Bioquell Qube

Compliance with EU Volume 4 Annex 1

1. Introduction

In August 2022, the European Union made a significant update by releasing a revised edition of Annex 1 to Volume 4 of the EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. This updated version specifically pertains to the "Manufacture of Sterile Medicinal Products," outlining essential compliance requirements.

This document is an abbreviated version that explains how the Bioquell Qube meets the requirements of Annex 1 based on Ecolab's current understanding.

2. Analysis of Bioquell Qube Compliance

2.1 Pressure Differences and Warnings – (Annex 1 Section No 4.16)

Requirement

Section	Requirement (Relevant extract)	Check
4.16 ***(BQ Doc Section 3.1)***	Indicators of air pressure differences should be fitted between cleanrooms and/or between isolators and their background. Set points and the criticality of air pressure differences should be considered within the CCS. Air pressure differences identified as critical should be continuously monitored and recorded. A warning system should be in place to instantly indicate and warn operators of any failure in the air supply or reduction of air pressure differences (below set limits for those identified as critical). The warning signal should not be overridden without assessment and a procedure should be available to outline the steps to be taken when a warning signal is given. Where alarm delays are set, these should be assessed and justified within the CCS. Other air pressure differences should be monitored and recorded at regular intervals.	

Response

The Bioquell Qube has a pressure transducer for each chamber including each QMTD Transfer Hatch which monitors the pressure difference between the chamber and the room. The pressure is monitored in real time and is displayed. The pressure can be recorded by a customer on their data acquisition system when connected to the Bioquell Qube. Full justification of the default set points, alarm settings and alarm delays are available, and the setpoints and alarm settings are customer alterable.

2.2 Observation of Production Process (Annex 1 Section No 4.17)

Requirement

Section	Requirement (Relevant extract)	Check
4.17 ***(BQ Doc Section 3.2)***	Facilities should be designed to permit observation of production activities from outside the Grade A and B areas (e.g. through the provision of windows or remote cameras with a full view of the area and processes to allow observation and supervision without entry). This requirement should be considered when designing new facilities or during refurbishment of existing facilities.	

Response

The Bioquell Qube has transparent window/doors on the front of the unit which allow observation of the activities being undertaken in the Bioquell Qube. In addition, there is a Camera option with the Bioquell Qube allowing observation of the work area from outside of the cleanroom. It should be noted that the Bioquell Qube's camera is a sealed webcam and it has a USB output, software is not provided. (The camera option should be considered)

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2.3 Separation of the Grade A Environment (Annex 1 Section No 4.18)

Requirement

Section	Requirement (Relevant extract)	Check
4.18 ***(BQ Doc Section 3.3)***	Isolators... should be designed to provide protection through separation of the Grade A environment from the environment of the surrounding room. The hazards introduced from entry or removal of items during processing should be minimized and supported by high capability transfer technologies or validated systems that robustly prevent contamination and are appropriate for the respective technology.	

Response

Entry Systems

Regardless of the configuration of the Bioquell Qube the entry into the Grade A environment will, as standard, require a Hydrogen Peroxide Vapour (HPV) bio-decontamination cycle. The cycle must be validated, and the load (items to enter the Grade A environment) must be consistent with the validation. This ensures that the items entering the Grade A environment will not introduce contamination.

There are other methods to introduce items into the Bioquell Qube aseptically, these include:

- Use of a Rapid Transfer Port (RTP), the Bioquell Qube as an option can be fitted with a 190 or 270mm RTP which enables items which have been pre-sterilised to enter directly into the Grade A environment.
- A number of different liquid transfer solutions can be used to allow liquid to enter the Bioquell Qube aseptically from containers sited outside the Bioquell Qube.

Exit Systems

Exit Transfer Hatch (QMTD)

The main exit system offered with the Bioquell Qube is the Bioquell Qube Material Transfer Device (QMTD). The QMTD allows items to be transferred out of the Bioquell Qube while maintaining the Grade A environment in the main chamber adjacent to it. It has the following features to ensure that contamination will not enter the Grade A environment when set as a positive pressure isolator:

Extensive testing has been conducted looking at the effectiveness of the contamination control design features. There were three sets of tests all conducted with the Bioquell Qube in a non-classified environment:

- Visualisation of airflow – smoke test
- Particle count tests
- Contamination test

The airflow results showed that the QMTD has positive airflows from the Grade A critical zone into the QMTD when the internal door, and out of the QMTD into the room when the outer door was opened.

The particle counting showed that at no point the QMTD fell below Grade A (ISO 5) both when the internal door was opened and shut and the external door was opened and shut including when multiple items were passed out, simulating a typical operation.

- The same simulation with multiple items being passed out was conducted with swabs, settle plates, active air sampler and contact samples in the QMTD and its door, and no growth was seen on any sample.
- Though not recommended, when the above was repeated passing items into the Grade A from the outside via the QMTD, similar results were seen, except on one run the QMTD fell to Grade B.

Alternative Exit Systems

There are alternative exit systems available with the Bioquell Qube. They include:

- A 190 or 270mm Rapid Transfer Ports (RTP) placed on the side of the chamber.
- The Main QHPV chamber loading door operating as a transfer isolator.

2.4 Grade A First Air Protection and unidirectional airflow (Annex 1 Section No 4.19)

Requirement

Section	Requirement (Relevant extract)	Check
4.19 ***(BQ Doc Section 3.4)***	The design of the technology and processes used should ensure appropriate conditions are maintained in the critical zone to protect the exposed product during operations. i. Isolators: a. The design of open isolators should ensure Grade A conditions with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing. b. The design of closed isolators should ensure Grade A conditions with adequate protection for exposed products during processing. Airflow may not be fully unidirectional in closed isolators where simple operations are conducted. However, any turbulent airflow should not increase risk of contamination of the exposed product. Where processing lines are included in closed isolators, Grade A conditions should be ensured with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing.	

Response

The Bioquell Qube according to the industry understanding and ISO 13408-6 definition is a closed isolator; however in Annex 1, a new definition has been used which conflicts with the ISO definition. Based on the Bioquell Qube configuration with bio-decontamination entry and QMTD exit, Ecolab defines the Bioquell Qube as a closed isolator system because the internal environment of the isolator is always separated from the external environment by a solid physical barrier. Refer to the extensive testing to support this position.

The Bioquell Qube is designed with downflow air which comes from the top of the Bioquell Qube's chamber and is uniform over the critical Grade A zone. After the airflow straighteners there are no objects which can be touched by the air prior to the critical working zone.

Smoke tests to visualise the airflow pattern were performed showing no turbulent flow, this is then repeated as part of the OQ conducted by Ecolab on site.

(For existing equipment a smoke test should be considered)

2.5 Glove Systems, their testing and Leak Testing (Annex 1 Section No 4.21)

Requirement

Section	Requirement (Relevant extract)	Check
4.21 ***(BQ Doc Section 3.5)***	The materials used for glove systems (for both isolators and RABS), should be demonstrated to have appropriate mechanical and chemical resistance... leak testing of the glove system... i. Isolators: a. For isolators, leak testing of the glove system should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined intervals. Generally glove integrity testing should be performed at a minimum frequency of the beginning and end of each batch or campaign. Additional glove integrity testing may be necessary depending on the validated campaign length. Glove integrity monitoring should include a visual inspection associated with each use and following any manipulation that may affect the integrity of the system. For manual aseptic processing activities where single unit or small batch sizes are produced, the frequency of integrity verification may be based on other criteria, such as the beginning and end of each manufacturing session. b. Integrity / leak testing of isolator systems should be performed at defined intervals.	

Response

The Ecolab patented glove sleeve system which is installed in the Bioquell Bioquell Qube has been tested for appropriate chemical and mechanical resistance. The sleeves have good chemical resistance with all Klercide products, and are mechanically classed to have Level B cut resistance, Level 4 abrasion resistance and level 1 puncture resistance, which is suitable for an isolator application.

The Bioquell Qube, as an option, has an integrated glove leak tester which can detect down to a 50µm hole.

The Bioquell Qube has a built-in pressure test routine. This can be run on the QHPV chamber only or the whole system.

(The Glove tester option should be fitted to comply)

2.6 Automated Bio-decontamination and glove presentation (Annex 1 Section No 4.22)

Requirement

Section	Requirement (Relevant extract)	Check
4.22 ***(BQ Doc Section 3.6)***	Decontamination methods (cleaning and bio-decontamination, and where applicable inactivation for biological materials) should be appropriately defined and controlled. The cleaning process prior to the bio-decontamination step is essential; any residues that remain may inhibit the effectiveness of the decontamination process. Evidence should also be available to demonstrate that the cleaning and bio-decontamination agents used do not have adverse impact on the product produced within the RABS or isolator. **i. For isolators** **The bio-decontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (e.g. gaseous or vaporized form). Gloves should be appropriately extended with fingers separated to ensure contact with the agent. Methods used (cleaning and sporicidal bio-decontamination) should render the interior surfaces and critical zone of the isolator free from viable microorganisms.**	

Response

(Note the first section of 4.22 is discussed in section 3.4 later in this document, this section covers the second half 4.22 i. which has been highlighted in bold)

The Bioquell Qube has an in-built Hydrogen Peroxide bio-decontamination system which allows hydrogen peroxide vapour bio-decontamination cycles to be run automatically. Ecolab can validate the Bioquell Qube and conduct Gassing Cycle Development (GCD) to validate the cycle using industry standard 6-log *Geobacillus stearothermophilus* biological indicators.

The Bioquell Qube's patented sleeve system has been designed with a number of features to ensure full bio-decontamination of the whole glove and sleeve, while in the designated hanging position.

(The new grey sleeve system should be fitted – standard since March 2021)

2.7 Downflow Air Speed (Annex 1 Section No 4.30)

Requirement

Section	Requirement (Relevant extract)	Check
4.30 ***(BQ Doc Section 3.7)***	The speed of air supplied by unidirectional airflow systems should be clearly justified in the qualification protocol including the location for air speed measurement. Air speed should be designed, measured and maintained to ensure that appropriate unidirectional air movement provides protection of the product and open components at the working position (e.g. where high-risk operations occur and where product and/or components are exposed). Unidirectional airflow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position, unless otherwise scientifically justified in the CCS. Airflow visualization studies should correlate with the air speed measurement.	

Response

The Bioquell Qube's airflow is set as a default average of 0.38m/s and can be set up to 0.42m/s when running at positive pressure. This is within the guidance value. The variation within the critical zone allowed during calibration is ±20%, at any single point.

(Note MKIII and earlier units the default average was 0.35m/s, this figure can be justified)

2.8 Disinfection Validation (Annex 1 Section No 4.34)

Requirement

Section	Requirement (Relevant extract)	Check
4.34 ***(BQ Doc Section 3.8)***	The disinfection process should be validated. Validation studies should demonstrate the suitability and effectiveness of disinfectants in the specific manner in which they are used and on the type of surface material, or representative material if justified, and should support the in-use expiry periods of prepared solutions.	

Response

The Bioquell Qube has an integral sporicidal bio-decontamination process. Ecolab has performed targeted efficacy testing on relevant Bioquell Qube surfaces with Klerwipe and Klercide products. The EN 16615 test standard was used for this testing, because it incorporates the application of the disinfectant with mechanical action (representing wiping or mopping) onto a surface. The test was modified to utilise Bioquell Qube surfaces and bacteria, yeast, fungal and bacterial spores, and viruses. The tests were conducted by an independent laboratory.

(Recommend the use of Klercide products as these have been validated for use with the Bioquell Qube)

2.9 Description of the Equipment design (Annex 1 Section No 5.1)

Requirement

Section	Requirement (Relevant extract)	Check
5.1 ***(BQ Doc Section 3.9)***	A written, detailed description of the equipment design should be available (including process and instrumentation diagrams as appropriate). This should form part of the initial qualification package and be kept up to date.	

Response

A detailed description is available for the Bioquell Qube in the Functional Design Specification.

2.10 Particle Counter Requirement (Annex 1 Section No 5.9)

Requirement

Section	Requirement (Relevant extract)	Check
5.9 ***(BQ Doc Section 3.10)***	Particle counters, including sampling tubing, should be qualified. The manufacturer's recommended specifications should be considered for tube diameter and bend radii. Tube length should typically be no longer than 1m unless justified and the number of bends should be minimized. Portable particle counters with a short length of sample tubing should be used for classification purposes. Isokinetic sampling heads should be used in unidirectional airflow systems. They should be oriented appropriately and positioned as close as possible to the critical location to ensure that samples are representative.	

Response

Ecolab provide a particle counter for the Bioquell Qube as an option. The isokinetic tube meets the manufacturer's requirements for diameter and minimum bend radii, and the tube is 700mm long. The design allows for the isokinetic cone to be moved in an arc to the most appropriate position for the activity being undertaken.

(A Level 3 option – active air head and particle counter with central isokinetic cone, swan neck, should be fitted to all chambers where critical operations are undertaken)

2.11 Hold Time of a Decontaminated Environment (Annex 1 Section No 8.18)

Requirement

Section	Requirement (Relevant extract)	Check
8.18 ***(BQ Doc Section 3.11)***	The duration of each aspect of aseptic preparation and processing should be minimized and limited to a defined and validated maximum time, including: iii. The holding time for a decontaminated environment, such as the RABS or isolator before use.	

Response

The Bioquell Qube has a feature called 'Aseptic Hold' on two or three chamber systems, which informs the operator visually that the Bioquell Qube has exceeded its validated maximum time. It is reset after each bio-decontamination cycle.

(The aseptic hold period should be validated for each application by the user)

2.12 Vial Crimping (Annex 1 Section No 8.26)

Requirement

Section	Requirement (Relevant extract)	Check
8.26 ***(BQ Doc Section 3.12)***	Where the equipment used to crimp vial caps can generate large quantities of non-viable particle, measures to prevent particle contamination such as locating the equipment at a physically separate station equipped with adequate air extraction should be taken.	

Response

Ecolab recommend that a Bioquell Qube configuration with two working chambers is used when crimping which are separated either by a door or an open module. In this way the crimping activity is kept physically separate from the filling, while being easy to pass vials from the filling station to where the crimping is taking place.

(If crimping is taking place this should take place in a separate module to filling and capping)

3. Analysis of Service Requirements Connected to the Bioquell Qube and its Use

3.1 Qualification (Annex 1 Section No 4.25)

Requirement

Section	Requirement (Relevant extract)	Check
4.25 ***(BQ Doc Section 4.1)***	Cleanroom and clean air equipment qualification is the overall process of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use. As part of the qualification requirements of Annex 15, the qualification of cleanrooms and clean air equipment should include (where relevant to the design/operation of the installation): i. Installed filter system leakage and integrity testing. ii. Airflow tests - volume and velocity. iii. Air pressure difference test. iv. Airflow direction test and visualisation. v. Microbial airborne and surface contamination. vi. Temperature measurement test. vii. Relative humidity test. viii. Recovery test. ix. Containment leak test.	

Response

The Installation Qualification (IQ), Operational Qualification (OQ), Gassing Cycle development and Performance Qualification (PQ), can all be completed by Ecolab technicians. The IQ and OQ is a standard protocol and covers items: i, ii, iii, iv and ix. Items vi, and vii are standard calibrated instruments, and v and viii are for the user to conduct.

(It is advisable that Ecolab conduct IQ, OQ and Gassing Cycle Development (GCD) on all new installations to ensure that it is set-up and validated correctly)

3.2 Routine Maintenance and Qualification (Annex 1 Section No 4.32)

Requirement

Section	Requirement (Relevant extract)	Check
4.32 ***(BQ Doc Section 4.2)***	The requalification of cleanrooms and clean air equipment should be carried out periodically following defined procedures. The requalification should include at a minimum the following: ▪ Cleanroom classification (total particle concentration). ▪ Integrity test of final filters. ▪ Airflow volume measurement. ▪ Verification of air pressure difference between rooms. Air velocity test (Note: For grade B, C and D the air velocity test should be performed according to a risk assessment documented as part of the CCS. However, it is required for filling zones supplied with unidirectional airflow (e.g. when filling terminally sterilized products or background to Grade A and RABS). For grades with non-unidirectional airflow, a measurement of recovery testing should replace velocity testing). The maximum time interval for requalification of Grade A & B areas, is 6 months. The maximum time interval for requalification of grade C & D areas, is 12 months. Appropriate requalification consisting of at least the above tests should also be carried out following completion of remedial action implemented to rectify an out of compliance equipment or facility condition or after changes to equipment, facility or processes as appropriate. The significance of a change should be determined through the change management process. Examples of changes to be considered include but are not limited to the following: i. Interruption of air movement which affects the operation of the installation. ii. Change in the design of the cleanroom or of the operational setting parameters of the HVAC system. iii. Special maintenance which affects the operation of the installation (e.g. change of final filters).	

Response

Ecolab has a maintenance programme for Bioquell Qubes which includes a 6 monthly check as required.

The annual maintenance is more in depth and checks other calibrations and functionality as well as a four-year cycle of part changes.

If there is any need for a service technician to make an intervention which could affect the filters or the airflow, then the client will be informed, enabling their change management process to determine whether the 6 month check procedure should be carried out.

(It is advised that a service agreement with 6 monthly check is in place)

3.3 Understanding the effectiveness of Vapour-phase Hydrogen Peroxide (Annex 1 Section No 4.36)

Requirement

Section	Requirement (Relevant extract)	Check
4.36 ***(BQ Doc Section 4.3)***	Where... vapour disinfection (e.g. Vapour-phase Hydrogen Peroxide)... the effectiveness of any fumigation agent and dispersion system should be understood and validated.	

Response

The validation of the Bioquell Qube by Ecolab ensures that the distribution is correct by use of Chemical Indicators and Biological Indicators.

(It is advised that Validation including Gassing Cycle Development is conducted by Ecolab to ensure compliance)

3.4 Determination of no adverse effects of the Decontamination process (Annex 1 Section No 4.22 & 10.8)

Requirement

Section	Requirement (Relevant extract)	Check
4.22	Decontamination methods (cleaning and bio-decontamination, and where applicable inactivation for biological materials) should be appropriately defined and controlled. The cleaning process prior to the bio-decontamination step is essential; any residues that remain may inhibit the effectiveness of the decontamination process. Evidence should also be available to demonstrate that the cleaning and bio-decontamination agents used do not have adverse impact on the product produced within the RABS or isolator.	
10.8	Any process (e.g. Vaporized Hydrogen Peroxide, Ultra Violet) used to decontaminate the external surfaces of sterility samples prior to testing should not negatively impact the sensitivity of the test method or the reliability of the sample.	

Response

The Klercide sterile water (WFI) is recommended for the cleaning of the Bioquell Qube. This will not come in direct contact with the product and so there will be no adverse impact on the product produced.

Test methods, which Ecolab has developed, show that none of the vessels which either the product is in, or will end up in, as well as the consumables the product may pass through or touch have any Hydrogen Peroxide in them as a result of the bio-decontamination cycle. This testing is available to clients.

(Ensure all materials and consumables which contact the product are known to be suitable, if not testing should be conducted)

For regional office details, please visit bioquell.com

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