SUBMED – Su Biyomedikal Sistemler ve Saglik Hizmetleri San. Ve Tic A. Ş.
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STERILIZATION PROCESS FOR SUBMED PRODUCTS

1. PURPOSE

This report demonstrates that the sterilization process in Su Biyomedikal Sistemler ve Sağlık Hizmetleri San. Ve Tic. A.Ş. (SUBMED). Ethylene Oxide Sterilize are capable of consistently steriling the products of SUBMED to a minimum sterility assurance level of 10^{-6} . This report has been prepared to describe the routine sterilization process in SUBMED.

2. KAPSAM /SCOPE

This report covers all products sterilized to Submed.

3. GENERAL DEFINITION OF STERILIZER

There are two ETO Sterilizers in Submed as TBT and MDS.

TBT ETO Sterilizer consist of 5 main part that are generator, cabin, jacket, turbination tank, neutralisation tank.Steam that is necessary for sterilization is produced with generator. Jacket system is providen protection of temperature of sterilization unit and incriased durableness of cabin.

Brand of Sterilizer : Turkuaz
Device Placement Address: Orhangazi mah. 1673. Sok. Kat: 3 No:20 Esenyurt İstanbul Türkiye

Model : TBT ETO PLUS 12000
Serial Number: 541001
Volume: 12 m^3

MDS ETO Sterilizer is consist of 5 main part that generator, nitrogen generator, cabin, jacket, turbination tank. Steam that is necessary for sterilization is produced with generator. Jacket system is providen protection of temperature of sterilization unit and incriased durableness of cabin. Nitrogen is used to increase the safety level in working with ethylene oxide.

Brand of Sterilizer : MDS
Device Placement Address: Orhangazi mah. 1673. Sok. Kat: 3 No:20 Esenyurt İstanbul Türkiye

Model : MDS S"8S1SD
Serial Number: MDS18.116
Volume: 22,5 m^3

4. GENERAL DEFINITION OF STERILIZER PROCESS

TBT Sterilizer has 12 m^3 volumes. 6 euro pallets can be placed in the sterilizer. Products are placed in boxes in the sterilizer. Preconditioning, conditioning, sterilization and aeration processes are done in the sterilizer.Preconditioning time, conditioning time, sterilization time, aeration time are 10, 2, 6,4 hours respectively.

MDS Sterilizer has 22,5 m^3 volumes. 8 euro pallets can be placed in the sterilizer. Products are placed in boxes in the sterilizer. Pre-conditioning is carried out in a separate room from sterilization, conditioning, ethylene oxide exposure and ventilation processes are carried out

in the MDS sterilization device. Preconditioning time, conditioning time, sterilization time, aeration time are 15, 4, 5,3 hours respectively.

%90 EtO %10 CO_2 gas is used to sterilize SUBMED products.

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5. STERILIZATION VALIDATION AND REVALIDATION STUDY

Sterilization (re)validation studies have been done appropriate to EN ISO 11135:2014. TBT Sterilizer and MDS sterlizer were installed in 2015, 2019 respectively. Sterilization validation studies were completed in 2016 for TBT, 2020 for MDS. Every year sterilization revalidation studies are done to check the validity of done sterilization validation studies with operational qualification, performance qualification and microbiological performance qualifications according to EN ISO 11135:2014.

Installation qualifications carried out manufacturer of the device and the acceptability controlled by Submed. Operational, physical and microbiological performance qualifications will be carried out by Submed and a physical and microbiological validation report is written. EN ISO 11135:2014 /Annex B/Overkill approach (Half-cycle approach) is chosen for the killing rate of the sterilization (re)validation studies.

5.1. INSTALLATION QUALIFICATION (IQ)

The characteristics of installation area will be reviewed by manufacturer of the sterilizer that is manufactures of the sterilizer in order to work of the user and system with maximum security precautions. The qualifications of all parts were contolled and the products compatibilities will be reported by manufacturer of the sterilizer at installation of the sterilizer.

5.2. OPERATIONAL QUALIFICATION (OQ)

The operational qualification is carried out by Submed. In this work, all applicable characteristics and process acceptability of the sterilizer will be tested which which were defined previously by manufacturer.

Probes are put in sterilizer to define temperature and humidity profile of empty sterilizer cycles. The probes are replaced in sterilizer for likely to present maximum temperature differential. other probes were distributes evenly within the chamber. Number of humidity and temperature sensors is defined according to EN ISO 11135-2014. For determination of the empty chamber temperature and relative humidity profile, after placing the probes inside the empty chamber, sterilizer was performed three times. Difference between set value and real value of relative humidity will be specified with the datas that are provide from the sterilization cyles. Temperature difference of sterilization phase between sterilizer set temperature and temperature in sterilizer is less than +/- 30C. (EN ISO 11135:2014 D.9.3.2 b 3)

5.3. PHYSICAL PERFORMANCE QUALIFICATION (PQ)

The temperature and humidity profiles of loaded chamber for all steps of sterilization process are measured by Submed. The number of temperature and humidity probes are determined with using the calculation is given on EN ISO 11135:2014, Annex C and Table C.1. The temperature and humidity interval which will be measured on sterilization load during exposure time is aimed between ± 5 ^{0}C, ± % 15 RH.

Different product boxes that will be sterilized were weighted and density was calculated for every different boxes. Worst-case density that is equal or more than density of product boxes that will be sterilized was calculated according to the list. Worst case product load were selected according to desing challenge and product density.

Temperature and humidity probes with products that have maximum density (reference load) are placed in sterilizer. Temperature and humidity probes are placed in primer packages. Some

probes are placed maximum and minimum temperature points in sterilizer other probes are divided equally in sterilizer.

Sterilizer are performed 3 times with temperature and humidity probes that were placed in loaded chamber.

5.4. MICROBIOLOGICAL PERFORMANS VALIDATION (MPQ)

The biogical indicators are used in sterilization (re)validation studies must be appropriate to EN ISO 11138. It is shown that the sterilization process is sufficient to inactivate the bioindicators which will be placed in load. The type pf biological indicator will be used is Bacillus atrophaeus which matches ATTC 9372 conditions and the indicators broth is Triptych Soya Broth (TSB). Microbial population in the biological indicators is minimum 10^6.

Products in scope of Submed Quality System that are to be sterilized have been grouped into product families taking in consideration their configuration, componentry and gas ventilation characteristics and wost-case points for sterilizer .Worst-case products that have difficult conditions for sterilization are grouped in a list. New product that have more difficult conditions for all products that will be sterilized and the product was choosen as representative product (PCD) of sterilization (re)validation. The biological indicators are put in the PCDs to have more difficult conditions. The PCDs are used as internal PCDs and they are used for sterilization (re)validation studies.

External PCDs are designed to check routin cycles. The bioindicators that have minimum 10^6 microbial population put in the external PCDs and after each sterilization cycle are tested to prove sterilization cycle.

Sterilization (re)validation studies were done minimum sterility assurance level of 10^{-6} (SAL) by using the internal and external PCDs.

The PCD numbers are defined according to according to EN ISO 11135:2014, Table C.3 and 3, positioned every validation cycle in load.

All PCDs are taken from the load by trained personnel for the sterility tests after the sterilization cycle has completed. The control of product bioburden is a part of the validation study. It is controlled regularly and after validation study. The SAL<10^6 are shown with bioburden tests before the validation study.

A fractional cycle , three half cycle and two full cycle (consecutive double aterilization) were done for microbiological performance validation at sterilization validation studies. Every year a half cycle and two full cycle (consecutive double aterilization) are done for microbiological performance validation at sterilization revalidation studies.

Sterility control for products and PCDs are performed after every end of cycle. Inoculated products (PCD) and products have not shown microbiological growth at half and full cycles. Also below tests are performed during microbiolagical performans qualifications at sterilization (re)validation studies.

- Bioburden Test
- BI Sterilite Test
- Product Sterility Test
- Etylene Oxide Residual Test
- Etylene Chlorhidrin Residual Test
- Product Sterility Test
- Material Performance Tests After Stability
- Packaging Performance Tests

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Sterilization (Re)Validation Final Reports include all tests, results, evaluations and the definition of routine sterilization cycle are published according to EN ISO 11135:2014 requirements. The consistency of the results of validation study with validation protocol, EN ISO 11135:2014 and meet the acceptance criteria evaluate in Sterilization (Re)Validation Final Report.

6. ROUTINE STERILIZATION PROCESS

Sterilization process is done for sterilizing products manufactured. SUBMED products are taken to the sterilization area and are prepared by the responsible personnel for the sterilization of the materials according to the TL.06.09 Sterilization Device Operating Instructions and then responsible personnel take out the products indicated in the instruction are output. Sterilization procedures and parameters are recorded by Sterilization Personnel with **FR.06.06 TBT Sterilization Form and FR.06.06-1 MDS Sterilization Form**.

Results of sterilization process in monitored by chemical and biological indicators. Indicators are placed inside sterilizer according to TBT **Sterilization Placement Plan (PL.05.03), MDS Sterilization Placement Plan (PL.05.03-1)**.

Sterilizer parameters like temperature and pressure are recorded with **FR.06.06 TBT Sterilization Form and FR.06.06-1 MDS Sterilization Form**. After sterilization, products are kept under quarantine in warehouse until biological indicator tests are completed. Products are not released during that time. Product release is only possible with the approval of Quality Management Representative. After sterilization, colour changes in chemical indicators are checked at first. Biological indicators for each bag and a control BI which is not EtO sterile are placed on incubator for 48 hours at 37 ^{o}C. These tests prove if sterility is assured or not. Results of biological indicator tests are recorded on **Biological Indicator Test Monitoring Form (FR.05.05)** by responsible personnels and this form is controlled by Quality Management Representative.

7. PRODUCT FINAL CONTROL

After production phase , sterilization processes are done for the products. Sterilization process records are checked on **FR.06.06 TBT Sterilization Form and FR.06.06-1 MDS Sterilization Form** by Quality Management Representative. After sterilization processes, biological indicator sterility test for every sterilization cyle are done by Quality Control Responsible and test results are recorded on **FR.05.05 Biological Indicator Test Monitoring Form**.

After sterilization processes , final controls of products are done according to **PL.05.02-3 Final Control Plan** by Quality Control Personnels. Control results are recorede on **FR.05.03-3 Final Control Form.**

Sterilization processes, BI sterility test results, steril product quantity, produced and comparison of steril and produced product quantities , physical views of product boxes and products , contents of products are controlled and recorded on **FR.05.03-3 Final Control Form.**

8. PRODUCT RELEASE

All processes from production planning to product release approval are followed and recorded by the responsible personnel in **FR.06.13 Production Follow-up Form**. With the **FR.06.13**

Production Follow-up Form, all used raw materials, packaging, labeling, quality control, sterilization processes are carried out and recorded by responsible personnels.

Release approval is required to exit the product. The Quality Management Representative or General Manager inspects all actual activities. If the actions are appropriate, specify release approval in **FR.06.13 Production Follow-up Form**. The release of the product without release approval does not occur

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