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Nuclear Medicine

Spore formers in Clean rooms

Nice to e-meet you

:)

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Isotopia's plant in Soreq-Yavne is a leading production center of a variety of cold kits for nuclear theranostics.

Our Soreq plant:

- Complies with cGMP regulation
- Complies with the Israeli MoH, EMA and FDA guidelines
- Offers comprehensive contract manufacturing services
- When leading companies are our clients, we are assured about the essential role we serve in advancing efficient healthcare.

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Soreq Plant

From new product development
to commercial product supply- World wide

CMO services:

- Qualified teams to support product development and registration processes
- Support the submission process with all necessary documents
- Use state-of-the-art Microbiology and Chemistry labs
- Are tailor-made to customer specifications (you can choose the batch size, packing size, filling volume, etc.)
- Offer advanced analytical testing methods and manufacturing procedures
- Locate reliable suppliers and conduct qualification audits
- Carry out equipment procurement and validation

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Introduction

4.14 Cleanrooms should be supplied with a filtered air supply that maintains a positive pressure and/or an airflow relative to the background environment of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have an air pressure difference of a minimum of 10 Pascals (guidance value). Particular attention should be paid to the protection of the critical zone. The recommendations regarding air supplies and pressures may need to be modified where it is necessary to contain certain materials (e.g. pathogenic, highly toxic or radioactive products or live viral or bacterial materials). The modification may include positively or negatively pressurized airlocks that prevent the hazardous material from contaminating surrounding areas. Decontamination of facilities (e.g. the cleanrooms and the heating, ventilation, and air-conditioning (HVAC) systems) and the treatment of air leaving a clean area, may be necessary for some operations. Where containment requires air to flow into a critical zone, the source of the air should be from an area of the same or higher grade.

Changes in Pressures

Sr.no	Room Name	Room No	Gradeification	Temperature	Relative Humidity	Previous pressure(±5pa)	Changed pressure(±5pa)
1	Autoclave room	#207	Grade D	21±3°C	<60%	15	15
2	Capping Room	#221	Grade D	21±3°C	<60%	27	30
3	Small compounding	#214	Grade B	21±3°C	<60%	60	55
4	Transfer Room	#222	Grade B	21±3°C	<60%	50	50
5	Pass-Through	#205	Grade B	21±3°C	<60%	39	45
6	A.L 2	#219	Grade B	21±3°C	<60%	39	45
7	Corridor	#201	N.C	N/A	N/A	N/A	N/A
8	Clean Corridor	#200	Grade C	21±3°C	<60%	28	30
9	Material Buffer - Oper. Storage	#210	C.N.C	<25	<60%	<5	<5
22	Equipment Washing	#217	Grade C	21±3°C	<60%	15	15
23	Clean tools	#218	Grade C	21±3°C	<60%	15	30
24	Washing Room	#216	Grade C	21±3°C	<60%	15	15
16	Cloak Room Lady	#203	N.C	N.A	N.A	<5	<5
17	Staff Enter Lady	#215	Grade C	21±3°C	<60%	17	25
18	Undress Lady	#203.1	Grade D	21±3°C	<60%	6	10
19	Preparation room LC-101	#208	Grade C	21±3°C	<60%	15	15
20	Weighing	#213	Grade C	21±3°C	<60%	15	15
21	Large Compounding	#212	Grade C	21±3°C	<60%	15	40
22	Equipment Washing	#217	Grade C	21±3°C	<60%	15	15
23	Clean tools	#218	Grade C	21±3°C	<60%	15	30
24	Washing Room	#216	Grade C	21±3°C	<60%	15	15
25	Filling Room	#220	Grade A	21±3°C	<60%	62	60

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The upgrading of HVAC system

- The project of upgrading the HVAC system was performed by BIOPHARMAX.
- After returning from the shutdown, a Performance qualification (PQ) was required.
- The PQ protocol was presented and approved.
- The PQ was performed in three phases and included viable environmental monitoring (contact, active, and passive monitoring), gowning monitoring, and non-viable particle monitoring.

Conclusion

- Biggest investment of ISOTOPIA
- Turnkey project of Biopharmax
- Minimal shutdown of the plant
- Guidance by an internal project manager
- Project meets the planned timeline
- The project was accompanied by the GMP inspectorate department of the Israeli Ministry of Health- managed by Rachel Shimonovich

Phases of performance qualification (PQ)

Pre-Phase: The rooms were cleaned and disinfected for 3 days before the starting of monitoring

Phase I

At rest conditions: Seven consecutive days of sampling, with no additional cleaning or disinfection in between.

Phase II.I- 10 days

In-Operation conditions: Production conditions with equipment running and with the maximum number of operators allowed in each room. The rooms were sampled for 10 days with additional monitoring points.

Phase II.I-20 days

In-Operation conditions: Additional 20 days under working conditions, the sampling was done according to routine monitoring.

Phase III

Routine conditions: From the end of phase II until the end of the calendar 2023 year

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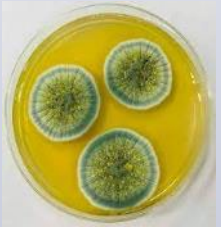
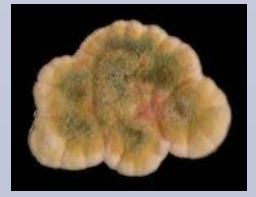
Appearance of spore formers

29.06.23: At Rest, Alert result at active monitoring Grade B: 6 CFU/m3

Penicillium chrysogenum



Aspergillus versicolor

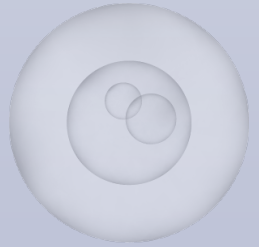


05.07.23: Spore formers started to appear at Grade C during Phase II

Penicillium chrysogenum

23.07.23: Action result at active monitoring Grade C, count of 157 CFU/m3.

Penicillium chrysogenum



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Appearance of spore formers

16.08.23

Ministry of Health Visit

Appearance of spore formers during the PQ monitoring

It was required to investigate every appearance of spore former

New form " Microbiological observations“ was created

August 2023:

Spore formers continue to appear

after Prochlor and Steri-perox 6%

04.09.23 Rooms sanitation using Hydrogen peroxide 6% fogging procedure

11.09.23 HVAC sanitation by quaternium ammonia September 2023

Consultants

08.10.2023 Rooms sanitation by Hydrogen Peroxide and peracetic acid

Filters were changed

Floor sealing

Ceiling sealing

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Conclusion and Corrective Actions

- Every single event of spore formers will be documented at “Microbiological observations”
- Special limits for spore formers

יש לנקוט פעולות ניקוי וחיטוי בחומר ספורוצידי במידה וב-2 תוצאות ניטור עוקבות מתקבלות הופעות חוזרות של זני עובשים או בצילוסים מעל הגבול המוגדר בטבלה מטה:

אזור	Class D	Class C	Class B
גבול מוגדר	במעקב	5 מושבות	2 מושבות

לאחר הניקוי וחיטוי בחומר ספורוצידי יש לבצע 3 ימי דיגום עוקבים, במידה ומתקבלת הופעה חוזרת של זני בצילוס או עובשים, הבטחת איכות תחליט לגבי המשך פעולות.

- In-house fogging machine

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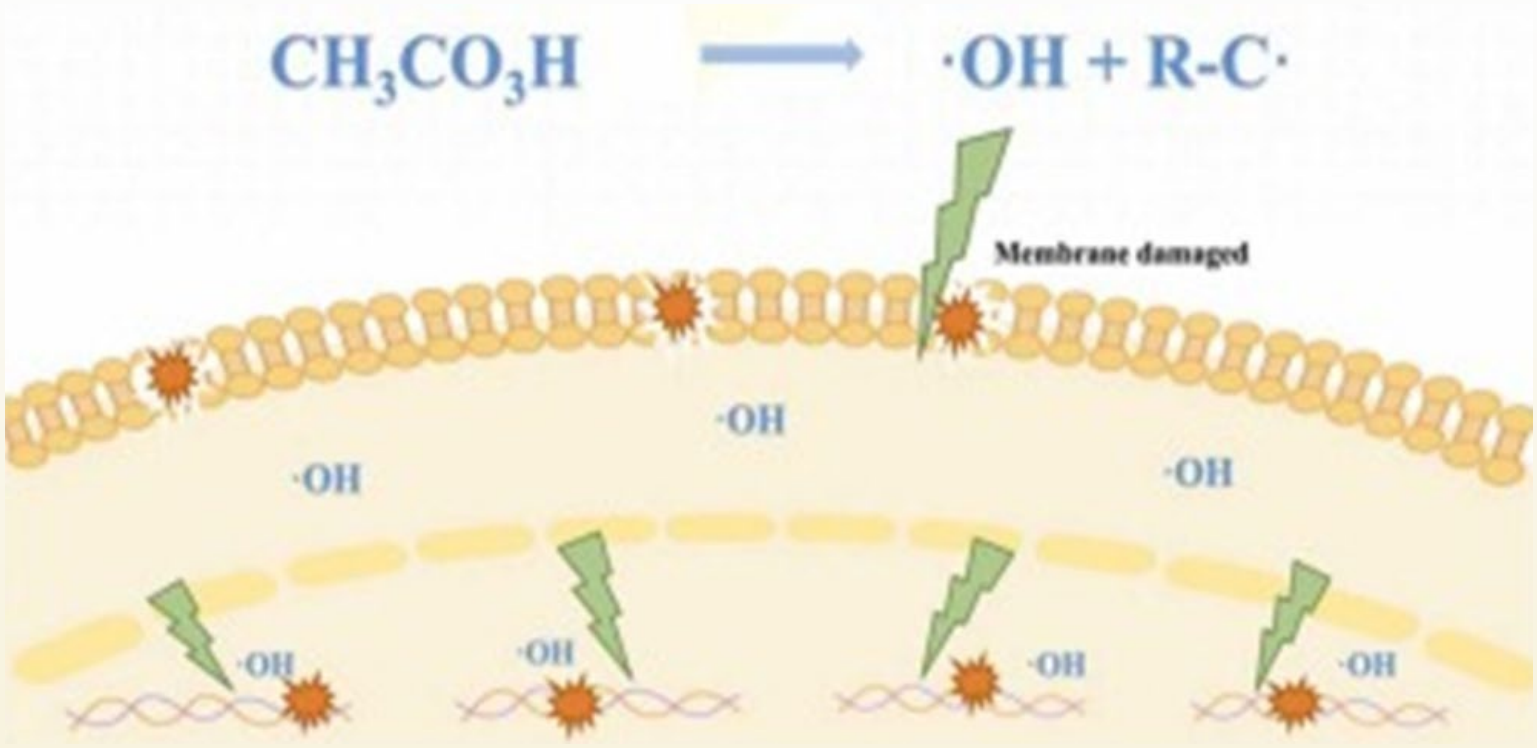
Questions ?

Thank you!

Influence of peracetic acid on Fungi types



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Results after Fogging with peracetic acid

CLASS D						CLASS C										CLASS B						
204/1S SDA-D	204/1S TSA-D	203/1S SDA-D	203/1S TSA	203/1B SDA	203/1B TSA	215/2B SDA	215/2B TSA	200/2B SD	200/2B TSA	200/1B SD	200/1B TSA	212/5B SDA	212/5B TSA	212/2B SD	212/2B TSA	222/3S SD	222/3S TSA	205/1B SD	205/1B TSA	222/2B SD	222/2B TSA	
טיפולב OX 08.10.23																						
												0	נראה בצילום 1	0	נראה בצילום 3	0	0			עובש* 1	0	11.10.23
עובש-1 , 21	עובש-1 , 46	עובש-1 , 2	עובש-1 , 10			0	1	0	0	0	1	1	9	1	מושבות דומות לבצילוס 2-4	0	0	0	0	0	0	12.10.23
דמויי 31	92	עובש 1	23	עובשים 2 , 9	0	עובש 1	עובש-1 , 3	0	עובש, 1	0	עובש, 1	2	7	7	בצילוס- 2 , 18	0	0	0	0	עובש 1	0	15.10.23
עובש 1	21	1	9		0		0		3		1		1		3	0	עובשים 1	עובש 1	עובשים 9	0	0	16.10.23
												0	0	0	1	0	0			0	עובש 1	17.10.23
9	76	0	0		0		0		12		5	0	5	1	7	0	0		0	0	0	18.10.23
עובשים 2 , 47	134	7	עובש 1 , 18		0		0		0		0	1	4	2	38	0	0		0	0	עובש 1	19.10.23
טיפולב OX 19.10.23																						
	עובשים 2 , 30		4		0		0		0		0		3		3		0		0		0	22.10.23

- 08.10.23 fogging sanitation with peracetic acid –InspecOX at rooms 212,222 and 219
- 19.10.23 Repeated fogging sanitation whole site

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Form: Microbiological Observations

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Microbiological observations

Date of sampling	Point	Class	Amount	Type of microorganism (morphology by approximation)	Identification

Reporting to the **production** department ❑

Reporting to the **quality assurance** department ❑

Reporting to the **engineering** department ❑

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Microbiological observations

Investigation of Production department:

	Name	Signature	Date
Written by			
Approved by			

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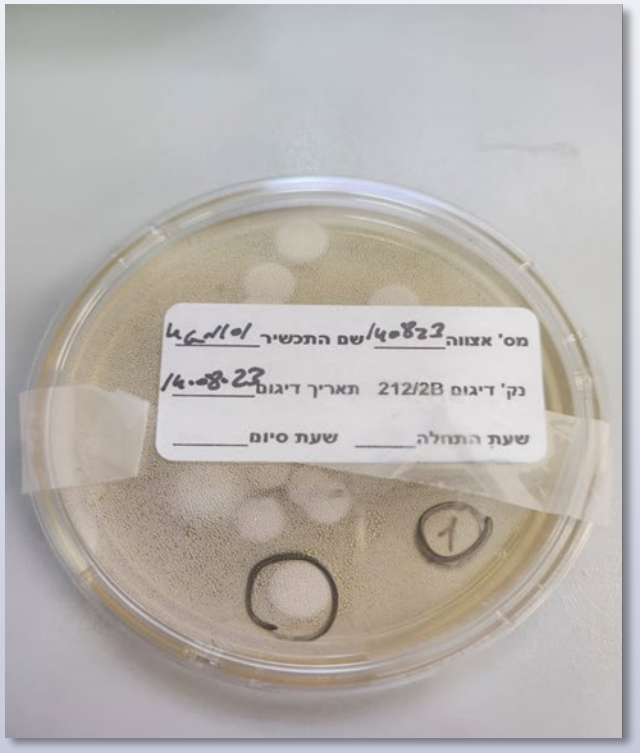
Microbiological observations

Investigation of Production department:

	Name	Signature	Date
Written by			
Approved by			

First Identification by morphology



Penicillium chrysogenum

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August 2023

ACTION	ALERT	212/3S SDA	212/3S TSA	תאריך	TOTAL	ACTION	ALERT	212/5B SDA	212/5B TSA	212/2B SDA	212/2B TSA	
50	25	0	0	01.08.23		100	50			0	1	01.08.23
50	25	0	1	02.08.23		100	50			0	1	02.08.23
50	25	0	0	03.08.23		100	50			0	0	03.08.23
50	25	12	6	06.08.23		100	50			21	20	06.08.23
50	25	1	4	07.08.23		100	50			0	1	07.08.23
50	25			07.08.23		100	50					07.08.23
50	25	0	0	08.08.23		100	50			1	0	08.08.23
50	25	0	0	09.08.23		100	50			0	0	09.08.23
50	25	3	13	10.08.23		100	50			1	8	10.08.23
50	25			10.08.23		100	50					10.08.23
50	25	6	43	13.08.23		100	50			94	TNTC	13.08.23
50	25	12	50	14.08.23		100	50			8	26	14.08.23
50	25	0	0	15.08.23		100	50			0	1	15.08.23
50	25			20.08.23		100	50					20.08.23
50	25			21.08.23		100	50	15	3			21.08.23
50	25	0	1	27.08.23		100	50	0	0	15	13	27.08.23
50	25	0	0	28.08.23		100	50	0	2	0	0	28.08.23
50	25	0	0	29.08.23		100	50	0	5	65	144	29.08.23
50	25	0	5	30.08.23		100	50	4	53	38	46	30.08.23
50	25	0	0	31.08.23		100	50	0	1	0	2	31.08.23

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September 2023

TOTAL	ACTION	ALERT	212/3S SDA	212/3S TSA	תאריך	TOTAL	ACTION	ALERT	212/5B SDA	212/5B TSA	212/2B SDA	212/2B TSA	
	50	25	5	11	06.09.23		100	50	90	180	11	12	06.09.23
	50	25	2	1	07.09.23		100	50					07.09.23
	50	25			11.09.23		100	50					11.09.23
	50	25	0	0	13.09.23		100	50	0	0	0	0	13.09.23
	50	25	0	0	14.09.23		100	50	1	5	6	30	14.09.23
	50	25	0	0	18.09.23		100	50	0	1	0	0	18.09.23
	50	25	מנוחה 4	מנוחה 1	18.09.23		100	50	In o. 43	In o. 67	In o. 105	In o.TNTC	18.09.23
	50	25	In o. 1	In o. 4	18.09.23		100	50					18.09.23
	50	25	In o. 0	In o. 0	19.09.23		100	50	0	0	0	2	19.09.23
	50	25			19.09.23		100	50	In o. 1	In o. 9	In o. 0	In o. 9	19.09.23
	50	25	1 דיגום2	2 דיגום 2	20.09.23		100	50	0	0	0	35	20.09.23
	50	25			20.09.23		100	50	In o. 0	In o. 0	In o. 0	In o. 0	20.09.23
	50	25			20.09.23		100	50	In o. 0	In o. 0	In o. 3	In o. 4	20.09.23
	50	25			20.09.23		100	50	In o. 1	In o. 1	In o. 4	In o. 9	20.09.23
	50	25			20.09.23		100	50			In o. 6	In o. 129	20.09.23
	50	25					100	50					

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9.10 Monitoring procedures should define the approach to trending. Trends can include, but are not limited to:

i. Increasing numbers of action limit or alert level breaches.

ii. Consecutive breaches of alert levels.

iii. Regular but isolated breaches of action limits that may have a common cause, for example, single excursions that always follow planned preventative maintenance.

iv. Changes in microbial flora type and numbers and predominance of specific organisms. Particular attention should be given to objectionable organisms or those that can be difficult to control such as spore-forming microorganisms.

9.31 Microorganisms detected in Grade A zone and Grade B area should be identified to species level and the potential impact of such microorganisms on product quality (for each batch implicated) and overall state of control should be evaluated. Consideration should also be given to the identification of microorganisms detected in Grade C and D areas (for example where action limits or alert levels are exceeded or where atypical or potentially **objectionable microorganisms** are recovered). The approach to organism identification and investigation should be documented.

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Thank you

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