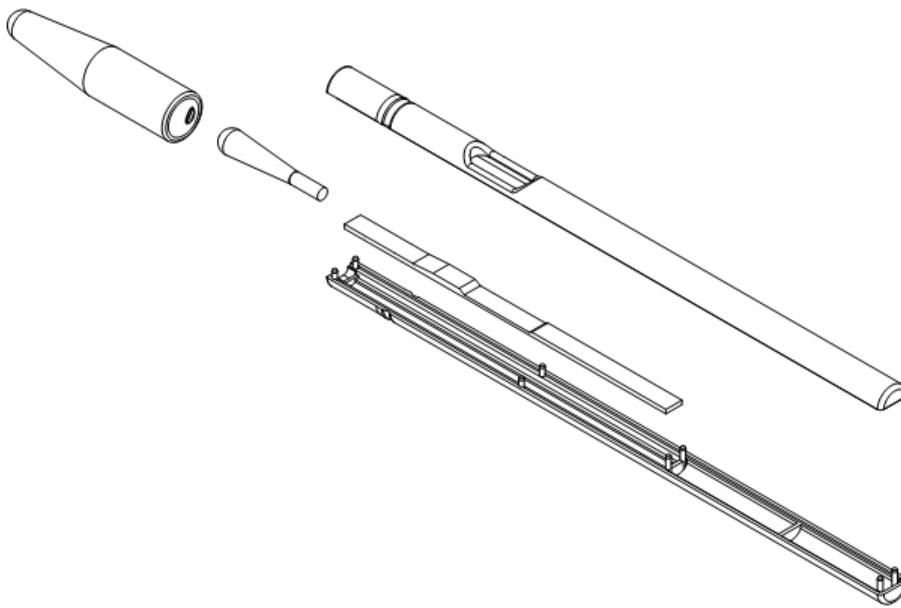


Figure 4: schematic representation of device assembly process

Figure 5 below shows a schematic representation of the assembled Lab-On-Time™ device:

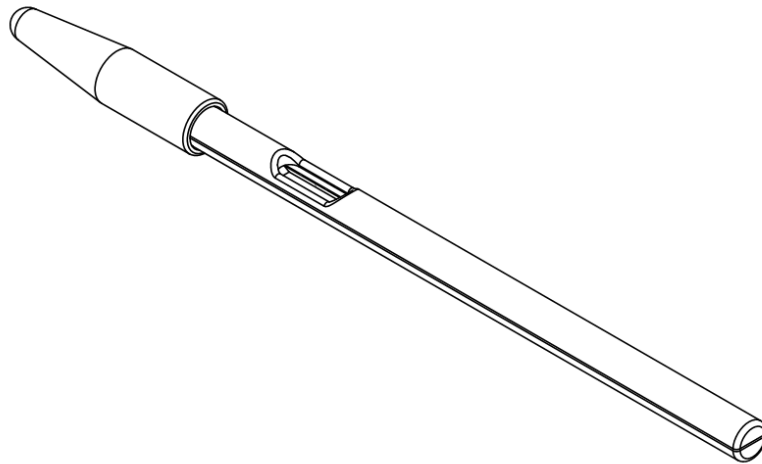


Figure 5: schematic representation of the assembled Lab-On-Time™ device

4 DEVICE PERFORMANCE AND TESTING

The Lab-On-Time™ device has been tested for the following performance parameters:

- I. Clinical performance
- II. Analytical performance
- III. Mechanical and fluidics performance
- IV. Storage stability

4.1 Clinical Performance

4.1.1 Sample correlation:

The specimen correlation used a specimen number (n) equal to 526 (122 positive specimens and 404 negative specimens confirmed by culture results). Specimens were rated as either positive or negative at 5 minutes. The clinical study was performed in the USA by ACRO Biotech, Inc., 9500 7th Street, Unit M, Rancho Cucamonga, CA 91730 USA. The subjects' age distribution was: 3-10 years old (55%), 10-16 years old (28%), and 16 years and older (17%). Clinical study results are presented in tables 2 and 3 below.

Table 2: Clinical Study of Lab-On-Time™ Strep A Device

Method		Culture		Total Results	
Strep A rapid test Strip	Results	Positive	Negative		
		Positive	116	9	125
		Negative	6	395	401
Total results		122	404	526	

Relative Sensitivity: 95.1% (95%CI:*89.6%-98.2%)

Relative Specificity: 97.8% (95%CI:*95.8%-99.0%)

Overall accuracy: 97.1% (95%CI:*95.3%-98.4%)

*Confidence Intervals

Table 3: Clinical Positive Culture Result of Lab-On-Time™ Strep A Device

Positive Culture Classification	Strep A Rapid Test/Culture	% Agreement
Rare	8/10	80.0%
1+	18/20	90.0%
2+	19/20	95.0%
3+	33/34	97.1%
4+	38/38	100.0%

4.2 Analytical Performance

4.2.1 Interfering Substances:

Device tips were spiked with 100ul interfering substances below at the starting concentration of 1% and then spiked with 10ul 0.5%BSA-PBS, 2.5E+07org/ml, or 1E+08org/ml Strep A (ATCC #19615 and ATCC #12365) samples. Test was performed according to the package insert in replicates. Test results were read at 5 minutes and are presented in Table 4 below.

- A: Cherry Halls cough drops
- B: Menthol Halls cough drops
- C: Robitussin cough syrup
- D: Dimetapp cough syrup
- E: Vicks Chloraseptic spray
- F: Cepacol Chloraseptic spray
- G: Listerine mouthwash
- H: Scope mouthwash

Table 4: Interfering Substance

0.5% BSA-PBS

Lot#:	A	B	C	D	E	F	G	H
BMT10001	3-*	3-	3-	3-	3-	3-	3-	3-

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

BMT10002	3-	3-	3-	3-	3-	3-	3-	3-
BMT10003	3-	3-	3-	3-	3-	3-	3-	3-
BMT10004	3-	3-	3-	3-	3-	3-	3-	3-
BMT10005	3-	3-	3-	3-	3-	3-	3-	3-
BMT10006	3-	3-	3-	3-	3-	3-	3-	3-

2.5E+07org/ml

Lot#:	A	B	C	D	E	F	G	H
BMT10001	3+**	3+	3+	3+	3+	3+	3+	3+
BMT10002	3+	3+	3+	3+	3+	3+	3+	3+
BMT10003	3+	3+	3+	3+	3+	3+	3+	3+
BMT10004	3+	3+	3+	3+	3+	3+	3+	3+
BMT10005	3+	3+	3+	3+	3+	3+	3+	3+
BMT10006	3+	3+	3+	3+	3+	3+	3+	3+

1E+08org/ml

Lot#:	A	B	C	D	E	F	G	H
BMT10001	3+	3+	3+	3+	3+	3+	3+	3+
BMT10002	3+	3+	3+	3+	3+	3+	3+	3+
BMT10003	3+	3+	3+	3+	3+	3+	3+	3+
BMT10004	3+	3+	3+	3+	3+	3+	3+	3+

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

BMT10005	3+	3+	3+	3+	3+	3+	3+	3+
BMT10006	3+	3+	3+	3+	3+	3+	3+	3+

Note: *all three test results were negative; **all three test results were positive

Conclusion: Substances tested showed no interference with the test. There were no apparent differences between the 6 tested product lots.

4.2.2 Cross Reactivity:

Aliquots (10ul) of the below microorganisms were spiked onto swabs and tested according to the package insert in duplicates. Test results were read at 5 minutes and presented in table 5 below

Group B Streptococcus	Concentration: 1E+07org/test
Group F Streptococcus	Concentration: 1E+07org/test
Streptococcus pneumonia	Concentration: 1E+07org/test
Streptococcus mutans	Concentration: 1E+07org/test
Staphylococcus aureus	Concentration: 1E+07org/test
Corynebacterium diphtheria	Concentration: 1E+07org/test
Candida albicans	Concentration: 1E+07org/test
Enterococcus faecalis	Concentration: 1E+07org/test
Neisseria meningitides	Concentration: 1E+07org/test
Neisseria sicca	Concentration: 1E+07org/test
Branhamella catarrhalis	Concentration: 1E+07org/test
Group C Streptococcus	Concentration: 1E+07org/test
Group G Streptococcus	Concentration: 1E+07org/test
Streptococcus sanguis	Concentration: 1E+07org/test
Staphylococcus epidermidis	Concentration: 1E+07org/test
Serratia marcescens	Concentration: 1E+07org/test
Klebsiella pneumonia	Concentration: 1E+07org/test
Bordetella pertussis	Concentration: 1E+07org/test
Neisseria gonorrhoea	Concentration: 1E+07org/test
Neisseria subflava	Concentration: 1E+07org/test
Hemophilus influenza	Concentration: 1E+07org/test
Pseudomonas aeruginosa	Concentration: 1E+07org/test

Table 5: Results of Cross reactivity

Treatment	Lab-On-Time™ Strep A Device		
	BMT10001	BMT10002	BMT10003
	5 minutes	5 minutes	5 minutes
Group B Streptococcus	3-*	3-	3-
Group F Streptococcus	3-	3-	3-
Streptococcus pneumonia	3-	3-	3-
Streptococcus mutans	3-	3-	3-
Staphylococcus aureus	3-	3-	3-
Corynebacterium diphtheria	3-	3-	3-
Candida albicans	3-	3-	3-
Enterococcus faecalis	3-	3-	3-
Neisseria meningitides	3-	3-	3-
Neisseria sicca	3-	3-	3-
Branhamellacatarrhalis	3-	3-	3-
Group C Streptococcus	3-	3-	3-

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

Group G Streptococcus	3-	3-	3-
Streptococcus sanguis	3-	3-	3-
Staphylococcus	3-	3-	3-
Epidermidis	3-	3-	3-
Serratiamarcescens	3-	3-	3-
Klebsiella pneumonia	3-	3-	3-
Bordetella pertussis	3-	3-	3-
Neisseria gonorrhoea	3-	3-	3-
Neisseria subflava	3-	3-	3-
Hemophilus influenza	3-	3-	3-
Pseudomonas aeruginosa	3-	3-	3-

Note: *all three test results were negative

Conclusion: No cross-reactivity could be detected with the above microorganisms under the test operating protocol.

4.2.3 Analytical Sensitivity:

Different Strep A strains were serially diluted in 0.5% BSA-PBS starting at 1.0E+08 organisms/ml to 1.0E+07 organisms/ml and 2.5E+07 org/ml. Each dilution was spiked (10 µ L) onto device tip and tested according to the package insert in replicates of three. Results were rated at 5 minutes and presented in Table 6 below.

Table 6: Analytical Sensitivity

1E+07org/ml

Lot#:	Strep A ATCC number							
	12202	12203	12204	12365	14289	19615	49399	51399
BMT10001	3+**	3+	3+	3+	3+	3+	3+	3+
BMT10002	3+	3+	3+	3+	3+	3+	3+	3+
BMT10003	3+	3+	3+	3+	3+	3+	3+	3+
BMT10004	3+	3+	3+	3+	3+	3+	3+	3+
BMT10005	3+	3+	3+	3+	3+	3+	3+	3+
BMT10006	3+	3+	3+	3+	3+	3+	3+	3+

2.5E+07org/ml

Lot#:	Strep A ATCC number							
	12202	12203	12204	12365	14289	19615	49399	51399
BMT10001	3+	3+	3+	3+	3+	3+	3+	3+
BMT10002	3+	3+	3+	3+	3+	3+	3+	3+
BMT10003	3+	3+	3+	3+	3+	3+	3+	3+
BMT10004	3+	3+	3+	3+	3+	3+	3+	3+
BMT10005	3+	3+	3+	3+	3+	3+	3+	3+

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

BMT10006	3+	3+	3+	3+	3+	3+	3+	3+
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1.0E+08org/ml

Lot#:	Strep A ATCC number							
	12202	12203	12204	12365	14289	19615	49399	51399
BMT10001	3+	3+	3+	3+	3+	3+	3+	3+
BMT10002	3+	3+	3+	3+	3+	3+	3+	3+
BMT10003	3+	3+	3+	3+	3+	3+	3+	3+
BMT10004	3+	3+	3+	3+	3+	3+	3+	3+
BMT10005	3+	3+	3+	3+	3+	3+	3+	3+
BMT10006	3+	3+	3+	3+	3+	3+	3+	3+

Note: **all three test results were positive

Conclusion: The detection limit for various Strep A strains are listed in the above table.

This study demonstrated that the 6 lots of the rapid diagnostic test device display acceptable sensitivities.

4.2.4 Dose Hook:

Strep A strains ATCC #19615 and ATCC #12365 (10 µ L) were spiked onto device tips and were tested according to the package insert in replicates of three. Test results were rated at 5 minutes and presented in Table 7 below.

Table 7: Dose Hook

Lot#:	Strep A Positive Sample			
	1.0E+09org/ml	1.0E+10org/ml	1.0E+11org/ml	1.0E+12org/ml
BMT10001	3+**	3+	3+	3+

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

BMT10002	3+	3+	3+	3+
BMT10003	3+	3+	3+	3+
BMT10004	3+	3+	3+	3+
BMT10005	3+	3+	3+	3+
BMT10006	3+	3+	3+	3+

Note: ** all three test results were positive.

Conclusion: Test results show that there was no dose hook effect for either of the six lots of Strep A device.

4.2.5 Variability (Inter/Intra/Day to day assay):

Samples of bacterial culture suspensions (10 µL each) were spiked onto swabs and tested according to the package insert. Five replicates for each specimen and concentration were tested each day for 3 consecutive days using six device lots. Test results were read at 5 minutes and are presented in Table 8 below.

Table 8: Test Variability

0.5% BSA-PBS

Day	Lot#:	1	2	3	4	5
Day 1	BMT10001	_*	-	-	-	-
	BMT10002	-	-	-	-	-
	BMT10003	-	-	-	-	-
	BMT10004	-	-	-	-	-
	BMT10005	-	-	-	-	-
	BMT10006	-	-	-	-	-
Day 2	BMT10001	-	-	-	-	-

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

	BMT10002	-	-	-	-	-
	BMT10003	-	-	-	-	-
	BMT10004	-	-	-	-	-
	BMT10005	-	-	-	-	-
	BMT10006	-	-	-	-	-
	Day 3	BMT10001	-	-	-	-
BMT10002		-	-	-	-	-
BMT10003		-	-	-	-	-
BMT10004		-	-	-	-	-
BMT10005		-	-	-	-	-
BMT10006		-	-	-	-	-

2.5E+07org/ml

Day	Lot#:	1	2	3	4	5
Day 1	BMT10001	+**	+	+	+	+
	BMT10002	+	+	+	+	+
	BMT10003	+	+	+	+	+
	BMT10004	+	+	+	+	+
	BMT10005	+	+	+	+	+
	BMT10006	+	+	+	+	+

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

Day 2	BMT10001	+	+	+	+	+
	BMT10002	+	+	+	+	+
	BMT10003	+	+	+	+	+
	BMT10004	+	+	+	+	+
	BMT10005	+	+	+	+	+
	BMT10006	+	+	+	+	+
Day 3	BMT10001	+	+	+	+	+
	BMT10002	+	+	+	+	+
	BMT10003	+	+	+	+	+
	BMT10004	+	+	+	+	+
	BMT10005	+	+	+	+	+
	BMT10006	+	+	+	+	+

1.0E+08org/ml

Day	Lot#:	1	2	3	4	5
Day 1	BMT10001	+**	+	+	+	+
	BMT10002	+	+	+	+	+
	BMT10003	+	+	+	+	+
	BMT10004	+	+	+	+	+
	BMT10005	+	+	+	+	+

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

	BMT10006	+	+	+	+	+
Day 2	BMT10001	+	+	+	+	+
	BMT10002	+	+	+	+	+
	BMT10003	+	+	+	+	+
	BMT10004	+	+	+	+	+
	BMT10005	+	+	+	+	+
	BMT10006	+	+	+	+	+
Day 3	BMT10001	+	+	+	+	+
	BMT10002	+	+	+	+	+
	BMT10003	+	+	+	+	+
	BMT10004	+	+	+	+	+
	BMT10005	+	+	+	+	+
	BMT10006	+	+	+	+	+

Note: “*” means negative result; “**” means positive result

Conclusion: The tables above show that different lots of Strep A device show similar performance and display no variability on a day to day comparative basis.

4.3 Mechanical and Fluidics Performance

4.3.1 Mechanical performance:

Mechanical performance of the Lab-On-Time™ Strep A Rapid Diagnostic Device was evaluated according to the following parameters:

- I. Swab tip vertical insertion depth into device cover

- II. Swab tip dislocation force
- III. Device cover-base opening force

In order to test these parameters, manufactured devices were mechanically secured at a horizontal position with 10cm of the swab tip end of the device overhanging. The swab tip was then enclosed by a noose linked to a hanging reservoir to which weight was added at a constant rate of 10gr/sec. The weight at which the device failed through cover-base split was recorded, followed by visual inspection to examine if the swab tip was dislocated from its holding groove in the device cover. Failed devices were further examined for swab tip protrusion from device cover by means of a micrometer.

All tested devices were required to fail at no less than 400gr (~4N), with the device tip held intact within the cover at that failure force. Swab tip protrusion from the cover needs to be no more than 4.50mm, which are 0.23mm above full swab tip penetration into the cover.

4.3.2 Fluidics performance:

The overall performance of the Lab-On-Time™ Strep A Rapid Diagnostic Device relies on efficient fluid transfer from the device's swab tip to the diagnostic test strip, facilitated by capillary forces driving fluid through the fiber comprising the swab tip to the sample pad of the diagnostic test strip. The critical factors affecting fluid transfer from the swab tip to the sample pad are sufficient overlap and contact between the distal part of the swab tip fiber and the fiber comprising the sample pad. In order to achieve optimal contact between the swab tip fiber and test strip sample pad, the following parameters have been optimized:

- I. Swab tip type and model
- II. Swab tip length
- III. Sample pad length
- IV. Swab tip insertion force and sample pad separation distance
- V. Device assembly force

4.3.2.1 Swab tip type and model:

Several manufacturers were considered and swabs of different types were evaluated for their performance in the Lab-On-Time™ Strep A RDT Device. Manufacturers included Puritan and Copan and different swab types, including polyester fiber-wound swabs and flocked swabs, were tested. The most appropriate swabs chosen for our device, based on both superior homogeneity and sample collection capability was Puritan's 25-3206-H flocked swab. These swabs have very uniform tips, displaying reproducible sorptivity and porosity, leading to consistent fluid flow in assembled devices

4.3.2.2 Swab tip length:

Swab tip length has a critical effect on both device fluidics and clinical sample collection. Short

swab tips tend to better overlap with the sample pad, at the expense of both - being too bulky to properly fit into the device cover's groove and making sample collection more challenging. On the other hand, longer swab tips lead to reduced overlap between the swab tip fiber and the sample pad but fit better into the device cover's groove and have improved sample collection capacity. The optimized swab tip length was found to be around 24mm for Puritan's 25-3206-H swabs.

4.3.2.3 Sample pad length:

Sample pad length was empirically set to 5mm, to allow sufficient overlap with the rear end of the swab tip for efficient capillary flow between the two.

4.3.2.4 Swab tip insertion force and sample pad separation distance:

The separation distance between the swab tip and the sample pad is largely determined by the penetration depth of the swab tip stem into its groove in the device cover. Full swab tip penetration assures optimal device performance, but due to swab tip variability that sometimes leads to some difficulty in driving the swab stem fully into its groove, the swab stem could protrude above device cover. Full swab stem penetration into the device cover groove is visually inspected and confirmed by measuring its protrusion with a micrometer (see 9.2.3.3 for further detail).

The device base that holds the test strip has an engineered groove designed to accommodate 4mm-wide, 80mm-long, and 0.80mm thick (sample pad area) strips. Strips that are wider or narrower than 4mm, which don't fit snugly into the device base groove are disqualified and removed during manufacturing. The internal distance between the device base and cover has been carefully calibrated to optimize the contact area between the swab tip and the diagnostic test strip, without generating excessive pressure that could act to obstruct fluid flow between them.

4.3.2.5 Device assembly force:

The force required to fully lock the pins of the device base to their matching holes in the cover has been recorded and the appropriate pneumatic piston and pressure (5-6bar) have been designed to deliver this force. Device lots are tested periodically for their mechanical failure force, which is an indication of proper device assembly - see 3.3.1 above for additional detail.

4.3.2.6 Fluidics performance testing:

The fluidics performance of the device is tested by recording the time it takes for the reagent to start flowing through the diagnostic test strip, indicated by first appearance of a liquid front beyond the conjugate pad. The time for first results reading - of both the control and test lines

- is also recorded. Rise of fluid through the swab tip, the sample pad and the conjugate pad, resulting in a fluid front beyond the conjugate pad, should be no longer than 90sec from test initiation by device dipping in reagent A tube. Time for first results reading (visible control line) should be no longer than 3min from test initiation.

4.4 Storage Stability

Storage stability of the Lab-On-Time™ Strep A Rapid Diagnostic Device was evaluated by accelerated aging using samples from three different lot batches. These were placed in an incubator with the temperature calibrated at 45°C and 55°C. Relative humidity (RH) calibrated at about 60%. A series of stability tests were performed at 0, 7, 14, 21, 28, 35, 42, 56, 77, 84 days at 45°C. Some of the performance study was performed at 0, 7, 14, 21, 28, 35, 42 days at 55°C, according to Arrhenius Plot (See below Table). Test devices were assayed using 0.5%BSA-PBS, 1E+07org/ml, 2.5E+07org/ml and 1E+08 org/ml strep A specimens (ATCC #19615 and ATCC #12365). Testing at each specific time interval consisted of 3 replicates for each specimen. The tests were performed according to the package insert. Results are presented in Table 9 below.

Arrhenius Formula:

$\ln K = -E_a/RT + \ln A$

“K” mean Rate constant

“A” mean Arrhenius constant

“E_a” mean Activation energy

“R” mean Gas constant

“T” mean Temperature in Kelvin

Table 9: Time line for Accelerate Stability Study

Day Temp.	0day	7days	14 days	21 days	28 days	35 days	42 days	56 days	77 days	84 days
45°C	√	√	√	√	√	√	√	√	√	√
55°C	√	√	√	√	√	√	√	N/A	N/A	N/A

Table 10: 45°C Accelerated Stability Summary

Day	Specimen	Lab-On-Time™ Strep A Device
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LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

		BMT10001	BMT10002	BMT10003
0	0.5%BSA-PBS	3-*	3-	3-
	1E+07org/ml	3+**	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
7	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
14	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
21	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
28	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
35	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
42	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
56	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
77	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
84	0.5%BSA-PBS	3-	3-	3-

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
Day	Specimen	Lab-On-Time™ Strep A Device		
		BMT10004	BMT10005	BMT10006
0	0.5%BSA-PBS	3-*	3-	3-
	1E+07org/ml	3+**	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
7	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
14	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
21	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
28	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
35	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
42	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
56	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
77	0.5%BSA-PBS	3-	3-	3-

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
84	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+

Table 11: 55°C Accelerated Stability Summary

Day	Specimen	Lab-On-Time™ Strep A Device		
		BMT10001	BMT10002	BMT10003
0	0.5%BSA-PBS	3-*	3-	3-
	1E+07org/ml	3+**	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
7	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
14	0.5%BSA-PBS	3-	3-	3-

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
21	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
28	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
35	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
42	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

Day	Specimen	Lab-On-Time™ Strep A Device		
		BMT10004	BMT10005	BMT10006
0	0.5%BSA-PBS	3-*	3-	3-
	1E+07org/ml	3+**	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
7	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
14	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
21	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
28	0.5%BSA-PBS	3-	3-	3-

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
35	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+
42	0.5%BSA-PBS	3-	3-	3-
	1E+07org/ml	3+	3+	3+
	2.5E+07org/ml	3+	3+	3+
	1E+08org/ml	3+	3+	3+

Note: * all three test results were negative; ** all three test results were positive

Conclusion: Lab-On-Time™ Strep A Rapid Test Device was stable at 45°C for 84 days and at 55°C for 42 days. These data were plotted on an Arrhenius Plot and the shelf life of this product was determined to be at least 24 months from the data of manufacture.

5 STANDARDS AND THEIR APPLICATION

5.1 List of applicable standards:

The following standards were used to prove the conformity of the Lab-On-Time™ Strep A Rapid Diagnostic Test Device with the essential requirements of the Directive 98/79/EC:

Standard	Description
EN 1041:2008	Information supplied by the manufacturer of medical device
ISO 13485:2012/AC:2012 (ISO 13485:2003)	Medical equipment - Quality management systems – Requirements for regulatory purposes
EN 13612:2002 / AC:2002	Performance evaluation of in-vitro diagnostic medical devices
EN 13640:2002	Stability testing of in vitro diagnostic reagents
EN 13641:2002	Elimination or reduction of risk of infection related to in vitro diagnostic reagents
EN 13975:2003	Sampling procedures used for acceptance testing of in vitro diagnostic medical devices – Statistical aspects
EN ISO 14971:2012	Medical devices – Application of risk management to medical devices (ISO 14971:2007, corrected version 2007-10-01)
EN ISO 15193:2009	In vitro diagnostic medical devices – Measurement of quantities in samples of biological origin – Requirements for content and presentation of reference measurement procedures
EN ISO 15194:2009	In vitro diagnostic medical devices - Measurement of quantities in samples of biological origin - Requirements for certified reference materials and the content of supporting documentation
ISO 15223-1:2012	Medical devices – symbols to be used with medical devices: Labels, labeling and information to be supplied – Part 1: General requirements
EN ISO 17511:2003	In vitro diagnostic medical devices – Measurement of quantities of biological origin – Metrological traceability of values assigned to

	calibrators and control materials
BS EN ISO 18113-1:2011	In-vitro diagnostic medical devices –Information supplied by the manufacturer (labeling) – Part 1: Terms, definitions and general requirements
BS EN ISO 18113-2:2011	Part 2: In-vitro diagnostic reagents for Professional use (ISO 18113-2 : 2009)
EN 23640:2013	In-vitro diagnostic medical devices: Evaluation of stability of in-vitro diagnostic reagents

5.2 Proof of the Essential requirements according to Annex 1 of the Directive 98/79/EC on in-vitro diagnostic medical devices:

ESSENTIAL REQUIREMENTS	Applicability (Y/N)	Applied Standards, procedures	References	Comments
A. GENERAL REQUIREMENTS				
1. Documentation concerning safe use: The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise, directly or indirectly, the clinical condition or the safety of the patients, the safety or health of users or, where applicable, other persons, or the safety of property. Any risks which may be associated with their use must be acceptable when weighed against the benefits to the patient and be compatible with a high level of protection of health and safety.	Y	EN ISO 14971:2012 EN 13640:2002 EN 13641:2002 EN ISO 18113-2:2011	Risk Analysis – Section 7 below; BMT SOP 110	Risk analysis, estimate and evaluation was performed. All risks were found to be acceptable
2. Documentation for design and construction: The solutions adopted by the manufacturer for the design and construction of the devices must conform to safety principles, taking account of the generally acknowledged state of the art. In selecting the most appropriate solutions, the manufacturer must apply the following principles in the following order: <ul style="list-style-type: none"> - eliminate or reduce risks as far as possible (inherently safe design and construction), - where appropriate take adequate protection measures in relation to risks that cannot be eliminated, - inform users of the residual risks due to any shortcomings of the protection measures adopted. 	Y	EN ISO 14971:2012 EN 13640:2002 EN 13641:2002 EN ISO 13485:2012 /AC:2012 EN ISO 15223-1:2012	Risk Analysis – Section 7 below; See enclosed "Instructions for use"	This test is an advanced test for which Analytical parameters have been shown to be similar if not better than other marketed tests

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<p>3. Specification of function: The devices must be designed and manufactured in such a way that they are suitable for the purposes referred to in Article 1(2)(b), as specified by the manufacturer, taking account of the generally acknowledged state of the art. They must achieve the performances, in particular, where appropriate, in terms of analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, including control of known relevant interference, and limits of detection, stated by the manufacturer.</p> <p>The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order.</p>	Y	EN ISO 13485:2012 /AC:2012 EN 13612:2002/AC:2002 EN ISO14971:2012	Risk analysis Stability testing, BMT SOP 108	Studies addressing the listed standards demonstrate that the test is suitable for its intended use
	Y	EN 13612:2002/AC:2002	Performance evaluation	ATCC ref material used to verify performance
<p>4. Maintenance of the function of the product during its lifetime: The characteristics and performances referred to in sections 1 and 3 must not be adversely affected to such a degree that the health or the safety of the patient or the user and, where applicable, of other persons, are compromised during the lifetime of the device as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use. When no lifetime is stated, the same applies for the lifetime reasonably to be expected of a device of that kind, having regard to the intended purpose and the anticipated use of the device.</p>	Y	EN 13612:2002/AC:2002 EN 13641:2002	Performance evaluation – See product stability studies 4.4	Stability studies show no loss of performance for at least 12 months
<p>5. Packaging , transportation and storage : The devices must be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected under storage and transport conditions (temperature, humidity, etc.) taking account of the instructions and information provided by the manufacturer.</p>	Y	EN 13612:2002/AC:2002 ISO 14971:2012 EN ISO 13485:2012/AC:2012 EN ISO 18113-1:2011 EN ISO 18113-2:2011	Risk Analysis – File, see section 7, See enclosed "instructions for use" Information supplied by manufacturer, labeling	Tests show good temperature tolerance (transport stability). Risk analysis rates hazards arising from transportation. Packaging designed to lower risks of damage during transport.
B. DESIGN AND MANUFACTURING REQUIREMENTS				
1. Chemical and physical properties				
1.1. The devices must be designed and manufactured in such a way as to achieve the characteristics and performances referred to in section A on the ‘General requirements’. Particular attention must be paid to the possibility of impairment of analytical performance due to incompatibility between the materials used and the specimens (such as biological tissues, cells, body fluids and micro-organisms) intended to be used with the device, taking account of its intended purpose.	Y	EN 13612:2002/AC:2002 ISO 14971:2012	Risk Analysis – File - see section 7, below	Cross reactivity studies showed no cross-reactivity with other bacteria which might manifest similar clinical symptoms
1.2. The devices must be designed, manufactured and packed in such a way as to reduce as far as possible the risk posed by product leakage, contaminants and residues to the persons involved in the transport, storage and use of the devices, taking account of the intended purpose of the products.	Y	EN 14971:2012 EN ISO 18113-2:2011 EN 13641:2002	Risk analysis BMT SOP 108 Stability studies Labeling and IFU	Hazard analysis has determined risk to be low and acceptable. Primary packaging has been chosen to minimize the risk of leakage during transport, storage and use of product .
2. Infection and microbial contamination				
2.1 The devices and their manufacturing processes must be designed in such a way as to eliminate or reduce as far as possible the risk of infection to the user or other persons. The design must allow easy handling and, where necessary, reduce as far as possible contamination of and leakage from the device	Y	ISO 14971:2012 ISO 13641:2002 ISO 18113-2:2011	Risk Analysis - see section 7, below	The test is for professional use only. Clinical specimens should be treated as

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	during use and, in the case of specimen receptacles, the risk of contamination of the specimen. The manufacturing processes must be appropriate for these purposes.				potentially infectious and used and disposed of in accordance to national regulations.
2.2	Where a device incorporates biological substances, the risks of infection must be reduced as far as possible by selecting appropriate donors and appropriate substances and by using appropriate, validated inactivation, conservation, test and control procedures.	Y	ISO 14971:2012 ISO 13641:2002 ISO 18113-2:2011	Risk Analysis – see section 7, below, MSDS	The biological substances in the device are of negligible risk for infection. Sources of materials of biological origin are carefully selected to minimize hazards.
2.3	Devices labeled either as ‘STERILE’ or as having a special microbiological state must be designed, manufactured and packed in an appropriate pack, according to procedures suitable for ensuring that they remain in the appropriate microbiological state indicated on the label when placed on the market, under the storage and transport conditions specified by the manufacturer, until the protective packaging is damaged or opened.	Y			The product components are sterilized, and it is adequately protected from microbial contamination by drying, addition of preservative and sealing in a protective pouch.
2.4	Devices labeled either as ‘STERILE’ or as having a special microbiological state must have been processed by an appropriate, validated method.	Y			The product components have been sterilized by a validated gamma irradiation protocol; product has been assembled in a clean room environment and tested for microbial bioburden
2.5	Packaging systems for devices other than those referred to in section 2.3 must keep the product without deterioration at the level of cleanliness indicated by the manufacturer and, if the devices are to be sterilized prior to use, reduce as far as possible the risk of microbial contamination.	Y	EN ISO 13485:2012 /AC:2012 ISO 14971:2012 ISO 18113-2:2011 EN ISO 13485:2012	Risk analysis Labeling Design and manufacturing information	The product is sealed in a coated, aluminum foil pouch.
	Steps must be taken to reduce as far as possible microbial contamination during selection and handling of raw materials, manufacture, storage and distribution where the performance of the device can be adversely affected by such contamination.	Y		Manufacturing and Quality documentation	Quality Management system defines measures to ensure correct handling of raw materials and manufacturing process
2.6	Devices intended to be sterilised must be manufactured in appropriately controlled (e.g. environmental) conditions.	Y			The product is manufactured in an ISO5 clean and controlled environment
2.7	Packaging systems for non-sterile devices must keep the product without deterioration at the level of cleanliness stipulated and, if the devices are to be sterilised prior to use, minimise the risk of microbial contamination; the packaging system must be suitable taking account of the method of sterilisation indicated by the manufacturer.	Y	EN ISO 13485:2012 ISO 14971:2012	Design and manufacturing information Risk analysis - see section 7	The product is sealed in a laminated aluminum foil pouch with added desiccant.

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				The product is gamma-sterilized according to a validated protocol
3. Manufacturing and environmental properties				
3.1	If the device is intended for use in combination with other devices or equipment, the whole combination, including the connection system, must be safe and must not impair the specified performances of the devices. Any restrictions on use must be indicated on the label and/or in the instructions for use.	N		The product (device) is used in conjunction with standard laboratory equipment.
3.2	Devices must be designed and manufactured in such a way as to reduce as far as possible the risks linked to their use in conjunction with materials, substances and gases with which they may come into contact during normal conditions of use.	Y	EN ISO 13485:2012 ISO 14971:2012 ISO 13641:2002	Risk analysis IFU Stability studies
3.3	Devices must be designed and manufactured in such a way as to remove or reduce as far as possible: - Risk of injury linked to their physical features (in particular aspects of volume x pressure, dimension and, where appropriate, ergonomic features). - Risks linked to reasonably foreseeable external influences, such as magnetic fields, external electrical effects, electrostatic discharge, pressure, humidity, temperature or variations in pressure or acceleration or accidental penetration of substances into the device. - Devices must be designed and manufactured in such a way as to provide an adequate level of intrinsic immunity of electromagnetic disturbance to enable them to operate as intended.	Y	ISO 14971:2012	Risk analysis IFU
		Y	ISO 14971:2012 ISO 13640:2002	Risk analysis Product stability study
		N		
3.4	Devices must be designed and manufactured in such a way as to reduce as far as possible the risks of fire or explosion during normal use and in single fault condition. Particular attention must be paid to devices whose intended use includes exposure to or use in association with flammable substances or substances which could cause combustion.	N		No risk of fire or explosion while using the product
3.5	Devices must be designed and manufactured in such a way as to facilitate the management of safe waste disposal.	Y	ISO 14971:2012 ISO 13641:2002	Risk analysis Elimination of risk of infection
3.6	The measuring, monitoring or display scale (including colour change and other visual indicators) must be designed and manufactured in line with ergonomic principles, taking account of the intended purpose of the device	Y	EN ISO 13485:2012 ISO 14971:2012	Device description Risk analysis
				The product is used to detect the presence of Streptococcus Group A in a specimen collected by a throat swab which is potentially infectious. Warnings are given in the IFU. The test is for professional use only.
				Risk of injury due to the use of the device is very low. Risk from chemical solutions used with the device has been rated in the Risk analysis as acceptable.
				No risk of electromagnetic interference with test
				Clinical specimens are of a potentially infectious nature and should be handled and disposed of according to local regulations. Warnings are given in the IFU
				Two distinct lines provide a positive result with the test which can be well seen by the user. A faint line at the minimum detection limit of the test might be seen but Risk analysis showed this to be

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

				acceptable.
4. Devices which are instruments or apparatus with a measuring function				
4.1	Devices which are instruments or apparatus having a primary analytical measuring function must be designed and manufactured in such a way as to provide adequate stability and accuracy of measurement within appropriate accuracy limits, taking into account the intended purpose of the device and of available and appropriate reference measurement procedures and materials. The accuracy limits have to be specified by the manufacturer.	Y	EN ISO 13485:2012 ISO 14971:2012 EN 13612:2002/AC:2002	Device description Risk analysis Performance Evaluation
4.2	When values are expressed numerically, they must be given in legal units conforming to the provisions of Council Directive 80/181/EEC of 20 December 1979 on the approximation of the laws of the Member States relating to units of measurement.	N	ISO 18113-2:2011 Information provided by the manufacturer – labelling, IFU	The test provides a qualitative YES/NO result only. It has reliable limit of detection of 1×10^5 organisms which is consistent for all batches. QC procedures are in place to ensure this and RA confirms it as acceptable.
5. Protection against radiation				
5.1	Devices shall be designed, manufactured and packaged in such a way that exposure of users and other persons to the emitted radiation is minimized.	N		No numerical quantitative results are obtained with this test
5.2	When devices are intended to emit potentially hazardous, visible and/or invisible radiation, they must as far as possible be: - designed and manufactured in such a way as to ensure that the characteristics and the quantity of radiation emitted can be controlled and/or adjusted - fitted with visual displays and/or audible warnings of such emissions	N		This test does not contain any energy and / or radiation sources, neither does it generate any.
5.3	The operating instructions for devices emitting radiation must give detailed information as to the nature of the emitted radiation, means of protecting the user, and on ways of avoiding misuse and of eliminating the risks inherent in installation.	N		This test does not contain any energy and / or radiation sources, neither does it generate any.
6. Requirements for medical devices connected to or equipped with an energy source				
6.1	Devices incorporating electronic programmable systems, including software, must be designed to ensure the repeatability, reliability and performance of these systems according to the intended use.	N		This test does not contain any energy and / or radiation sources, neither does it generate any.
6.2	Devices must be designed and manufactured in such a way as to minimise the risks of creating electromagnetic perturbation which could impair the operation of other devices or equipment in the usual environment. According to 2007/47/EC: For devices which incorporate software, or which are medical software in themselves, the software must be validated.	N		This test does not have any programmable electronic system
6.3	Devices must be designed and manufactured in such a way as to avoid, as far as possible, the risk of accidental electric shocks during normal use and in single fault condition, provided the devices are installed and maintained correctly.	N		This test does not incorporate any software
6.4	Protection against mechanical and thermal risks			No electromagnetic perturbation are to be expected with this device
6.4.1	Devices must be designed and manufactured in such a way as to protect the user against mechanical risks. Devices must be sufficiently stable under the foreseen operating conditions. They must be suitable to withstand stresses inherent in the foreseen working environment, and to retain this resistance during the expected life of the devices, subject to any	Y		Risk analysis Performance evaluation
				There are no mechanical risks for the user

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inspection and maintenance requirements as indicated by the manufacturer.				
Where there are risks due to the presence of moving parts, risks due to break-up or detachment, or leakage of substances, then appropriate protection means must be incorporated.	N	EN ISO 13485:2012 ISO 14971:2012		No mechanical risk from moving parts or breaking of kit components can be described
Any guards or other means included with the device to provide protection, in particular against moving parts, must be secure and must not interfere with access for the normal operation of the device, or restrict routine maintenance of the device as intended by the manufacturer.	N	EN 13612:2002/AC:2002		
6.4.2 Devices must be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from vibration generated by the devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.	N			No mechanical risks for the user due to vibration can be described
6.4.3 Devices must be designed and manufactured in such a way as to reduce as far as possible the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified performance.	N			No mechanical risks for the user due to noise emissions can be described
6.4.4 Terminals and connectors to electricity, gas or hydraulic and pneumatic energy supplies which the user has to handle must be designed and manufactured in such a way as to minimise all possible risks.	N			No risks to the user due to electricity, gas, hydraulic or pneumatic energy can be described
6.4.5 Accessible parts of the devices (excluding the parts of areas intended to supply heat or reach given temperatures) and their surroundings must not attain potentially dangerous temperatures under normal use.	N			There are no parts which could heat up during use of the device
7. Requirements for devices for self-testing				
Devices for self-testing must be designed and manufactured in such a way that they perform appropriately for their intended purpose taking into account the skills and the means available to users and the influence resulting from variation that can reasonably be anticipated in users' technique and environment. The information and instructions provided by the manufacturer should be easily understood and applied by the user.	N			The test is for professional use only
7.1 Devices for self-testing must be designed and manufactured in such a way as to: - ensure that the device is easy to use by the intended lay user at all stages of the procedure, and - reduce as far as practicable the risk of user error in the handling of the device and in the interpretation of the results.	N			The test is for professional use only
7.2 Devices for self-testing must, where reasonably possible, include user control, i.e. a procedure by which the user can verify that, at the time of use, the product will perform as intended.	N			The test is for professional use only
8. Information supplied by the manufacturer				
8.1 Each device must be accompanied by the information needed to use it safely and properly, taking account of the training and knowledge of the potential users, and to identify the manufacturer.	Y	BS EN ISO 18113-1:2011 EN ISO 15223-1:2012 EN ISO 18113-1:2011 EN ISO 18113-2:2011	Instructions for use Labelling Symbols	The Primary and Secondary packaging (including labelling) and IFU for the test were designed according to the quoted standards. Manufacturer is named on primary packaging, secondary packaging and IFU.
This information comprises the data on the label and in the instructions for use.	Y			
As far as practicable and appropriate, the information needed to use the device safely and properly must be set out on the device itself and/or, where appropriate, on the sales packaging. If individual full labelling of each unit is not practicable, the information must be set out on the packaging and/or in the	Y			

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<p>instructions for use supplied with one or more devices.</p> <p>Instructions for use must accompanied or be included in the packaging of one or more devices.</p> <p>In duly justified and exceptional cases no such instructions for use are needed for a device if it can be used properly and safely without them.</p> <p>The decision whether to translate the instructions for use and the label into one or more languages of the European Union shall be left to the Member States, except that, for devices for self-testing, the instructions for use and the label must include a translation into the official language(s) of the Member State in which the device for self-testing reaches its final user. Official language(s) of the Member State in which the device is for self-testing</p>	<p>Y</p> <p>N</p> <p>N</p>			<p>Intended use is detailed in IFU, on secondary packaging with symbols on primary packaging. IFU details how to perform the assay, gives background information, precaution, limitations and performance data</p>
<p>8.2 Where appropriate, the information to be supplied should take the form of symbols. Any symbol and identification color used must conform to the harmonized standards. In areas for which no standards exist, the symbols and color used must be described in the documentation supplied with the device.</p>	<p>Y</p>	<p>BS EN ISO 18113-1:2011 EN 15223-1:2012</p>	<p>IFU and sample labels are included in the technical file</p>	<p>Symbols are used. Explanatory table of symbols appears in IFU.</p>
<p>8.3 In the case of devices containing or a preparation which may be considered as being dangerous, taking account of the nature and quantity of its constituents and the form under which they are present, relevant danger symbols and labelling requirements of Directive 67/548/EEC (1) and Directive 88/379/EEC (2) shall apply. Where there is insufficient space to put all the information on the device itself or on its label, the relevant danger symbols shall be put on the label and the other information required by those Directives shall be given in the instructions for use.</p> <p>The provisions of the aforementioned Directives on the safety data sheet shall apply, unless all relevant information as appropriate is already made available by the instructions for use.</p>	<p>N</p> <p>Y</p>	<p>2001/58/EC and REACH REGULATION (1907/2006 CE + Commission Regulation EU No 109/2012</p>	<p>MSDS of kit</p>	<p>No dangerous materials are included in this device or kit.</p>
<p>8.4 The label must bear the following particulars which may take the form of symbols as appropriate:</p> <p>a) The name or trade name and address of the manufacturer. For devices imported into the Community with a view to their distribution in the Community, the label, the outer packaging, or the instructions for use shall contain in addition the name and address of the authorized representative of the manufacturer;</p>	<p>Y</p>	<p>BS EN ISO 18113-1:2011 EN 15223-1:2012 EN ISO 13485:2012</p>	<p>See enclosed samples of labels and instructions for use</p>	<p>The name and address of BMT's authorized EU representative appears on the IFU and on the secondary labeling.</p>
<p>b) The details strictly necessary for the user to uniquely identify the device and the contents of the packaging;</p>	<p>Y</p>			<p>All necessary symbols are included</p>
<p>c) Where appropriate, the word 'STERILE' or a statement indicating any special microbiological state or state of cleanliness;</p>	<p>Y</p>			
<p>d)The batch code, preceded by the word 'LOT', or the serial number;</p>	<p>Y</p>			<p>Primary and secondary labels carry a Lot number</p>

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e) If necessary, an indication of the date by which the device or part of it should be used, in safety, without degradation of performance, expressed as the year, the month and, where relevant, the day, in that order	Y	BS EN ISO 18113-1:2011	See enclosed samples of labels and instructions for use	Primary and outer packaging carry the expiration date of the test
f) In case of devices for performance evaluation, the words 'for performance evaluation only';	N			The test is for professional use only, not for performance evaluation
g) Where appropriate, a statement indicating the in vitro use of the device;	Y	BS EN ISO 18113-1:2011	See enclosed sample of labels	The IVD symbol appears on primary labels and outer packaging
h) Any particular storage and/or handling conditions;	Y	BS EN ISO 18113-1:2011	See enclosed sample of labels	Storage temperature appears on primary and outer packaging
i) Where applicable, any particular operating instructions;	Y	BS EN ISO 18113-1:2011	See enclosed sample of labels and instructions for use	IFU are included in the kit
j) Appropriate warnings and/or precautions to take;	Y	BS EN ISO 18113-1:2011	See enclosed Instructions for use	Warnings appear on IFU
k) If the device is intended for self-testing, that fact must be clearly stated	N		See enclosed Instructions for use	The test is for professional use only
8.5 If the intended purpose of the device is not obvious to the user, the manufacturer must clearly state the intended purpose in the instructions for use and, if appropriate, on the label.	Y	BS EN ISO 18113-1:2011	See enclosed samples of labels and the IFU	Intended use appears on primary packaging, outer packaging and on kit label
8.6 Wherever reasonable and practicable, the devices and separate components must be identified, where appropriate in terms of batches, to allow all appropriate action to detect any potential risk posed by the devices and detachable components.	Y	BS EN ISO 18113-1:2011	See enclosed samples of labels	
8.7 Where appropriate, the instructions for use must contain the following particulars:		BS EN ISO 18113-1:2011 EN 14971:2012	See enclosed sample of labels and instructions for use	
a) The details referred to in section 8.4 with the exception of points (d) and (e);	Y			
b) Composition of the reagent product by nature and amount or concentration of the active ingredient(s) of the reagent(s) or kit as well as a statement, where appropriate, that the device contains other ingredients which might influence the measurement	Y			
c) The storage conditions and shelf life following the first opening of the primary container, together with the storage conditions and stability of working reagents;	Y			
d) The performances referred to in section 3 of part A;	Y			
e) An indication of any special equipment required including information necessary for the identification of that special equipment for proper use;	Y			
f) The type of specimen to be used, any special conditions of collection, pre-treatment and, if necessary, storage conditions and instructions for the preparation of the patient;	Y			
g) A detailed description of the procedure to be followed in	Y			

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using the device;				
h) The measurement procedure to be followed with the device including as appropriate:	Y			
- The principle of the method,				
- The specific analytical performance characteristics (e.g. sensitivity, specificity, accuracy, repeatability, reproducibility, limits of detection and measurement range, including information needed for the control of known relevant interferences), limitations of the method and information about the use of available reference measurement procedures and materials by the user				
- The details of any further procedure or handling needed before the device can be used (for example, reconstitution, incubation, dilution, instrument checks, etc.),				
- The indication whether any particular training is required;				
i) The mathematical approach upon which the calculation of the analytical result is made;	N			
j) Measures to be taken in the event of changes in the analytical performance of the device;	N			
k) Information appropriate to users on:	Y			
- internal quality control including specific validation procedures,				
- the traceability of the calibration of the device;	N			
l) The reference intervals for the quantities being determined, including a description of the appropriate reference population;	N			
m) If the device must be used in combination with or installed with or connected to other medical devices or equipment in order to operate as required for its intended purpose, sufficient details of its characteristics to identify the correct devices or equipment to use in order to obtain a safe and proper combination;	N			
n) All the information needed to verify whether the device is properly installed and can operate correctly and safely, plus details of the nature and frequency of the maintenance and calibration needed to ensure that the device operates properly and safely; information about safe waste disposal;	N			
o) Details of any further treatment or handling needed before the device can be used (for example, sterilization, final assembly, etc.);	N			
p) The necessary instructions in the event of damage to the protective packaging and details of appropriate methods of re-sterilization or decontamination;	N			
q) If the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging and re-sterilization or decontamination, and any restriction on the number of reuses;	N			
r) Precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external electrical influences, electrostatic discharge, pressure or variations in pressure, acceleration, thermal ignition sources, etc.;	N			

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s) Precautions to be taken against any special, unusual risks related to the use or disposal of the device including special protective measures; where the device includes substances of human or animal origin, attention must be drawn to their potential infectious nature;	Y			
t) Specifications for devices for self-testing: <ul style="list-style-type: none"> - the results need to be expressed and presented in a way that is readily understood by a lay person; information needs to be provided with advice to the user on action to be taken (in case of positive, negative or indeterminate result) and on the possibility of false positive or false negative result, - specific particulars may be omitted provided that the other information supplied by the manufacturer is sufficient to enable the user to use the device and to understand the result(s) produced by the device, - the information provided must include a statement clearly directing that the user should not take any decision of medical relevance without first consulting his or her medical practitioner, - the information must also specify that when the device for self -testing is used for the monitoring of an existing disease, the patient should only adapt the treatment if he has received the appropriate training to do so; 	N			
u) Date of issue or latest revision of the instructions for use.	Y	BS EN ISO 18113-1:2011	See enclosed sample of labels and instructions for use	

6 DECLARATION OF CONFORMITY

EC Declaration of Conformity

Manufacturer:

Name: BIO MARKETING T, LTD
Address: 14 Ha'ilan St. Or-Akiva, PO Box 420, Zichron Ya'akov 3095203 Israel

Manufacturing Site:

Name: BIO MARKETING T, LTD
Address: 14 Ha'ilan St. Or-Akiva, PO Box 420, Zichron Ya'akov 3095203 Israel

European Representative:

Name: MedNet GmbH
Address: Borkstrasse 10, 48163 Muenster, Germany

Product Name: Strep A Rapid Test Device

Brand Name: Lab-On-Time™

Model: Device

Classification: Device for professional use only not listed under IVDD 98/79/EC Annex II

Conformity Assessment Route: IVDD 98/79/EC Annex III

We herewith declare that the above-mentioned products meet the transposition into national law, the provisions of the following EC Council Directives and Standards. All supporting documentation are retained under the premises of the manufacturer.

DIRECTIVES

General applicable directive:

DIRECTIVE 98/79/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 October 1998 on in-vitro diagnostic medical devices

Standards Applied:

IVDD 98/79 EC, EN ISO13485:2012/AC:2012, EN ISO14971:2012, EN 13975:2003, EN ISO18113-1:2011
EN ISO 18113-2:2011, EN 13612:2002/AC:2002, EN ISO 17511:2003, EN ISO 15193:2009, EN ISO
15194:2009, EN 13640:2002, EN 13641:2002 BS, EN ISO 15223-1:2012, EN 1041:2008

Place, Date of issue: in Or-Akiva on Nov 9th 2015

Signature:



Name: Idan Tamir, PhD

Position: Co-owner

7 RISK MANAGEMENT

7.1 Scope

This document identifies hazards associated with the Lab-On-Time™ Strep A Rapid Diagnostic Test Device manufactured by BMT BioMarketing, Ltd. The document does not cover any hazard that may be caused by any equipment or devices used in conjunction with the Lab-On-Time™ Strep A Rapid Diagnostic Test Device

7.2 Related documents

Standard ISO EN 14971:201

Quality Manual BMT-2015

7.3 Hazard assessment method

Hazard analysis was performed by Dr. Idan Tamir in consultation with external experts with wide knowledge in medical devices in general and in IV Diagnostic products in particular.

The process used was as follows:

- All known and relevant hazards were discussed and listed (See sec. 7.3.5. below).
- The hazards were rated for probability of occurrence and severity.
- A risk index was calculated for each hazard before mitigation by multiplying occurrence probability by its severity.
- The mitigation activities required to control each hazard were defined.
- A new rating for probability of occurrence and severity was assigned.
- A new risk index was calculated for each hazard before its mitigation by multiplying the probability by the severity.
- All of the above information is tabulated

7.3.1 Severity ranking Hazard assessment method:

Rating	Occurrence	Definition
1	Low	Unlikely to cause any damage to the user or the patient
2	Moderate	Likely to result in a medically reversible, treatable condition of the user or patient
3	Significant	Likely to result in a condition requiring severe intervention

7.3.2 Occurrence / Probability ranking:

Rating	Occurrence/ Probability	Definition
1	Low	Unlikely to occur
2	Medium	Can happen, but not frequently
3	High	Likely to occur frequently

7.3.3 Risk Index Ranking:

The severity and occurrence rankings will determine a Risk Index to be used for risk acceptability decisions and design verification acceptance criteria. The following matrix and Risk Index definitions shall be used.

		Severity			
		1	2	3	4
Occurrence	1	0	0	0	1
	2	0	0	1	2
	3	0	1	2	2
	4	1	1	2	3

green area – acceptable risk

red area - unacceptable risk

7.3.4 Risk Index Definitions – Risk Priority Number – RPN:

Level	Risk Index Definitions for Design	
0	Negligible Risk	Acceptable as implemented.
1	Tolerable Risk	Verified/validated to minimum performance level for a Level 1 risk and approved through design review; risk is typically deemed acceptable.
2	Undesirable Risk	Verified/validated to minimum performance level for a Level 2 risk and approved through design review. Additional actions may be taken to reduce risk. Risk may be deemed acceptable based on the device.
≥3	Intolerable Risk	Unacceptable as is based on the pre-established criteria for risk acceptability; re-design or reduction in occurrence typically required

7.3.5 Applicable Risk and Hazard Discussion and Listing:

- a) **What is the intended use and how is the medical device to be used?**
 The device is used as a screening tool for detection of Streptococcus Group A antigens in throat swab specimens or plate colony samples. The device is to be used by trained professional personnel only.
- b) **Is the medical device intended to come into contact with the patient?**
 Yes, the device is intended to contact the patient throat for clinical sample collection. The device components are sterilized, and the assembled device is inspected periodically and batch-wise for bioburden and the possible presence of pathogens.
- c) **Is there a mechanical risk to the patient's throat by the device during clinical sample collection?**
 The device is designed to have no sharp ends and when used according to the IFU and in professional hands poses no risk to the patient.
- d) **Is the medical device supplied sterile or intended to be sterilized by the user?**
 The device is supplied sterile, it is not intended to be cleaned, disinfected or sterilized by the user.
- e) **Is the device used with a calibrator or control which, if used inappropriately could cause an erroneous result?**
 The device has a built-in control so that the user cannot confuse usage of a control.
- f) **Is the medical device intended for use in conjunction with other medical technologies or instrument?**
 The device is not intended for use in conjunction with other laboratory equipment.
- g) **What is the probability that the result obtained will be false positive?**
 The probability is low as no cross-reactivity has been shown with 23 common microorganisms. Additionally, the false positive rate is determined by test specificity, which has been determined to be 97.8% in comparison with bacterial culture, indicating a low false positive rate.

h) What is the probability that result obtained will be false negative?

The false negative rate is determined by test sensitivity, which has been determined to be 95.1% with respect to bacterial culture, indicating that the probability of a false negative result is low. However, inappropriate sample collection by untrained personnel may have a negative impact on test sensitivity. It is therefore essential that the test should only be performed by trained professional staff.

i) Is the medical device intended to use in conjunction with medicines or other medical technologies?

No

j) Is the medical device susceptible to environmental influence?

The device is packed in a laminated aluminum foil pouch together with desiccant. The device does not have to be stored refrigerated and the test should be performed at ambient temperatures.

k) Does the medical device influence the environment?

Device disposal should be according to local environmental regulations. Proper caution should be exercised when disposing clinical samples and kit reagents.

l) Does shelf life of the device conform to its intended use?

The shelf life of the device is dictated by the shortest shelf life of any of its components. The most sensitive component is the test strip, which is at-least 24 months following manufacture assuming proper storage conditions are employed. The shelf life is indicated on the device label.

m) What will be the impact of a false negative test result on the patient?

Failure to detect Strep throat infection could cause unnecessary discomfort to the patient due to the delay in administering antibiotic therapy. The physician suspecting a strep throat infection in a specific patient though the device tests negative should send a throat swab to the lab for results confirmation

n) What will be the impact of a false positive test result on the patient?

A false positive result would cause the health provider to administer antibiotic medication unnecessarily.

o) Will use of this device be the only means of clinical condition diagnosis?

The device is intended to confirm other clinical observations and findings by the healthcare provider. Access to other laboratory results should assist in determining the final diagnosis.

p) Is the medical device intended for single use?

Yes.

q) Does use of the medical device require special training?

The device is to be used by trained and qualified healthcare providers (physician, nurse, etc.). The user should read and closely follow the instructions for use prior to attempting device usage.

r) What assures that the test has been properly performed?

The device has a built-in control which verifies that it is performing according to the manufacturer's design.

s) To what extent would failure on the part of the health provider to provide a quick diagnosis be dangerous or crucial to the patient?

Failure of timely drug administration will cause prolonged discomfort for the patient. Only in extremely rare cases will delay in treatment be dangerous to the patient.

7.3.6 Conclusion (overall evaluation):

After implementation of the risk control measures for every hazard, as shown in sec. 8 below, and after it was established that the mitigation activities reduce risk, it was concluded that the overall risk posed by the Lab-On-Time™ Strep A Rapid Diagnostic Test Device is at an acceptable level.

8 FMEA: DESIGN, PROCESS, USE

The below table summarizes risks associated with product manufacture and utilization and their mitigation

FMEA DPU										Action Results			
Item & Function	Potential Failure Mode	Potential Effect(s) of Failure	Severity	Potential Cause(s) of Failure(s)	Occurrence	Current Controls	RPN	Recommended Action	Responsibility	Action Taken	Severity	Occurrence	RPN
Bio-contamination	Buffer contaminated	Test fails to perform	3	Contaminated during manufacturing	2	Batch QC	1				3	1	0
Bio-incompatibility	Buffer gets in contact with skin	Minor skin irritation	1	Leaking buffer bottle	1	Batch visual inspection	0	IFU urges the use of protective equipment	Marketing team	IFU update	1	1	0
Incorrect chemical composition	Incorrect antibody concentration	Test sensitivity altered	1	Manufacturing error	1	Batch QC	0						0
Degradation	Antibodies degraded	Shelf-life shortened	2	Incorrect storage	2	Storage conditions and expiration date are clearly stated on the label	0	Batch QC	QC team	Sampling QC	1	1	0
Waste contamination	Test disposed of improperly	On-site staff exposure to hazardous material	2	User unaware of correct procedures	2	Clear disposal instructions in IFU	0	Clear labeling urges proper disposal routes	Marketing team	Labeling update	1	1	0
Subtotal Risk Priority Number							0	Resulting Subtotal Risk Priority Number					0

Item & Function	Potential Failure Mode	Potential Effect(s) of Failure	Severity	Potential Cause(s) of Failure(s)	Occurrence	Current Controls	RPN	Recommended Action	Responsibility	Action Taken	Severity	Occurrence	RPN
Inadequate labeling	Label contains inaccurate storage instructions/ batch data	Test degradation/ traceability impossible	2	Incorrect manual data input	1	Labeling process controlled	0						0
Inadequate IFU	Test performed not as designed	Invalid test result	3	Test instructions misinterpreted	1	IFU prepared in plain and clear language	0	Conduct frequent on-site user training and phone follow ups	Marketing team	Physicians and pharmacists training performed	1	1	0
Inadequate shelf life	Test fails to perform accurately	Invalid test result	3	Biocomponent degradation	1	Shelf life validated	0	Maintain samples of specific lots	QC team	Lot samples kept for real-time shelf-life testing	1	1	0
Batch non-homogeneity	Inconsistent test performance	Random invalid test result	2	Production error	2	Production standardization	0	Transfer to automated manufacturing	R&D team	Specific manufacturing tasks automated	1	1	0
Subtotal Risk Priority Number							0	Resulting Subtotal Risk Priority Number					0

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FMEA DPU										Action Results			
Item & Function	Potential Failure Mode	Potential Effect(s) of Failure	Severity	Potential Cause(s) of Failure(s)	Occurrence	Current Controls	RPN	Recommended Action	Responsibility	Action Taken	Severity	Occurrence	RPN
Inadequate packaging	Test fails to perform accurately	Invalid test result	3	Biocomponent Degradation due to external humidity, etc	1	Packaging designed to protect tests from damage	0	Accelerated aging for packaging testing	QC team	Improved package sealing	1	1	0
Problems related to sample collection, stability	Test result is obscured or not unequivocal	Invalid test result	3	Antigen degradation, inadequate sampling	1	Clear instructions in IFU	0	Conduct frequent on-site user training and phone follow ups	Marketing team	Physicians and pharmacists training performed	1	1	0
Test sensitivity and specificity	Failure to detect the correct antigen cut-off	Invalid test result	3	Antibody batch variability	1	QC using known concentrations of ATCC bacterial strains	0	Batch QC	QC team	Sampling QC	1	1	0
Subtotal Risk Priority Number							0	Resulting Subtotal Risk Priority Number					0

9 MANUFACTURING - QUALITY ASSURANCE & CONTROL

9.1 Product sterilization - overview

The Lab-On-Time™ Strep A Rapid Diagnostic Test Device is an integrated device for the diagnosis of strep throat in patients. As such, the device operates as both a swab and a diagnostic lateral flow test, which requires insertion of the device tip into the patient's throat for clinical sample collection. The EU Directive 98/79/EC on in vitro diagnostic (IVD) Medical Devices is mute regarding such combination devices and doesn't invoke a requirement for device sterilization with the involvement of a Notified Body. However, we have voluntarily elected to follow strict sterilization guidelines in order to assure the sterility and safety of our device.

9.2 Sterilization, manufacturing and assembly protocols

In order to comply with sterilization requirements for the entire device the following sterilization and assembly strategy has been implemented:

9.2.1 Device components pre-sterilization & validation:

All device components, excluding the diagnostic test strip, are initially subjected to sterilization according to the following protocols:

No.	Device part	Manufacturer Cat no.	Sterilization route	Sterilization dose	Responsibility
1	Swab	Puritan 25-3206-H	ETO	N/A	Provided sterile (CE-marked) by manufacturer
2	Device Cover	BMT-P2950001	Gamma irradiation	10 KGray	BMT
3	Device Base	BMT-P2950002	Gamma irradiation	10 KGray	BMT
4	Device Cap	BMT-P2950003	Gamma irradiation	10 KGray	BMT
5	Aluminum pouch	MG-10000	Gamma irradiation	10 KGray	BMT

Application of this protocol has been validated to provide sterile components for device assembly purposes. Furthermore, the effect of gamma irradiation on device components has been studied and was determined as non-destructive to both short- and long-term device function.

9.2.2 Swab tip manufacturing process:

Sterile 25-3206-H swabs provided by Puritan were subjected to the following manufacturing steps, all performed in a controlled ISO5 environment:

The first step to swab tip manufacturing involves the incorporation of citric acid to swab tips. The amount of citric acid incorporated into the swab tip has been carefully calibrated to provide the exact amount required for sodium nitrite solution acidification for optimal bacterial wall antigen (GAS antigen) extraction. The process of citric acid incorporation within the swab tip involves swab tip dipping in a citric acid solution in ethanol. This coating solution is freshly prepared by dissolving analytical grade citric acid monohydrate in absolute ethanol (BMT SOP 105, see also 2.6, above and Table 1 for additional detail) and stored in the dark at 4°C to minimize its degradation. Next, the swabs are air-dried in an ISO5-controlled environment for 20min and the tips cleaved to the right length (24.0±0.3mm) using a pneumatic guillotine, according to BMT SOP 106. Truncated swab tips are immediately used for device assembly. Swab tips are quality-controlled according to BMT SOP 110 - Lab-On-Time incoming and manufactured components inspection and QC.

9.2.3 Device assembly and QC:

Device components are assembled in an ISO5-controlled environment according to the Lab-On-Time™ Strep A Rapid Diagnostic Test Device assembly protocol described in Chapter 3, above, and in accordance with BMT SOP 107. Assembled devices are tested for fluidics, mechanical, analytical performance, and bioburden testing, as described in BMT SOPs 108 - QC testing for outgoing Lab-On-Time Strep A Rapid Diagnostic Test product - and also briefly in sections 4.2 and 4.3 above.

Specifically, the following tests are performed for 1% of each outgoing lot/batch:

9.2.3.1 Device fluidics testing:

The fluidics performance of the device is tested by registering the time it takes the reagent to start flowing through the diagnostic test strip and the time for first results reading of both the control and test lines. Rise of reagent fluid through the swab tip, the sample pad and the conjugate pad, as indicated by a fluid front emanating past the conjugate pad, should be no longer than 90sec from the time the swab tip of the device is dipped in the reagent tube. Initial results, as indicated by the appearance of the control line on the membrane, should be evident within 3min of test initiation. Positive test results should be apparent by 5min from test initiation and should reach a stable visual signal within 10min of test initiation (see also 9.2.3.2, below)

9.2.3.2 Device analytical performance:

The analytical performance of the device is tested by recording the results obtained using 1×10^5 inactivated Strep A bacteria suspension (ATCC #19615 and ATCC #12365) as positive control and 1×10^7 inactivated Strep C bacteria suspension (ATCC #9528) as a negative one, used separately on a batch of manufactured devices. The stock bacterial suspension is diluted to provide the required bacterial load in 10ul of a buffer, which are added to Reagent A in the reagent tube, followed by device dipping and stirring, all according to the

IFU. A faint Test line and a strong Control line should appear within 5min and become established 10min following test initiation.

9.2.3.3 Device mechanical performance:

As already described in 4.3.1 above, the mechanical performance of the Lab-On-Time™ Strep A Rapid Diagnostic Device is evaluated according to the following parameters:

- I. Device cover-base opening force
- II. Swab tip dislocation force from device cover
- III. Minimal swab stem protrusion above device cover

In order to test these parameters, manufactured devices were mechanically secured horizontally (results reading window facing down) to a support with 10cm of the swab tip end of the device overhanging. The swab tip is then secured by a noose to a hanging reservoir to which weight is added at a constant rate of 10gr/sec. The weight at which the device failed was recorded, followed by visual inspection to examine if the swab tip was dislocated. Failed devices were further examined for swab tip protrusion from device cover by means of a micrometer.

All tested devices were required to fail at no less than 400gr (~4N), with the device tip held intact within the cover at that failure force. Swab tip protrusion above the cover following device failure needs to be no more than 0.10mm (full swab stem penetration is indicated by overall cover thickness of 4.27mm).

The above tolerances provide assurance that the device doesn't disintegrate under normal clinical operation conditions and that even in the rare situation where it fails mechanically during normal operating conditions, the swab tip will remain attached to the device and won't dislodge, which otherwise could possibly cause it to be inhaled or ingested by the patient.

9.2.3.4 Bioburden testing:

In order to assure that the devices remain sterile following assembly, they were tested for both their bioburden and specific pathogenic microbiological presence.

- I. First, a validation study of the bioburden determination technique was performed to assure effective bacterial extraction from the device and establish the correction factor for bacterial cfu determination. The results of this study are presented in **Appendix A**.
- II. Second, microbial testing was performed for assembled devices to determine their level of contamination, according to the validated bioburden determination protocol. The representative results of such microbiological test are shown in **Appendix B**.
- III. Finally, possible contamination by the presence of common, specific pathogens was evaluated using established techniques for microbiological examination (**Appendix C**).

10 PACKAGING COMPONENT SPECIFICATIONS & LABELING

10.1 Packaging components specification

Kit components are presented in the below photographs and diagrams:

10.1.1 Lab-On-Time™ Strep A Rapid Diagnostic Test Device:

The assembled rapid diagnostic test device is shown in Fig. 6, below (diagnostic control line in blue shown for scaling purposes only).



Figure 6: Fully-assembled Lab-On-Time™ Strep A Rapid Diagnostic Test Device (diagnostic control line shown)

10.1.2 Desiccant bag:

Standard, 0.5gr desiccant bag is used per device to assure low level of humidity within the sealed pouch in order to prevent growth of microorganisms and diagnostic strip deterioration.

10.1.3 Reagent A tube:

Fig. 7 below shows the filled and capped Reagent A tube.



Figure 7: Filled and capped Reagent A tube

Reagent tube label is according to the below graphics (Figure 8):



Figure 8: Reagent A tube label

10.1.4 Instructions for use (IFU):

Please refer to section 11, below.

10.2 Aluminum foil pouch and device packaging

The laminated aluminum pouch is custom-manufactured printed and divided into two separate pouches connected by a perforated border. Each separate pouch is heat-sealed on three sides, allowing insertion of the Lab-On-Time™ Strep A Rapid Diagnostic Device, together with a silica gel desiccant bag into one pouch, while the Reagent A tube containing Reagent A is inserted into its the other pouch, as shown in Figure 9, below.

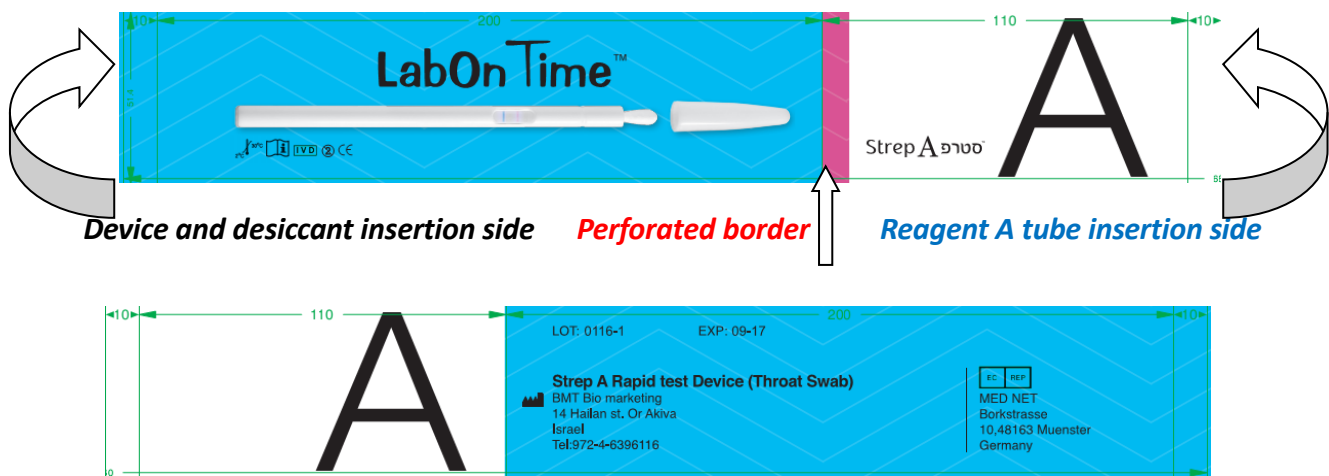


Figure 9: Front (top) and back (bottom) view of the laminated aluminum pouch, showing all required labels and directions for device and Reagent A tube insertion

Following the insertion of the test strip and desiccant bag, the device side of the aluminum pouch is immediately heat sealed, to avoid test strip deterioration and stamped with the batch number and expiration date. The device packed within its pouch is then transferred to the packaging department, where the filled Reagent A tube is inserted into the other pouch and the pouch is heat-sealed, as shown in Figure 10, below.



Figure 10: Device and Reagent A tube sealed in aluminum pouch

10.3 Outer packaging

Once both the device and reagent tube have been inserted into the aluminum pouch and the pouch has been heat-sealed, the pouch is folded along its perforated line and introduced, together with the IFU into the cardboard box shown in Figs. 11 (unfolded) and 12 (folded), below.

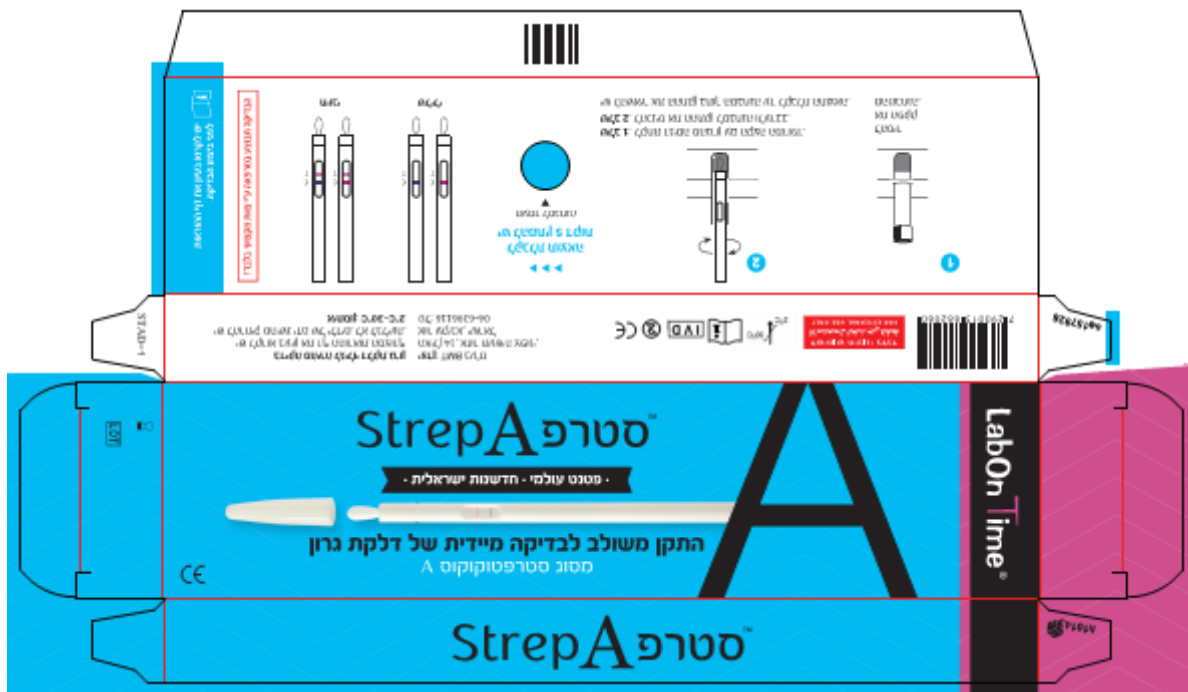


Figure 11: Outer packaging detail, unfolded box



Figure 12: Outer packaging detail, folded

The outer packaging provides all required markings (e.g. CE), symbols and additional information required by the IVD directive.

11 INSTRUCTIONS FOR USE (IFU)

Lab-On-Time™ Strep A Rapid Test Device (Throat Swab) Package Insert

An integrated rapid test device for throat swab specimen collection and qualitative detection of Strep A antigens. For professional in vitro diagnostic use only.

【INTENDED USE】

The Lab-On-Time™ Strep A Rapid Test Device is an integrated device for the collection of throat swab specimen and its rapid analysis by a chromatographic immunoassay for the qualitative detection of Strep A antigen to aid in the diagnosis of Group A Streptococcal infection.

【SUMMARY】

Streptococcus pyogenes is non-motile gram-positive cocci, which contains the Lancefield group A antigens that can cause serious infections such as pharyngitis, respiratory infection, impetigo, endocarditis, meningitis, puerperal sepsis, and arthritis.¹ Left untreated, these infections can lead to serious complications, including rheumatic fever and peritonsillar abscess.² Traditional identification procedures for Group A Streptococci infection involve the isolation and identification of viable organisms using techniques that require 24 to 48 hours or longer.^{3,4} The Lab-on-Time™ Strep A Rapid Test Device is an integrated device for throat swab sample collection and qualitative rapid analysis to detect the presence of Strep A antigen, providing results within 5 minutes. The test utilizes antibodies specific for whole cell Lancefield Group A Streptococcus to selectively detect Strep A antigens in a throat swab specimen.

【PRINCIPLE】

The Strep Lab-on-Time™ Strep A Rapid Test Device is an integrated device employing a qualitative, lateral flow immunoassay for the detection of Strep A carbohydrate antigen in a throat swab. In this test, antibody specific to Strep A carbohydrate antigen is coated on the test line region of the test. During testing, the extracted throat swab specimen reacts with an antibody to Strep A that is coated onto particles. The mixture migrates by capillary forces along the membrane to react with the antibody to Strep A on the membrane and generate a color line in the test line region. The presence of this color line in the test line region indicates a positive result, while its absence indicates a negative result. To serve as a procedural control, a colored line will always appear in the control line region, indicating that proper volume of specimen has been added and membrane wicking has occurred.

【REAGENT】

The test contains Strep A antibody coated particles and Strep A antibodies coated on the membrane.

【PRECAUTIONS】

- For professional in vitro diagnostic use only. Do not use after the expiration date.
- Do not eat, drink or smoke in the area where the specimens and kits are handled.
- Handle all specimens as if they contain infectious agents. Observe established precautions against microbiological hazards throughout the procedure and follow the standard procedures for proper disposal of specimens.
- Wear protective clothing such as laboratory coats, disposable gloves and eye protection when specimens are assayed.
- The used test should be discarded according to local regulations.
- Humidity and temperature can adversely affect results.
- Do not use test if pouch is damaged.
- The positive and negative controls contain sodium azide (NaN₃) as a preservative.
- Do not interchange external control solution bottle caps.

【STORAGE AND STABILITY】

Store as packaged in the sealed pouch at room temperature or refrigerated (2-30°C). The test is stable through the expiration date printed on the sealed pouch. The test must remain in the sealed pouch until use. **DO NOT FREEZE.** Do not use beyond the expiration date.

【SPECIMEN COLLECTION AND PREPARATION】

- Collect the throat swab specimen with the sterile Strep Lab-on-Time™ Strep A Rapid Test Device provided in the kit. Remove the device cap and use the device swab tip to swab the posterior pharynx, tonsils and other inflamed areas. Avoid touching the tongue, cheeks and teeth with the swab tip.⁵
- Testing should be performed immediately after the specimens have been collected.
- If a culture is desired, lightly roll the swab tip onto a Group A selective (GAS) blood agar plate before performing the rapid test using the provided Test Reagent tube.

【MATERIALS】

- | | |
|---|---|
| <ul style="list-style-type: none"> Strep A Rapid Test Device Package insert | <p style="text-align: center;">Materials Provided</p> <ul style="list-style-type: none"> Extraction tube with Extraction Reagent (1.2M Sodium Nitrite) Workstation |
|---|---|

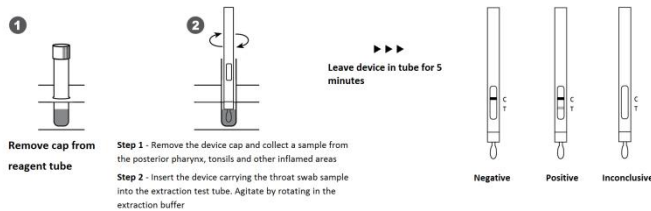
Materials Required But Not Provided

- Timer

【DIRECTIONS FOR USE】

Allow the test, reagents, throat swab specimen, and/or controls to reach room temperature (15-30°C) prior to testing.

- Remove the Strep A Rapid Test Device from the sealed foil pouch and use it as soon as possible. Best results will be obtained if the test is performed immediately after opening the foil pouch.
- Remove the Extraction tube containing Extraction Reagent from the second sealed foil pouch. The color of the extraction reagent is red.
- Insert the Strep A Rapid Test Device carrying the patient throat swab sample into the extraction test tube with the swab tip being dipped into the extraction buffer. Agitate the Strep A Rapid Test Device by rotating it at least 10 times for effective Strep A antigen extraction. Leave the Strep A Rapid Test Device in the extraction test tube and wait for the colored line(s) to appear. **Read the result in the Strep A Rapid Test Device results window between 5 and 10 minutes.** Do not interpret the result after 10 minutes.



【INTERPRETATION OF RESULTS】

(Please refer to the illustration above)

POSITIVE: * **Two lines appear.** One colored line should be in the control line region (C) and another apparent colored line should be in the test line region (T). A positive result indicates that Strep A was detected in the specimen.

***NOTE:** The intensity of the color in the test line region (T) will vary depending on the concentration of Strep A present in the specimen. Therefore, any shade of color in the test line region (T) should be considered positive.

NEGATIVE: **One colored line appears in the control line region (C).** No line appears in the test line region (T). A negative result indicates that Strep A antigen is not present in the specimen, or is present below the detectable level of the test. The patient's specimen should be cultured to confirm the absence of Strep A infection. If clinical symptoms are not consistent with results, obtain another specimen for culture.

INVALID: Control line fails to appear. Insufficient specimen volume or incorrect procedural techniques are the most likely reasons for control line failure. Review the procedure and repeat the test with a new test. If the problem persists, discontinue using the test kit immediately and contact your local distributor.

【QUALITY CONTROL】

Internal Quality Control

Internal procedural controls are included in the test. A colored line appearing in the control region (C) is an internal positive procedural control. It confirms sufficient specimen volume, adequate membrane wicking and correct procedural technique.

LAB-ON-TIME™ STREP A RAPID TEST DEVICE (THROAT SWAB)

External Quality Control

It is recommended that a positive and negative external control be run every 25 tests, and as deemed necessary by internal laboratory procedures. External positive and negative controls are supplied in the kit. Alternatively, other Group A and non-Group A Streptococcus reference strains may be used as external controls. Some commercial controls may contain interfering preservatives; therefore, other commercial controls are not recommended.

Procedure for External Quality Control Testing

1. Add 1 full drop of positive or negative control solution into the Extraction Tube containing the Extraction Reagent, holding the bottle upright.
 2. Place the Strep A Rapid Test Device into this extraction tube and agitate the device in the solution by rotating it at least 10 times.
 3. Continue with Step 3 of Directions For Use.
- If the controls do not yield the expected results, do not use the test results. Repeat the test or contact your distributor.

【LIMITATIONS】

1. The Strep A Rapid Test Device is for in vitro diagnostic use only. The test should be used for the detection of Strep A antigen in throat swab specimens only. Neither the quantitative value nor the rate of increase in Strep A antigen concentration can be determined by this qualitative test.
2. This test will only indicate the presence of Strep A antigen in the specimen from both viable and non-viable Group A Streptococcus bacteria.
3. A negative result should be confirmed by culture. A negative result may be obtained if the concentration of the Strep A antigen present in the throat swab is not adequate or is below the detectable level of the test.
4. Excess blood or mucus on the swab specimen may interfere with test performance and may yield a false positive result. Avoid touching the tongue, cheeks, and teeth⁵ and any bleeding areas of the mouth with the Strep A Rapid Test Device when collecting specimens.
5. As with all diagnostic tests, all results must be interpreted together with other clinical information available to the physician.

【EXPECTED VALUES】

Approximately 15% of pharyngitis in children ages 3 months to 5 years is caused by Group A beta hemolytic Streptococcus.⁶ In school-aged children and adults, the incidence of Strep throat infection is about 40%.⁷ This disease usually occurs in the winter and early spring in temperate climates.³

【PERFORMANCE CHARACTERISTICS】

Sensitivity and Specificity

Using three medical centers for evaluation, a total of 526 throat swabs were collected from patients

exhibiting symptoms of pharyngitis. Each swab was rolled onto a sheep blood agar plate, and then tested by the Strep A Rapid Test Strip (Throat Swab). The plates were further streaked for isolation, and then incubated at 37°C with 5-10% CO₂ and a Bacitracin disk for 18-24 hours. The negative culture plates were incubated for an additional 18-24 hours. Possible GAS colonies were subcultured and confirmed with a commercially available latex agglutination grouping kit. Of the 526 total specimens, 404 were confirmed to be negative and 122 were confirmed to be positive by culture.

Method	Culture		Total Results
	Positive	Negative	
Strep A Rapid Test Strip	116	9	125
	6	395	401
Total Results	122	404	526

Relative Sensitivity: 95.1% (89.6%-98.2%)* Relative Specificity: 97.8% (95.8%-99.0%)* Overall accuracy: 97.1% (95.3%-98.4%)* * 95% Confidence Intervals

Positive Culture Classification	Strep A Rapid Test/Culture	% Agreement
Rare	8/10	80.0%
1+	18/20	90.0%
2+	19/20	95.0%
3+	33/34	97.1%
4+	38/38	100.0%

Cross Reactivity

The following organisms were tested at 2.5 x 10⁷ organisms per test and were all found to be negative when tested with the Strep A Rapid Test Strip. No mucoid-producing strains were tested.

Group B Streptococcus Group F Streptococcus Streptococcus pneumoniae Streptococcus mutans Staphylococcus aureus Corynebacterium diphtheria Candida albicans Enterococcus faecalis	Neisseria meningitidis Neisseria sicca Branhamella catarrhalis Group C Streptococcus Group G Streptococcus Streptococcus sanguis Staphylococcus epidermidis	Serratia marcescens Klebsiella pneumoniae Bordetella pertussis Neisseria gonorrhoea Neisseria subflava Hemophilus influenza Pseudomonas aeruginosa
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7. Woods WA, Carter CT, Stack M, Connors Jr AF, Schlager TA. Group A Streptococcal Pharyngitis in Adults 30 to 65 years of age. Southern Medical Journal (May 1999), 491-492

	Attention, see instructions for use		Tests per kit		Authorized Representative
	For in vitro diagnostic use only		Use by		Do not reuse
	Store between 2-30°C		Lot Number		Catalog #
	Do not use if package is damaged				

BMT Biomarketing, Ltd
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 T: +972-4-6396116, F: +972-4-6396995



www.bmtdiagnostics.com

Effective date: 2016-12-25

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10. Woods WA, Carter CT, Stack M, Connors Jr AF, Schlager TA. Group A Streptococcal Pharyngitis in Adults 30 to 65 years of age. *Southern Medical Journal* (May 1999), 491-492.

13 INTELLECTUAL PROPERTY AND TRADE MARKS

13.1 Patent registration

A patent application covering the basic aspects our proprietary technology: "Devices for Biological Sample Collection and Analysis and Methods of Use Thereof" - PCT US1618148, claiming priority of US provisional application no. 62117211, filed on Feb 17, 2015, is now at National Phase in multiple territories

13.2 Trade marks

The Lab-On-Time™ is registered in both Israel and the USA

14 APPENDICES

14.1 Appendix A - Bioburden Technique Validation

Date of Receiving: December 28, 2015
 Date of Testing: January 11, 2016 Test No.: 55501
 Company Name: Biomarketing Code: 1322
 Address: האיילן 14 ת.ד. 420 מנר עקיבא
Petach Tikva 49511 Israel
 Contact: גילי
 Sample: Strep A Rapid Test 1, 2, 3
 Batch No.: 0116-1
 Test Report Version No.: 1



Hy Laboratories Ltd.
 Park Tamar, Rehovot, 7670606, Israel
 Tel: 972-8-9366475
 Fax: 972-8-9366474
www.hylabs.co.il
hylabs@hylabs.co.il



VALIDATION OF BIOBURDEN TECHNIQUE

Method: Hy-Labs Protocol 10-012 According to EN 1174-ISO 117 37-1
Product Inoculation with Known level of microorganisms.

Selected microorganism: *B.atrophaeus* (former *subtilis*) ATCC 9372
 Estimated inoculum: 100 cfu
 Actual inoculum: 95 cfu TSA Lot No.: 251931
 Removal Technique: Membrane Filtration
 Number of samples pooled: /
 Fluid extraction solution / Volume: 500

ASSAY RESULTS

Product Lot Number	Viable cfu on membrane	Results
Sample 1	74	74
Sample 2	85	85
Sample 3	65	65
Sample 4	/	/
Sample 5	/	/

Mean of cfu / sample: **1.27**

Correction factor for removal efficiency = $\frac{\text{Initial inoculum}}{\text{Recovery titer}} = 95/74.6 = \mathbf{1.27}$

cfu = colony forming units.

TSA = Tryptic Soy Agar.

Negative control of culture medium: Growth / No Growth

Technician: Meital Cohen Microbiology Technician Date: 18 FEB 2016
 Approved by: Kobi Buxdorf Ph.D. M.Sc. Head of the laboratory Date: 17.02.16

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14.2 Appendix B - Microbiological Testing

Date of Receiving: August 17, 2016
Date of Testing: August 21, 2016 **Test No.:** 59987
Company Name: Biomarketing **Code:** 1322 **Hy Laboratories Ltd.**
Address: תאילן 14 ת.ד. 420 אור עקיבא **Park Tamar, Rehovot, 7670606, Israel**
Contact: ניילי **Tel: 972-8-9366475**
Sample: BMT-011 **Fax: 972-8-9366474**
Batch No.: Production Batch **www.hylabs.co.il**
Test Report Version No.: 1 **hylabs@hylabs.co.il**



MICROBIOLOGICAL TEST

Estimation of Population of Microorganisms on Product (Bioburden)

Method: Hy Laboratories Protocol 10-003, based on ISO 11737-1-2.

Technique: Membrane Filtration.

ASSAY RESULTS

Samples	Viable cfu on Membrane		Correction Factor	Results (cfu/ Device)
	Total Aerobic Microbial Count			
	Bacteria	Yeasts and Molds		
1	0	0	1.27	0
2	1	0	1.27	1.27
3	0	0	1.27	0
/	/	/	/	/
/	/	/	/	/
/	/	/	/	/
/	/	/	/	/
/	/	/	/	/
/	/	/	/	/
/	/	/	/	/

Mean of cfu/ Device: **0.42**

TSA- Tryptic Soy Agar

Lot No.: 261124 Negative control of culture Media : Growth / No Growth

TSA- Tryptic Soy Agar

Lot No.: 261124 Negative control of work : Growth / No Growth

Technician:

Daniel Rososki
Biology Technician

28 AUG 2016

Date:

Approved by:

[Signature]

Date:

28 AUG 2016

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14.3 Appendix C - Microbiological Examination

Date of Receiving: January 19, 2016
 Date of Testing: January 19, 2016 Test No.: 55515
 Company Name: BMT Code: 1056
 Address: האיילון 14 תיך 420 אור טקיבא
 Contact: Dr. Idan
 Sample: BMT-002
 Batch No.: Production batch-1
 Test Report Version No.: 1



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Microbiological Examination of Nonsterile Products:
Microbial Enumeration Tests

According to Hy Laboratories SOP No. 10-021, based on Harmonized USP/EP Pharmacopeias.

ASSAY RESULTS

TEST	RESULTS (cfu / _____)
Total Aerobic Bacterial Count	-
Total Yeasts & Molds	-

... suitability of the method to this specific sample was not validated

TEST	RESULT	ID
<i>E. coli</i>	No Growth	-
<i>Salmonella</i>	No Growth	-
<i>S.aureus</i>	No Growth	-
<i>P.aeruginosa</i>	No Growth	-
<i>C.albicans</i>	-	-

I.D. = Final Identification

Negative control: Growth / No Growth

Technician: Daniel Rososhin
Microbiology Technician
 Approved by Kobi Buxdorf Ph.D.MBA
Head of Microbiology Service Lab

Date: 22.01.16
 Date: 31/01/16

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