RanD

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INNOVATION IN MEDICAL TECHNOLOGY

Medolla, 17th March 2021

Subject: information regarding Steril Milano issue

This report is being sent to the following EU Competent Authorities:

Austria	Federal Office for Safety in Healthcare - (BASG) Bundesamt für Sicherheit im Gesundheitswesen, Institute for Surveillance, Department Medical Devices Surveillance
Bulgaria	Bulgarian Drug Agency 8 Damyan Gruev Str., BG - 1303 Sofia
Croatia	Agency for Medicinal products and medical devices
Denmark	Danish Medicines Agency Axel Heides Gade 1, DK - 2300 - Kobenhavn,
France	Agence nationale de sécurité du médicament et des produits de santé (ANSM)
Germany	Federal Institute for Drugs and Medical Devices
Greece	National Organization for Medicines
Italy	Ministero della Salute
Lithuania	The State Health Care Accreditation Agency, under the Ministry of Health of the Republic of Lithuania
Norway	Statens legemiddelverk/ Norwegian Medicines Agency Postboks 6167 Etterstad
Netherlands	Dutch Health and Youth Care Inspectorate, IGJ Information Office (Meldpunt)
Poland	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Czech Rep.	State Institute for Drug Control
Romania	National Agency for Medicines and Medical Devices of Romania
Slovenia	JAZMP - Agency for Medicinal Products and Medical Devices of the Republic of Slovenia Slovenčeva ulica 22, SI - 1000 Ljubljana
Spain	Agencia Española de Medicamentos y Productos Sanitarios
Sweden	Swedish Medical Products Agency 'Läkemedelsverket' Department of Medical Devices
Switzerland	Swissmedic, Swiss Agency for Therapeutic Products Medical Devices Division
Turchia	The Ministry Of Health, Turkish Medicine and Medical Device Agency
UK	Medicines and Healthcare products Regulatory Agency

1. DESCRIPTION OF THE EVENT

On 15/02/2021, RanD S.p.A. received a notice of temporary shutdown of the activities of Monza and Reggiolo sites of the Steril Milano sterilizer, due to "a potential quality problem" under investigation. From 16/02, all lots in RanD warehouse were put in quarantine.

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On 18/02 we received a further more detailed communication indicating that from 2018 onwards our sterilization contractor Steril Milano had systematically falsified sterilization records in order to mask some unspecified sterilization cycle parameters deviations. The records that we received from such contractor were always conforming so we could not suspect this fraud. The falsification malpractice, perpetrated over the years was attributed to the previous company management. From 22/02 the Steril Milano starting sending us the raw data (not counterfeit) downloaded from their PLC of the sterilization parameters to allow us an assessment of the impact of the deviations during the sterilization cycles. RanD has critically analyzed every single sterilization lot provided by Steril Milano using the rationales described in the internal document "RAZIONALI DI ANALISI DEI LOTTI DI STERILIZZAZIONE COINVOLTI NELLA FRODE STERIL MILANO", in order to justify or not the acceptability of the deviations. Therefore, some production lots were released based on such critical evaluations.

2. ANALYSIS OF DATA AND EVALUATION OF THE RISKS ON HEALTH

Evaluation of the risk of non-sterile products

RanD has regularly critically analyzed all data received from Steril Milano. Our analyses take into account the following general starting considerations:

1. Since we started sterilizing at Steril Milano in 2017, we have never received any complaints from the field regarding patient infection following the use of our products.
2. Likewise, our periodic searches of PMS on the MAUDE, MIN SALUTE, BFARM and MHRA databases have never revealed incidents related to sterility problems reported by customers who, like us, sterilize at Steril Milano. Considering that thousands of sterilization cycles have been carried out on products of different nature and types in Steril Milano premises, it is believed that, given the systematic nature with which the fraud was perpetrated, if non-sterile products had actually been placed on the market, the problem would emerge at some point.
3. Our ETO sterilization cycle with OVERKILL method is extremely conservative, considering that it is validated according to ISO 11135 to kill a population of 10^6 CFU of Bacillus Atropheous, which is one of the most resistant microorganisms, in the most critical product in the most critical load. The routine bioburden of our devices is in the order of 10^1 - 10^2. Furthermore, in validation it has been shown that our products are sterile in half the time (half cycle) that is normally used during routine cycles. To date, we have obtained the original (not counterfeit) data from the last revalidation process that took place in 2019 and there is no evidence of tampering, so the revalidation was carried out adequately.
4. From the investigations conducted by Steril Milano, all the documentation relating to the management of biological indicators is correct and no non-conformities or signs of falsification have been found. However, the staff who managed them admitted that in some sporadic cases some IBs tested positive and that this result was not communicated to their respective customers. This has happened very rarely and has never affected all indicators of a given cycle. According to Steril Milano's records, none of the manufacturers that independently incubated and assessed their IBs ever communicated to Steril Milano that they had found positive IBs, although the sterilization cycles of all customers were impacted by the same problems. Our products are always placed in autoclaves in mixed loads, i.e. together with products from other manufacturers, so if other manufacturers had noticed non-sterile biological indicators, our goods would have been involved in the non-compliance, but this has never happened.
5. From a clinical point of view, it should also be considered that patients undergoing the treatments for which our devices are intended (hyperthermic perfusion) undergo pre- and post-operative courses of antibiotics.

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6. From the original data we are receiving these days, there has never been any non-compliance so far in the following two important parameters: the amount of EtO introduced into the autoclave (sometimes even slightly above the maximum limit) and the duration of time contact of the load with the EtO.
Taking into account all the above considerations, and the analyses of the out-of-specification parameters, the risk of having non-sterile products on the market has been estimated as "low", and it is outweighed by the benefits given by the treatment. Furthermore, patients undergoing hyperthermic perfusion treatments are generally exposed to massive doses of antibiotics. This aspect, in case of non-sterile product, would contribute to mitigate the harm.

Evaluation of the potential EtO residues over the limits

We have been able to ascertain that in some cases the degassing cycles have not been carried out in accordance with the specifications and it is possible, even if not ascertainable, that in some cases products with an ETO residue higher than the established limit have been placed on the market. However, the products currently on the market and in our warehouse have been treated a long time ago, so in the meantime the gas has certainly been able to evacuate naturally. To confirm this, we carried out a residual ETO test on 1 sample of lot F210016 (included in the sterilization lot 210203R2) which finished degassing on 08/02/2021 and for which the raw data indicated that 37 vacuum cycles less than the prescribed number were done. The report n ° 01423-21 received from Coronati Consulting lab. (our external qualified lab) shows that after 23 days from the end of the cycle the residual ETO is equal to 0.71 mg / device, therefore far below the threshold of 4 mg / device provided for by the 10993-7 standard. All other batches in stock were sterilized (and degassed) prior to this one. **In general, we believe that, at present, the lots in stock and on the market are not at risk of containing a residual ETO higher than the limit established for our devices.**

3. INVOLVED LOTS

The conclusions of our analysis have identified the following batches as potentially affected by the problem basically because Steril Milano has not provided us with the raw data yet, so a critical analysis is not possible at the moment. Steril Milano has however communicated that it will send us the remaining data by 19/03, so we believe we will be able to complete the analysis of everything on the market shortly.

LIST OF INVOLVED LOTS

- All lots starting with **F18** e **F19**
- The following lots:

R9900033	F200023
	FR20023
	F200174
R9900067	F200109
	F200110
	F200149
	F200273
	F200274
	F200180
	F200199

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	F200253
	F200262
	F200284
	F200316
	F200298
	F200304
	F200325
	F200316
	F200325
	F200369
	F210007
	F210110
	F200024
	F200038
	F200262
	F200253
	F200199
	F200081
	F200083
	F200273
	F200274
	F200109
	F200110
	F200180
	F200149
R9900071	F200014
	F200058
	F200084
	F200086
	F200097
	F200127
	F200225
	F200127
R9900084	F200125
	F200162
R9900086	F200004
	F200116
R9900088	F200095
	F200111

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R9900088	F200160
	F200166
	F200198
	F200201
	F200237
	F200263
	F200289
	F200329
	F200315
	F200317
	F200329
	F200372
R9900089	F200015
	F200082
	F200117
	F200117
	F200202
R9900093	F200252
	F200159
	F200252
R9900099	F200156
R9900101	F200075
R9900110	F200165
R9900111	F200112
R9900119	F200128
	F200230
	F200230
R9900120	F200158
	F200232
	F200232
	F200276
R9900127	F200146
	F200165
	F200288
R9900129	F200016

This is an exhaustive list of all the devices and lots involved, distributed world-wide. It is intended that not all of them are distributed in each notified Country. RanD has created a traceability list with the lots distributed in each Country that will be shared with the local distributor for end-users identification.

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4. IDENTIFICATION OF THE NOTIFIED BODY

TÜV SÜD Product Service GmbH (id. No. 0123)

5. POSSIBLE CORRECTIVE ACTIONS

Lots found to be non-compliant will be disclosed to distributors and customers with FSN and a recall will be made. Depending on the number of pieces involved, the different options will be evaluated:

- disposal of the pieces;
- re-sterilization in a new validated sterilizer, as our products are validated for double sterilization.

RAND has suspended sterilization in Steril Milano facility and is qualifying an alternative supplier. Should Steril Milano resume the sterilization activities, it will be necessary to proceed with a new qualification of the supplier through an on-site audit to assess the consistency of the corrective actions implemented.

Further corrective actions will be defined by RAND at the closure of the investigation.

6. FOLLOW UP

Updates will follow as soon as we receive further information from Steril Milano and in any case no later than 03/25/2021. Should we identify any non-sterile product, we will notify you immediately.

For any clarification we remain at your complete disposal. Here are our contacts:

[redacted] Regulatory Affairs Manager	Email: [redacted]	Tel. +39 0535 49283
[redacted] Quality Assurance Manager	Email: [redacted]	Tel. +39 0535 49283

Best regards

[redacted]

C.E.O.

RAND S.p.A.