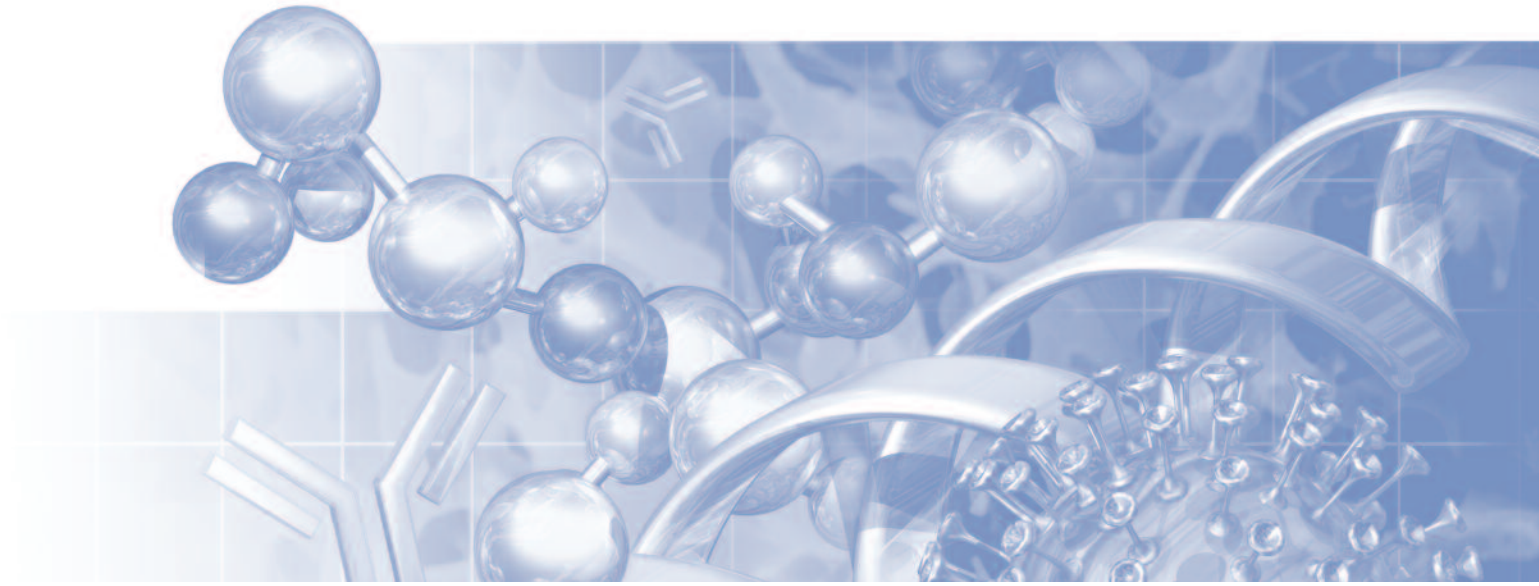
PALL Life Sciences

Validation Guide

USTR 2491a

Activated Carbon AKS Depth Filter Media



*Filtration. Separation. Solution.*SM

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1. Overview

1.1 Introduction

Activated Carbon Sheets are widely used in the pharmaceutical industry for decolorization and removal of other impurities.

This report contains validation data applicable to Pall Activated Carbon (AKS) depth filter media which is used in different formats and configurations such as:

- Flat sheets for use in filter presses
- Modules used in housings
- Capsules

This report contains a summary of tests carried out and results obtained by Pall. The data contained in this document are typical measured values, the correctness and reproducibility of which are controlled on a regular basis and confirmed by results of field applications.

This validation guide has been compiled for the users of Pall Activated Carbon (AKS) depth filter media as a basis and support for their own validation procedures.

The validation program included:

- Extractables testing
- Conductivity and pH
- TOC
- Phosphate ions
- Extractable cations
- Total extractables
- Endotoxin levels
- Biological reactivity

1.2 Summary of Conclusions

Table 1

Extractables Results

Activated carbon (AKS) depth filter media	Conductivity in µS/cm Rinsing Volume (L/m²)		pH Rinsing Volume (L/m²)		TOC in mg/L Rinsing Volume (L/m²)		PO_4^{-3} in mg/L Rinsing Volume (L/m²)		ppm Al in WFI Rinsing Volume (L/m²)		ppm Ca in WFI Rinsing Volume (L/m²)	
	0 – 5	50	0 – 5	50	0 – 5	50	0 – 5	50	0 – 5	50	0 – 5	50
AKS 1	< 1800	< 250	2.5 - 4.5	3.0 – 4.5	< 100	< 5	< 500	< 2	< 2	< 0.1	< 150	< 0.5
AKS 2	< 1000	< 100	4.0 – 6.0	3.5 – 6.0	< 50	< 5	< 100	< 2	< 0.3	< 0.05	< 150	< 0.5
AKS 4	< 1000	< 100	5.0 – 7.0	5.0 – 7.0	< 50	< 5	< 10	< 2	< 1	< 0.1	< 100	< 2
AKS 5	< 1500	< 100	4.0 – 6.0	4.0 – 6.0	< 50	< 5	< 5	< 0.5	< 0.1	< 0.02	< 100	< 0.5
AKS 6	< 1800	< 150	3.0 – 4.5	3.5 – 5.0	< 100	< 10	< 500	< 2	< 0.3	< 0.05	< 150	< 0.5
AKS 7	< 10000	< 200	2.0 – 4.0	3.0 – 4.5	< 100	< 5	< 150(	< 2	< 2	< 0.1	< 200	< 2
AKS 8	< 1000	< 100	5.0 – 7.0	5.0 – 7.0	< 50	< 5	< 10	< 0.5	< 0.1	< 0.05	< 200	< 10
AKS 9	< 1000	< 100	5.0 – 7.0	5.0 – 7.0	< 50	< 10	< 10	< 0.5	< 0.1	< 0.1	< 200	< 10

Activated carbon (AKS) depth filter media	ppm Mg in WFI Rinsing Volume (L/m²)		ppm Fe in WFI Rinsing Volume (L/m²)		ppm Ni in WFI Rinsing Volume (L/m²)		ppm Cu in WFI Rinsing Volume (L/m²)		ppm Cr in WFI Rinsing Volume (L/m²)	
	0 – 5	50	0 – 5	50	0 – 5	50	0 – 5	50	0 – 5	50
AKS 1	< 50	< 0.1	< 1	< 0.1	< 0.1	< 0.01	< 0.1	< 0.1	< 0.05	< 0.01
AKS 2	< 50	< 0.1	< 0.1	< 0.1	< 0.05	< 0.01	< 0.1	< 0.1	< 0.05	< 0.01
AKS 4	< 50	< 1	< 0.1	< 0.1	< 0.05	< 0.05	< 0.1	< 0.1	< 0.05	< 0.05
AKS 5	< 50	< 0.1	< 0.1	< 0.1	< 0.05	< 0.01	< 0.1	< 0.1	< 0.1	< 0.01
AKS 6	< 50	< 0.1	< 0.1	<0.1	< 0.05	< 0.01	< 0.1	< 0.1	< 0.05	< 0.01
AKS 7	< 50	< 0.1	< 0.2	< 0.1	< 0.05	< 0.02	< 0.1	< 0.1	< 0.05	< 0.01
AKS 8	< 50	< 0.5	< 1	< 0.5	< 0.05	< 0.05	< 0.5	< 0.5	< 0.5	< 0.5
AKS 9	< 100	< 0.5	< 0.1	<0.1	< 0.05	< 0.05	< 0.1	< 0.1	< 0.01	< 0.01

Total Extractables 21 CFR 177.2260

The total extractables of all Pall Activated Carbon (AKS) depth filter media were significantly below the CFR limits and therefore meets the requirements of 21 CFR 177.2260. Detailed reports are available upon request.

1.2.1 Endotoxin

Endotoxins

The endotoxin content of all tested sheets (except AKS 4) in human albumin without pre-rinsing was below 0.12 EU/mL.

The endotoxin level of AKS 5 and AKS 6 was below the detection limit of 0.06 EU/mL.

Pall Activated Carbon (AKS) depth filter media. Endotoxin Content in EU/mL

Table 2

Endotoxin Content of Tested Sheets

Activated Carbon (AKS) Depth Filter Media	Endotoxin Content (EU/mL)
AKS 1	< 0.12
AKS 2	< 0.12
AKS 4(1)	ND(2)
AKS 5	< 0.06
AKS 6	< 0.06
AKS 7	< 0.12
AKS 8	< 0.12
AKS 9	< 0.12

(1) AKS4 is not an activated carbon grade developed for the pharmaceutical market and therefore not optimized regarding endotoxins.

(2) ND = Not determined

1.2.2 Biological Reactivity Tests

All tested materials (except for AKS 4) have met the specifications for Biological Reactivity Tests, *in vivo*, listed in the current revision of the United States Pharmacopeia (USP) for Class VI - 121 °C Plastics.

Certificates and test reports are available upon request.

2. General Characteristics of Pall Activated Carbon (AKS) Depth Filter Media

This validation report describes the following depth filter media grades:

AKS 1 AKS 2 AKS 4 AKS 5 AKS 6 AKS 7 AKS 8 AKS 9

All of these depth filter media grades (except AKS 4) are manufactured under special production conditions that guarantee the highest purity possible. These conditions include such things as:

1. Specific cleaning and disinfection of the manufacturing line
2. The use of RO-water for final rinsing according to the specification

3. Typical Technical Data

Table 3
Typical Technical Data

Activated Carbon (AKS) Depth Filter Media	Weight per Unit Area (g/m^2)	Thickness (mm)	Ash Content (%)	Adsorption Substance A[1] (g/m^2)	Adsorption Substance B[2] (g/m^2)
AKS 1	1600	5.9	2	> 350	> 250
AKS 2	1600	5.8	2	> 200	> 100
AKS 4	1050	3.8	13	> 120	> 30
AKS 5	1300	4.5	0	> 200	> 30
AKS 6	1400	4.9	1	> 300	> 270
AKS 7	1600	5.8	2	> 330	> 220
AKS 8	1350	5.2	1	> 150	> 90
AKS 9	1350	4.6	1	> 150	> 80

(1) Representing molecules between 200 and 400 Dalton
(2) Representing molecules between 1000 and 1500 Dalton

4. Extractables

4.1 Method

In the adsorption process of pharmaceutical products, it is essential that the product composition be unaffected by extractables released from the Activated Carbon filters. An appropriate rinsing procedure after sterilization was therefore used to remove any extractable substances. The most common rinsing medium is Water for Injection (WFI).

Additionally, in many processes organic solvents are used to dilute the products. Therefore, in addition to WFI, 40% ethanol was chosen as a second extraction medium, representing other organic solvents.

For the extraction curves discussed in the following chapter, a filter with an effective filter area of 670 cm^2 was used. The flow rate was adjusted to 500 LMH ($L/m^2/hr$).

Samples for the determination of

- Conductivity
- pH
- TOC (Total Organic Carbon)
- Phosphate ions in WFI
- Cations (Al, Ca, Mg, Fe, Ni, Cu, Cr)

were taken at a rinsing volume of:

- 5 –10 L/m²
- after 50 L/m²
- after 100 L/m²

4.2 Conductivity and pH Value in WFI

4.2.1 Method

Conductivity and pH value are measured by a calibrated conductivity and pH meter.

4.2.2 Results

Table 4

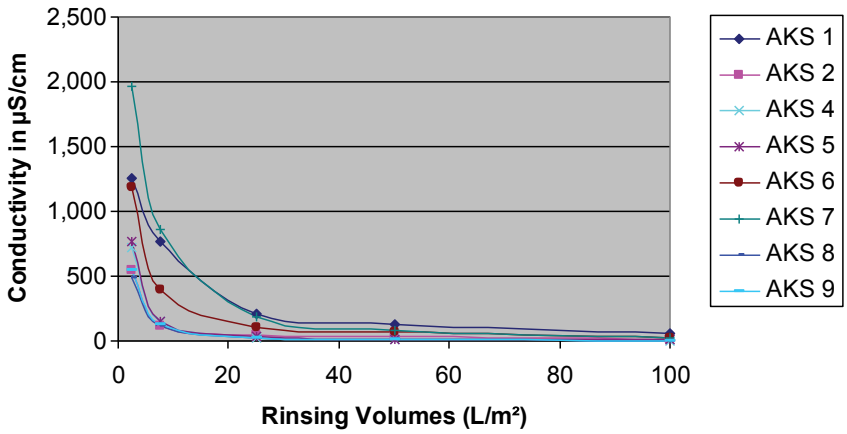
Conductivity shift and pH value in WFI

Pall Activated Carbon (AKS) depth filter media	Conductivity Shift in µS/cm Rinsing Volume (L/m²) 5 – 10	50	100	pH Value Rinsing Volume (L/m²) 5 – 10	50	100
AKS 1	724	124	56	3.0	3.7	4.2
AKS 2	118	32	8	4.8	4.5	4.8
AKS 4	151	9	4	5.9	5.7	5.8
AKS 5	154	12 5	4.6	4.9	5.3	
AKS 6	401	65	21	3.4	4.1	4.6
AKS 7	858	87	26	3.0	3.9	4.4
AKS 8	122	11	5	6.0	5.7	6.0
AKS 9	133	10 5	6.3	5.7	6.1	

Control WFI sample: pH value 5.5, conductivity < 1 µS/cm, TOC < 500 ppb

Figure 1

Conductivity in µS/cm after Rinsing with WFI



4.2.3 Conclusion

After a rinsing volume of 50 L/m², the pH value of WFI was between 3 and 7 depending upon the type of Powdered Activated Carbon (PAC) used in production.

The conductivity of the extract was between 20 and 250 µS/cm at this volume depending upon the type of PAC used in production.

Due to different activation processes, the initial pH and ion content of the PAC can vary and influences the parameters of the final Activated Carbon (AKS) depth filter media.

Pall recommends flushing with 50 L/m².

4.3 TOC (Total Organic Carbon) in WFI

4.3.1 Method

TOC (Total Organic Carbon) in WFI is the parameter characterizing organic extractables from the filters.

4.3.2 Results

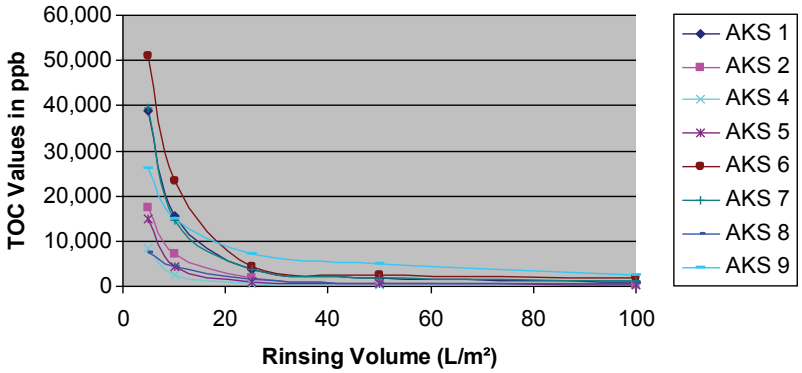
Table 5

TOC (Total Organic Carbon) in WFI

Activated Carbon (AKS) depth filter media	TOC (Total Organic Carbon) Rinsing Volume (L/m²) 5 – 10	50	100
AKS 1	15	2	1
AKS 2	7	0.7	< 0.5
AKS 4	2	< 0.5	< 0.5
AKS 5	4	0.5	< 0.5
AKS 6	23	2	2
AKS 7	15	2	1
AKS 8	4	0.7	0.5
AKS 9	15	5	2

Figure 2

TOC Values in ppb after Rinsing with WFI



4.3.3 Conclusion

After a rinsing volume of 100 L/m², the TOC in WFI is below 5 ppm for all Pall Activated Carbon (AKS) depth filter media.

Due to different activation processes, the initial TOC level of the PAC can vary and influences the parameters of the final Activated Carbon (AKS) depth filter media.

4.4 Phosphate Ions in WFI

4.4.1 Method

Phosphate ion determination according to Dr. Lange method: LCK 349.

4.4.2 Results

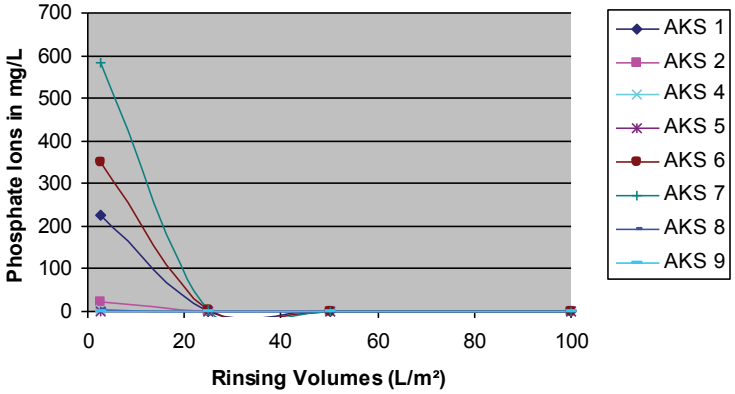
Table 6

Phosphate Ions in WFI

Activated Carbon (AKS) depth filter media	Phosphate Ions in mg/L Rinsing Volume (L/m²) 0 – 5	25	50
AKS 1	226	1.4	0.3
AKS 2	2	1.2	0.4
AKS 4	3	0.2	0.2
AKS 5	0.8	< 0.15	< 0.15
AKS 6	350	2	0.3
AKS 7	582	3	0.5
AKS 8	4	0.2	< 0.15
AKS 9	1	< 0.15	< 0.15

Figure 3

Phosphate Ion Values in ppb after Rinsing with WFI



4.4.3 Conclusion

After a rinsing volume of 50 L/m², the phosphate ion content is below 1 ppm for all Pall Activated Carbon (AKS) depth filter media.

Due to different activation processes, the initial phosphate ion content of the PAC can vary and influences the parameters of the final Activated Carbon (AKS) depth filter media.

4.5 Extractable Cations (Al, Ca, Mg, Fe, Ni, Cu, Cr)

4.5.1 Method

Cations (Al, Ca, Mg, Fe, Ni, Cu, Cr) extracted in ethanol and WFI are determined by AAS (atomic adsorption spectroscopy) by flame or graphite tube technique.

4.5.2 Results

Table 7

Al (ppm)

Activated Carbon (AKS) depth filter media	Al (ppm) in WFI Rinsing Volume (L/m²)			Al (ppm) in 40% Ethanol Rinsing Volume (L/m²)		
	5 – 10	50	100	5 – 10	50	100
AKS 1	0.23	0.040	0.022	0.10	0.008	< 0.005
AKS 2	0.039	0.013	0.005	0.048	0.013	0.009
AKS 4	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005
AKS 5	0.009	0.006	< 0.005	0.038	0.005	< 0.005
AKS 6	0.036	0.013	0.020	0.009	< 0.005	< 0.005
AKS 7	0.12	0.023	0.010	0.023	0.006	< 0.005
AKS 8	0.006	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005
AKS 9	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005

Figure 4

Al Values in ppm after Rinsing with WFI

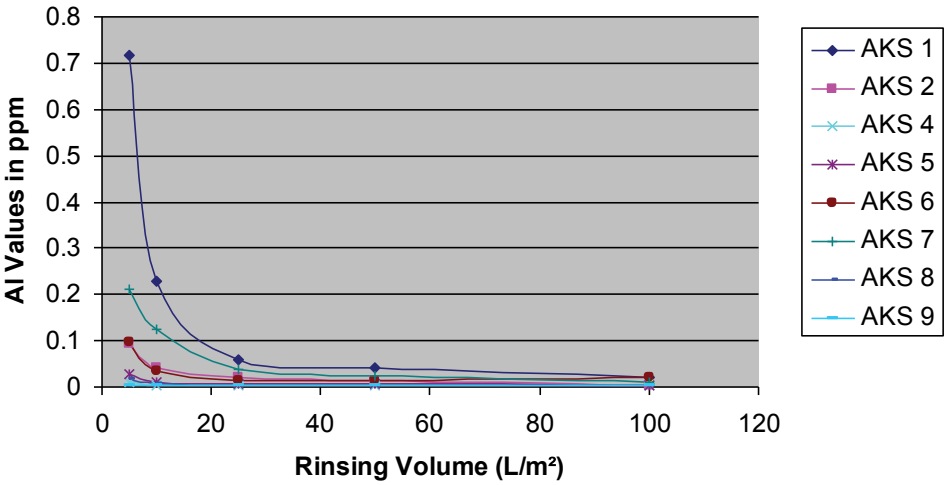


Figure 5

Al Values in ppm after Rinsing with EtOH

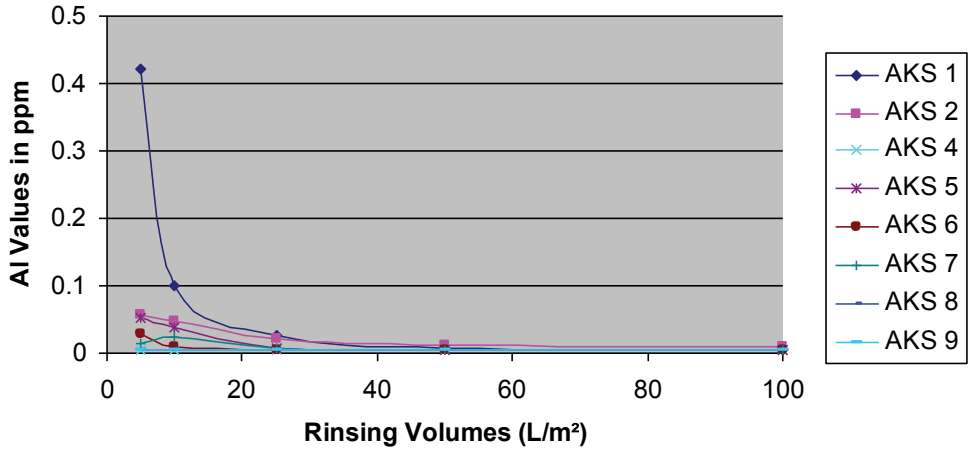


Table 8

Ca (ppm)

Activated Carbon (AKS) depth filter media	CA (ppm) in WFI Rinsing Volume (L/m²)			CA (ppm) in 40% Ethanol Rinsing Volume (L/m²)		
	5 – 10	50	100	5 – 10	50	100
AKS 1	11	0.09	0.05	11	0.45	0.06
AKS 2	7	0.21	0.07	9	0.53	0.11
AKS 4	7	0.41	0.19	5	0.95	0.57
AKS 5	12	0.11	< 0.05	13	0.66	0.17
AKS 6	15	0.23	0.05	15	0.72	0.08
AKS 7	12	0.31	0.08	8	0.61	0.09
AKS 8	9	0.81	0.33	7	1.3	0.58
AKS 9	10	0.77	0.33	5	1.1	0.68

Figure 6

Ca Values in ppm after Rinsing with WFI

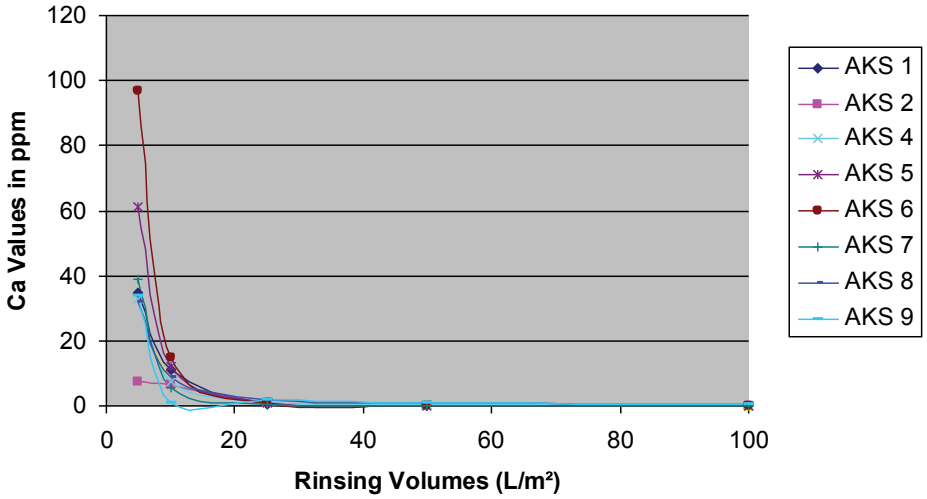


Figure 7

Ca Values in ppm after Rinsing with EtOH

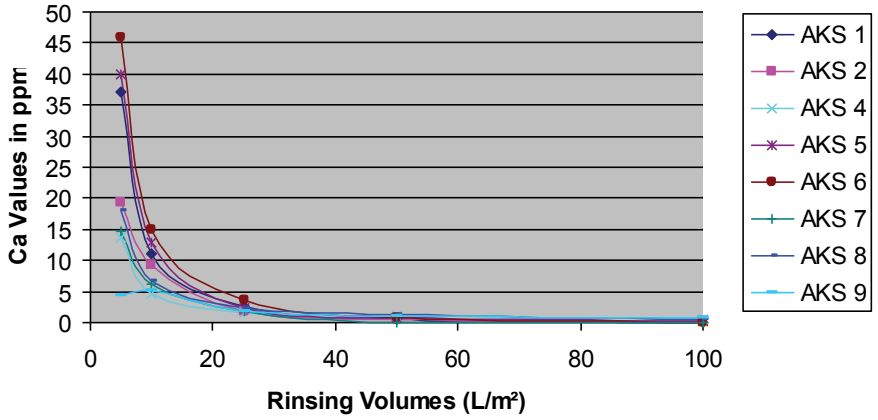


Table 9

Mg (ppm)

Activated Carbon (AKS) depth filter media	Mg (ppm) in WFI Rinsing Volume (L/m²)			Mg (ppm) in 40% Ethanol Rinsing Volume (L/m²)		
	5 – 10	50	100	5 – 10	50	100
AKS 1	2	< 0.05	< 0.05	2	0.11	< 0.05
AKS 2	2	0.06	< 0.05	2	0.09	< 0.05
AKS 4	2	0.11	0.05	2	0.30	0.16
AKS 5	2	< 0.05	< 0.05	3	0.15	< 0.05
AKS 6	4	0.06	< 0.05	4	0.18	< 0.05
AKS 7	3	< 0.05	< 0.05	2	0.20	< 0.05
AKS 8	3	0.18	0.06	3	0.27	0.08
AKS 9	3	0.12	< 0.05	3	0.27	0.10

Figure 8

Mg Values in ppm after Rinsing with WFI

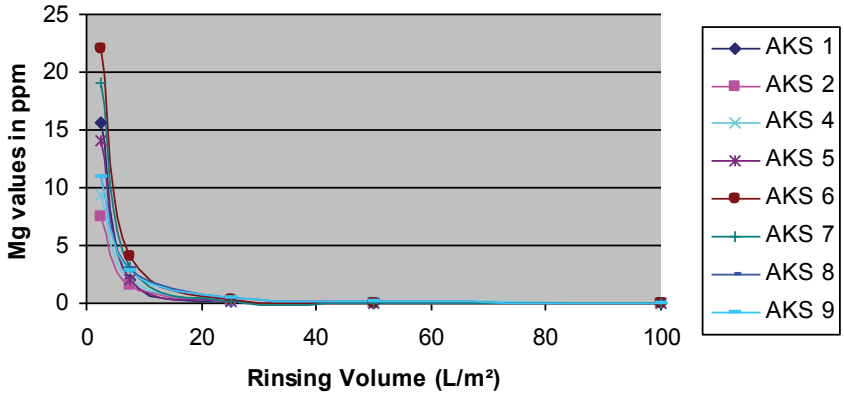


Figure 9

Mg Values in ppm after Rinsing with EtOH

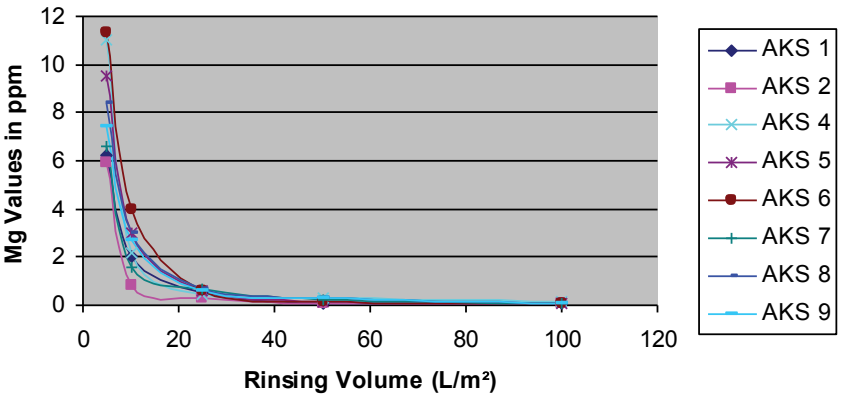


Table 10

Fe (ppm)

Activated Carbon (AKS) depth filter media	Fe (ppm) in WFI Rinsing Volume (L/m²)			Fe (ppm) in 40% Ethanol Rinsing Volume (L/m²)		
	5 – 10	50	100	5 – 10	50	100
AKS 1	0.07	< 0.05	< 0.05	0.27	0.09	0.05
AKS 2	< 0.05	< 0.05	< 0.05	0.05	< 0.05	< 0.05
AKS 4	< 0.05	< 0.05	< 0.05	0.06	0.05	< 0.05
AKS 5	< 0.05	< 0.05	< 0.05	0.06	< 0.05	< 0.05
AKS 6	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
AKS 7	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
AKS 8	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
AKS 9	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

Table 11

Ni (ppm)

Activated Carbon (AKS) depth filter media	Ni (ppm) in WFI Rinsing Volume (L/m²)			Ni (ppm) in 40% Ethanol Rinsing Volume (L/m²)		
	5 – 10	50	100	5 – 10	50	100
AKS 1	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005
AKS 2	0.006	< 0.005	< 0.005	0.006	< 0.005	< 0.005
AKS 4	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005
AKS 5	0.005	< 0.005	< 0.005	0.014	< 0.005	< 0.005
AKS 6	0.007	< 0.005	< 0.005	0.005	< 0.005	< 0.005
AKS 7	0.006	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005
AKS 8	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005
AKS 9	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005

Table 12

Cu (ppm)

Activated Carbon (AKS) depth filter media	Cu (ppm) in WFI Rinsing Volume (L/m²)			Cu (ppm) in 40% Ethanol Rinsing Volume (L/m²)		
	5 – 10	50	100	5 – 10	50	100
AKS 1	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
AKS 2	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
AKS 4	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
AKS 5	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
AKS 6	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
AKS 7	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
AKS 8	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
AKS 9	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

Table 13

Cr (ppm)

Activated Carbon (AKS) depth filter media	Cr (ppm) in WFI Rinsing Volume (L/m²)			Cr (ppm) in 40% Ethanol Rinsing Volume (L/m²)		
	5 – 10	50	100	5 – 10	50	100
AKS 1	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005
AKS 2	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005
AKS 4	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005
AKS 5	0.014	< 0.005	< 0.005	0.013	< 0.005	< 0.005
AKS 6	0.007	0.005	< 0.005	< 0.005	< 0.005	< 0.005
AKS 7	0.006	< 0.005	< 0.005	0.006	< 0.005	< 0.005
AKS 8	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005
AKS 9	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005

4.5.3 Conclusion

Table 14

Extractables Results

Activated carbon (AKS) depth filter media	Conductivity in µS/cm Rinsing Volume (L/m²)		pH Rinsing Volume (L/m²)		TOC in mg/L Rinsing Volume (L/m²)		PO_4^{-3} in mg/L Rinsing Volume (L/m²)		ppm Al in WFI Rinsing Volume (L/m²)		ppm Ca in WFI Rinsing Volume (L/m²)	
	0 – 5	50	0 – 5	50	0 – 5	50	0 – 5	50	0 – 5	50	0 – 5	50
AKS 1	< 1800	< 250	2.5 – 4.5	3.0 – 4.5	< 100	< 5	< 500	< 2	< 2	< 0.1	< 150	< 0.5
AKS 2	< 1000	< 100	4.0 – 6.0	3.5 – 6.0	< 50	< 5	< 100	< 2	< 0.3	< 0.0	< 150	< 0.5
AKS 4	< 1000	< 100	5.0 – 7.0	5.0 – 7.0	< 50	< 5	< 10	< 2	< 1	< 0.1	< 100	< 2
AKS 5	< 1500	< 100	4.0 – 6.0	4.0 – 6.0	< 50	< 5	< 5	< 0.5	< 0.1	< 0.0	< 100	< 0.5
AKS 6	< 1800	< 150	3.0 – 4.5	3.5 – 5.0	< 100	< 10	< 500	< 2	< 0.3	< 0.0	< 150	< 0.5
AKS 7	< 10000	< 200	2.0 – 4.0	3.0 – 4.5	< 100	< 5	< 1500	< 2	< 2	< 0.1	< 200	< 2
AKS 8	< 1000	< 100	5.0 – 7.0	5.0 – 7.0	< 50	< 5	< 10	< 0.5	< 0.1	< 0.0	< 200	< 10
AKS 9	< 1000	< 100	5.0 – 7.0	5.0 – 7.0	< 50	< 10	< 10	< 0.5	< 0.1	< 0.1	< 200	< 10

Activated carbon (AKS) depth filter media	ppm Mg in WFI Rinsing Volume (L/m²)		ppm Fe in WFI Rinsing Volume (L/m²)		ppm Ni in WFI Rinsing Volume (L/m²)		ppm Cu in WFI Rinsing Volume (L/m²)		ppm Cr in WFI Rinsing Volume (L/m²)	
	0 – 5	50	0 – 5	50	0 – 5	50	0 – 5	50	0 – 5	50
AKS 1	< 50	< 0.1	< 1	< 0.1	< 0.1	< 0.01	< 0.1	< 0.1	< 0.05	< 0.01
AKS 2	< 50	< 0.1	< 0.1	< 0.1	< 0.05	< 0.01	< 0.1	< 0.1	< 0.05	< 0.01
AKS 4	< 50	< 1	< 0.1	< 0.1	< 0.05	< 0.05	< 0.1	< 0.1	< 0.05	< 0.05
AKS 5	< 50	< 0.1	< 0.1	< 0.1	< 0.05	< 0.01	< 0.1	< 0.1	< 0.1	< 0.01
AKS 6	< 50	< 0.1	< 0.1	<0.1	< 0.05	< 0.01	< 0.1	< 0.1	< 0.05	< 0.01
AKS 7	< 50	< 0.1	< 0.2	< 0.1	< 0.05	< 0.02	< 0.1	< 0.1	< 0.05	< 0.01
AKS 8	< 50	< 0.5	< 1	< 0.5	< 0.05	< 0.05	< 0.5	< 0.5	< 0.5	< 0.5
AKS 9	< 100	< 0.5	< 0.1	<0.1	< 0.05	< 0.05	< 0.1	< 0.1	< 0.01	< 0.01

4.6 Total Extractables. 21 CFR 177.2260

4.6.1 Method

Under title 21 "Food and Drugs," (2) chapter 177, the Code of Federal Regulations of the FDA (Food and Drug Administration) is concerned with indirect food additives: polymers.

Subpart C: Substances for use only as components of articles intended for repeated use.

21 CFR 177.2260 refers to resin-bonded filters and states the limits for extractables in different extraction media and under different extraction conditions. The following limitations are stated here.

Table 15
Extraction Limitations

Extraction Solvent	Extraction Conditions	CFR Limits
deionized water	100 °C	< 4 % by weight of the filter
50 % ethanol	room temp.	< 4 % by weight of the filter
5 % acetic acid	room temp.	< 4 % by weight of the filter
n-hexane	reflux	< 4 % by weight of the filter

Although these regulations are not primarily intended for pharmaceutical products, they provide additional supportive data for the suitability of filters for pharmaceutical applications.

4.6.2 Results and Conclusion

The total extractables of all Pall Activated Carbon (AKS) depth filter media was significantly below the CFR limits and therefore meet the requirements of 21 CFR 177.2260.

Detailed reports are available upon request.

5. Endotoxins

5.1 Endotoxins

In filter manufacturing there is a potential risk of contamination by endotoxins. Therefore the verification of low endotoxin levels of the filter extracts is an important issue during validation.

5.1.1 Methods

Human Albumin LAL Gel Clot Test

For the extraction and desorption of endotoxins from filters, human albumin could be demonstrated as being most effective. Thus filtering a human albumin solution and demonstrating endotoxins are below detectable limit in the filtrate is used as a routine test in quality control.

Filtration of a human albumin solution without pre-rinsing was performed and an endotoxin specific LAL-gel clot test was used to determine the level of endotoxins in EU/mL (endotoxin units/mL).

5.1.2 Results

Table 16

Test Results in Human Albumin[1] without WFI Pre-rinse

P-series Depth Filter Media Grade	Endotoxin Content (EU/mL)
AKS 1	< 0.12
AKS 2	< 0.12
AKS 4[2]	ND[3]
AKS 5	< 0.06
AKS 6	< 0.06
AKS 7	< 0.12
AKS 8	< 0.12
AKS 9	< 0.12

(1) Control sample human albumin: < 0.06 EU/mL
(2) AKS 4 is not optimized regarding low endotoxin content.
(3) ND = Not determined

5.1.3 Conclusion

The endotoxin content of all tested sheets (except AKS 4) in human albumin without pre-rinsing was below 0.12 EU/mL.

The endotoxin level of AKS 5 and AKS 6 was below the detection limit of 0.06 EU/mL.

Detailed reports are available upon request.

6. Biological Reactivity Tests of Pall Activated Carbon (AKS) Depth Filter Media

6.1 Method

According to USP, the biocompatibility of a material can be checked in biological reactivity tests either *in vitro* or *in vivo*.

The Biological Reactivity Tests listed in the current revision of the United States Pharmacopeia (USP) for Class VI - 121 °C. Plastics are a combination of in vivo tests that are designed to determine the biological response of animals to specific extracts prepared from the material under test. The USP defines six plastic classes based on the response to these tests for which extracts, materials and routes of administration are specified. In testing of filter sheets, the following tests were performed:

- Acute systemic injection test
- Intracutaneous test
- Implantation test

As extraction media for systemic and intracutaneous injection, the following media are used:

- Saline
- Saline in alcohol
- Polyethylene glycol 400
- Sesame oil

The extraction is performed at 121 °C for 1 hour.

6.2 Results

All tested materials have met the specifications for Biological Reactivity Tests, in vivo, listed in the current revision of the United States Pharmacopeia (USP) for Class VI - 121 °C Plastics.

Certificates and test reports are available upon request.

7. Chemical Compatibility of Pall Activated Carbon (AKS) Depth Filter Media

7.1 Method

Chemical compatibility against different solvents is a critical parameter for materials used in API (Active Pharmaceutical Industry) manufacturing processes.

AKS 1 and AKS 2 activated carbon depth filter media were chosen to represent the two different groups of chemical and steamed activated carbon types.

The following solvents were taken each representing a specific product group:

Table 17
Solvents by Product Group

Solvent	Product Group
Ethanol	Alcoholic Solvents
Toluene	Aromatic Solvents
THF (Tetrahydrofuran)	Etheric Solvents
n-Hexane	Aliphatic Solvents
Acetone	Ketones
DMSO	Aprotic Solvents

In order to determine the chemical compatibility, the wet strength of the two activated carbon filter media (AKS 1 and AKS 2) was measured.

Sample preparation:
(a) Soaking for 5 minutes in H_2O (Standard Value)

(b) Soaking for 60 minutes in H_2O at room temperature (RT)

(c) Soaking for 60 minutes in described solvents (100%) at room temperature (RT)

7.2 Results

Table 18
AKS 1 Wet Strength Data

	AKS 1	
Solvent	Wet Strength [N](1)	Change of Wet Strength [%]
Standard Value	166	
H2O	173	< 5
Ethanol	241	+45
Toluene	246	+48
THF	246	+48
n-Hexane	262	+58
Acetone	249	+50
DMSO	168	< 5

(1) Data collected from three different measurements.

Table 19
AKS 2 Wet Strength Data

	AKS 2	
Solvent	**Wet Strength [N][(1)]**	**Change of Wet Strength [%]**
Standard Value	119	
H2O	120	< 5
Ethanol	198	+66
Toluene	202	+70
THF	212	+78
n-Hexane	218	+83
Acetone	193	+62
DMSO	129	+8

(1) Data collected from three different measurements.

7.3 Conclusion

Activated carbon filter sheets AKS 1 and AKS 2 are compatible with the tested solvents. With all tested solvents the wet strength increased or was comparable to the untreated carbon filter sheets.

PALL Life Sciences

Corporate Headquarters
Port Washington, NY, USA
+1.800.717.7255 toll free (USA)
+1.516.484.5400 phone
biopharm@pall.com e-mail

European Headquarters
Fribourg, Switzerland
+41 (0)26 350 53 00 phone
LifeSciences.EU@pall.com e-mail

Asia-Pacific Headquarters
Singapore
+65 6389 6500 phone
sgcustomerservice@pall.com e-mail

Visit us on the Web at www.pall.com/biopharm
E-mail us at biopharm@pall.com

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