GMP COMPLIANT ENVIRONMENTAL MONITORING SYSTEMS IN STEM CELL AND TISSUE LABORATORIES

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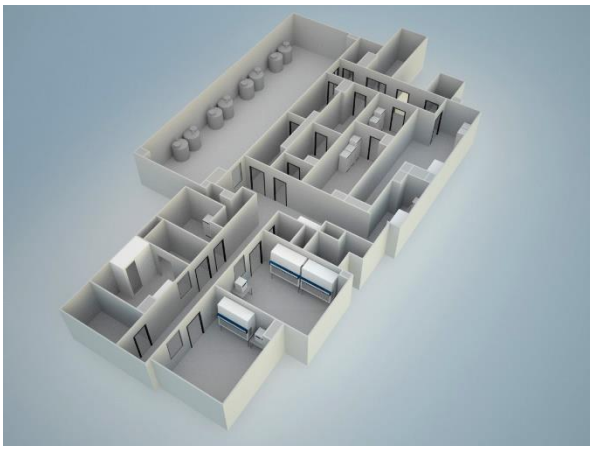
With advancing technology, many innovations in the field of health bring with them special applications. Stem cell based treatment services are undoubtedly the most lively and productive subject of the field in recent years. Stem cell studies need specifically controlled environments both because of their

complex structure and having special conditions in terms of attainment, production, storage and application. As in traditional pharmaceutical production facilities, many pieces of laboratory equipment are involved in stem cell production and application along with the clean rooms. In this relatively new field that is gaining even more importance in our country, production facilities should be monitored in terms of their compliance with regulations, efficiency, and quality. I would like to share with you the questions and answers we often encounter about these monitoring systems.

1. What are the equipment and parameters to be monitored in Stem Cell Laboratories?



All products and equipment directly involved in the production process of live cells must be included in the monitoring system. Here the work-flow in the laboratory needs to be handled from A to Z. For instance, all ambient conditions and equipment involved in the process starting from the differential pressure to adjacent rooms of GMP Grade B clean rooms that are directly involved in the production process at the first stage, to the production compliance of TRH, the monitoring of particle level in the GMP Grade A biosafety cabinet (BSC) and laminar air flow cabinets (LAF) in which the study is done and the cells are directly open to the atmosphere should be included.

The equipment and parameters included in monitoring in a general Stem Cell Laboratory are as follows:

	Temperature	Relative Humidity	Differential Pressure	Particles	Oxygen	Carbon Dioxide
GMP Grade C/B Production Air Lock (Airlock)	√	√	√			
GMP Grade B Production Corridor	√	√	√			
GMP Grade B Production room	√	√	√	√		
BSC (Grade A)				√		
LAF Cabinet (Grade A)				√		
Incubator	√				√	√
Drying Oven	√					
Refrigerator	√					
Deep Freeze	√					
Ultra Deep Freeze	√					
Cryogenic Tank	√					
Quarantine room	√	√	√			
Quality Control room	√	√				

Table 1 – Equipment and Parameters Included in Monitoring

Here are a few points to be noted:

- LAF cabinets for testing and/or control which are not directly involved in production do not need to be included in the online monitoring system. The aim of a GMP-compliant monitoring system is to directly monitor the

product and the environments in direct contact with the product. The same also applies to other laboratory equipment.

- By taking into consideration the specific circumstances of the site, the risk assessment should be carried out on-site. For example, a Grade B corridor that is used actively and in which the sample is processed, packaged, or tested should be treated as an active room. Particle monitoring should be performed in the room as well. Similarly, differential pressure monitoring across all actively used sterile rooms of the clean room will help reduce the risk.

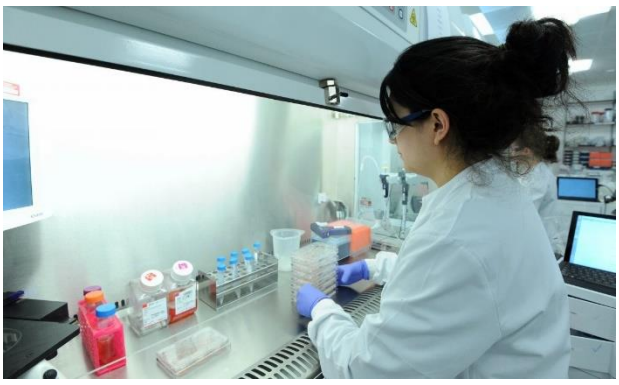
- Multiple sensors can be used in sensor placement, considering the device sizes and sections used independently and for different purposes.

- In clean rooms, the operator room and areas with cryogenic tanks should contain alarm towers that will warn the operators directly with auditory and visual alerts. These alarm towers must be coded to separately indicate the normal status, alarm status, and action status in green, yellow, and red, respectively.

- In cases where the site is not in use and the operator is not on the field, the alarm and warning parameters for protecting the samples and products can be transmitted to the persons by e-mail, SMS, voice message and other remote warning methods.

2. Are there any standards and regulations the monitoring systems are required to be compliant with?

Stem cell monitoring systems have areas classified as A, B, C and D as stated in GMP Annex 1 manual. In these areas, as in 6-month and 12-month qualification tests, continuous monitoring systems should be monitored in accordance with the heading “Cleanroom Monitoring” in GMP Annex 1. In addition, the risk-based approach for computerized monitoring systems is handled with all aspects and the validation process is clearly defined in the GAMP5 (Good Automated Manufacturing Practice Vol.5) document published by the International Pharmaceutical Engineering Association (ISPE). The ICHQ9 “Quality Risk Management” document, published in a process known as Risk International Conference on Harmonization (ICH), is also particularly helpful in the pre- and post-installation risk assessments.



3. We have a building monitoring system, do we still need an additional environmental monitoring system?

Perhaps the most common question in laboratory continuous monitoring systems is whether the data collected by the Building Management System/Building Automation (BMS) can be used in terms of quality as Environmental Monitoring System data. The BMS system is an automation that collects data for the regular control of the air conditioning system, the purpose of which is to control the heating, cooling, and air conditioning (HVAC) system.

Differences between Building Management Automation Systems (BMS) and Environmental Monitoring Systems (EMS) are outlined in Table 2.

	Building Automation (BMS)	Environmental Monitoring System
Purpose	The main purpose is to control the building air-conditioning system, fire detection system, and security system.	To detect any possible off-limit condition and to warn the operator in the production process.
Sensor Position	For environmental data, the sensor points are air returns, culverts, and service areas.	Sensor points in the field are selected by a risk-based approach, considering the worst-case scenario and with thermal mapping where necessary.
Warning and Control	Data is collected for purposes of establishing control parameters for HVAC and other systems and not for communication with operators.	Any possible warnings in the field are transmitted directly to the operators by means of alarm towers with audible, visual warnings. The system has no function to control. The goal is to collect and interpret the data accurately and to identify possible deviations.
Validation	Not necessary. Data accuracy and continuity are not top priority.	It is essential that the system is validated, and all errors, failures, and data loss scenarios are examined in Design Qualification and tested in IQ and OQ phases.
Calibration	Sensors are generally not subjected to regular calibration as long as they are functioning properly.	The sensors are calibrated at least once in the range of 6 months to 12 months.

Table 2 - Differences Between Building Automation System and Environmental Monitoring System

4. The equipment we use can measure and control all the necessary parameters. Can we monitor the system with this infrastructure?

Similar to building automation systems, equipment such as the Drying Oven, Incubator, Refrigerator, Deep Freeze and Cryogenic Tanks used in the laboratory can provide this data with their internal interfaces and can transfer this data to a central software by means of these interfaces if desired. However, GMP-compliant environmental monitoring systems provide a second level of security since they also monitor the potential sensor malfunctions and the data that controls the device just like a guard. Similarly, in the event of a failure in the GMP-compliant environmental monitoring system, it is possible to intervene in the process by means of the internal sensor of the device and prevent possible errors and losses.

5. We use a datalogger to collect all critical data. Is it enough?

Data collectors can play a key role in determining the trend of devices and the alarm and action limits. However, they cannot replace GMP-compliant environmental monitoring systems. Because, in order to be aware of this alarm in case of a possible alarm state, the data on the data collector must be transferred to the computer. This means the operators are notified of this alarm condition only after the intervention time period has expired. Usually we use data collection devices for heat mapping, worst case scenario and trend tracking. In GMP-compliant environmental monitoring systems, the aim is to inform the operator in the fastest and most effective way possible in case of a potential state of alarm.

6. Can data from Building Automation System (BMS) sensors differ from the GMP Compliant Environmental Monitoring System data?

In BMS systems, the sensor placement is done to collect enough data to enable the HVAC system to function most efficiently. Thus, for example, the temperature data is taken from the return air and/or the fresh air channels provided for the room. In this case, risk-based approach values measured at the selected point in the room may differ from the values at the selected point in BMS. If the sensitivity, calibration status, and hysteresis of the sensors are taken into consideration, the values may not be exactly the same. Since GMP-compliant monitoring systems are validated in accordance with GAMP5, each sensor is tested with a reference sensor at the time of operational qualification and the accuracy of the data is confirmed. Therefore, the data in the BMS and the Environmental Monitoring System being the same is not something to be expected.

7. Should Particle Monitoring Systems do 1 cubic meter air sampling? Should the alarms be set according to the limits in m3?

We often encounter this question not only for stem cell laboratories, but also for particle tracking systems in pharmaceutical manufacturing facilities. First of all, GMP Annex 1 provides guidance on both clean room classification and monitoring. From clause 4 to 7 of this document are given "Clean room and clean air device classification", and the classification table given in that section is shown here:

	Permissible particle limit of 1m3 of target particles of equal and larger diameter			
	At Rest		In Operation	
Grade	0.5 Micron	5.0 Micron	0.5 Micron	5.0 Micron
A	3520	20	3,520	20
B	3520	29	352,000	2,900
C	352,000	2,900	3,520,000	29,000
D	3,520,000	29,000	Not Defined	Not Defined

Table 3 - Particle Limits for Each Class in the GMP Annex 1 Manual

In clause 5 of GMP Annex 1, it is clearly stated that a minimum of $1m^3$ of air should be sampled for Grade A for qualification studies carried out in clean rooms. However, this is different in the case of continuous monitoring. Continuous monitoring is again carried out under the conditions set out in clauses 8 to 15 of GMP Annex 1. Here, in the 5th clause it's stated *"... Grade A areas should be monitored at any sample volume and measurement frequency which can trigger all kinds of interventions, transient events and all kinds of system disturbances by triggering off-limit alarms"* . Again, clause 12 states *"Sample volumes used for monitoring purposes using automated systems are generally a function of the sampling rate of the system used. The sample volume does not have to be the same as the one used for the official classification of clean rooms and clean air devices".* For this reason, considering the effect of the active usage area and the sample volume in the study area, samples should be taken every minute with different sample volumes and compared with the alarm limits and the operator must be warned in cases of over-flow.

About the Author

Hasim Solmaz is General Manager of Lighthouse Worldwide Solutions EMEA Operations located in Istanbul, Turkey. Hasim's focus is on cleanroom design and management concepts, environmental monitoring systems, pharmaceutical manufacturing and regulatory concerns. Hasim is a founding chair of Cleanroom Technologies Society of Turkey (TTD), head of delegation to ISO TC209 – Cleanrooms and associated controlled environments – and technical expert to ISO TC209 WG3 – Test methods.

Hasim was recently appointed as honorary chair of the International Confederation of Contamination Control Societies, ICCCS. He is an active member of ISPE, IEST and PDA and holds a Bachelor of Science degree with high honors in Atmospheric Science and Meteorological Engineering from Istanbul Technical University.