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APPLICATION NOTE

REAL-TIME DETECTION OF CFU GROWTH WITH THE SCANSTATION® SMART INCUBATOR EXPEDITES THE ENVIRONMENTAL MONITORING PROCESS

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Unit: ScanStation® - Software version:1.30

Introduction

In a time when an increasing number of laboratories are turning to rapid methods for their analysis, the responsibility is often on the end-user to validate an alternative method (eg. PCR, mass spectrometry) against the traditional, manually counted sample-on-agar cultures. INTERSCIENCE developed the ScanStation® (ISS) in the aim of providing advanced results, while still utilizing the traditional method (approved by the European Pharmacopoeia and the FDA). This system is an innovation based on the technology of end-point colony counters that have been used in

labs for over forty years[1,2]. By placing such a device inside of the incubation chamber, and automating the reading process, the culture growth monitoring in real time is now possible.

The ScanStation® collects images of each sample every 30 or 60 minutes during the whole duration of the incubation period. Those images, once analyzed by the monitoring software, are used to display a curve of the bacterial growth kinetics, available to the user in real-time. An example of this reporting is presented in **Figure 0**.
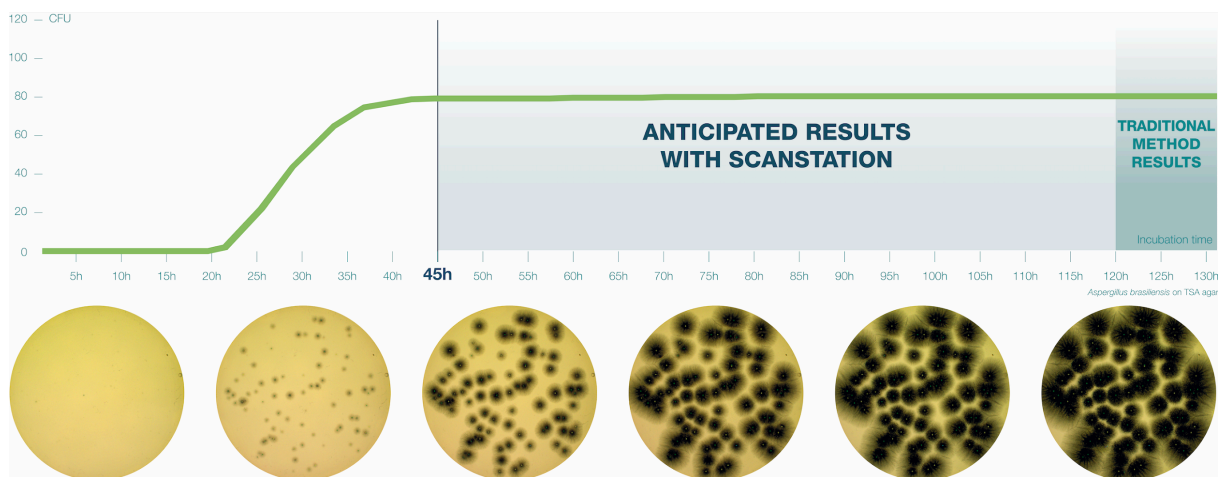

Figure 0: Example of report for A. brasiliensis on TCA medium by the ScanStation®. Above - growth curve established by CFU count in real time. Below - six pictures taken at different intervals of the 130-hour incubation period.

Real-time monitoring of bacterial and fungal growth affords a number of advantages beyond the advanced detection of colonies: switching from end-point to real time counting also increases the accuracy of the enumeration.

Firstly, the use of a "T0" image captured at the beginning of the incubation and effectively used as a "tare" for all subsequent counts reduces the number of false positives in case of debris/particles in the matrix, or writings on

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the plate, which are often falsely counted as CFUs during end-point enumeration (manual or automatic). Secondly, the detection and marking of colonies as soon as they appear on the Petri dish means that subsequent overgrowth or confluent growth are less likely to lead to false negatives.

The aim of this study is three-fold. First, we wish to assess the performance of the ISS by comparing the real manual with the automatic enumeration of pure cultures of the five organisms commonly tested for environmental monitoring in the pharmaceutical sector (*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans* and *Aspergillus brasiliensis*). Here it is important to note that, in order to avoid any inter- and intra-operator variation, which is very common with end-point counting[3,4], we are comparing the automatic ISS counts to a manual count based not on the traditional reading of the plates at the end of the incubation, but rather on the timelapse created by all the images collected during incubation. In a similar fashion as with replay footage in sports, the operator has access to a "back in time" function that should allow them to avoid any false positives and negatives. We will call this measure "true count".

Second, we also sought to model the "Time to Result" for these five of the pharmacopeial test strains, as defined as the duration of incubation at which the ISS can provide a stable and reliable Colony Forming Unit (CFU) count for 85% of the samples of each strain.

Third, we tested the ISS performance in real condition by performing air environmental monitoring. The correlation of the automatic count and true count, and the ''Time to Result'' were also analyzed for this purpose.

Methods

Context

The following five organisms commonly tested for environmental monitoring in the pharmaceutical sector were selected and studied at the INTERSCIENCE factory site, for a total of 114 samples:

- *Staphylococcus aureus* (ATCC 6538)

- *Escherichia coli* (ATCC 8739)

- *Pseudomonas aeruginosa* (ATCC 9027)

- *Candida albicans* (ATCC 10231)

- *Aspergillus brasiliensis* (ATCC 16404)

Protocol

Inoculation of samples

90 mm TSA plates: 100µL of *S. aureus, P. aeruginosa*, *C. albicans* and *A. brasiliensis* suspension were inoculated on a standard 90mm Petri dishes pre-filled with Tryptic Soy Agar (TSA) with an automatic spread plater and loaded them in the ScanStation® to start incubation.

Contact plates: 100µL of *E. coli* suspension was inoculated on 60 mm contact plates pre-filled with tryptic soy agar with an automatic spread plater and loaded in the ScanStation® to start incubation.

For the air environmental monitoring, 122 Petri dishes from different pharmaceutical industry laboratories were collected after inoculation of microorganisms present in the atmosphere by a passive sedimentation or using air sampler. These plates were incubated in the ScanStation® at 30-35°C for bacterial enumeration and then at 20-25°C for yeasts and molds for a total incubation time of 5 to 7 days.

Incubation

All the samples for each strain were incubated at the temperature and for the time listed in the table below:

Strain	Temperature (°C)	Time (days)
S. aureus	30-35	5
E. coli	30-35	5
P. aeruginosa	30-35	5
C. albicans	20-25	5
A. brasiliensis	20-25	5

During these five days, the Petri dish of each sample was taken in photo every 30 minutes. These images were then processed by the ScanStation® software version v1.30, which detected the apparition time of each colony and yielded a kinetics curve for each sample.

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Results

1. Manual vs. ScanStation® enumeration comparison

The following tables show the automatic and true count readings of the five pharmacopeial test strain colonies after growth. The manual readings were performed by manually counting CFUs on the unmarked timelapse of the growth as they appeared, therefore improving upon traditional end-point manual counting. Indeed, possible colonies hidden by an overlap in growth could be missed during classical readings on the Petri dish. This is the reason why the manual readings are qualified as "true count" in this study. All reading values are reported in the counted Colony Forming Unit (CFU) log. The difference between the automatic and real manual readings has been calculated and the average and the standard deviation per strain are given as follows:

Sample number	Enumeration (CFU log)		Difference (absolute value)
	TC	ISS	
2258	1.66	1.66	0,00
2259	1.54	1.53	0.01
2260	1.63	1.62	0.01
2261	1.61	1.62	0.01
2262	1.69	1.68	0.01
2263	1.59	1.56	0.03
2264	1.74	1.74	0,00
2265	1.75	1.74	0.01
2266	1.71	1.71	0,00
2267	1.65	1.62	0.03
2282	1.59	1.60	0.01
2283	1.60	1.62	0.02
2294	1.69	1.70	0.01
2295	1.68	1.69	0.01
2300	1.60	1.60	0,00
2301	1.71	1.72	0.01
2302	1.62	1.61	0.01
2303	1.62	1.65	0.03
2373	1.00	1.00	0,00
2374	0.78	0.78	0,00
2375	0.30	0.30	0,00
2376	1.08	1.04	0.04
2377	0.85	0.85	0,00

Sample number	Enumeration (CFU log)		Difference (absolute value)
	TC	ISS	
2378	0.85	0.85	0,00
2380	0.60	0.70	0.10
2381	0.60	0.60	0,00
2393	0.90	0.90	0,00
2394	1.04	1.04	0,00
2395	1.00	1.00	0,00
2396	0.90	0.90	0,00
2397	1.18	1.18	0,00
2398	0.70	0.70	0,00
3334	1.97	1.93	0.04
3335	2.01	1.95	0.05
3336	1.83	1.79	0.05
3337	1.87	1.80	0.07
3545	1.88	1.88	0,00
3546	1.83	1.83	0.01
3547	2.05	2.03	0.02
3548	2.07	2.06	0,00
3549	2.27	2.25	0.01
3562	1.68	1.67	0.01
3563	1.80	1.76	0.04
3564	2.13	2.10	0.04
3565	2.06	2.05	0.02
3566	2.13	2.17	0.03
3567	2.26	2.26	0,00
Average calculated difference			0.02
Standard deviation			0.02

Table 1: True count (TC) and automatic (ISS) comparison of *S. aureus*

Sample number	Enumeration (CFU log)		Difference (absolute value)
	TC	ISS	
2248	1.43	1.43	0.00
2249	1.52	1.52	0.00
2250	1.76	1.73	0.02
2251	1.65	1.65	0.00
2252	1.60	1.57	0.03
2253	1.76	1.76	0.01
2254	1.70	1.68	0.02
2255	1.69	1.69	0.00
2256	1.48	1.46	0.01
2257	1.67	1.64	0.03

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Sample number	Enumeration (CFU log)		Difference (absolute value)
	TC	ISS	
3472	2.23	2.20	0.03
3473	2.20	2.16	0.03
Average calculated difference			0.02
Standard deviation			0.01

Table 2: True count (TC) and automatic (ISS) comparison of *E. coli*

Sample number	Enumeration (CFU log)		Difference (absolute value)
	TC	ISS	
3460	2.28	2.06	0.22
3461	2.23	2.12	0.10
3462	2.00	1.88	0.12
3463	1.93	1.83	0.10
3556	1.94	1.81	0.13
3557	1.79	1.88	0.08
3559	2.29	2.09	0.21
3560	2.5	2.27	0.23
3561	2.48	2.24	0.24
8218	1.00	1.00	0.00
8219	0.95	1.00	0.05
8220	0.95	0.95	0.00
8221	1.04	1.04	0.00
8222	0.85	0.85	0.00
8223	1.00	1.00	0.00
8224	0.9	0.9	0.00
8225	0.78	0.7	0.08
8226	1.18	1.00	0.18
8227	0.9	0.85	0.06
8228	0.9	0.85	0.06
8229	0.95	0.95	0.00
8230	1.08	0.95	0.12
8231	1.11	1.00	0.11
Average calculated difference			0.09
Standard deviation			0.08

Table 3: True count (TC) and automatic (ISS) comparison of *P. aeruginosa*

Sample number	Enumeration (CFU log)		Difference (absolute value)
	TC	ISS	
3410	2.20	2.18	0.02
3411	2.38	2.33	0.05

Sample number	Enumeration (CFU log)		Difference (absolute value)
	TC	ISS	
3412	2.17	2.11	0.05
3413	2.12	1.99	0.13
8238	1.11	1.11	0.00
8239	0.78	0.78	0.00
8240	1.08	1.08	0.00
8241	1.15	1.15	0.00
8242	1.00	1.00	0.00
8243	1.08	1.08	0.00
8244	1.04	1.04	0.00
8245	1.04	1.04	0.00
8246	0.95	1.00	0.05
8247	1.00	0.95	0.05
8248	1.04	1.08	0.04
8249	0.78	0.85	0.07
8250	1.04	1.00	0.04
8251	1.00	1.00	0.00
Average calculated difference			0.03
Standard deviation			0.03

Table 4: True count (TC) and automatic (ISS) comparison of *C. albicans*

Sample number	Enumeration (CFU log)		Difference (absolute value)
	TC	ISS	
8258	1.00	1,00	0,00
8259	1.04	1.11	0.07
8260	0.78	0.78	0,00
8261	0.78	0.78	0,00
8262	1.11	1.11	0,00
8263	1.04	1.08	0.04
8264	1.18	1.18	0,00
8265	0.90	0.90	0,00
8266	0.78	0.78	0,00
8267	0.60	0.70	0.10
8268	0.78	0.90	0.12
8269	0.95	1,00	0.05
8270	0.48	0.30	0.18
8271	1.00	1.04	0.04
Average calculated difference			0.04
Standard deviation			0.06

Table 5: True count (TC) and automatic (ISS) comparison of *A. brasiliensis*

The calculated difference for all of the samples is close to 0 with a maximum of 0.24 and with a total average of all calculated differences equal to 0.04 and a standard deviation equal to 0.05. These results do not show a significant difference between the two enumeration modes. Furthermore, the following graph shows the correlation summarizing all manual and ScanStation® enumerations performed with these five pharmacopeial test strains.
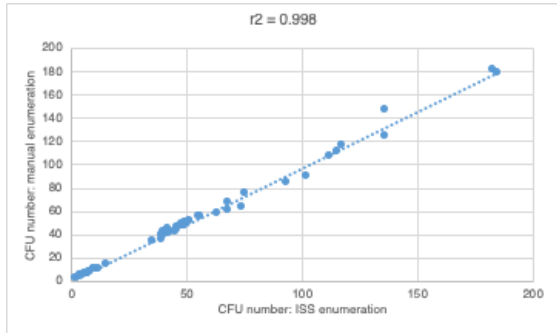

Figure 1: correlation graph of *S. aureus* manual and automatic enumeration
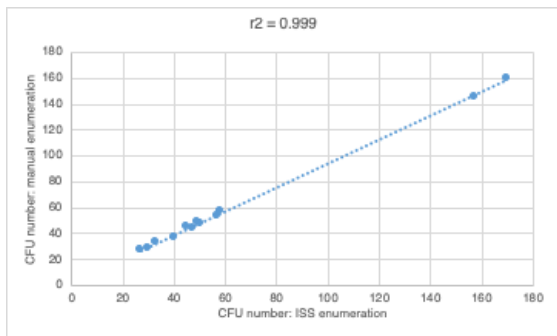
Figure 2: correlation graph of *E. coli* manual and automatic enumeration
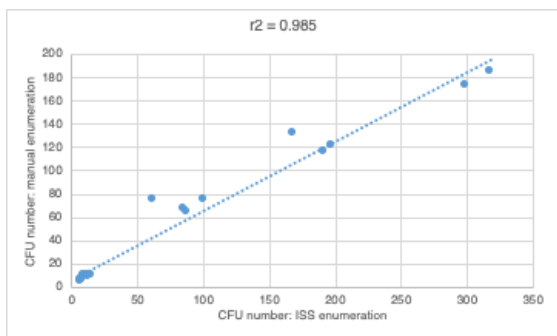
Figure 3: correlation graph of *P. aeruginosa* manual and automatic enumeration
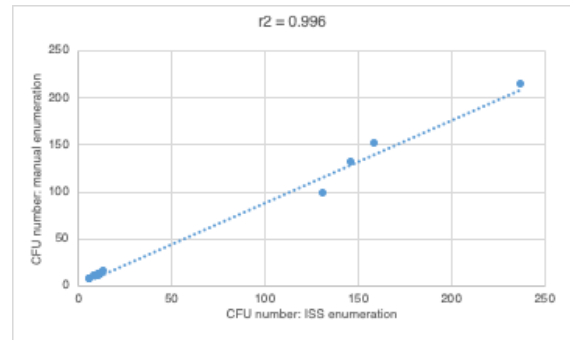
Figure 4: correlation graph of *C. albicans* manual and automatic enumeration
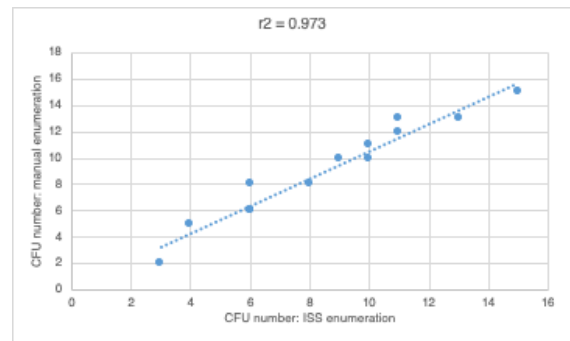
Figure 5: correlation graph of *A. brasiliensis* manual and automatic enumeration

The correlation coefficients R^2 are between 0.973 and 0.999, meaning there is not significant variation between true count and ScanStation® enumeration.

2. Time to Result

The ScanStation® captured an image of each sample every 30 minutes. These images were then processed by the ScanStation® counting software version v1.30, which detected the apparition time of each colony and yielded a kinetics curve for each sample. We aggregated those growth curves for each strain using Excel.

Figures 6 to 10 below show the aggregated growth curves for each of the five organisms tested in this study. The curves were normalized as a percentage of the total count for each sample for comparison purposes.
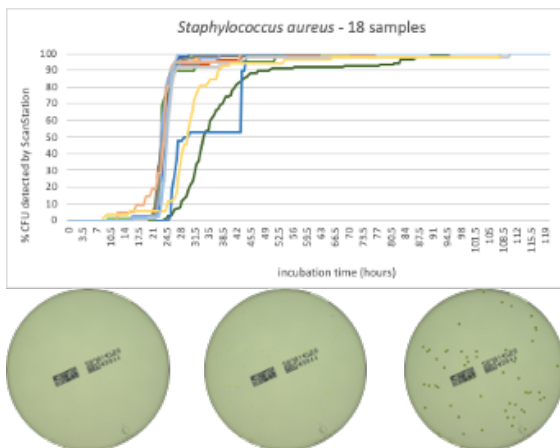
Figure 6: Aggregated growth curves of 18 samples of *S. aureus* and representative photos of real time growth of the sample #2264 at t = 0, t = 12.5 h and t = 21 h.
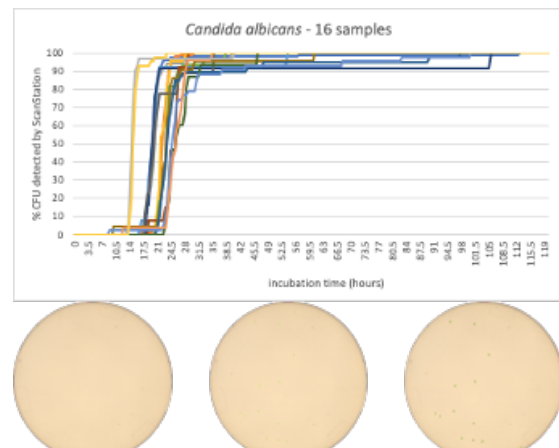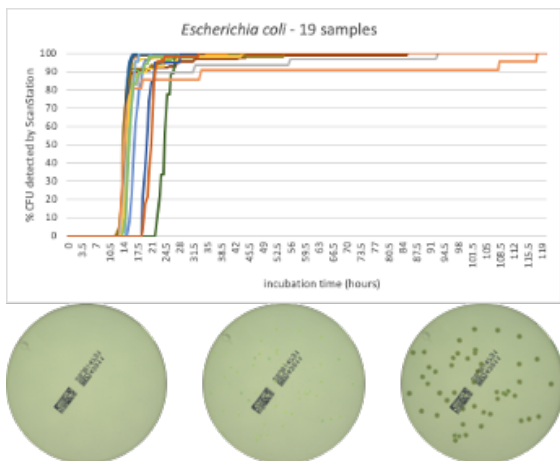

Figure 7: Aggregated growth curves of 19 samples of *E. coli* and representative photos of real time growth of the sample #2255 at t = 0, t = 8 h and t = 15.5 h.

Figure 8: Aggregated growth curves of 17 samples of *P. aeruginosa* and representative photos of real time growth of the sample #8221 at t = 0, t = 6 h and t = 12 h.

Figure 9: Aggregated growth curves of 16 samples of *C. albicans* and representative photos of real time growth of the sample #8241 at t = 0, t = 9 h and t = 12 h.
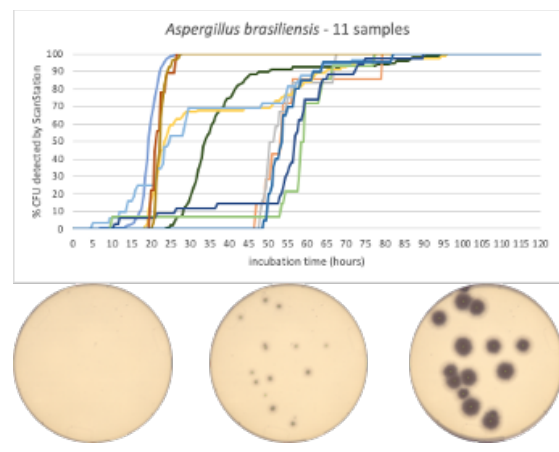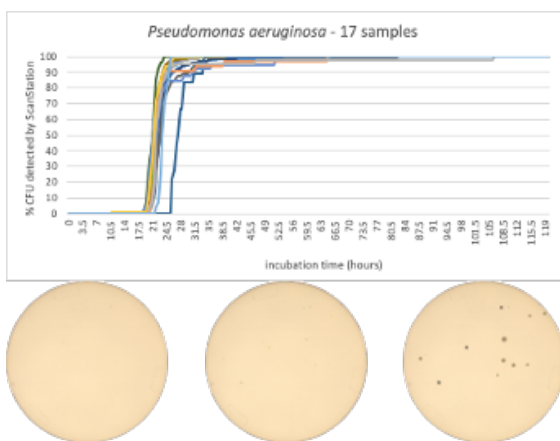

Figure 10: Aggregated growth curves of 11 samples of *A. brasiliensis* and representative photos of real time growth of the sample #8264 at t = 0, t = 16.5 h and t = 22.5 h.

Switching to real-time analysis of bacterial growth means that the user can anticipate the total number of Colony Forming Units (CFUs) on a Petri dish as soon as the growth curve has reached a plateau. In our study, we compared the early detection mean (defined as the incubation time when 85% of samples give a stable and accurate CFU count) to the classical 3 to 5 days (72 - 120 hours) recommended for environmental monitoring in the pharmaceutical industry[5], where the CFU number is recorded at the end of the incubation. We conservatively compared each of these early detection means to a 3-day and a 5-day incubation and found that real-time analysis with the ScanStation® could save 67% to 88% of incubation time compared to end-point reading. These results are detailed in **Figure 11**.
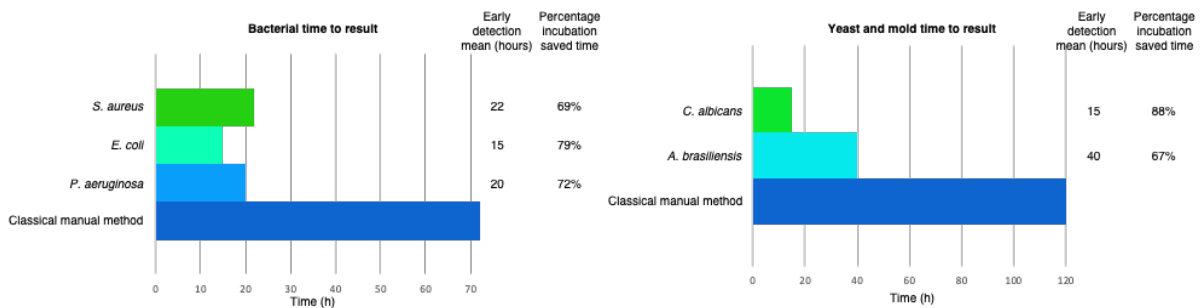
Figure 11: Early detection means (85% of samples at 100% of total CFU count) compared to end point reading at 72 hours (3 days) for the bacteria and at 120 hours (5 days) for the yeast and mold. Incubation time savings range from 67% for *A. basiliensis* to 88% *for C. albicans*.

3. ScanStation® performance evaluation in real environmental monitoring condition

3.1. Manual vs. ScanStation® enumeration comparison

The same method than for the pure culture enumerations presented in paragraph 1 was used for the enumeration comparison of the environmental monitoring by air sedimentation or by air sampler on Petri dishes. The following table shows the automatic and true count readings of the 122 Petri dishes after microbial growth. The difference between the automatic and real manual readings has been calculated and the average and the standard deviation are given as follows:

Sample number	Enumeration (CFU log)		Difference (absolute value)
	TC	ISS	
3170	1.38	1.38	0.00
3171	1.30	1.18	0.12
3172	1.59	1.57	0.02
3173	1.49	1.46	0.03
3174	1.59	1.54	0.05
3175	1.41	1.41	0.00
3176	1.45	1.45	0.00
3177	1.67	1.69	0.02
3178	1.79	1.74	0.05
3179	1.64	1.66	0.02
3180	1.76	1.72	0.04
3181	1.72	1.70	0.03
3183	1.52	1.51	0.01
3184	1.63	1.57	0.07
3191	1.32	1.38	0.06
3192	1.48	1.48	0.00
3193	1.32	1.36	0.04

Sample number	Enumeration (CFU log)		Difference (absolute value)
	TC	ISS	
3194	1.48	1.48	0.00
3195	1.57	1.46	0.11
3196	1.67	1.64	0.03
3198	1.46	1.41	0.05
3200	1.67	1.67	0.00
3201	1.61	1.59	0.02
3202	1.71	1.69	0.02
3204	1.66	1.62	0.04
3207	1.70	1.66	0.04
3208	1.20	1.20	0.00
3209	1.54	1.58	0.04
3210	1.48	1.40	0.08
3211	1.46	1.40	0.06
3212	1.48	1.46	0.01
3213	1.51	1.48	0.03
3218	1.66	1.67	0.01
3219	1.59	1.65	0.06
3223	1.70	1.66	0.04
3224	1.53	1.51	0.03
3226	1.54	1.51	0.04
3227	1.62	1.61	0.01
3228	1.63	1.61	0.02
3230	1.38	1.40	0.02
3231	1.40	1.36	0.04
3232	1.62	1.57	0.06
3233	1.60	1.52	0.08
3234	1.58	1.54	0.04
3235	1.43	1.40	0.03
3236	1.43	1.48	0.05

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Sample number	Enumeration (CFU log)		Difference (absolute value)
	TC	ISS	
3238	1.49	1.43	0.06
3239	1.45	1.45	0.00
3240	1.49	1.52	0.03
3241	1.20	1.15	0.06
3242	1.46	1.32	0.14
3243	1.54	1.46	0.08
3244	1.61	1.62	0.01
3245	1.51	1.52	0.01
3246	1.52	1.48	0.04
3249	1.68	1.62	0.06
3250	1.52	1.51	0.01
3251	1.56	1.54	0.01
3252	1.41	1.40	0.02
3253	1.58	1.51	0.07
3254	1.57	1.57	0.00
3256	1.46	1.43	0.03
3258	1.41	1.51	0.09
3259	1.56	1.51	0.05
3260	1.41	1.40	0.02
3261	1.36	1.30	0.06
3262	1.28	1.28	0.00
3264	1.49	1.45	0.04
3265	1.23	1.23	0.00
3266	1.49	1.45	0.04
3267	1.60	1.59	0.01
3268	1.68	1.70	0.02
3269	1.63	1.60	0.03
3895	1.62	1.61	0.01
3896	2.36	2.38	0.02
3897	1.70	1.70	0.00
3898	1.95	1.96	0.01
3899	1.81	1.81	0.01
3900	2.05	2.12	0.08
3902	1.76	1.77	0.01
3906	1.76	1.76	0.00
3907	1.97	1.96	0.01
3908	1.61	1.61	0.00
3909	1.69	1.72	0.03
3912	1.79	1.78	0.01
3913	1.69	1.68	0.01

Sample number	Enumeration (CFU log)		Difference (absolute value)
	TC	ISS	
3914	1.56	1.56	0.00
3915	1.53	1.51	0.03
3916	1.64	1.65	0.01
4158	0.48	0.48	0.00
4166	0.3	0.30	0.00
4168	0.00	0.00	0.00
4170	0.78	0.78	0.00
4172	0.30	0.48	0.18
4173	0.48	0.48	0.00
4176	0.78	0.78	0.00
4177	0.30	0.30	0.00
4178	1.04	1.00	0.04
4179	0.78	0.90	0.12
4180	0.78	0.70	0.08
4181	0.00	0.30	0.30
4182	0.30	0.30	0.00
4402	0.60	0.70	0.10
4403	1.08	1.00	0.08
4404	0.78	0.90	0.12
9072	1.00	0.95	0.05
9073	1.00	0.90	0.10
9074	0.30	0.30	0.00
9075	0.85	0.90	0.06
9076	0.78	0.78	0.00
9077	1.52	1.52	0.00
9078	0.48	0.48	0.00
9079	0.95	0.95	0.00
9080	1.04	1.04	0.00
9081	1.38	1.40	0.02
9082	2.08	2.07	0.01
9083	1.54	1.54	0.00
9084	1.45	1.43	0.02
9086	0.90	0.90	0.00
9087	1.28	1.26	0.02
9090	0.85	0.85	0.00
9091	0.95	0.95	0.00
Average calculated difference			0.03
Standard deviation			0.04

Table 6: True count (TC) and automatic (ISS) comparison of the air monitoring 122 Petri dishes.

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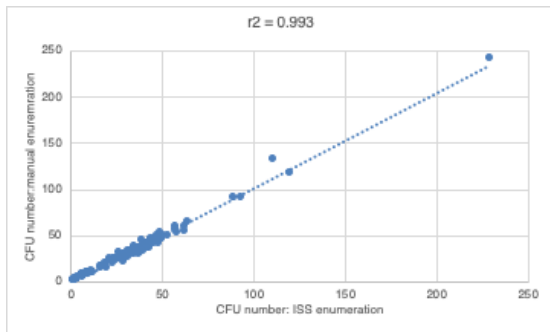

Figure 12: correlation graph of the air monitoring 122 Petri dishes manual and automatic enumeration.

The correlation coefficient R^2 is equal to 0.993, meaning there is not significant variation between true count and ScanStation® enumeration.

3.2. Time to result

The graphs of real time growth have also been performed for each sample. A time to result (TTR) has been implemented when the CFU value reached 85% of the final result.
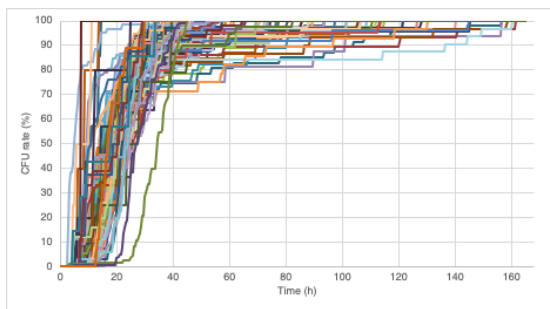
Figure 13: Aggregated growth curves of the 122 Petri dishes air monitoring.

The time of first detection varies from 3h to 16h with an average equal to 8.3 h ± 1.9. Furthermore, the 85% of result is reached after an average time of 35.2 h ± 10.1. This large range of values is explained by the intrinsic conditions of the plated samples. Indeed, these samples were analyzed following real laboratory conditions and therefore suffered from different stress conditions with a different

impact on microbial growth. However, TTR reading still allows a result anticipation and therefore it gives the possibility to the user to define in advance a corrective action, if necessary.

3.3. Representative photos of a real time air monitoring on TSA medium

Example of the sample 3900:

| t=0h | t=7.5h | t=58.5h |
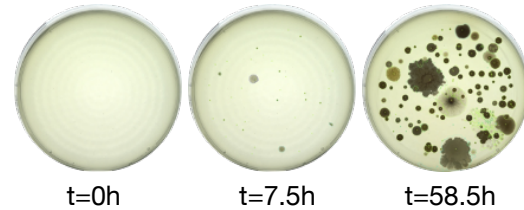
Discussion

The ScanStation® performs the enumeration of a sample by detecting the dynamic formation of each colony. This method yields counts that are as close as possible to the real number of colonies on the plate. Indeed, the possibility to monitor the colony growth in real time prevents the missing of overlapped colonies that would have happened with a classical automatic end-point colony counter, or manually (false negative). Furthermore, the T0 picture of the plate taken as it is loaded into the ScanStation® and before any growth starts is used as a tare reference for the analysis. Therefore, this first picture allows the possibility to remove all initial particles (bubbles in agar, solid fragments from sample…) that could be present on the plate, and to take into account only the dynamic apparition of colonies, thus reducing false positives.

In this study, the "true count" was performed by an operator who analyzed the video generated by the ScanStation® software. In a similar manner to the ScanStation® which prevents false positive or false negative counts better than an end point colony counter, this operator provided count results that are closer to the real colony number than a classical plate reading. This is the reason why the true count was selected as the best method in this study for the comparison of the ScanStation® enumeration performance.

The comparison of ScanStation® and true count enumerations of five of the pharmacopeial test strains shows a strong correlation. Indeed, the correlation coefficient R^2 is very close to 1 for all the five tested strains

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(figures 1 to 5). This result demonstrates that the ScanStation® enumeration method is accurate and reliable. Therefore, the ScanStation® is a relevant equipment which can be integrated in the quality control laboratory of a pharmaceutical production company. Indeed, the raw material and/or the end product control is a critical step of the pharmaceutical production because it ensures the safety and the quality of the medical product as directed by the FDA 21CFR211.84 and ICH Q7[6,7]. The quality control consists in monitoring the microbiological load present in the raw material, and to determine whether the end product falls within a very strict limit for that bacterial load. Thus the ScanStation® can perform this monitoring in real time and if the threshold is reached, an anticipated alert could be engaged, allowing an accurate stock management.

The real time colony growth monitoring by the ScanStation® highlights the three phases of microorganism growth. The first phase is the lag phase where the colonies are not visible yet, followed by the short log phase where the colony number increases rapidly, and finally the stationary phase where no more colony number variation is observed; after that comes the death phase where the number of colonies decreases exponentially[8]. These three first phases are modelized in Figure 0. The pharmacopoeia directives[9] impose a minimum of five days of incubation to give a conform result of microbiological culture. These five days ensure the possibility to reach the stationary phase without missing any colony. The time to result study of five of the pharmacopeial test strains and the air environmental monitoring in the ScanStation® shows that the stationary phase is actually reached a long time before these recommended five days. This result demonstrates that the ScanStation® can be used for environmental monitoring and bioburden analysis to provide, after a validation, an anticipated result confirming that a cleanroom is sterile and fit for pharmaceutical production. Furthermore, in the case of a contamination, the ScanStation® also provides an early detection of the contaminant, giving the opportunity to engage an anticipated alert. Taking the example of *E. coli* performed in this study (figure 9, table 6), the early detection average occurs after 40 hours of incubation. It

means that a contaminant could be detected 105 hours before the classical method recommended by the pharmacopoeia directives. Therefore, if it is necessary, the production could be stopped significatively earlier, which would in turn reduce manufacturing disruption costs[10].

Conclusion

In light of the results discussed in this study, which show a significantly high correlation between the ScanStation® automatic CFU count and the "true count" as verified by a human operator with all the pictures taken during the incubation cycle, we confidently recommend the use of the ScanStation® for environmental monitoring, or bioburden analysis. Furthermore, the Time to Result study gives us insights into the growth kinetics of each of the five main pharmacopeial strains which can be used, if replicated and validated in the lab where it would be intended to be installed, to shorten the detection time for environmental monitoring and therefore reduce production costs in the pharmaceutical industry. The ScanStation® is particularly fit for FDA-regulated laboratories, as the 21CFR part 11-compliant software offers full data integrity and traceability to the user.

On our end, further research is planned to assess the fit of the ScanStation® in other applications such as the Food and Cosmetics industries.

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