FIGURE 2. The PennTech RW-250 rotary vial washer washing chamber. Photograph courtesy of PennTech Machinery Corporation, Warminister, Pennsylvania, USA.

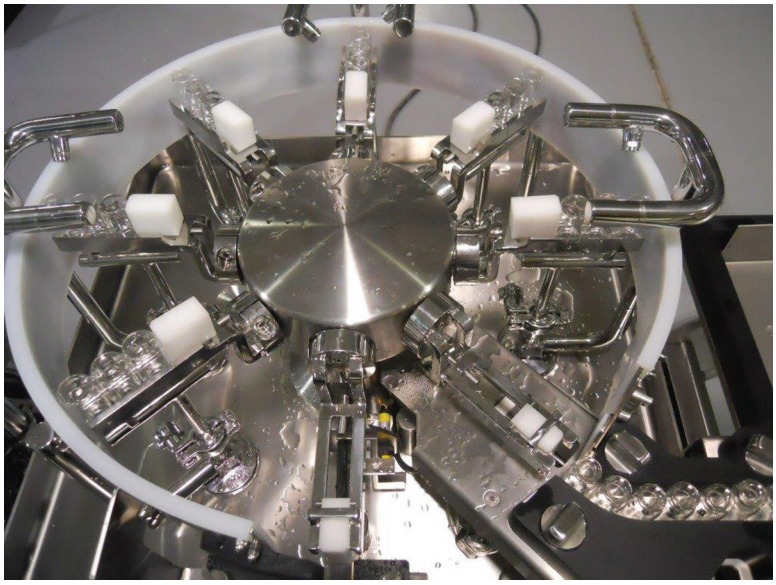


FIGURE 3. The PennTech RW-500 rotary vial washer. Photograph courtesy of PennTech Machinery Corporation, Warminister, Pennsylvania, USA.

SIDEBAR. Validation of a Rotary Vial Washer for Terminally Sterilized Product Manufacture.

Andrew Sully, Mark Meredith 1. Cardiff and Vale University Health Board, Cardiff

Introduction

The introduction of a Penntech RW-500 rotary vial washer was to be employed to further automate terminal sterilisation product manufacture. Validation was carried out in accordance with Annex 15 EU GMP.
In order to perform Performance qualification (PQ) on the equipment there were no published studies available to ensure effective machine performance. Discussion with our MHRA GMP inspector and manufacturer required a series of tests to demonstrate effective performance.

Aims

The introduction of a new rotary vial washer used in the process of manufacture of terminally sterilised products requires validation in accordance with GMP to ensure verification of performance.

A PQ protocol was required to test the effectiveness of the machine with regard to the manufacture of terminally sterilised parenteral products.

Method

10ml and 100ml Type 1 Glass vials were washed in accordance with the 0.1% vial dryness test acceptance criteria. Samples were taken at the beginning and end of the wash cycle and tests performed below:

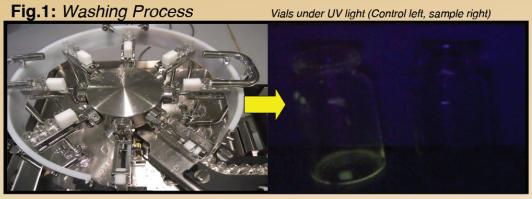
- Vials were soaked in Riboflavin 0.02% w/v solution, agitated to ensure coverage and left to dry in an oven at 60C for 24hours. Post washed vials were observed under UV light at 360nm for any signs of chemical contamination.
- 0.25ml of Duke Particle standard (50μm) added and agitated under grade A laminar air flow and covered.Vials dried at 60^{o}C until no visual water present. Post washed spiked vials and unspiked /unwashed vial (controls) were tested using particle free water and tested in accordance with the BP Subvisible test[1] using a HIAC Royco 9703 Liquid Particle counter.
- Endotoxin challenge vials were prepared containing approximately 100EU/ml of Endotoxin Control Standard (Charles River), vortexed, dried in a vacuum oven at 60C and 25mmHg until no visual water detected. Post washed spiked vials and unwashed spiked vials (control) had 1ml of LAL reagent water, vortexed and tested using the Endosafe PTS system.

Results

Chemical contamination studies did not detect Riboflavin by the presence of fluorescence in washed vials under UV light at 360nm and effective residue removal by the washer was evident as in (Fig. 1).

Fig.1: *Washing Process*

Vials under UV light (Control left, sample right)



The level of contamination observed was much higher than vials used in normal operation. Effective particulate removal of 50μm was observed in 10ml and 100ml containers (3.4 and 3.0 log reduction). Compliance with the BP sub visible particulate test was evident as shown below in (Fig. 2).

Fig. 2

Vials		Mean Particle counts: Unwashed / unspiked (n=3)	Spiked Unwashed (n=3)	Washed vials (n=12)	BP limits
10ml vials	10 µm	5	26.7	16.4	6000
	25 µm	1.7	745	0.4	600
	50 µm	0.0	1907	0.85	n/a
100ml bottles	10 µm	0.83	1.5	0.18	25
	25 µm	0	0.83	0.01	3
	50 µm	0	9	0.01	n/a

Results (continued)

The machine is reported to obtain a three log reduction in bacterial endotoxin which was observed in both vial sizes as seen in (Fig. 3).

Endotoxin log reduction results observed in washed vials is a minimum value as actual values were at the limit of sensitivity of the system.

Vials received pre-washed from the supplier showed endotoxin values that were also undetectable.

Fig. 3

Vials	Endotoxin EU/ml: Unwashed / unspiked (n=3)	Spiked Unwashed (n=3)	Spike Washed (n=6)	Log Reduction
10ml vials	<0.05	103	<0.05#	3.3
100ml bottles	<0.05	83.3	<0.05#	3.2

Limit of sensitivity

Conclusion

- The machine was able to demonstrate verification of operation in worst case conditions.
- The washer was able to reduce Endotoxin levels to undetectable limits and the use of depyrogenation processes for terminally sterilised manufacture was not justified on the basis of these results in addition with supporting data for pre-sterilisation bioburden and Endotoxin testing in final product.

Acknowledgments:
The authors would like to thank Biopharma Process Systems and Penntech for their information and advice

References
1. British Pharmacopoeia volume 1 (2011) Appendix XIII A. Particulate Contamination: Sub-visible Particles [online] available at http://www.pharmacopoeia.co.uk/bp2011/ixbin/bp.cgi?a=display&r=vIy5m38HLjz&n=9&id=928&tab=search. Last accessed 19.05.2011

GIG CYMRU NHS WALES | Bwrdd Iechyd Prifysgol Caerdydd a'r Fro | Cardiff and Vale University Health Board

Poster presented at: The National Health Services Quality Assurance Annual Symposium for Pharmacy Technical Services; September 2012; Ashford, Kent, England. Reprinted with permission of authors.

TABLE 1. A Comparison of PennTech[a] Rotary Vial Washer Models RW-250 and RW-500.

Model number	RW-250	RW-500
Style	Semiautomatic	Fully automatic
Vial range (mL)	2-100	2-100
Maximum speed	70 Vials per minute	120 Vials per minute
Footprint	45" × 50"	46" × 65"
Recirculation package	Not applicable	Available

[a]PennTech Machinery Corporation, Warmisister, Pennsylvania, USA.

TABLE 2. A Comparison of Steriline[a] Rotary Vial Washer Models RA-V4, RA-A4, RA-AV4, and RA-K4.

Commodity Ampules	**RA-V4**	**RA-A4**	**RA-AV4**	**RA-K4**
1-2 mL	NA	100 ppm	100 ppm	NA
5-10 mL	NA	50 ppm	50 ppm	NA
20-30 mL	NA	50 ppm	50 ppm	NA
Tubing vials				
2R-4R	150 ppm	NA	150 ppm	NA
6R-8R	120 ppm	NA	120 ppm	NA
10R-15R	100 ppm	NA	100 ppm	NA
20R-30R	70 ppm	NA	70 ppm	NA
Molded vials				
50H	30 ppm	NA	NA	NA
100H	15 ppm	NA	NA	NA
Cartridges/ syringes				
1-2 mL	NA	NA	NA	150 ppm
5-10 mL	NA	NA	NA	100 ppm
20-30 mL	NA	NA	NA	50 ppm

[a]Steriline s.r.l., Como, Italy
NA = Not applicable, ppm = parts per minute, R = tubing glass, H = molded glass.

TABLE 3. Rotary vial washers of interest to compounding pharmacists

Name and model number(s) of the device(s):	PennTech RW-250 Vial Washer
Manufacturer and location:	PennTech Machinery Corporation, Ivyland, Pennsylvania, USA
Type of device(s) (technology):	Rotary vial washer The PennTech rotary vial washer model RW-250 is a compact semiautomatic vial washer with a simple but robust design. That washer (and its supporting validation documents) adhere to cGMP guidelines and quality requirements. After having been cleaned, the vials are discharged onto a tray for further processing. To optimize WFI consumption so that the vials are effectively cleaned without wasting water, the RW-250 is equipped with individually programmable intermittent-spray manifolds that ensure that each type of vial washed is scrubbed by water and air for only as long as necessary. The effective matching of the size of each spray manifold orifice to the volume of the vial is essential to that process. The necessary change parts can be changed quickly and increase the washer's efficiency. The delivery of water and air is provided via a dedicated nonpenetrating manifold system.
USP Chapter <797> /cGMP compliant:	Yes, strictly adheres to *USP* Chapter <797>/cGMP guidelines.
Design and features:	The throughput of the RW-250 is typically 20-70 vials per minute, depending on the vial format. The typical batch size ranges from 1000-8000 vials. The vial range is from 2-100 mL (glass or plastic) (change parts are required). This washer includes 6 stations for water (RO/DI, WFI) and sterile-air blowing. Optionally, for those using bagged WFI, a WFI supply skid with a 21-gal (80-L) tank is available with a heating element that can increase the temperature of the WFI up to 80°C. The skid includes a sanitary centrifugal pump that provides the vial washer with 5 bar (about 73 psi) of water pressure. The RW-250, which is manufactured to operate with minimal maintenance, is specifically and intrinsically designed to achieve a 3-log endotoxin removal for compounding pharmacies, clinical studies, contract manufacturing organizations, and start-up companies. Changes in format parts are made manually. A user-friendly HMI allows simple programmable selections (e.g., the outfeed pusher movement and the setting of the number of indexes per minute) to be made. A comprehensive operator's manual includes "as built" 3-dimensional exploded assembly drawings and a complete bill of materials. Also supplied are material and welding certificates, relevant isometric drawings, a complete set of instructions for operations and maintenance, electrical drawings, and all the necessary PLC/HMI programs.
Allen-Bradley (Rockwell Automation, Inc., Milwaukee, Wisconsin) PLC/HMI:	Yes
Procedure for use:	The operator places the appropriate number of vials in front of the vial pusher and then moves the vials into the awaiting vial holder. When the vial holder has been fully loaded with vials, the turret (which moves clockwise 45 degrees at every index) makes 1 index to the next station. There are 8 stations, 6 of which are dedicated to a specific washing or air-drying function. The vials are inverted between stations 1 and 2 and remain inverted until they arrive at station 7. Between stations 7 and 8, the vials are turned upright. When the turret index has stopped, the air and water sprays operate for a predetermined time.
Manufacturer's contact information:	PennTech Machinery Corporation www.penntech-corp.com Kain Johnson 215-396-2200 kjohnson@penntech-corp.com
Name and model number(s) of the device(s):	PennTech RW-500 Vial Washer
Manufacturer and location:	PennTech Machinery Corporation, Ivyland, Pennsylvania, USA
Type of device(s) (technology):	Rotary vial washer The PennTech rotary vial washer model RW-500, which is a fully automated version of the RW-250, is designed for larger batch sizes.
USP Chapter <797> /cGMP compliant:	Yes, strictly adheres to *USP* Chapter <797>/cGMP guidelines.
Design and features:	The throughput is up to 120 vials per minute, depending on the vial format. The typical batch size ranges from 10,000-25,000 vials. The vial range is 2-100 mL (change parts are required). The RW-500 includes 6 stations for water (RO/DI, WFI) and sterile-air blowing. A rotary infeed table enables automatic loading of the vials into the vial holders. Features include the recycling of WFI, intermittent spraying, and an automatic lid lift mechanism. The changeover time is 15 minutes or less. The RW-500 is controlled by an Allen-Bradley (Rockwell Automation, Inc., Milwaukee, Wisconsin, USA) CompactLogix PLC that provides full control and monitoring of the machine. The machine includes a user-friendly Allen-Bradley (Rockwell Automation, Inc.) PanelView 600+ operator interface. A menu guides the operator through the operations of the machine. Fault conditions are displayed to inform the operator of the status during the washing process. All pipes in contact with WFI and sterile air are constructed of AISI type 316L stainless steel; their internal surfaces are electropolished. Orbital welding is applied wherever possible. Silicone seals are used throughout the piping system. All water pipes and manifolds are pitched 10 mm per meter to prevent water stagnation after shutdown. No dead-legs are present in the entire piping system, which is designed to run from high to low to prevent water stagnation. A 1-piece transparent polycarbonate cover permits visual verification of the flow of every nozzle. Safety features are in place to prevent water spraying when the cover is not located over the washing chamber. The RW-500 features water manifolds with CNC-drilled orifices instead of penetrating needles that move in and out of the vials and that, over time, may hit the neck finish of a vial and bend and cause glass chipping. Bent nozzles can jeopardize the validation of the batch.

TABLE 3. Rotary vial washers of interest to compounding pharmacists continued.

Allen-Bradley (Rockwell Automation, Inc., Milwaukee, Wisconsin) PLC/HMI:	Yes
Procedure for use:	The vials are positioned onto the rotary infeed table and are fed single-file to the infeed belt, from which they are fed into a cassette. Only when a cassette is loaded with the correct number of vials can the index switch be triggered. The servomotor-controlled central column indexes and inverts the vials, which are centered exactly with the internal spray pipe. The vials index around the machine and pause at each of the 6 stations for a sterile-air blow or a virgin-WFI spray; the inside and outside of each vial are thoroughly scrubbed. At the end of the seventh station, the vials are positioned upright before they are fed out of the machine via an outfeed pusher (precisely programmed outfeed movements are assured for every vial size). The clean items are then immediately available for manual or automatic tray loading.
Manufacturer's contact information:	PennTech Machinery Corporation www.penntech-corp.com Kain Johnson 215-396-2200 kjohnson@penntech-corp.com
Name and model number(s) of the device(s):	Steriline RA-V4, RA-A4, RA-AV4, RA-K4
Manufacturer and location:	Steriline s.r.l., Como, Italy
Type of device(s) (technology):	Rotary washers for injectable drug containers The Steriline RA series of rotary washers is designed to process vials, ampoules, cartridges, and syringes with an output of up to 9000 pieces per hour (150 pieces per minute). The containers are loaded into holders that manage them throughout the cleaning process. All Steriline RA series washers rotate with an intermittent motion and are equipped with nozzles that are lifted to enter the mouth of each container and then spray the appropriate washing and drying fluids; this, with the computer-controlled recipe parameters, ensures a highly repetitive washing cycle. At the end of the production cycle, the containers are automatically discharged either into trays or directly into a depyrogenation tunnel for further processing.
USP Chapter <797> /cGMP compliant:	Yes, as with all Steriline equipment, RA series washers are designed under GMP with the use of those washers in current cGMP environments in mind.
Design and features:	Steriline developed this small-footprint RA series of rotary washers for use in pharmacies, clinical manufacturing, laboratories, and research and development. The integrated control system in RA series washers includes an HMI and a PLC for the automatic control of all functional parameters according to various container sizes and types. Individual washing cycles can be programmed for each container type and process variables (e.g., temperature, pressure, fluid-spraying time, cycle speed). Each process parameter is defined in the software, and parameters are password protected. Because of their compact and flexible design, any of the RA series washers can be fully integrated with a Steriline compact depyrogenation tunnel with a single control package. A Steriline filler/capper with an isolator and exterior glassware washer can be added to provide a complete compact filling solution.
Allen Bradley (Rockwell Automation, Inc., Milwaukee, Wisconsin, USA)PLC/HMI:	Yes, PLC; Siemens (Munich, Bavaria), Allen-Bradley (Rockwell Automation, Inc.), and other brands of controllers and interfaces are available on customer request.
Procedure for use:	The containers are loaded onto an infeed section that automatically inserts each component into a gripper; this ensures that there is no glass-to-glass contact. With an intermittent motion, a group of up to 4 containers indexes to the first washing station. While in that first indexing step, the group of containers is turned upside-down for processing. At each of the 6 processing stations, the turret hesitates while nozzles are lifted to penetrate the mouth of each container and spray either the appropriate water for washing or sterile-air for drying; this ensures a complete and highly repetitive washing cycle for each container. Then those containers are automatically discharged at the end of the production cycle either into trays or directly on a depyrogenation tunnel infeed conveyor belt.
Manufacturer's contact information (phone number, hours of availability, time zone):	Steriline systems are distributed in North America by AWS Bio-Pharma Technologies, LLC, though a network of regional sales staff. Contact AWS Bio-Pharma Technologies at 877-297-7763 or at www.AWSBioPharma.com.

Abbreviations: cGMP = current good manufacturing practices, WFI = water for injection, USP = United States Pharmacopeia, RO = reverse osmosis, DI = deionized, HMI = human-machine interface, PLC = programmable logic controller, CNC = computer numerical control, GMP = good engineering practice.