L- Ornithine-L-Aspartate Bacterial Endotoxin Analysis Method Validation Report

Jingjing Pharmaceutical Co., Ltd.

★ Purpose

This document is developed to judge whether the limit of bacterial endotoxin of L-Ornithine-L-Aspartate is reasonable, it is to verify that this method is suitable for bacterial endotoxin test of L-Ornithine-L-Aspartate. The bacterial endotoxin test of L-Ornithine-L-Aspartate can ensure the accuracy and reliability of the test results according to this test method and test conditions.

★ Scope

This document is applicable to the Validation for bacterial endotoxin test of L-Ornithine-L-Aspartate.

★ Responsibilities

1. Responsibilities of Validation Team

1.1 Be responsible for the approval of validation scheme and report.

1.2 Be responsible for the coordination of validation to ensure the smooth implementation of the projects specified in this Validation scheme.

1.3 Be responsible for the daily management of validation.

2. Mobility Department

2.1 Be responsible for power and energy supply to ensure the normal operation of public facilities.

2.2 Be responsible for the calibration of instruments, meters, measuring tools, etc., and stick certificates on the calibrated instruments and meters.

3. Responsibilities of Quality Control

3.1 Be responsible for drafting, training, and implementing validation scheme and related SOP.

3.2 Be responsible for inspection, monitoring, data collation, summary, and analysis in validation work.

3.3 Be responsible for the preparation of standards and reagents required for validation.

3.4 Be responsible for change control and deviation investigation in the validation process of the department.

3.5 Be responsible for drafting the validation report.

4. Responsibilities of Quality Assurance

4.1 Be responsible for the reviewing of validation protocol and validation report.

4.2 Be responsible for the management of deviation investigation, change control and risk analysis during validation.

4.3 Be responsible for reviewing and evaluating the validation results.

4.4 Be responsible for filing and maintaining the validation documents.

4.5 Be responsible for the issuance of validation certificates.

5. Responsibilities of Public Support Department

5.1 Be responsible for the supply of materials required for this validation

★ Reference documents

1. *Good Manufacturing Practice* (2010 Revision) Chapter 10 Quality Control and Quality Assurance;

2. Quality control laboratories and material systems in the "Drug GMP Guidelines";

3. General Rule 1143 of the Pharmacopoeia of the People's Republic of China (2020 edition, Part IV).

★ Description

Bacterial endotoxin test is a method that uses tachypleus amebocyte lysate (TAL) to detect or quantify bacterial endotoxin produced by Gram-negative bacteria, to judge whether the limit of bacterial endotoxin in test samples meets the requirements. Bacterial endotoxin test includes two methods, namely gel method and photometric method, and the test can be performed using either method for the detection of the test samples. In case of dispute, the results of gel method shall prevail unless otherwise specified. This experiment adopts gel method, and the operation process should prevent the contamination of microorganisms and endotoxin. The amount of bacterial endotoxin is expressed in endotoxin unit (EU), and 1EU is equivalent to one international unit of endotoxin (IU). Bacterial endotoxin national standard strain was extracted from Escherichia coli, which was used to calibrate, recheck, and arbitrate the sensitivity of TAL and calibrate the titer of bacterial endotoxin working standards. Bacterial endotoxin test water means that the endotoxin content is less than 0.015 EU/ml (for gel method). The vessels used in the test need to be treated to remove possible exogenous endotoxin. Heat-resistant vessels are usually treated by dry heat sterilization (250°C, at least 1 hour).

★Contents

1 Confirmation of Instruments

Instrument Name	Manufacturer	Model	Self-numbering	Calibration		Calibration certificate number
				Date of Calibration	Validity Period	
Purification workbench	Suzhou Huada Instrument Equipment Co., Ltd	HW-CJ-2F	10-Q-006			
Electric Constant Temperature Drying Oven	Tianjin Taist Instrument Co., Ltd	WHLL-65B	TD-ZK-008	2022.04.25	2023.04.24	RGGH22-JZ02514
Endotoxin Gel Method Instrument	Tianjin Tianda Tianfa Technology Co., Ltd	ET-96	TD-ZK-033	2022.04.25	2023.04.24	RGGH22-JZ02525
Electronic balance	METTLER TOLEDO	ME104TE	EM-ZK-012	2022.04.26	2023.04.25	LXZT22-01465

2 Confirmation of Standards and Reagents

Name of standard and reagent	Manufacturer	Batch number	Specifications	Marked potency	Date of manufacture	Expiry date
National standard for bacterial endotoxins	China Food and Drug Control Research Institute	150601-201886	1ml/piece	80EU/piece		
Bacterial endotoxin working standard	Zhanjiang Andus Biological Co., Ltd	2203020	1ml/piece	10EU/piece	2022.03.20	2025.02
TAL	Zhanjiang Andus Biological Co., Ltd	2112220	0.65ml/piece	0.125EU/ml	2021.12.22	2024.11
	Zhanjiang Andus Biological Co., Ltd	2202162	0.65ml/piece	0.06EU/ml	2022.02.16	2025.01
	Xiamen tachypleus amebocyte lysate biotechnology Co., Ltd	21071035	0.1ml/piece	0.125EU/ml	2021.07.07	2023.07.06
	Xiamen tachypleus amebocyte lysate biotechnology Co., Ltd	22091036	0.1ml/piece	0.06EU/ml	2022.09.23	2024.09.22
Water for bacterial endotoxin test	Zhanjiang Andus Biological Co., Ltd	2205171	50ml/bottle	------	2022.05.17	2025.04

3. Validation of analytical method

2.1 Reexamination and Verification of Labeling Sensitivity of TAL

The sensitivity review of TAL is shown in SOP-012-JYF012, *Standard Operating Procedures for Bacterial Endotoxin Testing*.

2.2 Verification of Interference Initial Screening

2.2.1 Purpose

2.2.1.1 This test is a screening test for the compatibility between drugs and TAL. Through the reaction between a series of sample solutions containing endotoxin concentration and TAL, the concentration without interference to TAL was preliminarily screened.

2.2.1.2 This test can reduce the blindness of interference test.

2.2.2 Operating procedures

2.2.2.1 Determination of test sample limits

The quality standard requires that the limit value of L-Ornithine-L-Aspartate is L=0. 0006 EU/mg.In order to improve the quality of the drug, L=0.0009EU/mg was selected for interference screening.

2.2.2.2 Minimum effective concentration of test sample(c= λ /L)

Test sample limit (EU/mg)	0.006
Test concentration (mg/ml)	21

In the interference screening test, L=0.006EU/mg selects TAL with sensitivity λ of 0.125EU/ml for testing.

2.2.2.3 Preparation of each reaction solution

a.Preparation of solution A

Weigh 420mg of the test sample and dissolve it in 2.5ml of BET water to obtain a solution with a concentration of 168mg/ml. Prepare 134.4mg/ml, 67.2mg/ml, 42mg/ml, and 21mg/ml solutions of the test sample using BET water for later use.

b.Preparation of solution C

10 EU/ml bacterial endotoxin working standard was dissolved in BET water and mixed evenly in a vortex mixer for 15 minutes, then four concentrations of endotoxin standard solutions of 2 λ, λ, 0.5 λ and 0.25 λ were prepared, and each dilution step should be mixed evenly in the vortex mixer for 30 seconds.

c.Preparation of solution B

Take 0.4ml of 42mg/ml test sample solution and add it to a test tube. Take 0.4ml of 0.5EU/ml endotoxin standard solution and mix well in the same test tube to obtain a mixture containing 21mg/ml test sample and 0.25EU/ml endotoxin. Dilute the above mixture by 2, 4, and 8 times with a sample solution of 21mg/ml to obtain standard endotoxin control solutions with endotoxin concentrations of 0.125EU/ml, 0.06 EU/ml, and 0.03EU/ml, respectively, and a test sample concentration of 21mg/ml.

d. Preparation of Solution D

Bacterial endotoxin test water

Note: A is the test solution; B is the interference test series; C is the control series for the sensitivity of TAL; D is the negative control.

2.2.2.4 Sample addition and reaction

a. Turn on the TAL and accurately aspirate 0.1ml and 0.05ml PET water using pipettes, respectively, to dissolve the TAL again.

b. Take the corresponding solutions A and C of BET water volume equivalent to the reconstituted TAL and add them to the TAL reaction tube, with 2 tubes parallel for each concentration; Four parallel tubes are used for each concentration of solution B.

c. In addition, take BET water with the same volume as the reconstituted TAL BET water as the negative

control solution and add it to theTAL reaction tube, parallel to 2 tubes.

2.2.3 Acceptable criteria

Solution A and D were negative. When Es were 0.5 λ ~ 2 λ (including 0.5 λ and 2 λ) and Et were 0.5 Es ~ 2Es (including 0.5 Es and 2Es), it was considered that the test sample had no interference at this concentration

2.2.4 Confirmation Report

Confirmation of Interference Initial Screening

<table>
<tr><td>Name of Experiment</td><td colspan="6">Interference Initial Screening</td></tr>
<tr><td>Solution A</td><td colspan="2">－－</td><td>Solution D</td><td colspan="3">－－</td></tr>
<tr><td rowspan="4">Solution C</td><td>0.25</td><td>0.125</td><td>0.06</td><td>0.03</td><td>End point concentration of reactants</td><td>Es (EU/ml)</td></tr>
<tr><td>＋＋</td><td>＋＋</td><td>＋＋</td><td>－－</td><td>0.06EU/ml</td><td>0.06</td></tr>
<tr><td>0.125</td><td>0.06</td><td>0.03</td><td>0.015</td><td>End point concentration of reactants</td><td>ES (EU/ml)</td></tr>
<tr><td>＋＋</td><td>＋＋</td><td>＋＋</td><td>－－</td><td>0.03EU/ml</td><td>0.03</td></tr>
<tr><td rowspan="2">Solution B (21mg/ml)</td><td>0.25</td><td>0..125</td><td>0.06</td><td>0.03</td><td>End point concentration of reactants</td><td>Et (EU/ml)</td></tr>
<tr><td>＋＋＋＋</td><td>＋＋＋＋</td><td>＋＋＋＋</td><td>－－－－</td><td>0.06EU/ml</td><td>0.06</td></tr>
<tr><td>Formula</td><td colspan="6">Es=antilg(∑X/2) Et=antilg(∑X/4)</td></tr>
<tr><td>Conclusion</td><td colspan="6">A TAL with a sensitivity of 0.125EU/ml was used for bacterial endotoxin testing on a test sample with a concentration of 21mg/ml, which showed no interference.</td></tr>
<tr><td>Remark</td><td colspan="6">Please refer to the original record for details.</td></tr>
<tr><td>Verified by</td><td colspan="3">Jiancong Li</td><td>Date</td><td colspan="2">2022.11.12</td></tr>
<tr><td>Reviewed by</td><td colspan="3">Cunjing Wu</td><td>Date</td><td colspan="2">2022.11.12</td></tr>
</table>

2.3 Interference Test Confirmation

2.3.1 Purpose

By comparing the degree of difference in the reaction between the TAL from two manufacturers and the endotoxin in the aqueous solution and the endotoxin in the test solution, it is determined whether there is

interference from the test sample at that concentration.

2.3.2 Operating procedures

2.3.2.1 Determination of limit values for test samples

According to the initial screening results, interference tests were conducted with solution concentrations of 21mg/ml and 67.2mg/ml, respectively.

2.3.2.2 Selection of test samples

a. Conduct experiments on three consecutive batches of test samples produced.

b. According to the results of the interference screening test, the test sample showed no interference at concentrations of 21mg/ml (sensitivity of TAL is 0.125EU/ml)

2.3.2.3 Minimum effective concentration of test substance

According to the pharmacopoeia, it is necessary to calculate the concentration of the test article at MVD, that is, the minimum effective dilution concentration. The formula c= λ /L can be used, and λ is the labeled sensitivity (EU/ml) of the TAL reagent in the gel method; The minimum effective concentrations of the test substance are 21mg/ml.

2.3.2.4 Preparation of various reaction solutions

a. Preparation of Solution A

Weigh 420mg of the test sample and dissolve 2.5ml of BET water to obtain a solution with a concentration of 168mg/ml. Prepare 134.4mg/ml, 67.2mg/ml, 42mg/ml, and 21mg/ml solutions of the test sample using BET water for later use.

b. Preparation of Solution C

10 EU/ml bacterial endotoxin working standard was dissolved in BET water and mixed evenly in a vortex mixer for 15 minutes, then four concentrations of endotoxin standard solutions of 2 λ, λ, 0.5 λ and 0.25 λ were prepared, and each dilution step should be mixed evenly in the vortex mixer for 30 seconds.

c.Preparation of solution B

Take 0.4ml of 42mg/ml test sample solution and add it to a test tube. Take 0.4ml of 0.5EU/ml endotoxin standard solution and mix well in the same test tube to obtain a mixture containing 21mg/ml test sample and 0.25EU/ml endotoxin. Dilute the above mixture by 2, 4, and 8 times with a sample solution of 21mg/ml to obtain standard endotoxin control solutions with endotoxin concentrations of 0.125EU/ml, 0.06 EU/ml, and 0.03EU/ml, respectively, and a test sample concentration of 21mg/ml.

d. Preparation of Solution D

Bacterial endotoxin test water

Note: A is the test solution; B is the interference test series; C is the control series for the sensitivity of TAL; D is the negative control.

2.3.2.5 Sample addition and reaction

a. Turn on the TAL and accurately aspirate 0.1ml and 0.05ml PET water using pipettes, respectively, to

dissolve the TAL again.

b. Take the corresponding solutions A and C of BET water volume equivalent to the reconstituted TAL and add them to the TAL reaction tube, with 2 tubes parallel for each concentration; Four parallel tubes are used for each concentration of solution B.

c. In addition, take BET water with the same volume as the reconstituted TAL BET water as the negative control solution and add it to theTAL reaction tube, parallel to 2 tubes.

2.3.3 Acceptable criteria

Solution A and D were negative. When Es were 0.5 λ ~ 2 λ (including 0.5 λ and 2 λ) and Et were 0.5 Es ~ 2Es (including 0.5 Es and 2Es), it was considered that the test sample had no interference at this concentration

2.2.4 Confirmation Report

Confirmation of interference test

TAL Manufacturer Zhanjiang Andus Biological Co., Ltd

Name of Experiment	Interference test			Number of tests	1st time	
Solution A	－－		Solution D	－－		
Solution C	0.25	0.125	0.06	0.03	End point concentration of reactants	E_S (EU/ml)
	＋＋	＋＋	＋＋	－－	0.06EU/ml	0.06
	0.125	0.06	0.03	0.015	End point concentration of reactants	E_S (EU/ml)
	＋＋	＋＋	＋＋	－－	0.03EU/ml	0.03
Solution B (21mg/ml)	0.25	0.125	0.06	0.03	End point concentration of reactants	E_t (EU/ml)
	＋＋＋＋	＋＋＋＋	＋＋＋＋	－－－－	0.06EU/ml	0.06
Formula	Es=antilg(∑X/2)			Et=antilg(∑X/4)		
Conclusion	A TAL with a sensitivity of 0.125EU/ml was used for bacterial endotoxin testing on a test sample with a concentration of 21mg/ml, which showed no interference.					
Verified by	Jiancong Li			Date	2022.11.12	
Reviewed by	Cunjing Wu			Date	2022.11.13	

Jing Jing Pharmaceutical Co., Ltd.

Confirmation of interference test

TAL Manufacturer : Xiamen tachypleus amebocyte lysate biotechnology Co., Ltd

<table>
<tr><td>Name of Experiment</td><td colspan="3">Interference test</td><td>Number of tests</td><td colspan="2">1st time</td></tr>
<tr><td>Solution A</td><td colspan="2">－－</td><td>Solution D</td><td colspan="3">－－</td></tr>
<tr><td rowspan="4">Solution C</td><td>0.25</td><td>0.125</td><td>0.06</td><td>0.03</td><td>End point concentration of reactants</td><td>E_S (EU/ml)</td></tr>
<tr><td>＋＋</td><td>＋＋</td><td>－－</td><td>－－</td><td>0.125EU/ml</td><td>0.125</td></tr>
<tr><td>0.125</td><td>0.06</td><td>0.03</td><td>0.015</td><td>End point concentration of reactants</td><td>E_S (EU/ml)</td></tr>
<tr><td>＋＋</td><td>＋＋</td><td>－－</td><td>－－</td><td>0.06EU/ml</td><td>0.06</td></tr>
<tr><td rowspan="2">Solution B (21mg/ml)</td><td>0.25</td><td>0.125</td><td>0.06</td><td>0.03</td><td>End point concentration of reactants</td><td>E_t (EU/ml)</td></tr>
<tr><td>＋＋＋＋</td><td>＋＋＋＋</td><td>－－－－</td><td>－－－－</td><td>0.125EU/ml</td><td>0.125</td></tr>
<tr><td>Formula</td><td colspan="6">Es=antilg(∑X/2) Et=antilg(∑X/4)</td></tr>
<tr><td>Conclusion</td><td colspan="6">A TAL with a sensitivity of 0.125EU/ml was used for bacterial endotoxin testing on a test sample with a concentration of 21mg/ml,which showed no interference.</td></tr>
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</table>

Appendix 7:Confirmation of interference test

TAL Manufacturer Zhanjiang Andus Biological Co., Ltd

Name of Experiment	Interference test			Number of tests	2nd time	
Solution A	－－		Solution D	－－		
Solution C	0.25	0.125	0.06	0.03	End point concentration of reactants	E_S (EU/ml)
	＋＋	＋＋	＋＋	－－	0.06EU/ml	0.06
	0.125	0.06	0.03	0.015	End point concentration of reactants	E_S (EU/ml)
	＋＋	＋＋	－－	－－	0.06EU/ml	0.06
Solution B (21mg/ml)	0.25	0.125	0.06	0.03	End point concentration of reactants	E_t (EU/ml)
	＋＋＋＋	＋＋＋＋	＋＋＋＋	－－－－	0.06EU/ml	0.06
Formula	Es=antilg(∑X/2)			Et=antilg(∑X/4)		
Conclusion	A TAL with a sensitivity of 0.125EU/ml was used for bacterial endotoxin testing on a test sample with a concentration of 21mg/ml, which showed no interference.					
Verified by	Jiancong Li			Date	2022.11.12	
Reviewed by	Cunjing Wu			Date	2022.11.13	

Jing Jing Pharmaceutical Co., Ltd.

Confirmation of interference test

TAL Manufacturer : Xiamen tachypleus amebocyte lysate biotechnology Co., Ltd

<table>
<tr><td>Name of Experiment</td><td colspan="3">Interference test</td><td>Number of tests</td><td colspan="2">2nd time</td></tr>
<tr><td>Solution A</td><td colspan="2">－－</td><td>Solution D</td><td colspan="3">－－</td></tr>
<tr><td rowspan="4">Solution C</td><td>0.25</td><td>0.125</td><td>0.06</td><td>0.03</td><td>End point concentration of reactants</td><td>E_S (EU/ml)</td></tr>
<tr><td>＋＋</td><td>＋＋</td><td>－－</td><td>－－</td><td>0.125EU/ml</td><td>0.125</td></tr>
<tr><td>0.125</td><td>0.06</td><td>0.03</td><td>0.015</td><td>End point concentration of reactants</td><td>E_S (EU/ml)</td></tr>
<tr><td>＋＋</td><td>＋＋</td><td>－－</td><td>－－</td><td>0.06EU/ml</td><td>0.06</td></tr>
<tr><td rowspan="2">Solution B (21mg/ml)</td><td>0.25</td><td>0.125</td><td>0.06</td><td>0.03</td><td>End point concentration of reactants</td><td>E_t (EU/ml)</td></tr>
<tr><td>＋＋＋＋</td><td>＋＋＋＋</td><td>－－－－</td><td>－－－－</td><td>0.125EU/ml</td><td>0.125</td></tr>
<tr><td>Formula</td><td colspan="6">Es=antilg(∑X/2) Et=antilg(∑X/4)</td></tr>
<tr><td>Conclusion</td><td colspan="6">A TAL with a sensitivity of 0.125EU/ml was used for bacterial endotoxin testing on a test sample with a concentration of 21mg/ml, which showed no interference.</td></tr>
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Jing Jing Pharmaceutical Co., Ltd.

Confirmation of interference test

TAL Manufacturer Zhanjiang Andus Biological Co., Ltd

<table>
<tr><td>Name of Experiment</td><td colspan="3">Interference test</td><td>Number of tests</td><td colspan="2">3rd time</td></tr>
<tr><td>Solution A</td><td colspan="2">－－</td><td>Solution D</td><td colspan="3">－－</td></tr>
<tr><td rowspan="4">Solution C</td><td>0.25</td><td>0.125</td><td>0.06</td><td>0.03</td><td>End point concentration of reactants</td><td>E_S (EU/ml)</td></tr>
<tr><td>＋＋</td><td>＋＋</td><td>＋＋</td><td>－－</td><td>0.06EU/ml</td><td>0.06</td></tr>
<tr><td>0.125</td><td>0.06</td><td>0.03</td><td>0.015</td><td>End point concentration of reactants</td><td>E_S (EU/ml)</td></tr>
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<tr><td>＋＋＋＋</td><td>＋＋＋＋</td><td>＋＋＋＋</td><td>－－－－</td><td>0.06EU/ml</td><td>0.06</td></tr>
<tr><td>Formula</td><td colspan="3">Es=antilg(∑X/2)</td><td colspan="3">Et=antilg(∑X/4)</td></tr>
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Confirmation of interference test

TAL Manufacturer : Xiamen tachypleus amebocyte lysate biotechnology Co., Ltd

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<tr><td>＋＋＋＋</td><td>＋＋＋＋</td><td>－－－－</td><td>－－－－</td><td>0.125EU/ml</td><td>0.125</td></tr>
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</table>

Conclusion: This validation conducted interference screening tests using a test solution with a concentration of 21mg/ml and a TAL with a sensitivity of 0.125EU/ml, The results showed no interference.

Based on the initial screening results, interference tests were conducted using two different manufacturers' horseshoe crab reagents with concentrations of 21mg/ml , and the results met the requirements.