Dynamiker Biotechnology (Tianjin) Co., Ltd.

Dynamiker *Aspergillus* Galactomannan Assay

Catalogue No.: DNK-1402-1

User Manual / 96 tests

CONTENTS

1. INTENDED USE

Dynamiker Aspergillus Galactomannan Assay is based on competitive Enzyme-linked Immunosorbent Assay (ELISA). It is used for the quantitative detection of Aspergillus galactomannan antigen in human serum and bronchoalveolar lavage fluid (BAL), offering a diagnostic reference for Aspergillus infection. The kit is intended for professional use only.

2. PRINCIPLE

Pipette the treated serum or BAL and the anti-galactomannan antibody respectively into wells coated with galactomannan antigen and then incubate. After removing the unbound material by washing, pipette the conjugate into wells and incubate. Again, after removing the unbound material by washing, the substrate solution is added and incubated. Then the stopping solution is added to terminate the color development. The result is measured at 450nm using an ELISA microplate reader. The intensity of color development is negatively proportional to the concentration of galactomannan antigen tested.

3. SUMMARY AND EXPLANATION

With the wide application of broad-spectrum antibiotics, corticosteroid, immunosuppressant, anti-tumor drugs, as well as the prevalence of AIDS and the development of organ transplantation, the invasive fungal diseases (IFD), with a high mortality, is increasing and complicated. The invasive Aspergillosis (IA) is rapidly increasing. The susceptible population is mainly people who receive immunosuppressive therapy, such as hematopoietic stem cell transplantation patients, hematic malignant carcinoma patients, solid organ transplantation patients, bone marrow transplantation patients as well as long-term chemotherapy and corticosteroid therapy patients and severe AIDS patients.

The clinical symptom of IA is non-specific. There are no identical features in CT scan and X-ray. The difficulty of early diagnosis and timely treatment results in a high mortality of 60%~100% [1]. The presence of galactomannan antigen against Aspergillus indicates a prior Aspergillus infection.

4. KIT COMPONENTS

No.	Component	Content	Quantity
R1	Microtiter Strips	12 breakable strips with 8 wells each; coated with *Aspergillus* galactomannan antigen	1 plate/ 12×8 wells
R2a	Standard a (0.25 μg/L)	Galactomannan antigen in PBS with protein; Preservative: 0.05% ProClin300	1×1mL
R2b	Standard b (0.5 μg/L)	Galactomannan antigen in PBS with protein; Preservative: 0.05% ProClin300	1×1mL
R2c	Standard c (1 μg/L)	Galactomannan antigen in PBS with protein; Preservative: 0.05% ProClin300	1×1mL

R2d	Standard d (2.5 μg/L)	Galactomannan antigen in PBS with protein; Preservative: 0.05% ProClin300	1×1mL
R2e	Standard e (5 μg/L)	Galactomannan antigen in PBS with protein; Preservative: 0.05% ProClin300	1×1mL
R3	Anti-Galactomannan Antibody	Anti-galactomannan antibodies, stabilized with protein stabilization solution;	1×8mL
R4	Conjugate	Goat-anti-rabbit antibodies, conjugated with HRP; stabilized with protein stabilization solution	1×12mL
R5	Sample Treatment Solution	EDTA Solution	1×10mL
R6	Concentrated Washing Solution (20×)	PBS and Tween 20 Preservative: 0.05% ProClin300	1×12mL
R7	Sample Dilution Solution	PBS with protein and Tween 20 Preservative: 0.05% ProClin300	1×5mL
R8	Substrate Solution	Tetramethylbenzidine (TMB)	1×12mL
R9	Stopping Solution	2M H_2SO_4	1×8mL
R10	Control A	Galactomannan antigen in PBS with protein; Preservative: 0.05% ProClin300; 2.5μg/L-5.0μg/L	1×1mL
R11	Control B	Galactomannan antigen in PBS with protein; Preservative: 0.05% ProClin300; < 0.5μg/L	1×1mL
M1	Plate Sealer	Adhesive membrane of microtiter plate	1 sheet

5. STORAGE AND STABILITY

Item	Storage	Stability
Microtiter Strips coated with *Aspergillus* galactomannan antigen	after opening, stored in the sealed bag with desiccant at 2~8℃	4 weeks
Standards (a, b, c, d and e)	after opening, stored at 2~8℃	4 weeks
Controls (A and B)	after opening, stored at 2~8℃	4 weeks
Anti-Galactomannan Antibody	after opening, stored at 2~8℃	until expiry date
Conjugate	after opening, stored at 2~8℃	until expiry date
Sample Treatment Solution	after opening, stored at 2~8℃	until expiry date

Concentrated Washing Solution	after opening, concentrated solution (20×) stored at 2~8℃	until expiry date
	after dilution, washing solution stored at 2~30℃	2 weeks
Sample Dilution Solution	after opening, stored at 2~8℃	until expiry date
Substrate Solution	after opening, stored at 2~8℃ in dark	until expiry date
Stopping Solution	after opening, stored at 2~30℃	until expiry date

6. WARNINGS FOR USERS

6.1. For in vitro diagnostic use.
6.2. For professional use only.
6.3. Do not pipette by mouth.
6.4. Use of this test kit with samples other than human serum and BAL fluid is not recommended.
6.5. Wear protective clothing, including lab coat, eye/face protection and disposable gloves (synthetic, non-latex gloves are recommended) and handle the kit reagents and patient samples with the requisite Good Laboratory Practices. Wash hands thoroughly after performing the test.
6.6. Do not smoke, drink, or eat in areas where specimens or kit reagents are being handled.
6.7. Avoid splashing samples or solutions.
6.8. Biological spills not containing acid should be wiped thoroughly with an effective disinfectant. Disinfectants that can be used include (but are not limited to) a solution of 10% bleach (0.5% solution of sodium hypochlorite), 70% ethanol. Materials used to wipe up spills may require biohazardous waste disposal.
CAUTION: Do not place solutions containing bleach in the autoclave.
6.9. Spills containing acid should be appropriately absorbed (wiped up) or neutralized with sodium bicarbonate, and the area rinsed and wiped dry; if it contained biohazardous material, wipe the area with one of the chemical disinfectants.
6.10. Dispose of all specimens and materials used to perform the test as though they contain an infectious agent. Laboratory chemical and biohazardous wastes must be handled and discarded in accordance with all local, regional and national regulations.

7. PRECAUTIONS FOR USERS

7.1. FROZEN SERUM OR BAL FLUID SAMPLES STORED IN UNKNOWN CONDITIONS MAY GIVE INACCURATE RESULTS DUE TO CONTAMINATION WITH FUNGUS AND/OR BACTERIA.
7.2. Do not use kit or any kit reagents after the stated expiration date.
7.3. Do not mix reagents from other kits that have different lot numbers.
7.4. Bring all reagents to room temperature for at least 30 minutes before use.
7.5. Mix thoroughly every reagent before use.
7.6. Mix thoroughly the Concentrated Washing Solution (R6) before preparing the Working Washing Solution, exercising care to avoid microbial contamination.
7.7. Do not conduct the test in the presence of reactive vapors (acids, alkalis, aldehydes) or dust,

which could affect the enzymatic activity of the Conjugate.

7.8. For manual pipetting of controls and specimens, use individual pipette tips to prevent carryover of samples.

7.9. To ensure adequate washing of the wells, comply with the recommended number of wash cycles and ensure that all wells are completely filled and soak 40 seconds, then completely emptied. Washing should not be performed manually with a squeeze bottle.

7.10. Do not allow the microplate to dry between the end of the wash cycle and addition of reagents.

7.11. Do not use the same container for the Conjugate and Substrate Solution.

7.12. Do not allow Conjugate or Substrate Solution to come into contact with metal or metallic ions.

7.13. Avoid exposing the Substrate Solution to strong light during storage or incubation. Do not allow the substrate solutions to come into contact with an oxidizing agent.

7.14. Avoid contact of the Stopping Solution with any oxidizing agent. Do not allow the Stopping Solution to come into contact with metal or metallic ions.

7.15. Use clean, dust-free materials (tubes, tips, containers, etc.) to minimize the possibility of contamination with Aspergillus spores from the environment. Because galactomannan is heat-stable, sterilization of material used does not guarantee the absence of contaminating antigen. Pyrogen-free materials are optimal, but standard material can be used with adequate precautions.

7.16. Limit exposure of solutions (sera, BAL fluid, Sample Treatment Solution, Conjugate) or open containers (plates, tubes, pipettes) to the air.

7.17. Do not pour any unused Conjugate back into the original container.

7.18. The Substrate TMB Solution must be colorless. The appearance of a blue color indicates the reagent is contaminated and should not be used.

8. MATERIALS NEEDED BUT NOT SUPPLIED

8.1 ddH2O: for the dilution of concentrated washing solution

8.2 Absorbent paper

8.3 Disposable gloves

8.4 Pipette tips (200μL, 300μL, 1000μL)

8.5 Pipette (100uL, 1000uL)

8.6 Centrifuge (10000 x g)

8.7 Polypropylene centrifuge tubes (0.6mL or 1.5mL, sealed and gas-tight)

8.8 Vortex mixer

8.9 Water bath or Heat block

8.10 Incubator

8.11 Semi-automatic plate washer (Recommended)

8.12 Microplate reader

9. SAMPLE COLLECTION AND STORAGE

This test is performed on serum or BAL fluid.

9.1. SERUM

Collect blood samples according to standard laboratory procedures. Serum samples must be uncontaminated with fungal spores and/or bacteria. Transport and store samples in sealed tubes, unexposed to air. After initial opening, samples may be stored at 2-8°C for 48 hours prior to testing. For longer storage, store the serum at -20°C or less.
Avoid repeated freezing and thawing.

9.2. BAL FLUID

Collect BAL fluid samples according to standard laboratory procedures. BAL fluid samples must be collected in sterile saline and may be tested on neat samples (as is) or supernatants from centrifuged samples (10,000 rpm for 10 min).
BAL fluid samples must be uncontaminated with fungal spores and/or bacteria. Transport and store samples in sealed tubes, unexposed to air. After initial opening, samples may be stored at 2-8°C for up to 48 hours. For longer storage, store the BAL samples at -20°C or less.
Avoid repeated freezing and thawing.

10. FLOW CHART OF TESTING PROCEDURE

Samples pretreatment:

300μL of serum + 100μL of sample treatment solution OR
400μL of BAL(BAL no need heating only centrifuge)

⇩ Vortex for 10 sec
⇩ 100℃ for 3 min
⇩ 10,000×g for 10 min 4℃

Collect 50μL of supernatant

⇩

Addition of sample/standards/controls:

Add 50μL supernatant/ standards/ controls + 50μL anti-galactomannan antibody into microtiter wells

⇩ Shake plate for 10 sec
⇩ 37℃ for 90 min

Wash:

Wash 3×300μL (1:20)

⇩

Conjugate: 100μL/ well except substrate blank

Addition of conjugate:

⇩ 37℃ for 30 min

Wash 3×300μL (1:20)

⇩

Addition of substrate solution:

TMB solution: 100μL/ well

⇩ 37℃ for 15 min+ light-proof

Termination of the reaction:

Stopping solution: 50μL/ well

⇩ In 5 min

Measurement:

Read OD at 450nm

11. SAMPLE TREATMENT

11.1 Treatment of Serum

1. Pipette 300μL of serum into the centrifuge tube.
2. Pipette 100μL of sample treatment solution (R5) into each tube.
3. Vortex the centrifuge tube for 10 sec. Heat the tube at 100℃ for 3 min in water bath. Tightly close the tube to prevent opening during heating.
4. Water bath option:

If using a boiling water bath: heat tubes for 3 minutes at 100°C. Tubes must be placed in the water bath only when the prescribed temperature is reached.

5. Heat block option:

Heat tubes for 3 minutes in a heat block at 100°C. Tubes must be placed in the block only when the prescribed temperature is reached. The heat block should be opened at least 20 min before using to make the temperature stable. The size of centrifuge tubes should fit well with the well in the heat block. Do not rely on the temperature displayed by the apparatus, please check that the temperature complies with specifications by using a calibrated thermometer which will be fitted into a tube containing mineral oil: 100°C must be reached inside the tube in a heat block.

6. Centrifuge the heated tube for 10 min at 10,000×g (at 4 ℃ if centrifuge is refrigerated).
7. Collect 50μL of supernatant for detection.

11.2 Treatment of BAL

1. Pipette 400μL of BAL into the centrifuge tube.
2. Vortex the centrifuge tube for 10 sec.
3. Centrifuge the tube for 10 min at 10,000×g (at 4 ℃ if centrifuge is refrigerated).
4. Collect 50μL of supernatant for detection.

NOTE: The BAL samples do not need sample treatment solution (R5) and heating.

12. ELISA PROCEDURE

12.1 Bring all reagents under room temperature (20-25℃) for 30 min before test. Put the microtiter strips(R1) back to the refrigerator and take out after sample treatment.

12.2 Take the microtiter strips out of the sealed bag (R1). Return the unused strips and reseal the pouch tightly, stored at 2-8℃.

12.3 Prepare washing solution:

Dilute the concentrated washing solution (20×) at 1:20 ratio with ddH2O (e.g. 1mL conc. washing solution + 19mL ddH2O). The resultant washing solution is stored at 2~30℃ for up to 2 weeks. Adequate washing solution should be prepared for the entire test.

12.4 Add 50μL of standards (a, b, c, d and e), Controls (A and B) and samples into each well of the microtiter strips coated with Aspergillus galactomannan antigen separately, and then add 50μL of anti-galactomannan antibody (R3) into each well. Do not add the anti-galactomannan antibody (R3) before the standards, controls and samples. Add 100μL of sample dilution solution (R7) into one well as the substrate blank.

	1	2	3	4	5	6	7	8	9	10	11	12
A	Substrate blank	Sample 1	Sample 9									
B	Standard A	Sample 2	……									
C	Standard B	Sample 3										
D	Standard C	Sample 4										
E	Standard D	Sample 5										
F	Standard E	Sample 6										
G	Control A	Sample 7										
H	Control B	Sample 8										

12.5 Shake the plate well for 10 sec. Cover the microtiter plate with a plate sealer and incubate it at 37℃ for 90 min.

12.6 Remove the plate sealer and aspirate the incubation solution. Wash the wells 3 times with 300μL/ well washing solution each time. The soak time is 40 sec. After each wash, invert the microtiter plate and dry it by tapping on the absorbent paper.

12.7 Add 100μL of conjugate (R4) into each well except the substrate blank.

12.8 Cover the microtiter plate with a plate sealer and incubate it at 37℃ for 30 min.

12.9 Repeat step 10.6.

12.10 Add 100μL of substrate solution (R8) into each well including the substrate blank.

12.11 Incubate the microtiter plate at 37℃ and light-proof for 15 min without sealing.

12.12 Add 50μL of stopping solution (R9) into each well in the same order and at the same speed of the substrate solution addition. Shake the microtiter plate gently to mix.

12.13 Read OD at 450nm within 5 min after addition of the stopping solution.

13. DATA ANALYSIS

The standard curve is displayed between concentration of galactomannan as X-axis (logarithmic scale) and optical density as Y-axis (linear scale). The standard curve is plotted by a logarithmic regression using X (Logarithmic) and Y (Linear). Determine the concentration of

galactomannan in serum or BAL against the standard curve.

Example Calculation:

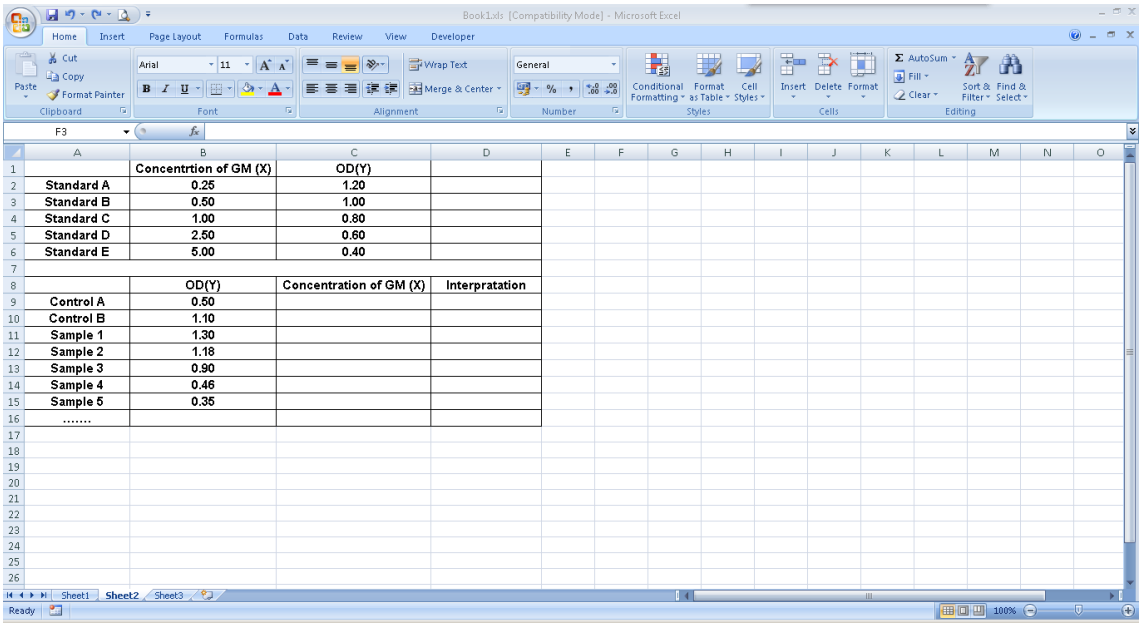
Sample	OD(Y)	Concentration of GM (X) μg/L
Standard A	1.20	0.25
Standard B	1.00	0.50
Standard C	0.80	1.00
Standard D	0.60	2.50
Standard E	0.40	5.00
Control A	0.50	Unknown
Control B	1.10	Unknown
Sample 1	1.30	Unknown
Sample 2	1.18	Unknown
Sample 3	0.90	Unknown
Sample 4	0.46	Unknown
Sample 5	0.35	Unknown

Option 1. Plot the standard curve with the software of Microplate Reader

Take OD as Y-axis (Linear) and Concentration of Galactomannan as X-axis (Logarithmic) respectively, then choose Logarithmic regression to get the standard curve. The concentration of Galactomannan for samples will be calculated against the standard curve.

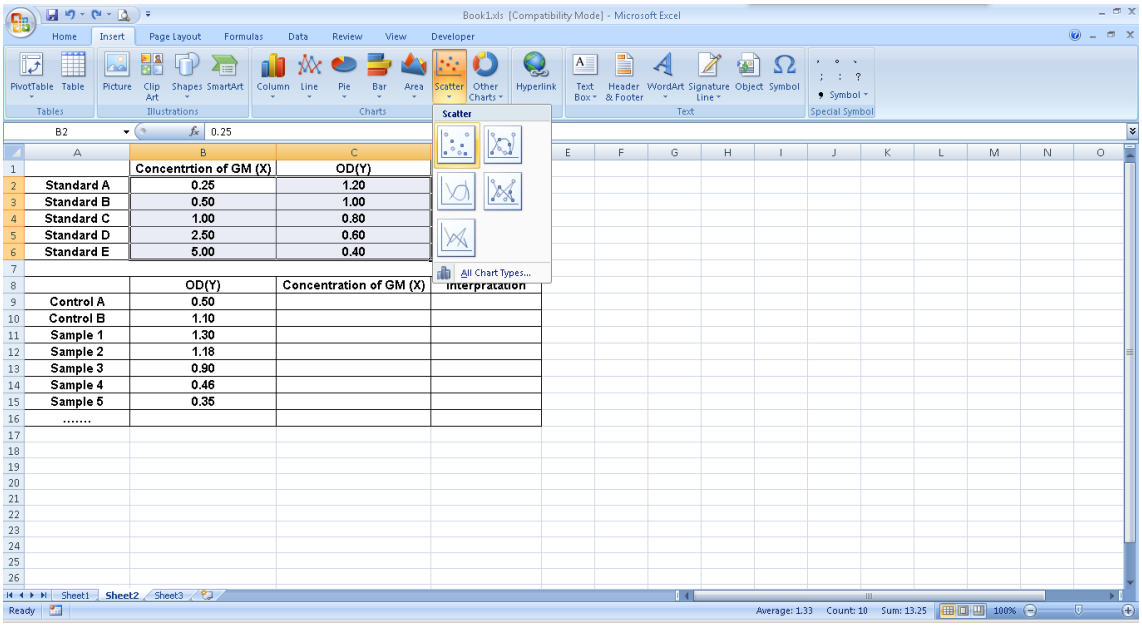
Option 2. Plot the standard curve with Excel

1. Input all the OD value and concentration of standard a-e on Excel.

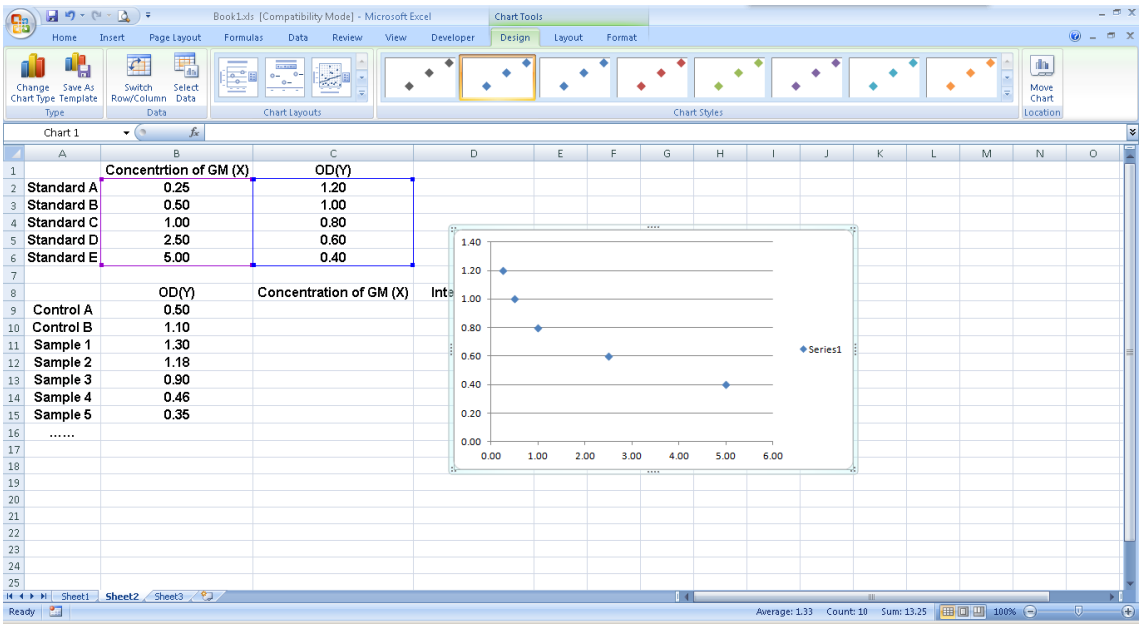


	A	B	C	D
1		Concentrtion of GM (X)	OD(Y)	
2	Standard A	0.25	1.20	
3	Standard B	0.50	1.00	
4	Standard C	1.00	0.80	
5	Standard D	2.50	0.60	
6	Standard E	5.00	0.40	
7				
8		OD(Y)	Concentration of GM (X)	Interpratation
9	Control A	0.50		
10	Control B	1.10		
11	Sample 1	1.30		
12	Sample 2	1.18		
13	Sample 3	0.90		
14	Sample 4	0.46		
15	Sample 5	0.35		
16	.....			

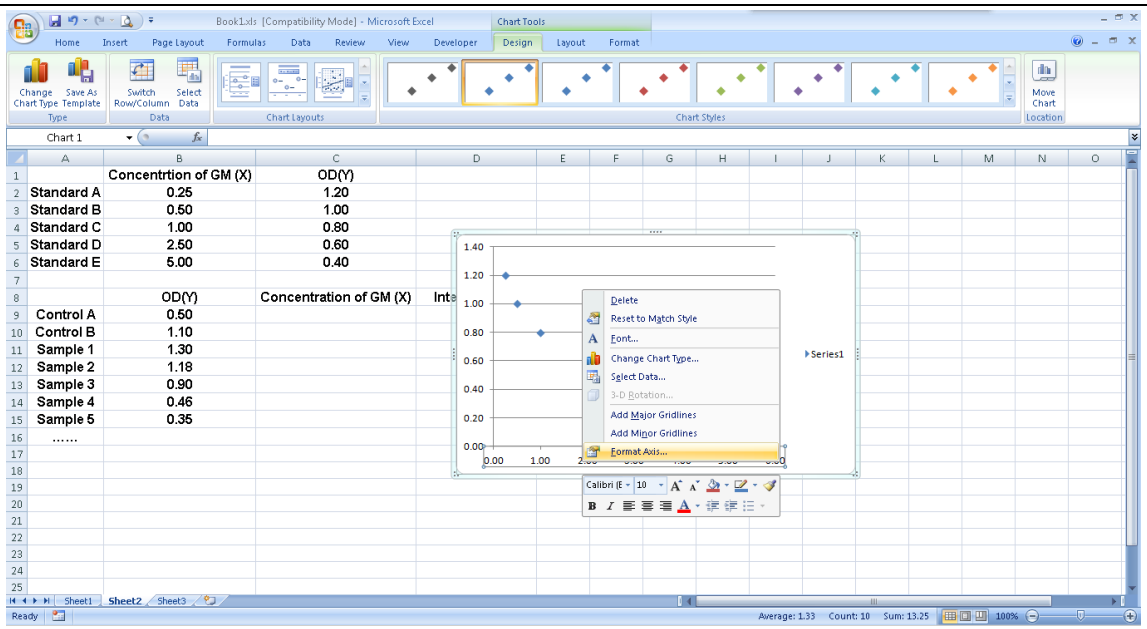
2. Select the values of both Concentration of GM (X) and OD (Y) for standard a-e, and then insert the first SCATTER.



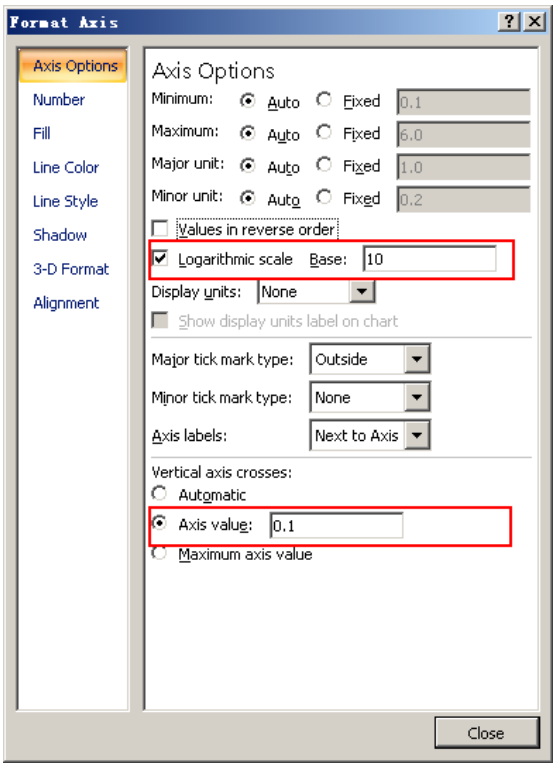
Note: The value of Concentration of GM (X) should be listed in the left of the OD (Y), otherwise the X-axis and Y-axis will be reversal and give false calculation.

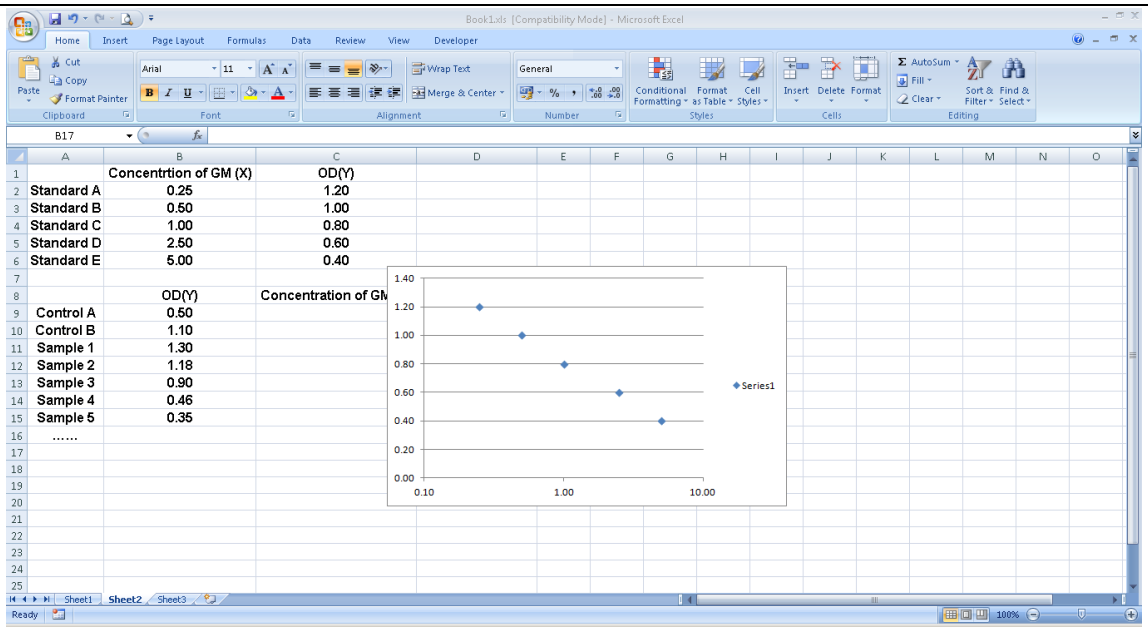


3. Select the X-axis by left click, and then right click to choose “Format Axis…”.

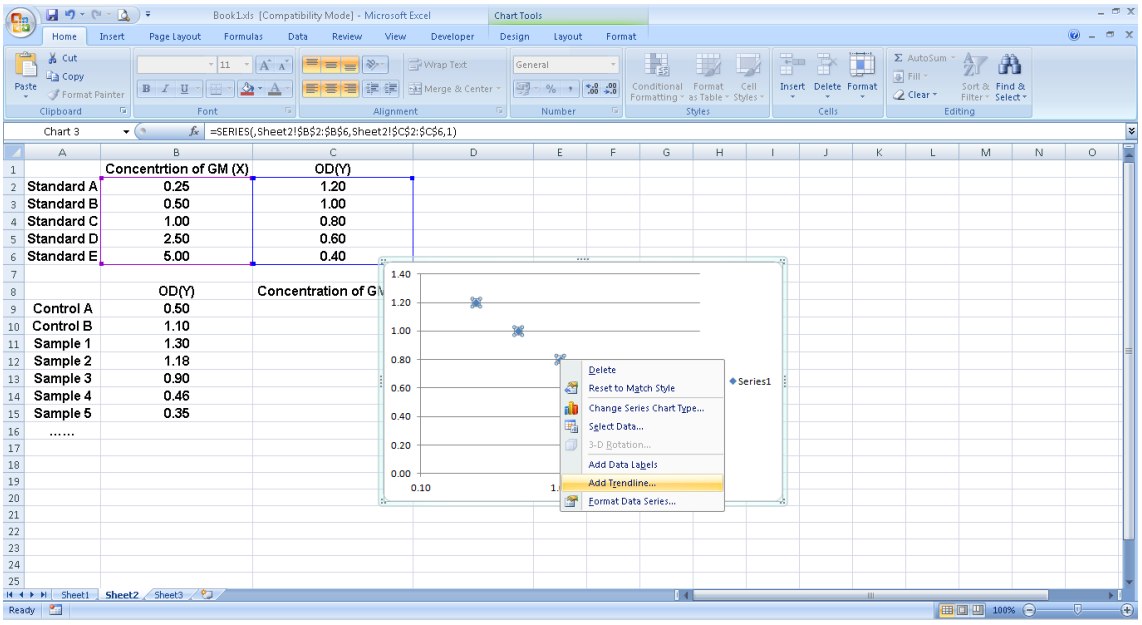


4. Select “Logarithmic scale” and change “Axis value” to 0.1.

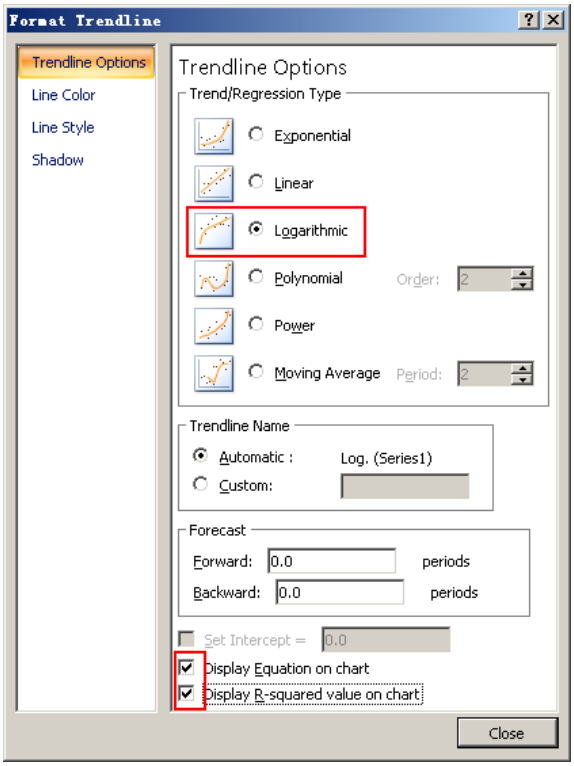


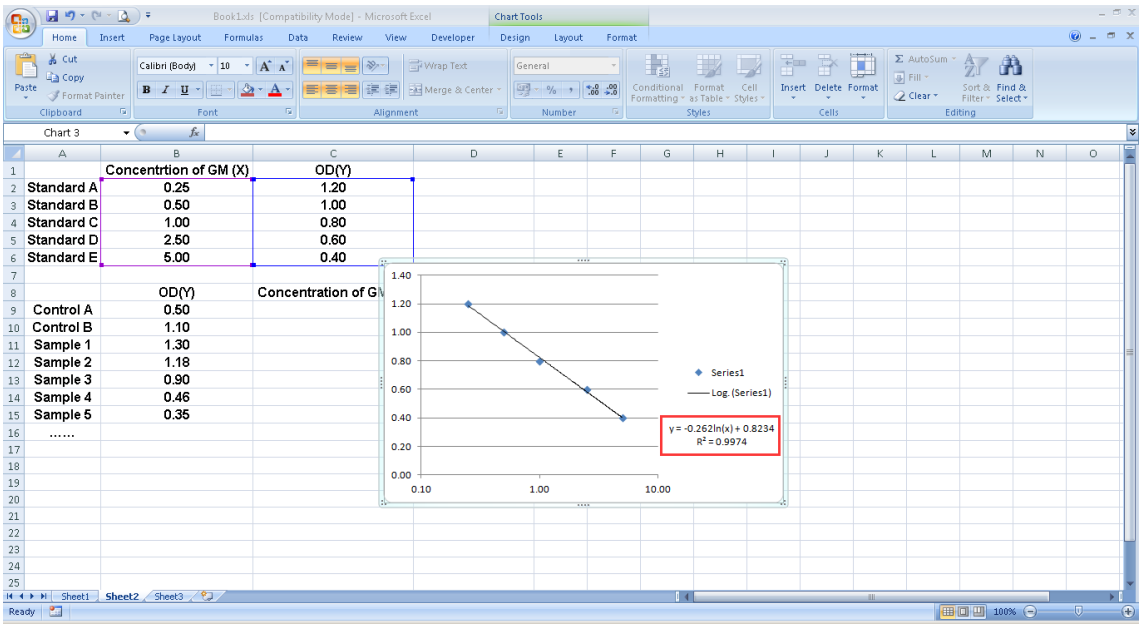


5. Select one of the point by left click and then right click to choose “Add Trendline…”.



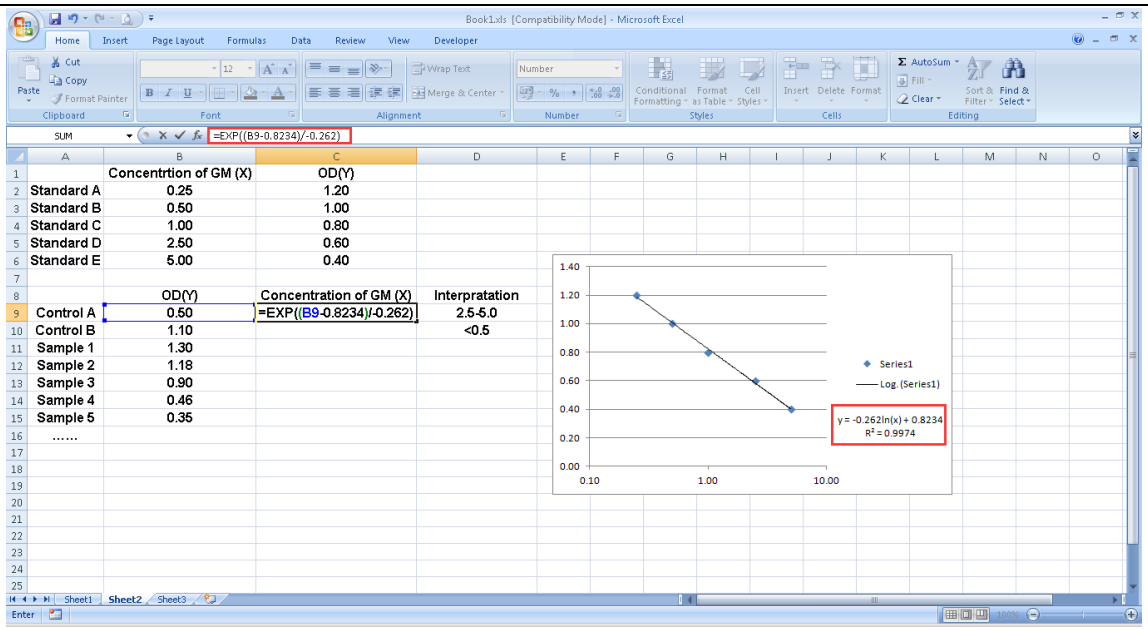
6. Select “Logarithmic”, “Display Equation on chart” and “Display R-square value on chart”. Then get the standard curve, Equation and R-square.
The correct Equation should be Y= a*ln(X) + b. R-square should be ≥0.98.

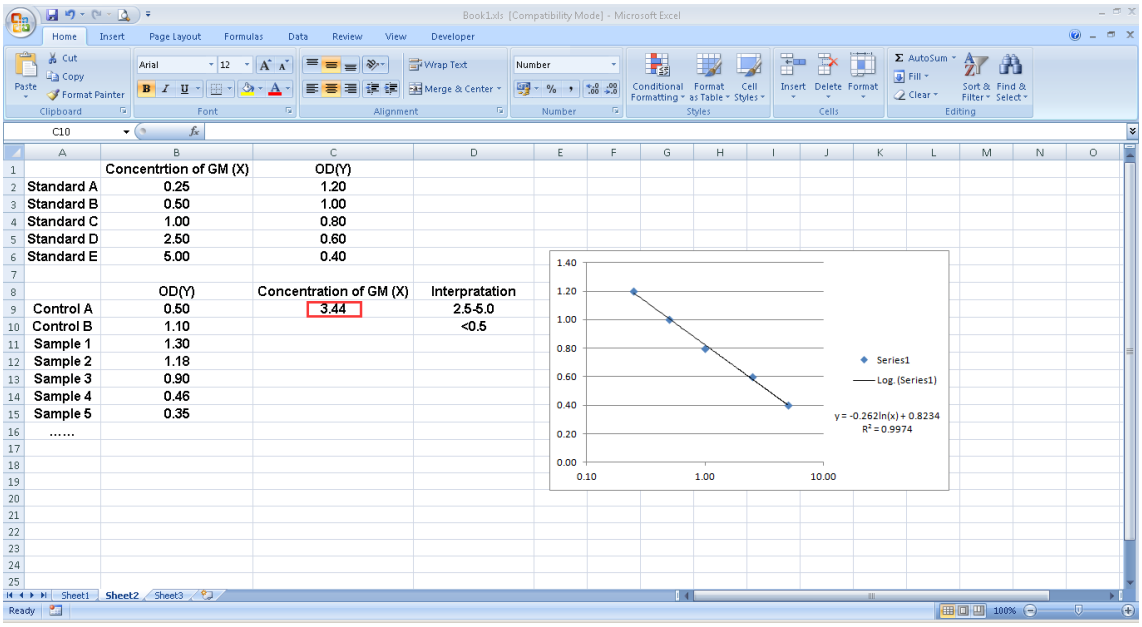




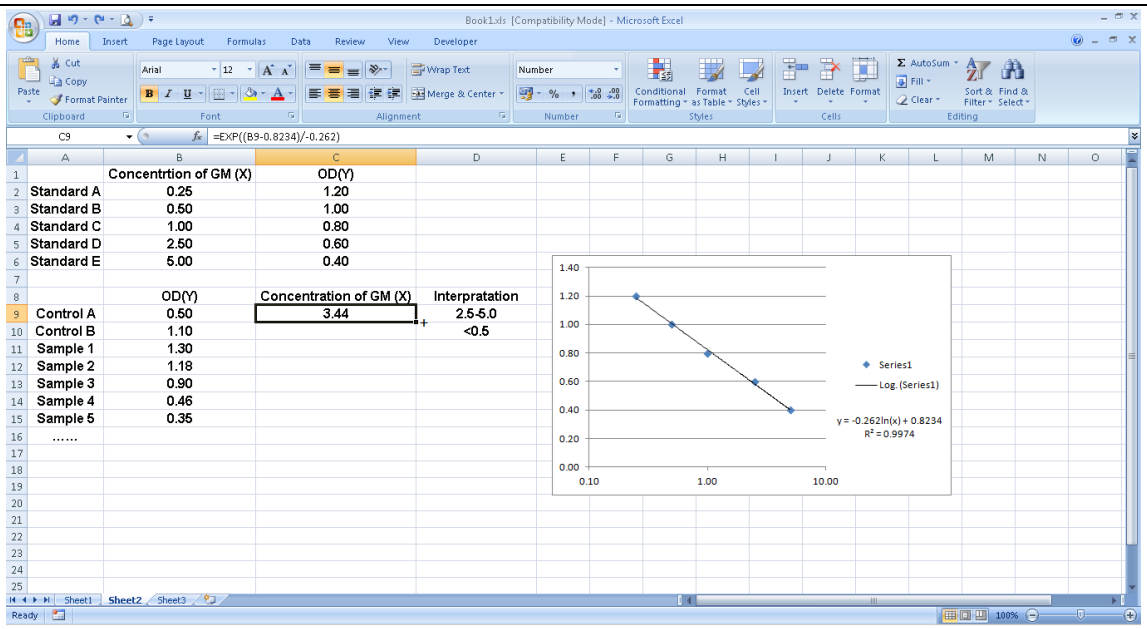
7. Calculate the concentration of GM (X) for controls and samples by using the Equation "X= EXP ((Y-b)/a)". In this example, a = -0.262, b = 0.8234. Then X= EXP ((Y-0.8234)/-0.262).

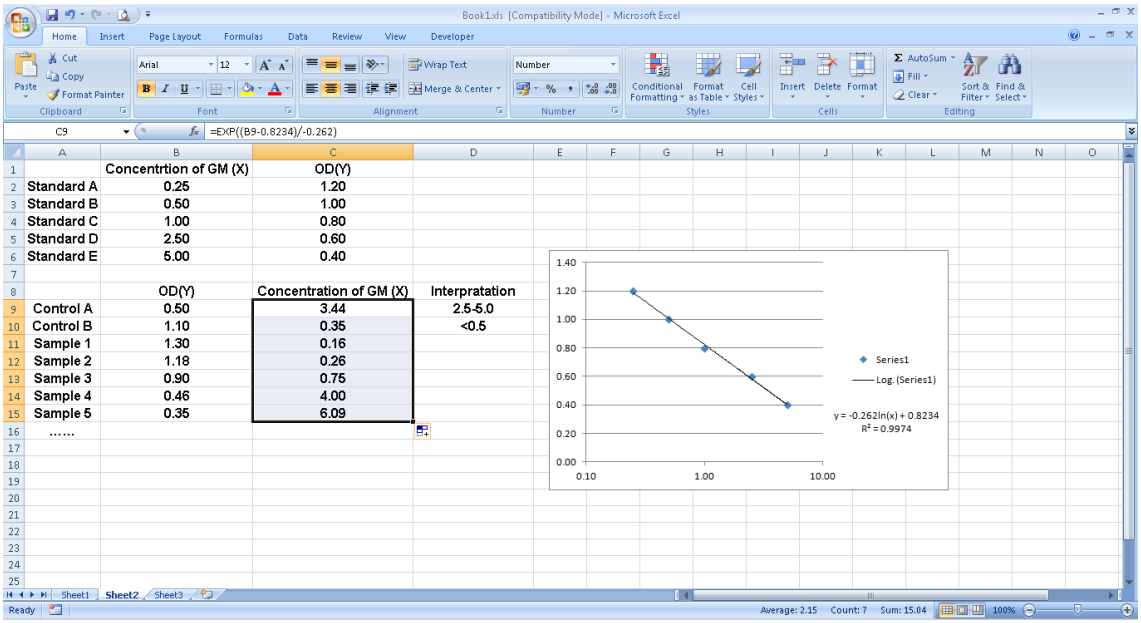
Note: The Equation "EXP" maybe different in different Excel with non-English languages, please check and use the right one.



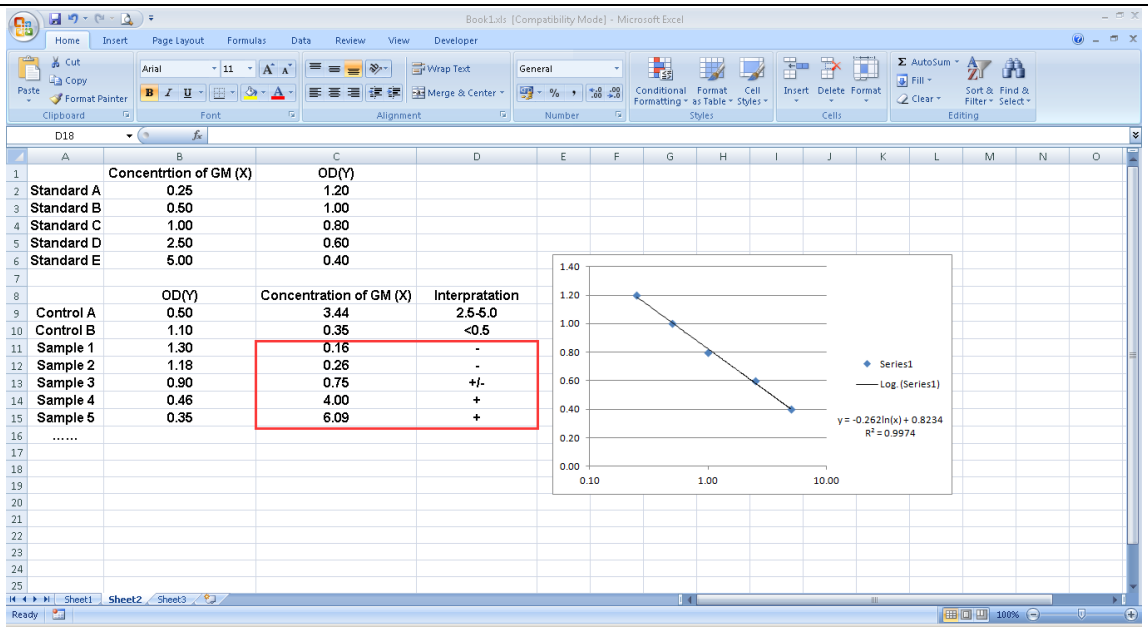


8. Calculating the Concentration of GM (X) for Control B and other samples by dragging the cell of Control A, when the cursors becomes a cross “+”, at the lower right corner.





9. Input the interpretation according to the cut-off and send report.



	Concentrtion of GM (X)	OD(Y)
Standard A	0.25	1.20
Standard B	0.50	1.00
Standard C	1.00	0.80
Standard D	2.50	0.60
Standard E	5.00	0.40

	OD(Y)	Concentration of GM (X)	Interpratation
Control A	0.50	3.44	2.5-5.0
Control B	1.10	0.35	<0.5
Sample 1	1.30	0.16	-
Sample 2	1.18	0.26	-
Sample 3	0.90	0.75	+/-
Sample 4	0.46	4.00	+
Sample 5	0.35	6.09	+
.....			

14. QUALITY CONTROL

14.1 Substrate Blank: the OD must be < 0.2;

14.2 Control A: The concentration must be 2.5μg/L-5.0μg/L;

14.3 Control B: The concentration must be < 0.5μg/L;

14.4 The r2 of the standard curve must be ≥ 0.98;

14.5 If these criteria are unmet, the test needs to be re-performed.

15. INTERPRETATION OF RESULTS

15.1 Concentration of galactomannan < 0.65μg/L indicates a negative result.

15.2 Concentration of galactomannan ≥ 0.85μg/L indicates a positive result.

15.3 0.65μg/L ≤ Concentration of galactomannan < 0.85μg/L indicates an inconclusive result. It is recommended to resample within a week.

Note:

(1) When the concentration of galactomannan is beyond the range of the standard curve:

OD sample > Standard R2a, it indicates a negative result.

OD sample < Standard R2e, it indicates a positive result. The sample is recommended being diluted and retested.

(2) If the square of correlation coefficient of the regression equation (r2) is lower than 0.98, it indicates the standard curve is unacceptable and a new test is needed.

16. CLINICAL PERFORMANCE

A total of 82 hematological patients at risk of invasive Aspergillosis were tested by this assay including one proven patient, 28 probable patients, 23 possible and 30 patients with no IFD as control. [2]

Sensitivity: 79.3%

Specificity: 83.0%

17. LIMITATIONS OF THE PROCEDURE

17.1 A negative test from serum and/or BAL samples cannot rule out the diagnosis of Invasive Aspergillosis. Serum samples from patients at risk for Invasive Aspergillosis should be tested twice a week.

17.2 The Procedure and the Interpretation of Results must be followed when testing samples for the presence of galactomannan antigen. The user of the kit is advised to read the package insert carefully prior to conducting the test. In particular, the test procedure must be carefully followed for sample and reagent pipetting, plate washing, and timing of the incubation steps.

17.3 Failure to add specimen or reagent as instructed in the procedure could result in a falsely negative test. Repeat testing of additional samples should be considered where there is clinical suspicion of Invasive Aspergillosis or procedural error

17.4 Contamination of negative patient specimen wells by positive control/patient specimen wells is possible if the contents of one well spill over into another well due to rough handling of the microplate or poor pipetting technique while adding reagents

17.5 The concomitant use of mold-active anti-fungal therapy in some patients with Invasive Aspergillosis may result in reduced sensitivity with Dynamiker Aspergillus Galactomannan Assay.

17.6 The Dynamiker Aspergillus Galactomannan Assay has not been evaluated for use with plasma or other sample types such as urine or CSF.

17.7 The performance of the Dynamiker Aspergillus Galactomannan Assay has not been established for manual reading and/ or visual result determination.

17.8 Cross-reactivity of BAL fluid samples with Mycoplasma pneumoniae or anaesthetic drugs/lubricants used to numb the neck/throat area for the aspiration process has not been evaluated.

17.9 Positive reactions with no clinical signs

The following should be considered with regard to the early galactomannan antigen detection in serum or BAL before the appearance of clinical and/or radiological signs. Positive test results without clinical signs are usually observed and they have been shown to correspond to «true positive» tests in patients for whom Proven or Probable Invasive Aspergillosis diagnosis is established later on.

However, in some particular cases, specific factors should be taken into account when interpreting the test:

1) Positive test results with no clinical signs have been reported, especially in young children. Although some of these cases could be related to real circulation of Aspergillus antigens, most cases can be considered to be false-positives.

2) Galactofuranose has been demonstrated in various foods, particularly cereals, cereal products and cream desserts. Unlike human milk, cow's milk formulas frequently contain high concentrations of galactomannan. Dietary factors must therefore be taken into account in interpretation of the course of antigenemia in young children, and more generally in all patients with an altered intestinal barrier. Any case of positive antigenemia not accompanied by clinical signs should be interpreted even more cautiously in this population of patients.

3) There have been reports of positive galactomannan test results in patients receiving

piperacillin/ tazobactam. There have also been reports of certain lots or batches of piperacillin/ tazobactam that have been found to be positive for galactomannan antigen. Therefore, positive test results in patients receiving piperacillin / tazobactam should be interpreted cautiously and confirmed by other diagnostic methods. Detection of galactomannan has also been reported in some batches of amoxicillin associated with clavulanic acid parenteral preparations. Therefore, semi-synthetic ß-lactam treatments should be taken into account when interpreting the test.

Nevertheless, as Aspergillus Galactomannan Assay can detect galactomannan antigen well before clinical or radiological signs appear, the occurrence of Invasive Aspergillosis cannot be ruled out. Therefore, patients treated with piperacillin/tazobactam with positive test results should be followed carefully.

4) Positive reactions in the absence of clinical signs may be observed in patients receiving products containing galactomannan, either parenterally or orally (in the presence of an alteration of the intestinal barrier). The presence of galactomannan in these products can often be explained by the use of a fermentation process based on fungal microorganisms. A positive result will not be observed in a patient, however, unless the serum concentration of exogenous galactomannan reaches or exceeds the test's detection threshold.

Thus, if there is a suspicious positive result in the absence of other clinical signs, we recommend investigating the products that the patient is taking and notably their production processes and the origin of the raw materials used.

18. REFERENCE

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19. MANUFACTURER

Company Name: Dynamiker Biotechnology (Tianjin) Co., Ltd.
Registration Address: No.101-2, 14th Building, Ecological Science Park
No. 2018 Zhongtian Revenue, Eco-City TEDA, Tianjin 300467, P. R. China

[EC REP]

Company Name: Wellkang Ltd.
Address: Suite B, 29 Harley Street, LONDON W1G 9QR, England, United Kingdom

[SYMBOLS USED]

Symbol	Description
	Use By

LOT	Batch Code
	Manufacturer
	Keep Away from Sunlight
2 °C 8 °C	Temperature Limitation
IVD	In Vitro Diagnostic Medical Device
EC REP	Authorized Representative in the European Community
CE	CE Mark

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