How does Fedegari answer to Annex 1 requirements?

V.Mascherpa, Senior R&D Consultant, Fedegari Group

Agenda

EudraLex & Annex 1 Overview

Analysis of the Fedegari design criteria according to Annex 1

Q & A

EudraLex

- **10 Volumes** with several Annexes, containing *"**The rules governing medicinal products in the European Union**".*
- EudraLex is a ***system of Rules***, thanks to the various Directives, including 2003/94/EC "laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use".

- The basic legislation is supported by a series of *Guidances* that are published in the other volumes

Body of European Union legislation

The body of EudraLex is compiled in Volume 1 and Volume 5 of the publication "*The rules governing medicinal products in the European union*":

- **Volume 1** - *EU pharmaceutical legislation for medicinal products for human use*
- **Volume 5** - *EU pharmaceutical legislation for medicinal products for s*

Guidelines

- The basic legislation is supported by a series of *Guidances* that are published in the other volumes of the "*The rules governing medicinal products in the European union*"

- **Volume 4** contains a *"Guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively.c*

… In short, this Volume is often referred to as "GMPs".

Annexes to EudraLex Vol. 4

Annex 1 to EudraLex Volume 4 deals (formally as "*guidance" to a "guidance*") with the Manufacture of Sterile Products.

N. B. The restriction *"Medicinal Sterile Products"* still present in the title of the final document, issued Aug. 23, 2022, is negated by the Scope (Clause 1) and Principles (Clause 2) of the document itself.

Other very important Annexes to EudraLex Volume 4 are:
Annex 11: *Computerised Systems*
Annex 15: *Qualification and Validation*
Annex 17: *Real Time Release Testing and Parametric release*

Annex 1- Manufacture of sterile medicinal product

First issue in 1971

Several targeted updates

Full review (started 2015)

- QRM Principles;
- New sections;
- Restructured to give more logical flow;
- Added detail to a number of the previous sections to provide further clarity

Publication of the final and definitive version
August 22, 2022

In force on August 25, 2023 *

* August 25, 2024 for point 8.123 related to *Lyophilizer sterilization and barrier technology*.

What is new? Close up on major changes

"The GMP/GDP Inspectors Working Group and the PIC/S Committee jointly recommend that the current version of annex 1, on the manufacture of sterile medicinal products, is revised ***to reflect changes in regulatory and manufacturing environments****. The new guideline should* ***clarify*** *how manufacturers can take* ***advantage of new possibilities deriving from the application of an enhanced process understanding*** *by using innovative tools as described in the ICH Q9 and Q10 guidelines.*

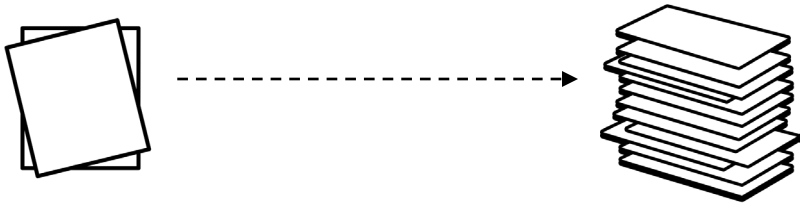
The revision of Annex 1 should also ***take into account related changes in other GMP chapters and annexes*** *as well as in other regulatory documents. The revised guideline will seek to* ***remove ambiguity and inconsistencies*** *and will* ***take account of advances in technologies****."*

Annex 1 2022, Reason for changes

What is new? Close up on major changes

The current version of Annex 1 2022 has become much longer and more detailed than the previous edition of 2007.

Its dense fifteen pages become fifty-eight in the soon-in-force document.



The new text is enriched with **explanations**, **descriptions**, and **details**. This "**content enrichment**" regards all the chapters.

… about the content enrichment

Chapter no. 4 (**Premises**) is almost *twice long* as, and much more *detailed* than the corresponding parts in Annex 1 2008.

Barrier technologies, e.g. *Restricted Access Barrier System* (RABS) and Isolators

Cleanroom and **Grades** of cleanroom

Transfer of equipment and materials

Chapters no. 5 (***Equipment***), no. 6 (***Utilities***), no. 7 (***Personnel***) and the part of no. 8 (***Production and Sterile Technologies***) dealing with aseptic preparation and processing are undergoing a remarkable amplification and revision.

What is new? Close up on major changes

The new Annex 1 is enriched with new and important concepts not previously used

- **QRM** → Quality Risk Management
- **CCS** → Contamination Control Strategy
- **CAPA** → Corrective and Preventive Actions
- **PQS** → Pharmaceutical Quality System

What is new? Impact on sterilization

As far as the sterilization proceedings are concerned, the new Annex 1 (issued 2022) expresses the **demand to ameliorate the present average level of safety and quality in the manufacture of the sterile products by means of a standardization at the state-of-the-art**.

As far as heat sterilization is concerned, most innovations are a photograph of the present top-level manufacturing practice

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Section 4- Premises

*4.1 The **manufacture of sterile products** should be carried out in **appropriate cleanrooms**, entry to which should be through change rooms that act as airlocks for personnel and airlocks for equipment and materials. Cleanrooms and change rooms **should be maintained to an appropriate cleanliness standard** and **supplied with air that has passed through filters of an appropriate efficiency**. Controls and monitoring should be scientifically justified and should effectively evaluate the state of environmental conditions of cleanrooms, airlocks and pass-through hatches.*

*This clause demands for strict isolation of clean areas. Fedegari double-end sterilizers are provided with a sophisticated **door interlock system**. Basic features are:*

a) the two doors cannot be unlocked simultaneously;

b) the unlocking of the clean side door may be subject to the completion of a successful sterilization cycle after any previous unlocking of the opposite door.

Section 4- Premises

*4.5 In cleanrooms and critical zones, **all exposed surfaces should be smooth, impervious and unbroken** in order to minimize the shedding or accumulation of particles or micro-organisms.*

*Exposed materials of the **clean side front of the Fedegari sterilizer** are exclusively polished stainless steel, smooth plastic, and glass.*

*"**Coplanarity**" is a strict design criterion for shaping the clean side front of Fedegari sterilizers.*

Section 4- Premises

*4.6 To **reduce accumulation of dust** and to **facilitate cleaning** there should be no recesses that are difficult to clean effectively, therefore **projecting ledges**, **shelves**, **cupboards** and **equipment should be kept to a minimum**. Doors should be designed to **avoid recesses** that cannot be cleaned. Sliding doors may be undesirable for this reason.*

No projecting ledges, shelves, cupboards and equipment are present on the clean side front of Fedegari sterilizers.
*Space around the door is rectilinear and large enough for **easy cleaning operations**.*
***Sliding doors** are not prohibited: they are only the object of a generic warning. In fact, they are almost exclusively preferred by users due to the absence of parts to lubricate and driving chains in their mechanism.*
***Exposed materials in moving rolls** are FDA approved.*

Section 4- Premises

*4.8 **Ceilings** should be **designed** and **sealed** to prevent contamination from the space above them*

Fedegari sterilizers are designed with full height and tight clean side front panels; these panels are sealable to false ceilings.

Section 4- Premises

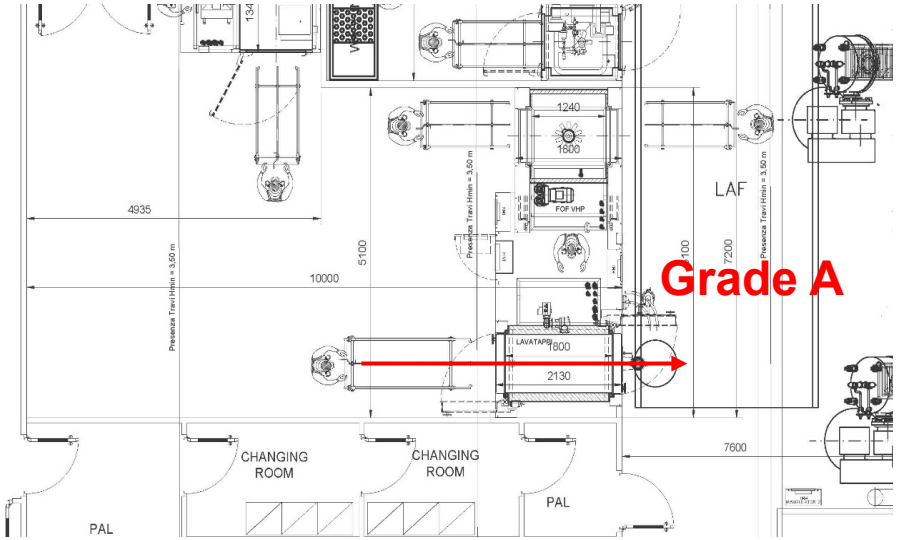
4.9 ***Sinks and drains should be prohibited in the grade A and grade B areas****. In other cleanrooms, air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade cleanrooms should be fitted with traps or water seals designed to prevent back flow and should be regularly cleaned, disinfected and maintained.*

In Fedegari sterilizers neither sinks nor drains are in the clean area.

The design of sink and drain is custom tailored according to URSs to comply with the solution locally adopted for preventing any backflow.

Section 4- Premises

*4.11 The **transfer of materials**, **equipment**, and **components** into **the grade A or B areas** should be carried out via a **unidirectional process**. Where possible, items **should be sterilised and passed into these areas through double-ended sterilisers** (e.g. through a double-door autoclave or depyrogenation oven/tunnel) sealed into the wall. Where sterilisation upon transfer of the items is not possible, etc. etc.*



Double-end Fedegari sterilizers are sealable to walls between areas of different grades.

Note: The other requirements of the clause only affect the organization of the manufacturers of sterile products.

Section 4- Premises

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. … 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, etc.*

- *Fedegari customizes the design and manufacturing of sterilizers for pathogenic or highly toxic materials to* ***prevent risks of environmental contamination****.*
- *The basic design criterion is to* ***lock any free discharge*** *of vapors, gases and liquids from such sterilizers as soon as the loading door has been opened till the completion of a successful sterilization.*
- *In addition, or as an alternative, if expressly requested by URSs, the solution is adopted to decontaminate or treat fluids leaving the sterilizer, prior, during or after the sterilization of a risky load.*

Section 5- Equipment

*5.3 As far as practicable, **equipment**, **fittings** and **services should be designed and installed so that operations, maintenance, and repairs can be performed outside the cleanroom**. If maintenance has to be performed in the cleanroom, and the required standards of cleanliness and/or asepsis cannot be maintained, then precautions such as restricting access to the work area to specified personnel, generation of clearly defined work protocols and maintenance procedures should be considered. Additional cleaning, disinfection and environmental monitoring should also be considered. If sterilisation of equipment is required, it should be carried out, wherever possible, after complete reassembly.*

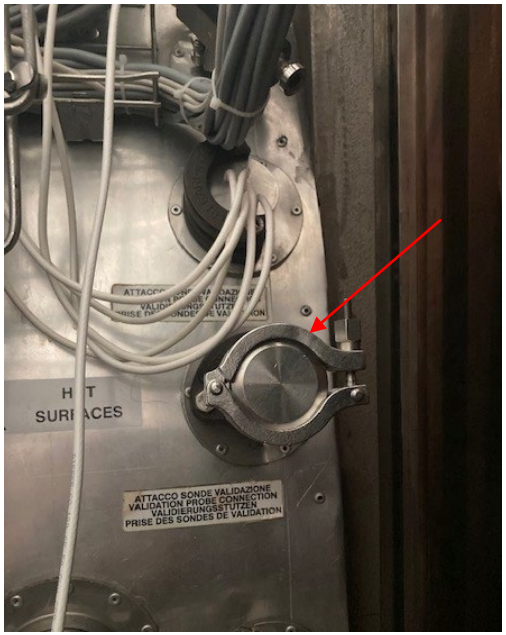
*All the **inspectable components** of Fedegari sterilizers are included in a "**technical compartment**", the so-called "technical space".*

*The technical compartment is **tightly isolated** from the clean area to which the sterilizers are unloaded.*

No maintenance personnel is thus necessary for routine intervention during aseptic operations.

Section 5- Equipment

*5.6 All equipment such as **sterilisers**, air handling systems (including air filtration) and water systems **should be subject to qualification, monitoring and planned maintenance**. Upon completion of maintenance, their return to use should be approved*



*Fedegari sterilizers are equipped with **validation ports**, accessible form the technical compartment.*

***Any** pre-validation **activity** prior to the commissioning is **recorded** and the relevant documentation is part of the supply.*

Section 6- Utilities

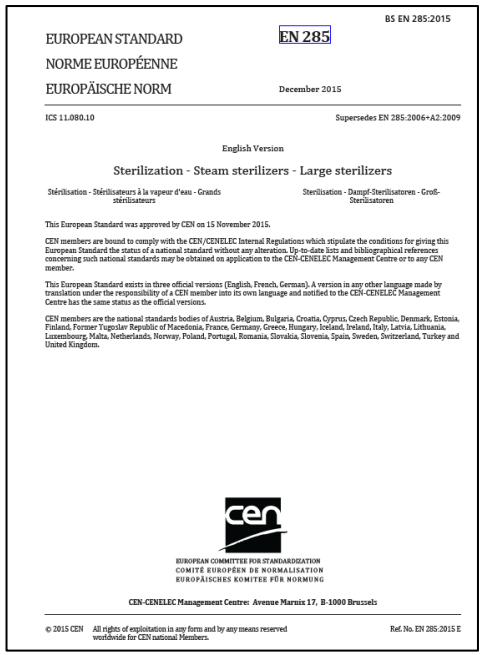
6.6 ***Pipes, ducts and other utilities <u>should not be present</u> in cleanrooms****. If unavoidable, then they should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean. Installation should allow cleaning and disinfection of outer surface of the pipes.*

Technical compartment

In Fedegari sterilizers all pipes and ducts and utilities connection are included in the ***technical compartment****.*

Steam used as a direct sterilising agent

6.16 Feed water to a pure steam (clean steam) generator should be appropriately purified. ***Pure steam generators should be designed, qualified and operated in a manner to ensure that the quality of steam produced meets defined chemical and endotoxin levels****.*



BS EN 285:2015

EUROPEAN STANDARD
NORME EUROPÉENNE
EUROPÄISCHE NORM

EN 285

December 2015

ICS 11.080.10

Supersedes EN 285:2006+A2:2009

English Version

Sterilization - Steam sterilizers - Large sterilizers

Stérilisation - Stérilisateurs à la vapeur d'eau - Grands stérilisateurs

Sterilisation - Dampf-Sterilisatoren - Groß-Sterilisatoren

This European Standard was approved by CEN on 15 November 2015.

CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration. Up-to-date lists and bibliographical references concerning such national standards may be obtained on application to the CEN-CENELEC Management Centre or to any CEN member.

This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the CEN-CENELEC Management Centre has the same status as the official versions.

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CEN-CENELEC Management Centre: Avenue Marnix 17, B-1000 Brussels

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Ref. No. EN 285:2015 E

Fedegari sterilizers may use steam either from a ***central source****, or from an* ***embedded generator****.*

In the case of steam from a central source, the in-battery ***steam pipes*** *to the chamber are fitted with* ***ports suitable for the quality tests*** *required by the user on the steam.*

Annex 1 does not give limits for non-condensable gases, dryness value and superheat.

These limits of non-condensable gases, dryness value and superheat are fixed in EN285:2015 as ***worst case for testing*** *the sterilizers and therefore are referred to in EN-ISO/TS 17665-2 as minimum quality requirement for the steam fed to sterilizers complying with EN285:2015.*

Steam used as a direct sterilising agent

6.17 Steam used as a direct sterilising agent should be of suitable quality and should not contain additives at a level that could cause contamination of product or equipment. For a ***generator supplying pure steam*** *used for the direct sterilisation of materials or product-contact surfaces (e.g. porous hard-good autoclave loads),* ***steam condensate should meet the current monograph for WFI of the relevant Pharmacopeia*** *(microbial testing is not mandatory for steam condensate). A suitable sampling schedule should be in place to ensure that representative pure steam is obtained for analysis on a regular basis. Other aspects of the quality of pure steam used for sterilisation should be assessed periodically against validated parameters. These parameters should include the following (unless otherwise justified): non-condensable gases, dryness value (dryness fraction) and superheat.*

Section 6- Utilities

*The condensate from the steam produced by **Fedegari embedded generators** complies with the pureness requirement as WFI, provided that the steam generator is fed with water of the suitable quality. The same is true for the content of non-condensable gases in the steam, and the superheat.*

Furthermore, the design of Fedegari embedded steam generators guarantees compliance of the connected Fedegari sterilizer with the drying requirements stated for the sterilizer in Paragraph 8.3 of European Standard EN 285:2015 if tested as described in Clause 20.

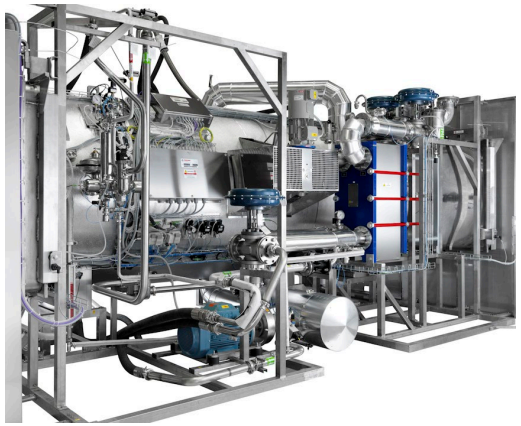
This does not involve that the steam produced by the Fedegari embedded generators will always comply with the dryness value requirements for the steam stated in Clause 21 of European Standard EN 285:2015.

Heating and cooling systems

*6.21 Major **items of equipment associated with hydraulic, heating and cooling systems should**, where possible, be **located outside the filling room**. There should be appropriate controls to contain any spillage and/or cross contamination associated with the system fluids.*

*6.22 Any **leaks from these systems** that would present a risk to the product **should be detectable** (e.g. an indication system for leakage).*

Technical compartment



*Steam generators and / or chillers, when present, are located in the **technical compartment** of Fedegari sterilizers, which is tightly isolated from higher-grade zones.*

Section 7- Personnel

*7.2 Only the **minimum number of personnel required should be present in cleanrooms**. The maximum number of operators in cleanrooms should be determined, documented and considered during activities such as initial qualification and APS, so as not to compromise sterility assurance.*

*As already seen, **all the inspectable components of Fedegari sterilizers are included in the technical compartment** tightly isolated from the clean area to which the sterilized items are unloaded. No maintenance personnel are thus necessary for routine intervention during aseptic operations.*

*The **unloading operations of sterilized items from the clean side door** of the sterilizers are made easier and ergonomic by the combination of internal and external trolleys, a standard feature for Fedegari sterilizers.*

Section 8- Production and specific technologies

*8.34 Where possible, **finished product should be terminally sterilised**, using a **validated and controlled sterilisation process**, as this provides a greater assurance of sterility than a validated and controlled sterile filtration process and/or aseptic processing. Where it is not possible for a product to undergo terminal sterilisation, consideration should be given to using post-aseptic processing terminal heat treatment, combined with aseptic process to give improved sterility assurance.*

*This clause further strengthens the assessment in the European Pharmacopoeia, that **terminal sterilization by heat is the method of choice to produce sterile products** rather than filtration and aseptic process.*

Section 8- Production and specific technologies

*8.35 The **selection**, **design** and **location** of the equipment and **cycle/programme** used for sterilisation should be based on **scientific principles** and data which demonstrate **repeatability** and **reliability** of the sterilisation process. All **parameters** should be **defined**, and **where critical**, these should be **controlled**, **monitored** and **recorded**.*

STERILIZATION CONTROL

n.	parameters	value
1	MIN STERILIZATION TEMPERATURE	120.0
2	MAX STERILIZATION TEMPERATURE	122.0
3	CONTROL TEMPERATURE	121.0
4	EXPOSURE TIME	20:00
5	MAX OFF TIME STERILISATION	5:00
6	MAX EXCESS STERILIZ.TIME	5:00
7	Z COEFF. FOR F(T,z) CALC.	10.00
8	REFER.T FOR F(T,z) CALCUL.	121.11
9	F(T,z) CALC.LOWEST TEMPERATURE	100.0

PHASE/GROUPS PARAMETERS

n.	n. phase	parameters	value
1	1	AUXILIARY OUTPUT	0
2	1	AUXILIARY OUTPUT TIMED (s)	0
3	1	AUXILIARY HEATING	3
4	1	AUXILIARY HEATING TEMPERATURE	110
5	1	MAX.HEATING DURATION	999
6	1	AUXILIARY CONTROL	0
7	2	TARGET PRESSURE	0.10
8	2	VACUUM VALVE OPENING PRESSURE	1.25
9	2	MAX.PHASE TIME	10
10	2	AUXILIARY HEATING	3
11	2	AUXILIARY HEATING TEMPERATURE	110
12	2	DEPRESSURIZE AIR FILTER	0
13	3	DURATION VACUUM, STEAM INJECT.	3
14	3	MIN.PRESSURE RISE	0.00
15	3	CHAMBER PRESSURE RISE	0.10
16	3	AUXILIARY HEATING	3
17	3	AUXILIARY HEATING TEMPERATURE	105
18	3	MAX.ALLOWED TEMPERATURE	123
19	3	PREPARE AIR FILTER	0
20	4	STERILIZATION START DELAY	0
21	4	MAX.HEATING DURATION	40
22	4, 5	STERILIZE AIR FILTER	0

*Fedegari controllers allow a **precise management of all the process parameters chosen by final users** (temperatures, time and or equivalent time F, heating and cooling rates, pressure, pressure change rates, etc.)*

Section 8- Production and specific technologies

8.36 ***All sterilisation processes should be validated****. Validation studies should take into account the product composition, storage conditions and maximum time between the start of the preparation of a product or material to be sterilised and its sterilisation.*

Continuous monitoring*,* ***repeatable control*** *and* ***independent recording of process physical data****, as well as storing them in non-volatile memories, are basic features of Fedegari process controllers. The availability of these data for comparison is the first step of validation.*

The ***effectiveness of sterilization*** *involve firstly the* ***demonstration of temperature distribution****, both in empty chamber and with effective load patterns, and the* ***demonstration of heat penetration*** *with effective load patterns.*

A correct temperature distribution is demonstrated by the so called "temperature mapping", and may be performed either as Type Test, if applicable and with reference to empty chamber only, or as Factory Acceptance Test. In any case, the temperature mapping should be repeated after the installation in the user's site, as it depends partially on the quality of the steam in use.

Temperature distribution studies with effective load patterns and heat penetration studies depend on the availability of real products and refer exclusively to these ones.

Section 8- Production and specific technologies

*8.36 (cont'd) Before any sterilisation process is adopted, its **suitability** for the product and equipment, and its **efficacy** in consistently achieving the desired sterilising conditions in all parts of each type of load to be processed should be **validated** notably by **physical measurements** and where appropriate by **Biological Indicators** (BI).*

*Moist-heat sterilizers demand for the **previous removal of air** and the **presence of condensing steam or liquid water** in contact with the microorganisms to inactivate. For dry-heat sterilizers only, the attainment of the specified heat penetration means achieving the desired sterilizing conditions.*

*For moist-heat sterilizers it has either to be respected the **maximum equilibration time** required by the European Standard EN 285:2015 (that is not possible with all "families" of load), or the efficacy of the actual exposure condition is to be demonstrated by the **inactivation** of suitable and properly located **biological indicators**. These cases are detailed in Clause 8.11 od EN ISO Standard 17665-1:2006.*

*Fedegari sterilizers provide **validation ports** for temperature mapping and heat distribution studies.*

Section 8- Production and specific technologies

*8.36 (end) For **effective sterilisation**, the whole of the product, and surfaces of equipment and components should be subject to the required treatment and the process should be designed to ensure that this is achieved*

*Fedegari sterilizers provide a **detailed routine monitoring and recording of physical data** within the chamber and the loads.*

After completing validation, it will be possible to recognize the routine accomplishment of the required treatment from physical measurement only.

Differently from the case of sterilization by gases and vapors, the routinary use of biological indicators will be necessary only very seldom in heat sterilization practice.

.

Section 8- Production and specific technologies

*8.37 Particular **attention** should be given when the adopted product **sterilisation method** is **not described in** the current edition of the **Pharmacopoeia**, or when it is used for a product which is not **a simple aqueous solution**. Where possible, heat sterilisation is the method of choice.*

Oily solutions are no longer considered "easy to sterilize": This is obtained by simply removing a single word in the new Clause 8.37. In fact, they can be an easy case only if the content of water is enough to generate inside containers such an amount of steam that could fill all the volume of the container. We are not talking about a big quantity, as the specific volume of steam under current moist-heat sterilization condition is almost eight hundred ninety times more than of liquid water at ambient temperature.

Oily solutions no longer equated to aqueous solutions

Oily solutions can be "simple" only if the amount of water contained is sufficient to develop steam

Section 8- Production and specific technologies

8.39 The validity of the sterilizing process should be reviewed and verified at scheduled intervals based on risk. Heat sterilization cycles should be revalidated with a minimum frequency of at least annually for load patterns that are considered worst case. Other load patterns should be validated at a frequency justified in the CCS.

8.40 Routine operating parameters should be established and adhered to for all sterilization processes, e.g. **physical parameters** and loading patterns.

*Clauses 8.39 and 8.40 are related to **well-established common sterilization practices** both in Europe and elsewhere.*

*Clause 8.39 also summarizes the **primary role of physical parameters** for evaluating the efficacy-in-routine of a sterilization process.*

Section 8- Production and specific technologies

8.41 There should be **mechanisms** in place to detect a sterilization cycle that does **not conform** to the validated parameters. Any **failed sterilization** or sterilization that deviated from the validated process (e.g. have longer or shorter phases such as heating cycles) should be **investigated**.

Same concept of clause 7.2 (*Fault indication system*) of EN 285:2015 about the design and validation of the control and alarm system of sterilizers

*The requirements are targeted to the correct **design** and **validation of the control and alarm** system of sterilizers. The first one may also be regarded as a "bridge" toward parametric release, asking for an automatic detection of any deviation. The final sentence is targeted to organizational aspects in manufacturing sterile products. Thanks to Fedegari TH4, it is possible to **define "critical" alarms**. The user can easily and thoroughly investigate the causes thereof when occurring.*

Section 8- Production and specific technologies

The requirements of **Clauses 8.42** and **8.43**, related to **Biological Indicators**, are under the responsibility of the final user.

The **use of BIs** in routine for heat sterilization was and remains not necessary even in the case that their role has been essential in the validation exercise.

Even when BI results are necessary, they alone "*do not give assurance of sterilization*" and the conformity to validated physical parameters "should" not be overridden.

The requirements of **Clause 8.44** don't directly affect the design of sterilizers, as they are related to **labelling of products**, **equipment** and **components** before and after the sterilization process. But they include two new points

Section 8- Production and specific technologies

8.45 **Sterilization records** should be **available for each sterilization run**. Each cycle should have a **unique identifier**. They should be reviewed and approved as part of the batch certification procedure.

```
25/06/21 16:32:39                FILE: 74_[illegible]1.prg
DATE FORMAT: DD/MM/YY HH:MM:SS
LANGUAGE: ENGLISH(ENG)
1||SERIAL NUMBER: NF8200
- PRODUCT CODE: Preliminary test
- BATCH No.: 21.06.21_02
- ID. STERILIZER: RES02_FOAF
PROGRESSIVE N.:       3524

PROGRAM            74
sterilization w/o drying
FILE      74_[illegible]
PROGRAMMER [illegible]
OPERATOR   [illegible]

PRODUCT CODE     Preliminary test
BATCH No.        21.06.21_02
ID. STERILIZER   RES02_FOAF
NOTES
Only pearled



MODEL                            FOAF3sp.
SERIAL NUMBER                    NF8200
LANGUAGE                         ENGLISH(ENG)
DATE AND TIME FORMAT             DD/MM/YY HH:MM:SS
TEMPERATURE UNIT                 0 (°C)
PRESSURE UNIT                    0 (bar)
P/G LIBRARY SW VERSION           T4LIB2Xa.00.00
PROGRESSIVE N.                         3524
```

Generation of records of physical data is a standard feature of Fedegari sterilizers

Sterilization by heat

8.50 ***Each heat sterilisation cycle should be recorded*** *either electronically or by hardcopy,* ***using equipment with suitable accuracy and precision****. The system should have* ***safeguards*** *and/or* ***redundancy*** *in its control and monitoring instrumentation to detect a cycle not conforming to the validated cycle parameter requirements and abort or fail this cycle (e.g. by the use of duplex/double probes connected to independent control and monitoring systems*

In addition to digital recording of physical data, Fedegari sterilizers include as a standard also a graphic representation of the process. The largeness of the graphic scale, the accuracy and the precision of the measurements are equal to, or better than specified by the European Standard EN 285:2015.

Redundancy of recording probes requested (or at least suggested) by clause 8.50 is at present an available option for Fedegari sterilizers; it may be foreseen that it will become a standard.

Section 8- Production and specific technologies

*8.51 The **position** of the **temperature probes** used **for controlling** and/or **recording** should be determined during the validation and selected based on system design and in order to correctly record and represent routine cycle conditions. **Validation studies** should be designed to demonstrate the suitability of system control and recording probe locations and should include the verification of the function and location of these probes by the use of an independent monitoring probe located at the same position during validation.*

*In most cases, Fedegari sterilizers provide **four "product" and/or recording temperature probes independent of the control sensors** (one fixed in the drain and three flexible).*
The total number is defined by URSs and Functional Specification.
It is the responsibility of the user to comply in routine with the position of the temperature probes as determined during the validation for each load pattern.

Section 8- Production and specific technologies

8.52 ***The whole of the load should reach the required temperature before measurement of the sterilising time-period starts****. For sterilisation cycles controlled by using a* ***reference probe within the load****, specific consideration should be given to ensuring the load probe temperature is controlled within defined temperature range prior to cycle commencement.*

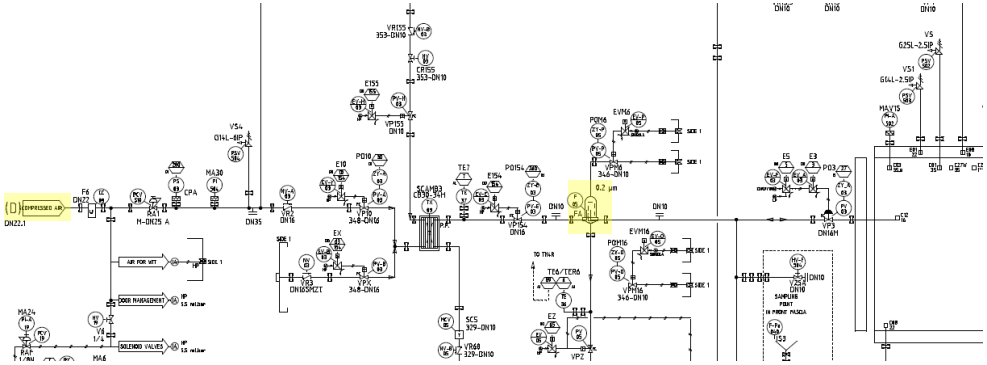
Fedegari sterilizer controllers commence the measurement of the sterilizing time ***only after all*** *the probes programmed for monitoring the load (the so-called "****product" probes****)* ***have reached the required temperature****. It is the responsibility of the user to locate these probes in routine at the same positions determined during validation for each load pattern.*

The ***option*** *is also provided to* ***delay the measurement of the sterilizing time-period*** *after all the programmed probes have reached the required temperature. This delay can tentatively correspond to the actual equilibration time.*

In addition, Clause 8.52 adds the less obvious warning that "the probe within the load", if present, shall not commence the cycle in a too warm condition. This may become critical in cycles for liquids.

Section 8- Production and specific technologies

8.53 After completion of the high temperature phase of a heat sterilisation cycle, precautions should be taken against contamination of a sterilised load during cooling. Any cooling liquid or gas that comes into contact with the product or sterilised material should be sterilised.



*Air (or other ballasting gas) is entering Fedegari sterilizers only through one or more **sterilizing filters**. This filter (or these filters) may be sterilized* in situ *and tested for efficiency by methods defined by the filter manufacturer and integrated in the control system of the sterilizer.*

Section 8- Production and specific technologies

8.53 After completion of the high temperature phase of a heat sterilisation cycle, precautions should be taken against contamination of a sterilised load during cooling. Any cooling liquid or gas that comes into contact with the product or sterilised material should be sterilised.

*If the sterilizer includes, on request, **spray cooling phases**, the **cooling water must be sterile** and is in most cases supplied by an external loop. If an "on board" water sterilization circuit is supplied with the sterilizer (the old R3 cooling), the spray cooling phase is prevented from starting until the sterilization of the cooling water has been completed, but this feature is now very unusual.*

Any different management of the precautions against final recontamination is responsibility of the user.

Section 8- Production and specific technologies

*8.54 In those cases where **parametric release** has been **authorized**, a robust system should be applied to the product lifecycle validation and the routine monitoring of the manufacturing process. This system should be periodically reviewed. Further guidance regarding parametric release is provided in Annex 17.*

PARAMETRIC RELEASE TABLE

Training

Phase	Name	UM	Min	Set	Max
13	F0 minimo totale MIN{bf[TE2],bf[TE4]}	min.	15	-	-
13	F0 massimo totale MAX{bf[TE2],bf[TE4]}	min.	-	-	25

PARAMETRIC RELEASE REPORT

1 = Parameter compliant
0 = Parameter not compliant
? = Parameter not evaluated

Phase	Name	UM	Min	Set	Max	Value	R
13	F0 minimo totale	min.	15	-	-	16	1
13	F0 massimo totale	min.	-	-	25	16	1

PROGRAM START TIME 06/12/18 10:56:03
PROGRAM END TIME 06/12/18 11:46:47
STERILIZATION N. 516 OK
MIN STERILIZ. TEMPERATURE °C 120.1 (4)
MAX STERILIZ. TEMPERATURE °C 121.0 (2)
STERIL. PHASE DURATION min.ss 12:31
F(T,z) MIN: 15.9 (4)
F(T,z) MAX: 16.1 (2)

WITH PARAM.RELEASE TABLE: OK

*The on-board control and recording devices of Fedegari sterilizers provide the user with information for a quick and transparent **comparison of physical data of any run with the validated process tolerances**: this may help greatly for parametric release.*

Furthermore, additional SW options provide functions that enable a direct comparison, either graphical or numerical, of actual data runs with validated process parameters stored as reference.

Moist heat sterilization

8.55 ***Moist heat sterilisation can be achieved using steam****, (****direct or indirect contact****), but also includes other systems such as* ***superheated water systems*** *(****cascade or immersion cycles****) that could be used for containers that may be damaged by other cycle designs (e.g. Blow-Fill-Seal containers, plastic bags).*

8.56 The items to be sterilised, other than products in sealed containers, should be ***dry****,* ***packaged in a protective barrier system*** *which allows removal of air and penetration of steam and* ***prevents recontamination*** *after sterilisation. All loaded items should be dry upon removal from the steriliser. Load dryness should be confirmed by visual inspection as a part of the sterilisation process acceptance*

Section 8- Production and specific technologies

*Fedegari sterilizers are equipped with **controlling, monitoring and recording systems** that allow the **continuous knowledge of physical conditions in the loading space of the sterilizer**.*

*It is the **responsibility of the user** to define the conditions of temperature and time required for the treatment of a product and validate the correspondence of them with biologically effective sterilizing conditions.*

It is also responsibility of the user to proper select wrapping materials.

*Fedegari sterilizers provide the user with **several drying methods** to prevent recontamination after sterilization and removal of the product from the chamber. The final choice and validation of the selected method is the responsibility of the user.*

Section 8- Production and specific technologies

*8.57 For **porous cycles** (hard goods), time, temperature and pressure should be used to **monitor the process and be recorded**. Each sterilised item should be inspected for damage, packaging material integrity and moisture on removal from the autoclave. Any item found not to be fit for purpose should be removed from the manufacturing area and an investigation performed.*

*Fedegari sterilizers are equipped with **controlling**, **monitoring** and **recording systems** that allow the **continuous knowledge of physical conditions** in the loading space of the sterilizer.*

*It is the **responsibility of the user** to define the conditions of temperature, time and vacuum required for the treatment of a product and evaluate the possible damage to the treated products.*

Confirmation of the importance of monitoring also pressure in “porous cycles”

Items sterilized should be inspected and rejecting them immediately if no longer “fit for purpose”.

Section 8- Production and specific technologies

*8.58 For **autoclaves capable of performing prevacuum sterilisation cycles**, **the temperature should be recorded at the chamber drain throughout the sterilisation period**. Load probes may also be used where appropriate, but the controlling system should remain related to the load validation. For steam in place systems, the temperature should be recorded at appropriate condensate drain locations throughout the sterilisation period.*

*Fedegari sterilizer controllers monitor and record **continuously** both temperature and pressure.*

*In the case of **pure steam process**, the temperature is controlled by pressure, i.e. the supply of steam to the chamber is controlled by the actual chamber pressure, thanks to the one-to-one relationship between saturated steam pressure and temperature.*

Section 8- Production and specific technologies

*8.58 For **autoclaves capable of performing prevacuum sterilisation cycles**, **the temperature should be recorded at the chamber drain throughout the sterilisation period**. Load probes may also be used where appropriate, but the controlling system should remain related to the load validation. For steam in place systems, the temperature should be recorded at appropriate condensate drain locations throughout the sterilisation period.*

*When the control of pressure chamber is intrinsically independent of temperature, as in the case of "**counterpressure" processes**, the control temperature probes are other than the monitoring temperature probes.*

*The clause also states that the **recording of drain temperature during the sterilization period** is required if the autoclave is "capable of performing prevacuum sterilization cycles". **Air-over-steam** cycles are obviously excluded, but the form of the sentence may cause ambiguities for mixed FOAF type autoclaves.*

Section 8- Production and specific technologies

8.59 ***Validation of porous cycles*** *should include a calculation of* ***equilibration time***, ***exposure time***, ***correlation of pressure and temperature*** *and the* ***minimum/maximum temperature range during exposure. Validation of fluid cycles*** *should include* ***temperature***, ***time and/or*** F_0. ***Critical processing parameters*** *should be subject to defined limits (including appropriate tolerances) and be confirmed as part of the sterilisation validation and routine cycle acceptance criteria.*

Fedegari sterilizer controllers ***monitor*** *and* ***record continuously*** *both temperature and pressure.*

All the ***data*** *necessary for the* ***calculation*** *of the* ***equilibration time*** *can be extracted from the cycle process report.*

It is the responsibility of the end user to correctly analyze and use this information.

Section 8- Production and specific technologies

F_0 is not admitted for replacing exposure time for porous loads.

Equilibration time is not applied to liquid loads.

The question whether a minimum temperature shall always be reached in a sterilization cycle, even when F_0-monitored, is left open by this clause. But EMA Guideline 2019 is very clear on this point: it must!

Section 8- Production and specific technologies

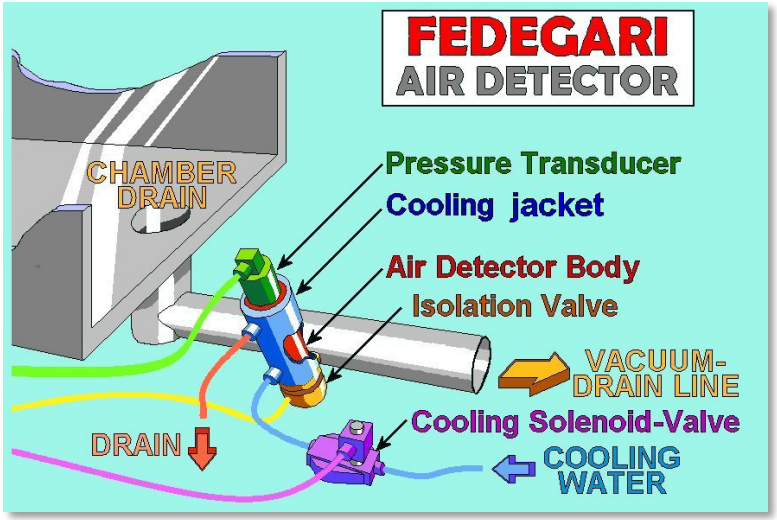
8.60 ***Leak tests on the steriliser*** *should be carried out periodically (normally weekly) when a vacuum phase is part of the cycle or the system is returned, post-sterilisation, to a pressure lower than the environment surrounding the steriliser.*

Fedegari sterilizers are equipped with ***vacuum leak test program*** *that can* ***detect a chamber leak****, if present.*

It is the responsibility of the user to select the applicable parameters for the test, the maximum time interval between two tests, and perform them.

Section 8- Production and specific technologies

*8.61 There should be **adequate assurance of air removal** prior to and during sterilisation when the sterilisation process includes air purging (e.g. porous autoclave loads, lyophilizer chambers). For autoclaves, this should include an air removal test cycle (normally performed on a daily basis) **or** the use of an air detector system. Loads to be sterilised should be designed to support effective air removal and be free draining to prevent the build-up of condensate.*



*Fedegari sterilizers can be equipped with an **Air Detector System for monitoring the residual presence of air before the commencement of the sterilization phase**.*

Section 8- Production and specific technologies

8.62 ***Distortion and damage of non-rigid containers*** *that are terminally sterilised, such as containers produced by Blow-Fill-Seal or Form-Fill-Seal technologies, should be prevented by appropriate cycle design and control (for instance setting correct pressure, heating and cooling rates and loading patterns).*

This clause formalizes as a "should" the ***current User's requirement for sterilization of non-rigid containers****.*

Fedegari "counterpressure" sterilizers provide a very ***large flexibility for the cycle development*** *and the* ***selection*** *of most suitable* ***pressure profile*** **versus** ***temperature****.*

Section 8- Production and specific technologies

*8.63 Where **steam in place systems are used for sterilisation** (e.g. for fixed pipework, vessels and lyophilizer chambers), the system should be appropriately designed and validated to assure all parts of the system are subjected to the required treatment. The system should be monitored for temperature, pressure and time at appropriate locations during routine use to ensure all areas are effectively and reproducibly sterilised. These locations should be demonstrated as being representative of, and correlated with, the slowest to heat locations during initial and routine validation. Once a system has been sterilised by steam in place, it should remain integral and where operations require, maintained under positive pressure or otherwise equipped with a sterilising vent filter prior to use.*

*This clause describes the current **"state-of-the-art" for steaming in place** and formalizes that this practice **should be validated and** monitored according to the same criteria of "porous cycles"*

Section 8- Production and specific technologies

*8.64 In **fluids load cycles where superheated water** is used as the **heat transfer medium**, the heated water should consistently reach all of the required **contact points**. Initial qualification studies should include **temperature mapping of the entire load**. There should be **routine checks on the equipment** to ensure that nozzles (where the water is introduced) are not blocked and drains remain free from debris.*

*In the so called "**static full water immersion**" **autoclaves superheated water** is the sole heat transfer medium and the requirement obviously strictly applies to them.*

*The **Fedegari superheated water autoclaves** circulate water at high flow-rate and spray it through fine-dispersion nozzles, so that the **heating medium in contact with the product is an intimate mixture of liquid superheated water and steam at the same temperature**.*

*The penetration of the heating medium to all the required contact points shall be demonstrated and validated by a suitable **temperature mapping of the entire load.***

Section 8- Production and specific technologies

*8.65 **Validation** of the sterilisation of **fluids loads in a superheated water autoclave** should include **temperature mapping** of the entire load and **heat penetration and reproducibility studies**. All parts of the load should heat up uniformly and achieve the desired temperature for the specified time. Routine temperature monitoring probes should be correlated to the worst case positions identified during the qualification process.*

*This clause photographs the **current "state-of-the art" for the validation of fluid loads**.*

*Fedegari superheated water autoclaves provide a **temperature uniformity** and **stability** during the exposure phase that is better than the commonly required band (- 0 °C / + 1 °C with reference to the "minimum sterilization temperature").*

Agenda

EudraLex & Annex 1 Overview

Analysis of the Fedegari design criteria according to Annex 1

Q & A

Thank you

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