

3.2.S.4.1 SPECIFICATION

The drug substance (DS) is routinely tested for (b)(4)

(b)(4) as shown in the Table S.4.1-1.

(b)(4)

3.2.P.5.1 SPECIFICATION(S)

The drug product (DP) is tested for release for appearance, identification, potency, excipients, purity and impurities, safety and pH, as shown in the Table P.5.1-1.

Table P.5.1-1 Kamada-API Drug Product Specifications and Release Tests

Test	Specification	Analytical Procedure
Appearance	The solution is clear and colorless to yellow-green. May contain a few particles.	Visual inspection
Identification		
(b)(4)	(b)(4)	
Potency		
Total Active API Content		
Active API Content		
Specific Activity		
Excipients		
Sodium Chloride (as NaCl) Phosphate	(b)(4)	
Purity and Impurities		
(b)(4)	(b)(4)	
Residual TnBP ¹		
Residual Tween 80 ¹		
(b)(4)		
Safety		
Bacterial Endotoxin	(b)(4)	(b)(4)
Pyrogenicity	Pass	Rabbit pyrogen test
Sterility	Pass	Membrane filtration
General Safety Test	Meets Requirements	Mice and guinea pigs toxicity (21 CFR 610.11)
General tests		
pH	(b)(4)	(b)(4)
Extractable Volume		(b)(4)

(b)(4)

As per (b)(4) in case of dispute, the final decision is based on the (b)(4) technique.

(b)(4)

Table P.5.3-73 Challenge with *C. sporogenes* (Sterility Test)

Parameter	Kamada-API Lot No.			Positive Control			Negative Control
	6112001	6112006	6115003	I	II	III	
Challenge Titer (CFU)	27	17	29	27	17	29	---
Growth Medium	FTM	FTM	FTM	FTM	FTM	FTM	FTM
Incubation Temp. (°C)	30-35	30-35	30-35	30-35	30-35	30-35	30-35
Days Incubation Until Growth Detected	2	2	2	2	2	2	No Growth After 5 Days
Culture Purity	Pure	Pure	Pure	Pure	Pure	Pure	---
Inoculated microorganism was confirmed to be the challenged microorganism?	Yes	Yes	Yes	Yes	Yes	Yes	---

Table P.5.3-74 Challenge with *B. subtilis* (Sterility Test)

Parameter	Kamada-API Lot No.			Positive Control			Negative Control
	6112001	6112006	6115003	I	II	III	
Challenge Titer (CFU)	25	20	69	25	20	69	---
Growth Medium	FTM	FTM	FTM	FTM	FTM	FTM	FTM
Incubation Temp. (°C)	30-35	30-35	30-35	30-35	30-35	30-35	30-35
Days Incubation Until Growth Detected	2	2	2	2	2	2	No Growth After 5 Days
Culture Purity	Pure	Pure	Pure	Pure	Pure	Pure	---
Inoculated microorganism was confirmed to be the challenged microorganism?	Yes	Yes	Yes	Yes	Yes	Yes	---

Table P.5.3-75 Challenge with *B. subtilis* (Sterility Test)

Parameter	Kamada-API Lot No.			Positive Control			Negative Control
	6112001	6112006	6115003	I	II	III	
Challenge Titer (CFU)	25	20	7	25	20	7	---
Growth Medium	TSB	TSB	TSB	TSB	TSB	TSB	TSB
Incubation Temp. (°C)	20-25	20-25	20-25	20-25	20-25	20-25	20-25
Days Incubation Until Growth Detected	2	2	3	¹	¹	¹	No Growth After 5 Days
Culture Purity	Pure	Pure	Pure	¹	¹	¹	---
Inoculated microorganism was confirmed to be the challenged microorganism?	Yes	Yes	Yes	¹	¹	¹	---

¹ No growth after 5 days as discussed above.

Table P.5.3-77 Challenge with *C. albicans* (Sterility Test)

Parameter	Kamada-API Lot No.			Positive Control			Negative Control
	6112001	6112006	6115003	I	II	III	
Challenge Titer (CFU)	24	17	18	24	17	18	---
Growth Medium	TSB	TSB	TSB	TSB	TSB	TSB	TSB
Incubation Temp. (°C)	20-25	20-25	20-25	20-25	20-25	20-25	20-25
Days Incubation Until Growth Detected	2	2	3	2	2	3	No Growth After 5 Days
Culture Purity	Pure	Pure	Pure	Pure	Pure	Pure	---
Inoculated microorganism was confirmed to be the challenged microorganism?	Yes	Yes	Yes	Yes	Yes	Yes	---

(b)(4)

Table 2.3-30 Manufacturers [Kamada-API]

Company	Responsibility
Kamada Ltd.	Manufacture and Quality Control of DP
Beit Kama	Labeling and packaging
MP Negev 85325	Lot release
(b)(4)	

From: McCormick, William
Sent: Tuesday, November 17, 2009 1:14 PM
To: Virata, Maria Luisa
Subject: RE: Kamada - endotoxin testing

Question 1 -

Companies use multiple (b)(4) test configurations within the same license all the time. But they **do not present nor do we advocate use of alternate reagent configurations for testing the same manufacturing stage**. And, especially not for Lot Release where full validation is required. One method (configuration) is selected, developed and validated. If there is ever a "dispute" then my concern would be that there is something insufficient about the validation study or that there is an inconsistency in the sample being tested. These concerns are not addressed/refereed through use of an alternate method.

In my view, "Dispute" level resolution is way above routine testing for Lot Release.

Question 2 -

Specifications should be method specific. If the spec that you present below is a Lot Release spec then it should be based upon capability of performing the assay as per the (b)(4) configuration. What you describe below is not a typical specification or justification.

From: Virata, Maria Luisa
Sent: Tuesday, November 17, 2009 11:16 AM
To: McCormick, William
Subject: FW: Kamada - endotoxin testing

Dear Dr. McCormick,

I was at your CMC Review lecture for the Impurities - Pyrogens and Endotoxin Testing last Oct. 22. Hope that it is ok to ask for your help in our BLA review re: endotoxin and pyrogen tests.

We are reviewing a BLA for a new company, Kamada Ltd, (based in Israel) which is seeking US licensure for the first time for their Alpha-1-Proteinase Inhibitor product. They listed two endotoxin methods as lot release tests: the (b)(4). They stated that the (b)(4) method is used for testing process intermediates and drug substance samples, while the (b)(4) method is for testing (b)(4) and drug product samples. They also stated that these methods are based on (b)(4) and also stated in a footnote "as per (b)(4), in case of dispute, the final decision is based on the (b)(4) technique". Do we normally allow a company to use 2 endotoxin methods for lot ?

Kamada also justifies that their specification of (b)(4) was "based on the drug product specification limit of (b)(4) and the sensitivity limit of the kit used for the (b)(4) assay". Is this a typical justification?

Hope to hear from you soon as I am currently writing my midcycle review memo on these issues.

Thanks,
Liza

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Pages 9 through 19 redacted for the following reasons:

(b)(4)

Table P.5.4-2 Drug Product Release Test Results of Conformance Lots (Cont.)

Test	Specification	RP Lots		SP Lots				RP Lot
		(b)(4)						
Safety								
Bacterial Endotoxin	(b)(4)	< 1	< 1	< 1	< 1	<1	<1	<1
Pyrogenicity	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Sterility	Sterile	Pass	Pass	Pass	Pass	Pass	Pass	Pass
General Safety Test ¹	Meets requirements	Pass	Pass	Pass	Pass	Pass	Pass	Pass
General Tests								
pH	(b)(4)	6.9	6.9	6.9	6.9	6.9	7.0	6.9
Extractable Volume	(b)(4)	Pass	Pass	Pass	Pass	Pass	Pass	Pass

RP – Recovered Plasma; SP – Source Plasma.

¹ Determined after lots release to gather data prior to marketing.