Parametric Release and Annex 1

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PARAMETRIC RELEASE: bibliography

- USP NF 41, General Chapter 1222: TERMINALLY STERILIZED PHARMACEUTICAL PRODUCTS - PARAMETRIC RELEASE
- Annex 17 to the EU Guide to Good Manufacturing Practice
  Title: Parametric Release
- FDA Guidance for Industry Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes

PARAMETRIC RELEASE: preamble

It is recognised that a comprehensive set of **in-process tests and controls** *may provide greater assurance of the finished product meeting specification than finished product testing.*

Parametric release may be authorized for certain specific parameters as an alternative to routine testing of finished products.

Annex 17, EU GMP

PARAMETRIC RELEASE: preamble

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

Annex 1 (Revision 2022)

PARAMETRIC RELEASE: its meaning

"Parametric release is a practice to release finished product that relies on process control in lieu of end product testing to establish that a product is safe, pure, efficacious, and of suitable strength for commercial or clinical use. Parametric release is based on demonstrating that in-process conditions relevant to the establishment of key product quality attributes were attained and maintained throughout the relevant manufacturing steps. One attribute for which in-process controls would replace end product testing is sterility."

USP 41, General chapter 1222

PARAMETRIC RELEASE: And Sterility Testing

STERILITY TESTING

The sterility test is a harmonized compendial test. It must be understood that while execution of the test is required for the release of sterile products where parametric release has not been approved, it cannot prove the sterility of the materials tested.

It should be recognized that parametric release is the default mode of sterile product release.

USP 41, General chapter 1222

PARAMETRIC RELEASE: Its limit

A major limitation of *Sterility Test* is that it is based on a limited sample.

Table 3. Minimum Number of Articles to be Tested in Relation to the Number of Articles in the Batch

Number of Items in the Batch*	Minimum Number of Items to be Tested for Each Medium (unless otherwise justified and authorized)**
Parenteral preparations	
Not more than 100 containers	10% or 4 containers, whichever is the greater
More than 100 but not more than 500 containers	10 containers
More than 500 containers	2% or 20 containers, whichever is less
♦*For large-volume parenterals*	2% or 10 containers, whichever is less
Antibiotic solids	
Pharmacy bulk packages (<5 g)	20 containers
Pharmacy bulk packages (≥5 g)	6 containers
Bulks and blends	See *Bulk solid products*♦

PARAMETRIC RELEASE: An example of failure

Sampling plan: Devonport incident example

The Daily Telegraph

LONDON, TUESDAY, MARCH 7, 1972. Printed in LONDON and MANCHESTER 4 p

'Life or death' Ministry warning

HOSPITAL DRUG ALERT AS 5 DIE

Race to find 500 drip-feed bottles

DAILY TELEGRAPH REPORTERS

A "LIFE or death" hunt for 500 bottles of dextrose drip-feed solution was ordered last night by the Department of Health as emergency inquiries began into the recent deaths of five patients at Devonport hospital, Plymouth.

The patients had all been given the solution manufactured by Evans Medical Ltd., of Speke, Liverpool. In a joint statement the firm and the Department of Health said a batch of the solution may have been contaminated.

About 660 bottles of the suspect solution were distributed in May—and only 156 have been traced so far. A Health Department spokesman said: "This is a matter of life and death.

"We have moved as fast as possible to get the widest possible warnings out about the danger of this batch of the solution in the national interest."

"It is vital for everyone stocking this solution to make sure that not even a single bottle from the suspect batch is allowed to be used. Every bottle on the shelves must be checked."

The suspect batch is the 5 per cent. dextrose solution marked D 1192/C.

It is fed through the veins of hospital patients who cannot eat, including those who have just had major operations.

Mixed delivery

The Department of Health say bottles of the solution are normally distributed in boxes of twelve and it is possible that a warehouseman making up deliveries could have mixed bottles from the contaminated batch with bottles from unaffected batches.

As experts at the Devonport Hospital, Plymouth, began their inquiry into the five deaths last night, a South Western Regional Hospital Board spokesman said the patients had "one common denominator." Each had been given an infusion of the 5 per cent. dextrose solution manufactured by Evans Medical Ltd.

But there was nothing to say these people did not die from other causes, he added.

Two other patients in Devonport hospital are believed to be suffering from the effects of an infusion with the dextrose. One is understood to be seriously ill.

Four of the Devonport hospital patients who died were men and their names have not yet been disclosed. The fifth, was Mrs Gillian Myatt, 33, mother of two children, who lived at Acre Place, Stoke, Plymouth.

Death mystery

When the inquest on Mrs Myatt opened yesterday at Plymouth, Dr A. C. Hunt, consultant pathologist, said he could give no cause for her death.

He told the coroner: "Information was given to me that the batch of infusion fluid supplied to the hospital was dangerously contaminated."

Asked why Mrs Myatt died, Dr Hunt replied: "It possibly was due as a result of being given some of that fluid."

He added that the fluid was a proprietary brand supplied to many hospitals.

The coroner, Mr W. E. J. Major, was told that Mrs Myatt went into the hospital on February 25 and died on March 1.

Dr Hunt said that death was due to collapse following an operation for thrombosis in an artery in the left leg. The dextrose solution fed to Mrs Myatt was suspected by one of the doctors at the hospital and he asked for it to be examined.

Difficult to recognise

In answer to questions from the coroner, Dr Hunt agreed that if any other patients died as a result of the contaminated solution, their bodies would have been disposed of by now.

The condition would be very difficult to recognise, and death would have been accounted for by natural causes.

The inquest on Mrs Myatt was adjourned.

Later, announcing the hospital inquiry, Mr Major said the five deaths had been comparatively recent. The bodies had either been buried or cremated.

"We must bear in mind—as Dr Hunt said at the inquest—that it is quite possible the persons who may have had an injection of this stuff may have been so seriously ill that they would have died anyway.

"As Dr Hunt again told me, they would not have had this injection unless they had been seriously ill."

Mr Eric Sewell, spokesman for the South West Regional Hospital Board, said last night: "It is possible that other hospitals which have been using this batch of solution may be alerted to examine recent case histories of people who have died."

Asked if people who had been given infusions from the suspect solution and had now left hospital were considered to be at any risk, Mr Sewell said: "This is what any inquiries are all about.

"If the alert detective work carried out at Devonport hospital is followed in the same way, the answer might not take too long to find—one way or another."

Dr Denis Cahal, senior principal medical officer at the Department of Health, said on television last night that the distribution of the faulty solution was "just a human error—one of those accidents which sometimes occur."

Dr Cahal said that it would be about two days before all the bottles of batch D 1192/C were located. Most of them were believed to be in south-west England.

Joint statement

The joint statement issued last night by the Department of Health and the dextrose manufacturer, Evans Medical, said:

A sub-batch of 5 per cent. dextrose solution for intravenous feeding, manufactured by Evans Medical Ltd., of Speke, Liverpool, is suspected of being faulty.

The sub-batch number is D 1192/C and it was distributed in May, 1971.

The manufacturers have taken all possible steps to ensure that any bottles remaining from this sub-batch, which originally consisted of approximately 660 bottles, be returned to them.

So far 156 bottles have been accounted for and an unknown number may have been used since the sub-batch was issued.

The Department of Health and Social Security ask all hospital pharmacies, wholesale pharmacists, doctors and any other people who have in their possession any 5 per cent. dextrose solution manufactured by Evans of Speke, to check their stocks immediately and to return any bearing the number D 1192/C to the manufacturers.

They should not use any of the preparations bearing this number in any circumstances.

Glaxo subsidiary

Evans Medical Ltd. was founded nearly 200 years ago and is now a Glaxo subsidiary.

It manufactures several hundred lines of standard drugs for hospitals and the pharmaceutical trade. Few of its products can be bought over the counter at a chemists.

A spokesman said last night that 5 per cent. dextrose solution was purely restricted to hospital use and could not be bought at High Street pharmacies.

Guy's Hospital said last night that it had received the warning from the Department of Health, but that it did not have any 5 per cent. dextrose in stock.

A spokesman at St. Thomas' said an immediate check was being made.

Cyanide Threat—P6

In 1971, bottles were autoclaved at the same time. A fault on the machine resulted in only the bottles on the top two shelves being sterilised properly. Those on the lower shelf were not. There were quality control checks – but the assessed bottles were only taken from the top shelf so the failure wasn't detected and the whole batch was issued for use.

STERILITY TEST

Sterility testing by cultivation of finished units drawn from the batch is limited in its ability to detect contamination because of the following: (1) the small number of samples required for testing, which restricts the ability to capture those microorganisms dispersed in a large volume, and (2) the limited ability of the prescribed culture media to stimulate growth of all potential microorganisms. Typically, these tests will detect only major errors in the manufacturing process that result in contamination of a large number of product units.

PARAMETRIC RELEASE:

It is **unlikely** that a completely **new product** would be considered as suitable for PR because a period of satisfactory results will form part of the acceptance critera.

Annex 17, EU GMP

PARAMETRIC RELEASE: An FDA warning letter

WARNING LETTER

Lernapharm (Loris) Inc.

MARCS-CMS 552525 – SEPTEMBER 04, 2018

Your response states that you do not perform finished product sterility testing because you maintain written records and validation procedures for your parametric release "sterilization program."

Your response is inadequate. Your firm lacks an adequate sterilization method. You have not demonstrated an ongoing state of control and your products, which purport to be sterile, are produced using manufacturing methods that are inappropriate to support this claim.

In addition, parametric release is only appropriate for robust sterilization methods (e.g., steam sterilization). The robust sterilization method must also be augmented by a strong sterility assurance program, an extensive ongoing characterization of batch process control, and a vigilant quality system. See FDA's Compliance Policy Guide (CPG) **(b)(4)** entitled, **(b)(4).**

U.S. FOOD & DRUG ADMINISTRATION

PARAMETRIC RELEASE: How to apply it

In a parametric release program, sterility assurance is achieved by

- process,
- facility,
- systems engineering,
- the establishment of appropriate risk-based user requirement specifications

It is conclusively demonstrated by

- the establishment,
- control,
- monitoring of process parameters

that confirm those user requirements are met.

PARAMETRIC RELEASE: How to apply it

PARAMETRIC RELEASE

It is a possibility when:

- the mode of sterilization is well understood,
- the physical parameters of processing are well defined, predictable and measurable,
- the lethality of the cycle has been microbiologically validated

CONCLUSION

STERILITY TEST

PARAMETRIC RELEASE

PARAMETRIC RELEASE: Annex 1?

Annex 1 (2022)

*8.35 …**All parameters** should be defined, and where critical, these should be controlled, **monitored** and **recorded**.*

*8.41 …Any failed sterilization or sterilization **that deviated from the validated process** should be investigated!*

Annex 17 (2018)

*4.16 Routine monitoring of the **sterilizer should demonstrate that the validated conditions necessary to achieve the specified process is achieved in each cycle**. Critical processes should be specifically monitored during the sterilization phase.*

In summary, the above sections indicate we require a system that monitors the whole of the sterilization process and can compare the in-process results against validated results.

PARAMETRIC RELEASE: Annex 1?

Do autoclaves have such a system? Typically, not!!

It's common for autoclaves to have alarms that are generated when specific conditions are exceeded, such as time.

Additionally, it's common for more specific alarms to be present in the sterilization phase, covering min and max values of temperature, pressure and time.

But it's not common that alarms can be configured to ensure the validated conditions of an overall process are being maintained.

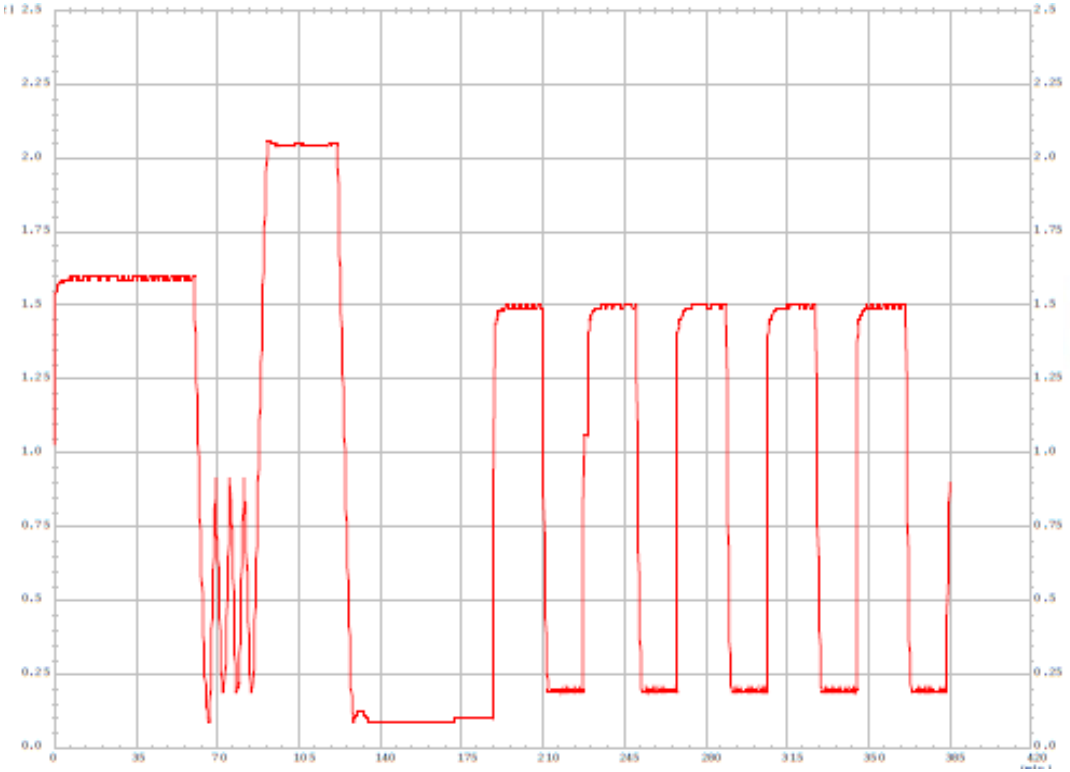
For example, to monitor the min and max time of a steam pulse or a depressurization rate or duration. Typically, alarms are in place to identify machine faults, not necessarily to monitor the validated process.

PARAMETRIC RELEASE/Annex 1: Case Study (Stoppers in bags)

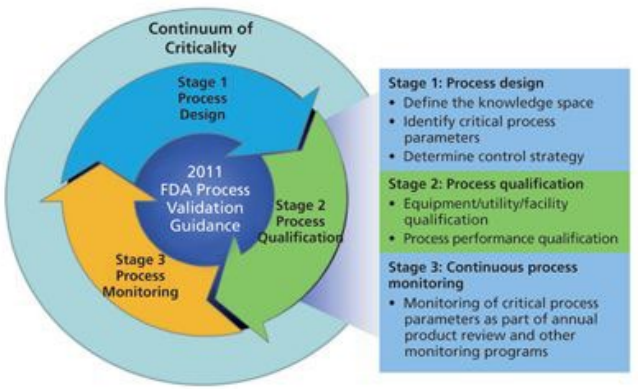
What at first seems a simple load, in fact requires a lot of different autoclave functions to process it correctly.

Any deviation from the validated process can cause multiple different issues, such as packaging integrity issues, load dryness issues and more.

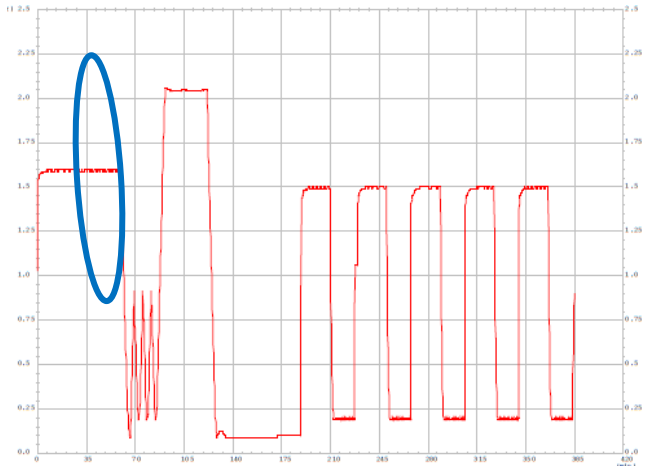
PARAMETRIC RELEASE/Annex 1: Case Study (Stoppers in bags)



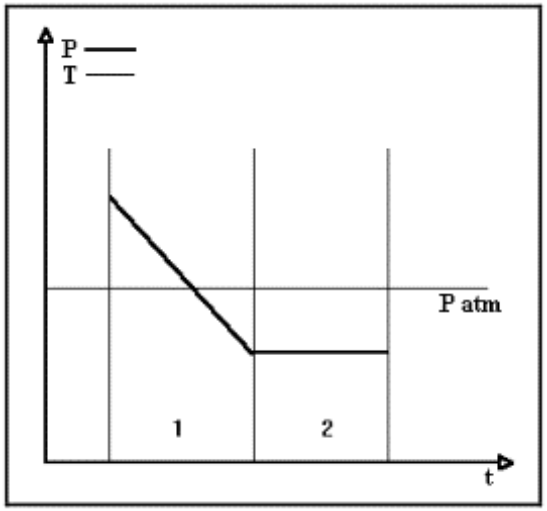
CPPs + CQAs



PARAMETRIC RELEASE/Annex 1: Case Study (Stoppers in bags)

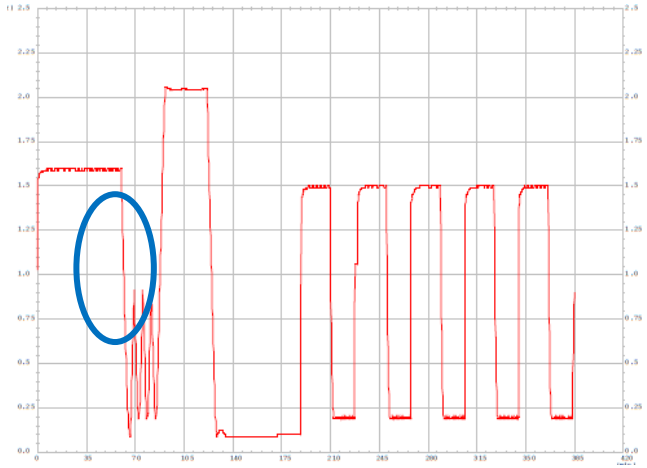


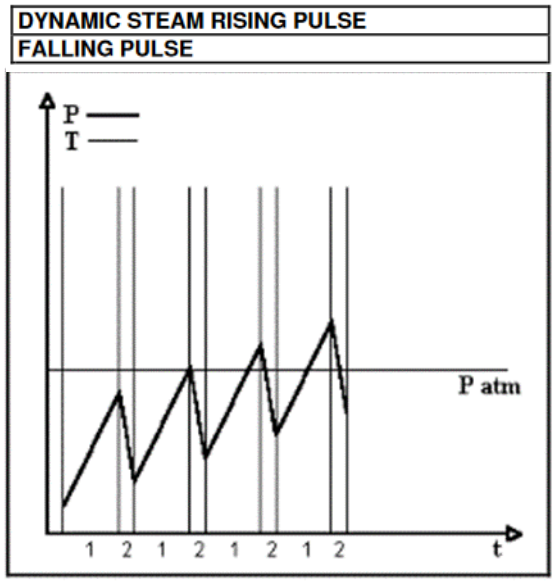
FUNCTION: **MODULATED DEPRESSURIZATION BY VACUUM PUMP**



Stage	Critical Process Parameters	Critical Quality Attributes
Modulated Depressurization	Target Pressure	Reaches pressure in correct time window
	Negative Pressure Gradient	Maintains correct pressure gradient
	Duration Vacuum	Maintains pressure widow during duration
	Auxiliary heating configuration	Activates correct auxiliary heating

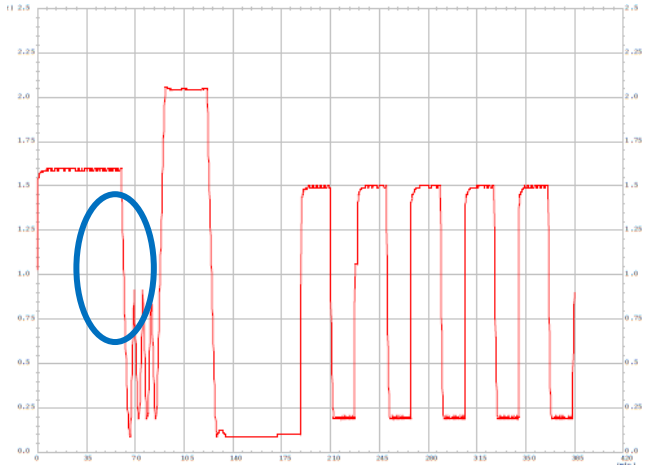
PARAMETRIC RELEASE/Annex 1: Case Study (Stoppers in bags)



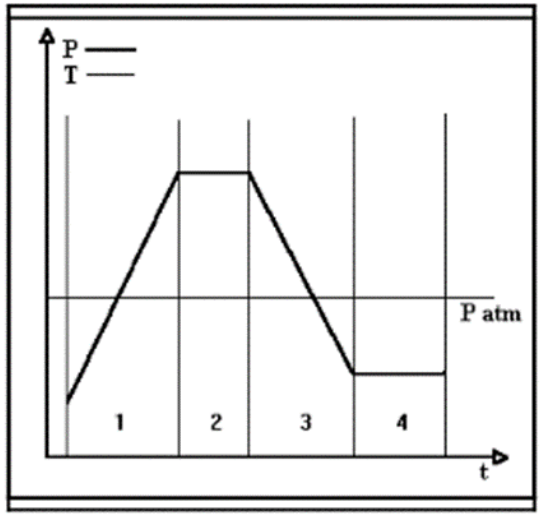


Stage	Critical Process Parameters	Critical Quality Attributes
Pulsed Air Removal	Target Pressure (positive)	Reaches pressure in correct time window
	Target Pressure (negative)	Reaches pressure in correct time window
	Auxiliary heating temperature	Maintains correct temperature window

PARAMETRIC RELEASE/Annex 1: Case Study



MODULATED STEAM RISING PULSE
DYNAMIC STEAM PRESSURE HOLD
MODULATED FALLING PULSE
TIMED VACUUM



Stage	Critical Process Parameters	Critical Quality Attributes
Modulated Air Removal	Target Pressure (positive)	Reaches pressure in correct time window
	Positive Pressure Gradient	Maintains correct pressure gradient
	Pressure(+) hold duration	Achieves correct phase duration
	Target Pressure (negative)	Reaches pressure in correct time window
	Negative Pressure Gradient	Maintains correct pressure gradient
	Pressure(-) hold duration	Achieves correct phase duration
	Auxiliary heating configuration	Activates correct auxiliary heating

PARAMETRIC RELEASE/Annex 1: Case Study (Stoppers in bags)

[redacted] REQUIREMENTS

Cycle Parameters	Minimum	Set Point	Maximum
Critical Parameters			
Exposure Time (min:sec)	-1%	11:00	+1%
Exposure Temperature (°F)	248.0	250.0	252.5
Exposure Temperature Delta (°F within each minute)	≤ 4.0 between TE #9 and TE #10[1]		
Exposure Pressure (psia)	-2.9	49.8	+2.9
Exposure Pressure (psia)	≤ 1.0 between TP #1 and TP #2[2]		
End of Cycle Load Monitors (F_0, minutes)	≥17.4	N/A	≤43.1
End of Cycle Load Monitors Delta (F_0, minutes)	≤ 1.0 maximum range among TE #2, TE #3 and TE #4[3]		
Non-Critical Parameters			
Heat Up Time (min:sec)	-1%	26:00	+1%
Cooling Time (min:sec)	-1%	60:00[4]	+1%
Cooling Pressure (psia)	-2.9	49.0	+2.9

FEDEGARI PROPOSAL

Phase	Name	UM	Min	Set	Max
3	EXPOSURE TIME (te-tb)/60	MIN:SEC	10:53=	-	11:06=
3	EXPOSURE TEMP M[TE2]&M[TE3]&M[TE4]	F	~~248.0=~~	-	252.5=
3	EXP. TEMP MIN m[TE2]&m[TE3]&m[TE4]	F	248=	-	-
3	EXPOSURE TEMP DIFF M[TE9-TE10]	F	-	-	4=
3	EXP. PRESS. MAX M[TP]&M[TP2]	PSIA	-	-	52.7=
3	EXP. PRESS. MIN m[TP]&m[TP2]	PSIA	46.9=	-	-
3	EXP. PRESS. DIFF. M[TP-TP2]	PSIA	-	-	1.0=
57	F0 END OF CYCLE ef[~~TB1~~]&ef[TE2]&ef[TE3]	F0	17.4=	-	43.1=
57	F0 CYCLE DIFF. MAX{ef[TE2-TE3],ef[TE3-TE4],ef[TE4-TE2]}	F0	-	-	1.0=
2	HEAT UP TIME (te-tb)/60	MIN:SEC	25:45=	-	26:15=
5,6	COOLING TIME (te-tb)/60	MIN:SEC	59:24=	-	60:36=
5,6	COOLING PRESS. MAX M[TP]&M[TP2]	PSIA	-	-	61.9=
5,6	COOLING PRESS. MIN m[TP]&m[TP2]	PSIA	46.1=	-	-

PARAMETRIC RELEASE/Annex 1:

12/04/18 14:01:32 FILE: 20_3S2-003B-1.prg
DATE FORMAT: MM/DD/YY HH:MM:SS
LANGUAGE: ENGLISH(ENG)
1||SERIAL NUMBER: NA2389AV - MANUAL PRINT
- PRODUCT CODE: FEDEGARI
- BATCH No.: 2 CC 2.3
- ID. STERILIZER: - USER NAME: QLT
PROGRESSIVE N.: 405 - PAGE: 21/21

PARAMETRIC RELEASE REPORT

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

Phase	Name	UM	Min	Set	Max	Value	R
3	Exp. Time	Min:Sec	10:54=	-	11:06=	11:00	1
3	Exp. Temp. Max.	F	-	-	252.5=	249.9	1
3	Exp. Temp. Min.	F	248.0=	-	-	249.3	1
3	Exp. TE9/TE10 Diff	F	-4.0=	-	4.0=	-0.2	1
3	Exp. Press. Max.	PSIA	-	-	52.7=	50.1	1
3	Exp. Press. Min.	PSIA	46.9=	-	-	49.1	1
3	Exp. Press. Diff.	PSIA	-1.0=	-	1.0=	0.1	1
57	F0 Min. End of Cyc	F0	24.8=	-	-	41.7	1
57	F0 Max. End of Cyc	F0	-	-	53.3=	42.3	1
57	F0 TE2/TE3 Diff.	F0	-1.0=	-	1.0=	0.3	1
57	F0 TE3/TE4 Diff.	F0	-1.0=	-	1.0=	0.3	1
57	F0 TE4/TE2 Diff.	F0	-1.0=	-	1.0=	-0.6	1
2	Heat up Time	Min:Sec	34:39=	-	35:21=	35:00	1
5,6	Cooling Time	Min:Sec	59:24=	-	60:36=	60:01	1
5,6	Cooling Press. Max	PSIA	-	-	51.9	50.3	1
5,6	Cooling Press. Min	PSIA	46.1=	-	-	47.0	1

PARAMETRIC RELEASE/Annex 1:

12/04/18 16:55:49 FILE: 20_3S2-003B-1.prg
DATE FORMAT: MM/DD/YY HH:MM:SS
LANGUAGE: ENGLISH(ENG)
1||SERIAL NUMBER: NA2389AV - MANUAL PRINT
- PRODUCT CODE: FEDEGARI
- BATCH No.: 2 CC 2.4
- ID. STERILIZER: - USER NAME: QLT
PROGRESSIVE N.: 407 - PAGE: 20/20

PARAMETRIC RELEASE REPORT

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

Phase	Name	UM	Min	Set	Max	Value	R
3	Exp. Time	Min:Sec	10:54=	-	11:06=	3:00	0
3	Exp. Temp. Max.	F	-	-	252.5=	244.8	1
3	Exp. Temp. Min.	F	248.0=	-	-	242.0	0
3	Exp. TE9/TE10 Diff	F	-4.0=	-	4.0=	-5.8	0
3	Exp. Press. Max.	PSIA	-	-	52.7=	48.0	1
3	Exp. Press. Min.	PSIA	46.9=	-	-	45.2	0
3	Exp. Press. Diff.	PSIA	-1.0=	-	1.0=	-1.7	0
57	F0 Min. End of Cyc	F0	24.8=	-	-	8.9	0
57	F0 Max. End of Cyc	F0	-	-	53.3=	12.5	1
57	F0 TE2/TE3 Diff.	F0	-1.0=	-	1.0=	-1.5	0
57	F0 TE3/TE4 Diff.	F0	-1.0=	-	1.0=	-2.1	0
57	F0 TE4/TE2 Diff.	F0	-1.0=	-	1.0=	3.6	0
2	Heat up Time	Min:Sec	34:39=	-	35:21=	24:18	0
5,6	Cooling Time	Min:Sec	59:24=	-	60:36=	18:33	0
5,6	Cooling Press. Max	PSIA	-	-	51.9	48.7	1
5,6	Cooling Press. Min	PSIA	46.1=	-	-	43.6	0

PARAMETRIC RELEASE/Annex 1:

```
PROGRAM START TIME    19/01/22 11:22:28
PROGRAM END TIME      19/01/22 11:48:22
STERILIZATION N.           2629 OK
MIN STERILIZ. TEMPERATURE   °C     120.2 ( 2)
MAX STERILIZ. TEMPERATURE   °C     120.9 ( 2)
STERIL. PHASE DURATION  min.ss    20:00
STERILIZATION TIME      min.ss    20:00

WITH PARAM.RELEASE TABLE: NOT OK
ACCEPTANCE REQUESTED


         PARAMETRIC RELEASE TABLE

TEST

Phase Name               UM      Min     Set     Max
2     Vacuum value       bar     -       -       0.1
      (te-tb)/60
3     Sterilization temp °C      -       -       121.5
      M[TE2]



         PARAMETRIC RELEASE REPORT

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

Phase Name               UM      Min     Set     Max     Value  R
2     Vacuum value       bar     -       -       0.1     3.7    0
3     Sterilization temp °C      -       -       121.5   107.1  1



   OPERATOR'S SIGNATURE          _____________________


   SUPERVISOR'S SIGNATURE        _____________________


   Q.A. SIGNATURE                _____________________
```

PARAMETRIC RELEASE/Annex 1: Case Study (Stoppers in bags)

To keep under control the cycle in terms of:

- critical parameters (validation approach)
- early diagnosis of malfunction (maintenance approach)

It is a fast procedure for investigating a failure giving you:

- ❖ the chance to avoid an additional review by a supervisor
- ❖ an easy detection of the wrong performance

Thank you!