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Validation of the Growth Direct™ system to perform pharmaceutical water bioburden analysis

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The validation of the Growth Direct system is described for the automated incubation and counting of microbial colonies on R2A media plates derived from a water bioburden test. The validation strategy and sample data are given to demonstrate that the technology is accurate for enumerating microorganisms, accurate and precise for microbial recovery and equivalent to the current compendia test for water testing.

Key words: Rapid Micro Method, water validation, Growth Direct, TR33.

Introduction

Pharmaceutical water testing comprises a significant percentage of the workload in the quality control department. Each water sample test is divided into two phases: first sampling/setting up the test and secondly reading and recording the test result(s). The second phase involves a highly trained analyst performing the very repetitive task of data collection and collation for which they may be overqualified. A reduction in the analyst involvement on the testing effort would be a benefit to the department in that other higher value activities could be performed by the same person. The introduction of automation to this process would add significant benefit. The Growth Direct™ (GD) system is an automated colony counter that can be linked into a two-way LIMS system to upload sample work-lists and download results, thus removing automatically these time-consuming, laborious tasks from the analyst. This paper describes the validation of the system as an automated colony counter applied to pharmaceutical water testing.

GD technology

The GD system uses a proven technology that is based on the same principles and procedures as that defined in the European Pharmacopoeia (Ph. Eur.) monographs for purified water and highly purified water using R2A at 30–35°C[1]. The system automates the compendial incubation and visual colony counting method for water testing by replacing detection by the human eye with sensitive digital imaging. The technology uses the same media and sampling methods as the current water testing methods and is able to deliver faster results by detecting microscopic colonies well before they become visible to the naked eye. This is achieved by imaging the intrinsic cellular auto-fluorescence of the bacterial colony. The growth of microscopic colonies are detected by the GD system by detecting and tracking the increase in their inherent auto-fluorescence over time. The technology is based on the fact that all microbial cells emit yellow-green fluorescence when illuminated by blue light at 460–490 nm due to the presence of fluorescent biomolecules inclusive of (ribo)flavins and flavoproteins[2]. Like adenosine triphosphate or DNA, these molecules are ubiquitous in living systems in all the kingdoms of life including microorganisms. This permits the detection of the same broad range of species as are detected by the visual colony counting method.

Growing micro-colonies exhibit increasing auto-fluorescence and size over time which the system detects and records. The system discriminates growing microbial colonies from inanimate fluorescent debris as these objects do not change in signal intensity or size.

The imaging method does not harm the cells and, as such, is a non-destructive method, thus the micro-colonies can grow

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into visible colonies for use in subsequent microbial identification.

Validation rationale

The GD technology uses standard mixed cellulose–ester 0.45 μm filtration membranes and standard media (R2A) and incubation parameters for microbial growth to allow a colony-forming unit (CFU) to grow into a colony and be counted. As the methods are comparable to the compendial method, this technology can be viewed as a rapid micro method rather than an alternative method. Effectively, the GD system performs as an automated incubation and colony counting system. The key functional parts are, therefore, only the qualification of the incubators and the qualification of the colony counting technology.

The new release of the *PDA Technical Report TR33 2013 Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods* contains the following text[3].

> "Some alternative or rapid technologies may be considered as automated traditional or compendial microbiological test methods, especially when the results are in colony forming units (CFU). These technologies may be qualified for their intended use without the need for demonstrating certain method validation requirements as specified in Section 5.0 of this Technical Report. For these technologies, at least accuracy and precision assessments should be performed, in addition to method suitability and equivalence/comparability studies. A risk assessment should be performed to determine the required testing that would support the validation of the alternative or rapid technology."

The validation steps of the GD system can be divided into five sections.

1. The Installation/Operational Qualification (IOQ) phase concentrates on the validation of the system's hardware and software components to confirm that they are all functioning according to the design specification. This includes the calibration and temperature mapping of the incubators.
2. The Performance Qualification (PQ) is subsequently carried out to validate the growth promotion properties of the media in association with the accuracy of colony enumeration by the software.
3. The Time to Result Qualification (TTRQ) phase consists of the determination of the timepoint at which the system result is shown to be comparable to the compendial test method. For this work, the natural flora from the facility should to be tested rather than the United States Pharmacopeia (USP)/Ph. Eur. organisms that are favoured during the PQ. The USP/Ph. Eur. defined organisms grow very quickly and are not indicative of the organisms seen in the facilities' water system. Some of these may have a long lag phase and slow doubling time that could lead to false negatives if the TTR was set from the speed of the pharmacopoeial organism growth rates. During this testing, it is also recommended to include some examples of stressed organisms to ensure the worst case scenario for microorganism detection are met.
4. The method suitability for the product evaluates interference, either to the growth of the organisms or interference of the product on the detection system of the GD system itself.
5. The final phase of the validation is the verification of equivalence to the traditional method by running both tests in parallel for a defined period of time.

Table 1. IOQ content.

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Sections 3, 4 and 5 can be merged into the same experimental design if required. This paper describes the approach used and data generated during the performance of a water test validation on the GD system.

Installation/Operation Qualification (IOQ)

The component testing performed during the IOQ are shown in **Table 1**. The majority of the testing focuses on the performance of the software to verify the correct steps and sequences. The key hardware test consists of temperature mapping of the two incubators. The mapping was performed with 10 Ellab temperature probes (Ellab, Hillerød, Denmark) placed throughout the incubator with both a full and empty load pattern of test cassettes. The temperature profiles for the empty incubator at 22.5 and 32.5°C are shown in **Table 2**. The temperature range seen for both incubators over 24 hours at all test points was 0.7°C. The same range was seen when testing the full load pattern.

Performance Qualification (PQ)

The PQ phase of the validation utilises microorganisms for the qualification of growth promotion, system accuracy for colony detection and precision of the colony detection. The organisms are presented in a neutral buffer such as Fluid A, buffered saline or peptone broth to take out any inhibitory actions on the organisms. The USP/Ph. Eur. suite of organisms can be used as examples of the spectrum of organisms required to be tested (**Table 3**).

The accuracy of the CFU count is determined by filtering the organisms through the GD filtration kit, transferring the membrane filter onto the GD R2A cassettes and running the cassettes on the GD system to generate a system CFU count. The cassettes are then removed and the colonies on the membrane surface counted by the analyst. Due to analyst to analyst variation in enumeration of colonies, the cassette colony count is performed by three analysts and the mean value obtained is then compared to the GD system count. The results of

Table 2. Temperature mapping profiles for the two incubators at their specified set points.

Probe location		13-14560: set at 22.5°C empty			13-14413: set at 32.5°C empty		
		Mean temperature (°C)	Minimum temperature (°C)	Maximum temperature (°C)	Mean temperature (°C)	Minimum temperature (°C)	Maximum temperature (°C)
H8 S1	Front	22.5	22.4	22.6	32.4	32.3	32.4
H6 S1	Right front	22.5	22.5	22.6	32.5	32.5	32.5
H4 S1	Right side	22.5	22.5	22.6	32.5	32.4	32.6
H10 S1	Left front	22.5	22.5	22.6	32.6	32.5	32.6
H2 S1	Right back	22.6	22.5	22.7	32.6	32.4	32.7
H10 S13	Left front	22.6	22.6	22.7	32.6	32.6	32.6
H6 S13	Right front	22.6	22.6	22.7	32.6	32.6	32.6
H12 S13	Left back	22.7	22.6	22.7	32.6	32.6	32.6
H12 S1	Left back	22.7	22.6	22.7	32.6	32.6	32.6
H14 S1	Back	22.7	22.6	22.7	32.6	32.5	32.7
H2 S13	Right back	22.7	22.7	22.7	32.6	32.6	32.7
H8 S13	Front	22.8	22.7	22.8	32.7	32.7	32.7
H4 S13	Right side	22.8	22.8	22.8	32.7	32.6	32.8
H2 S25	Right back	22.8	22.8	22.8	32.8	32.7	32.9
H6 S25	Right front	22.8	22.8	22.9	32.8	32.8	32.9
H4 S25	Right side	22.8	22.8	22.9	32.9	32.8	33.0
H14 S25	Back	22.9	22.8	22.9	32.9	32.8	33.0
H10 S25	Front	23.1	23.0	23.1	32.9	32.8	33.0
Global mean		**22.8**	**22.4**	**23.1**	**32.7**	**32.3**	**33.0**

Table 3. USP/Ph. Eur. test organisms for use in the PQ.	
Test microorganism	**ATCC* number[3]**
Bacillus subtilis	6633
Staphylococcus aureus	6538
Escherichia coli	8739
Pseudomonas aeruginosa	9027
Candida albicans	10231
Aspergillus brasiliensis	16404
* ATCC: American Type Culture Collection.	

the GD system count and the mean of the analyst count can then be directly compared.

The accuracy and precision of the method is determined using six replicates for each of the organisms of choice, run in three independent tests (**Table 3**). For the control, a parallel run is also performed using the standard in-house method. Incubation was for 5 days at 30–35°C.

System count accuracy

The results for the enumeration accuracy are listed in **Table 4** and the correlation shown in **Figure 1**. A very good correlation is seen on the 1:1 line between the manual and system count for the test organisms that grow to a discrete colony shape that is easy to count. For the spreading organisms, *A. brasiliensis* and *B. subtilis*, the difference in counts is seen with the GD system giving higher CFU counts. The graph also shows the 1 standard deviation bars around the operator visual counts that are wide due to the variability in accurately counting merging colonies. The accuracy of the GD system was verified by interrogating the image series created at 4-hour intervals for each plate and visually verifying that each colony detected by the system was in fact a discrete entity. Using lower spike numbers and counting earlier in the incubation period would help improve the accuracy of the human read.

Method accuracy

The results for the test methods, plate count and GD are shown in **Table 5**. The mean CFU count for each series of six replicates was calculated and the percentage recovery determined and then compared to the control method. The acceptance criteria were set to a recovery of ≥70%. All organisms passed recovery testing.

Precision

Precision estimates are usually stated as a standard deviation or a coefficient of variation (CV) and the % CV are listed in **Table 6**. All the CVs were well below the benchmark of 35% as described in TR33; however, six of the GD and nine of the plate count sets failed the specification of ≤15% stated in USP 12234 and Ph. Eur. 5.1.6[5] with the maximum CV at 27%. Due to the well-known difficulty of obtaining a homogenous distribution of microorganisms in a test sample, it is not surprising that some tests failed the 15% CV value. However, as both the compendial and the GD methods show similar

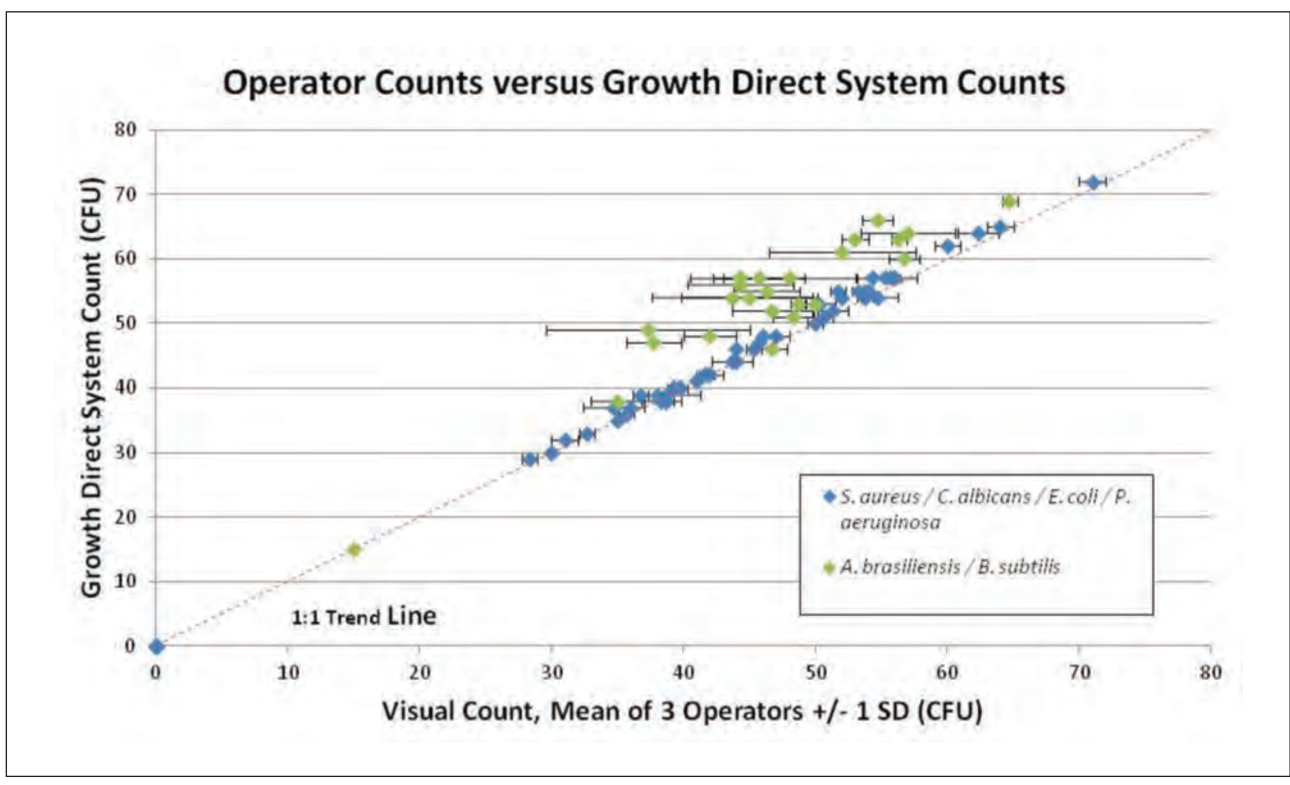

Figure 1. Correlation of system CFU counts compared to the mean CFU count and standard deviation of three analysts on the same cassette.

Table 4. Accuracy and precision raw data.

Method	Operator	Replicate	*B. subtilis* CFU	*S. aureus* CFU	*A. brasiliensis* CFU	*P. aeruginosa* CFU	*C. albicans* CFU	*E. coli* CFU
GD	1	1	53	57	54	29	40	37
GD	1	2	38	48	49	33	40	42
GD	1	3	61	64	54	39	57	55
GD	1	4	60	51	52	37	44	57
GD	1	5	55	55	57	32	57	54
GD	1	6	56	57	57	36	52	35
GD	2	1	56	58	56	33	42	42
GD	2	2	56	40	60	39	39	56
GD	2	3	47	53	57	39	56	47
GD	2	4	64	56	67	34	57	54
GD	2	5	66	50	43	36	44	48
GD	2	6	65	42	49	46	50	50
GD	3	1	69	58	81	41	65	53
GD	3	2	57	73	85	34	46	62
GD	3	3	56	61	84	34	48	61
GD	3	4	50	60	72	38	50	43
GD	3	5	54	55	78	30	53	54
GD	3	6	62	63	60	46	52	49
GD	4	1	63	55	51	30	44	47
GD	4	2	63	72	57	30	55	50
GD	4	3	69	54	46	42	55	38
GD	4	4	66	54	64	39	48	45
GD	4	5	53	46	48	46	53	41
GD	4	6	51	65	47	38	39	62
PC	1	1	56.0	61.3	52.7	47.3	48.0	47.0
PC	1	2	51.0	48.0	55.3	43.0	29.0	55.0
PC	1	3	44.0	45.0	42.7	32.0	35.0	56.0
PC	1	4	48.0	52.7	57.0	44.0	52.7	50.0
PC	1	5	34.0	50.0	50.0	42.7	44.0	50.3
PC	1	6	60.0	47.3	67.3	28.7	53.3	50.3
PC	2	1	59.0	49.7	54.0	37.0	50.7	43.3
PC	2	2	63.0	40.0	54.0	30.7	36.3	49.7
PC	2	3	52.3	39.0	43.3	39.0	47.0	52.0
PC	2	4	68.3	38.3	78.7	59.7	52.0	53.0
PC	2	5	44.7	47.0	60.0	32.7	51.0	42.7
PC	2	6	52.0	44.7	62.0	35.0	41.0	44.0
PC	3	1	47.0	56.0	56.7	41.0	53.0	48.3
PC	3	2	72.3	52.0	56.7	42.0	43.0	59.7
PC	3	3	54.3	46.0	62.0	40.3	56.0	53.7
PC	3	4	64.7	67.3	52.0	44.7	57.3	42.0
PC	3	5	60.0	65.7	53.0	47.3	52.6	61.0
PC	3	6	57.3	59.0	49.3	47.7	54.3	44.3
PC	4	1	53.0	51.0	76.7	24.7	45.0	47.7
PC	4	2	54.0	71.7	63.0	40.0	47.3	46.7
PC	4	3	63.3	84.3	66.0	32.3	62.0	43.3
PC	4	4	53.7	53.7	51.6	27.7	57.7	35.3
PC	4	5	60.7	53.0	61.3	29.0	71.3	54.7
PC	4	6	38.7	55.7	65.0	38.7	61.0	49.3

PC: plate count.
Note: the PC data are averages of counts by three operators

Table 5. Accuracy of method.

Operator	GD count	Plate count	% recovery
B. subtilis	53.8	48.8	110.2
	59	56.6	104.2
	58	59.3	97.8
	60.8	53.9	112.8
S. aureus	55.3	50.7	109.1
	49.8	43.1	115.5
	61.7	57.7	106.9
	57.7	61.6	93.7
A. brasiliensis	53.8	54.2	99.3
	55.3	58.7	94.2
	76.7	55	139.5
	52.2	63.9	81.7
P. aeruginosa	34.3	39.6	86.6
	37.8	39	96.9
	37.2	43.8	84.9
	37.5	32.1	116.8
C. albicans	48.3	43.7	110.5
	48	46.3	103.7
	52.3	52.7	99.2
	49	57.4	85.4
E. coli	46.7	51.4	90.9
	49.5	47.5	104.2
	53.7	51.5	104.3
	47.2	46.2	102.2

numbers of excursions, there is no evidence that one is better or worse than the other.

An alternative recommended test is the F-test used to compare the repeatability variances of both test methods in **Table 6**. No significant difference in repeatability precision between test methods was found for any of the six microorganisms. The p-values were calculated by means of the FDIST function in Excel using the variance ratio and the degrees of freedom for each variance as entries for the FDIST function (*PDA J Pharm Sci Technology*, In press).

Time to result qualification

Following confirmation of the efficacy of the performance of the instrument, the time required to confirm a negative result was defined. In order to do this, a TTR qualification was carried out.

The USP <1231> states that plates for water testing should be incubated for between 48 and 72 hours, however, the Ph. Eur. states that this time should be greater than or equal to 5 days at 30–35°C, therefore, these timings should form the basis for the TTR qualification.

A broad range of pharmacopeial organisms, environmental isolates and contaminated water samples were used, including stressed samples, e.g. stressed by temperature, pH, etc. Each analysed sample consisted of 5–150 CFU of the test organism for each test. The test samples were repeated in triplicate using both GD R2A cassettes and traditional R2A Petri plates.

The Petri plates were read at 7 days per standard operating procedure, GD cassettes were incubated for up

Table 6. Precision: summary statistics by method, operator and microorganism (six replicates).

Method	Operator	Average (CFU)					
		B. subtilis	*S. aureus*	*A. brasiliensis*	*P. aeruginosa*	*C. albicans*	*E. coli*
GD	1	53.8	55.3	53.8	34.3	48.3	46.7
GD	2	59.0	49.8	55.3	37.8	48.0	49.5
GD	3	58.0	61.7	76.7	37.2	52.3	53.7
GD	4	60.8	57.7	52.2	37.5	49.0	47.2
PC	1	48.8	50.7	54.2	39.6	43.7	51.4
PC	2	56.6	43.1	58.7	39.0	46.3	47.5
PC	3	59.3	57.7	55.0	43.8	52.7	51.5
PC	4	53.9	61.6	63.9	32.1	57.4	46.2
Method	**Operator**	**Coefficient of variation (%)**					
		B. subtilis	*S. aureus*	*A. brasiliensis*	*P. aeruginosa*	*C. albicans*	*E. coli*
GD	1	15	10	6	11	17	21
GD	2	13	15	15	12	16	10
GD	3	11	10	12	15	13	13
GD	4	12	16	13	17	13	18
PC	1	19	11	15	19	23	7
PC	2	15	11	20	27	14	10
PC	3	15	14	8	7	10	15
PC	4	16	22	13	19	17	14

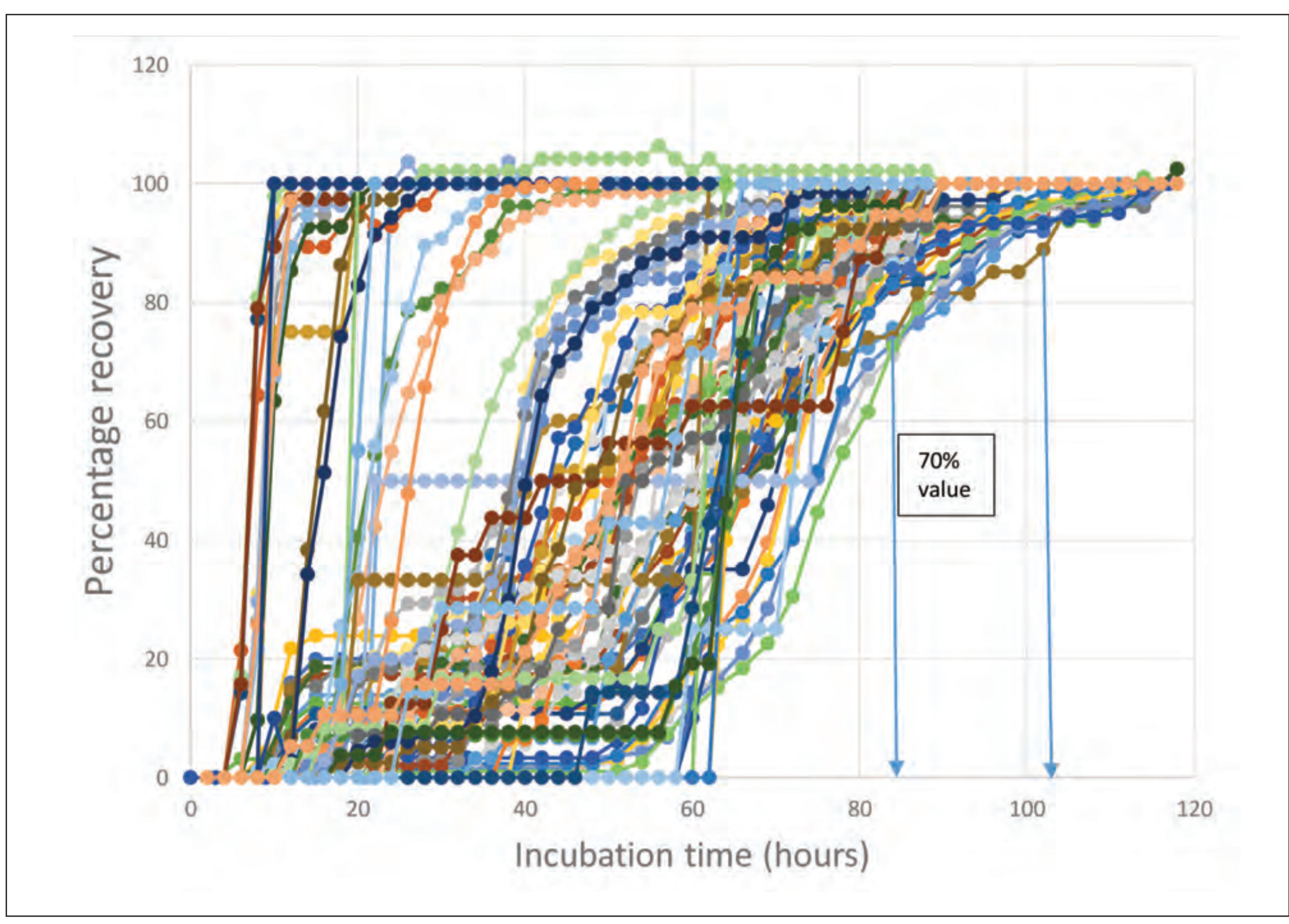

Figure 2. Estimation of TTR from all test samples run on the GD system. Each line represents the colony detection curves for each individual test sample expressed as a percentage of the control count for the same sample.

to 5 days. The colony detection profiles from the GD system were downloaded and analysed as the percentage recovery compared to the control method. The TTR can, therefore, be considered as the point at which the recovery is greater than 70% of the manual reference method. For the test samples in the study, the TTR determined to be 84 hours as shown in **Figure 2**. The data demonstrates that in the natural flora present in the water samples, there were a spectrum of organisms that had lag times ranging from 6 to 60 hours.

To add extra confidence, a later time point was taken and 96 hours was selected for the GD system TTR. This time gives equivalent results in approximately 60% of the traditional method incubation time.

Method suitability

Method suitability was performed as described in Ph. Eur. 2.6.12[6] and USP chapters <61>[7] and <1227>[8]. The testing can be split into two separate procedures when considering water testing, growth promotion verification and equivalence verification.

Growth promotion verification

Growth promotion verification was performed by inoculating water samples characteristic of the testing sites in their testing volume of 1 or 200 mL with USP/Ph. Eur. organisms and specific local environmental isolates at <100 CFU. The strains were filtered by the GD method and the traditional method, membranes placed on the appropriate R2A agar cassette or Petri plate, and incubated at 30–35°C for 96 hours on the GD system and 7 days for the control method. At the end of incubation, the CFU counts were collected and the percentage recovery calculated for the GD system result versus the traditional method. Acceptable recovery of the inoculated organisms on the GD of 70% or greater mean CFU of that obtained by the compendia method was exhibited for each test strain (see **Figure 3**).

Equivalence verification

In the last stage of validation, actual water sample testing was performed side by side between the GD system versus the manual method. Ten test sites were sampled at least 20 times to give at least 200 results. The test method was the same as described in the Growth Promotion section. Acceptance was deemed to be 50% to 200% recovery of the control media as defined in Ph. Eur. 2.6.12, total viable aerobic count where a factor >2 is defined.

For the water site shown (**Figure 4**), the agreement between CFU levels and trend detection was excellent with all GD results >50% of the side-by side control. Nine other sample sites were followed for 20 days and all exhibited equivalent detection between the two methods at 96 hours final incubation for the GD.

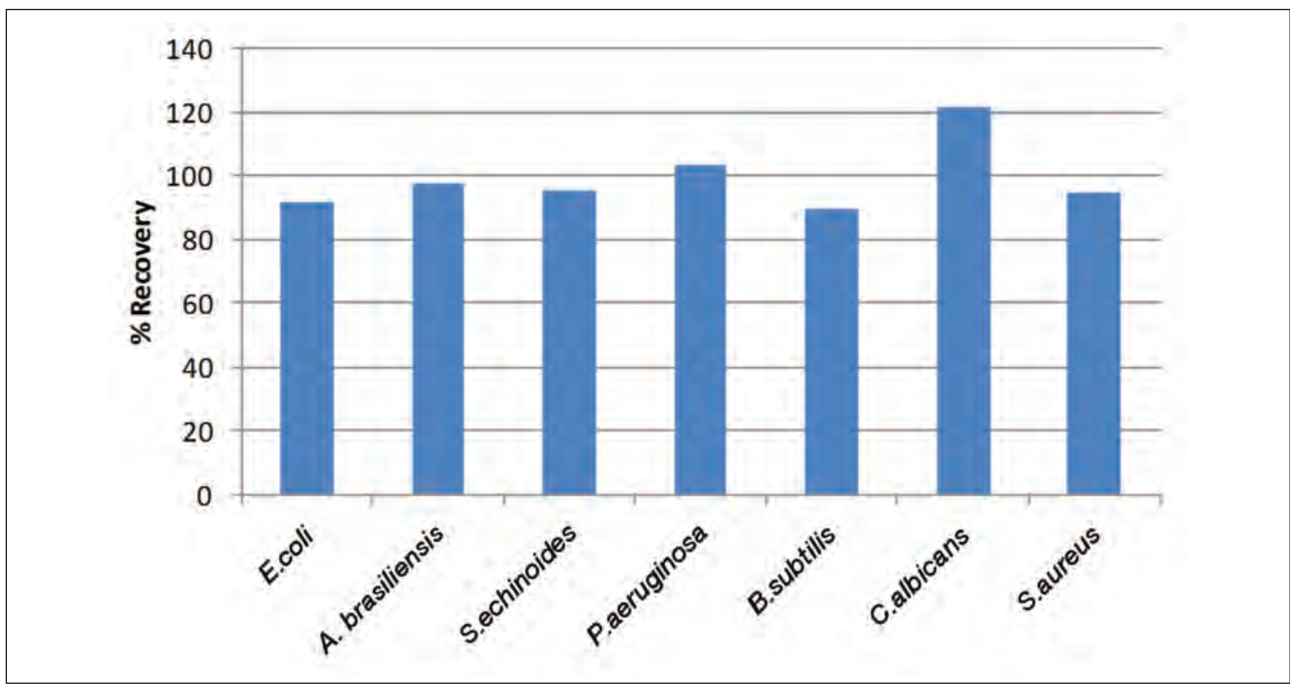

Figure 3. Growth promotion of inoculated organisms on the GD system versus the compendial method show comparable results. Data shows the percentage recovery of the GD method compared to the traditional method.

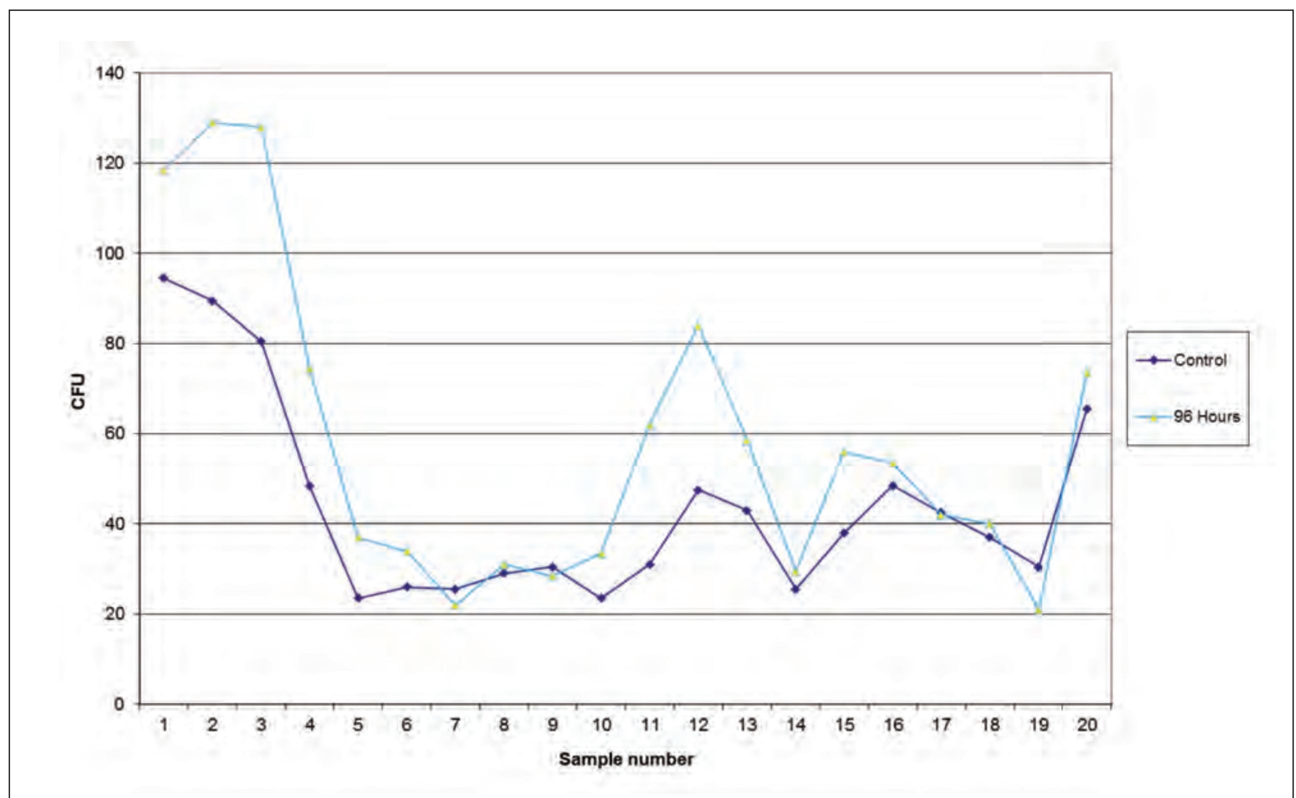

Figure 4. Water trending for a reverse osmosis sample site. CFU/200mL water sample size using the control method at 7 days and the GD method at 96 hours end point.

Discussion

The paper introduces the validation strategy for the GD system, an automated colony counter, for the analysis of water samples in a pharmaceutical environment. As the system is based on the compendial test method for water, the validation focuses primarily on those components that are different, e.g. the colony detection and enumeration algorithms and the automated incubation step. For the verification of the method, a simple approach to test the accuracy and precision of the method was chosen as

suggested in the current PDA TR33 document.

The data show that the camera detection and associated algorithms accurately enumerate the microorganism colonies on the membrane surface and that the R2A media recovers organisms from both standard diluents and real world samples at equivalent levels to the standard method. The precision of the enumeration method is equivalent to or better than that seen with the traditional method.

With the GD system, a faster result can be obtained by 96 hours rather than the 7 days used in the traditional in-house method at the site. If the action level were 1 CFU, then detection of an issue could be determined in <60 hours and would be flagged by the system to the analyst.

In summary, the GD system has used a proven validation strategy that uses a minimal validation approach following the process defined in the PDA TR33 report.

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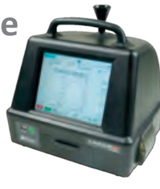
Monitoring
Lasair III



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