



# *INSTALLATION QUALIFICATION OPERATIONAL QUALIFICATION AND CYCLE DEVELOPMENT*





# *LA CALHENE VALIDATION DEPARTMENT - missions*

- ↪ EXTERNAL SERVICES:*
- ↪ On site qualification of special isolator systems -  
example filling line isolator*
- ↪ On site qualification of "standard" isolator  
systems - example sterility test suites*
- ↪ On site qualification of auxiliary equipment  
example GLT, TLT, RTD*
- ↪ Technical support for PQ*
- ↪ On site post qualification training*



# *LA CALHÈNE VALIDATION DEPARTMENT (2)*

- ↪ INTERNAL SERVICES:*
- ↪ Qualification of La Calhène standard equipment  
DPTe BETA BAG, GLT, RDT, TLT, sterilizers*
- ↪ Validation support for sterile packaging facility*
- ↪ Validation of sterilization of beta bag systems*
- ↪ Development and qualification of Bis for  
confinement systems*



# *QUALIFICATION PROTOCOLS*

- ⇒ Protocols are prepared using an “industry standard” format*
- ⇒ Sent to customer for approval at least 5 weeks prior to start of qualification*



# INSTALLATION QUALIFICATION (1)



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## ETUDES & DEVELOPPEMENT VALIDATION

C	1/4	TESTS GUIDE	NSCA 161/16		LC reference :	37K53E
	IQ		Page	Rev. Page	Customer reference :	45382135/392
			8/49	C	Customer :	MSD

N°	TESTS	REFERENCE DOCUMENT	FICHES DE CONTROLE INSPECTION NOTES NSCA 161/31		VALIDATION MANAGER	
			N°	Page	Name	Date & Visa
			1.0	Documentation review	NSCA 161/16	1 (1/4 to 4/4)
2.0	Utility connection check	NSCA 161/16	2 (1/1)	7	J. NOTTINGHAM	
3.0	P&ID check					
	1. Component and identification check	NSCA 161/16	N/A	N/A	J. NOTTINGHAM	
	2. Component conformity check	NSCA 161/16	3 (1/15 to 15/15)	8 to 22	J. NOTTINGHAM	

INSPECTIONS / TESTS	LA CALHENE		CUSTOMER	
	NAME	DATE & VISA	NAME	DATE & VISA
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# INSTALLATION QUALIFICATION (2)



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## ETUDES & DEVELOPPEMENT VALIDATION

C	2/4	TESTS GUIDE	NSCA 161/16		LC reference :	37K53E
	IQ		Page	Rev. Page	Customer reference :	45382135/392
			9/49	C	Customer :	MSD

N°	TESTS	REFERENCE DOCUMENT	FICHES DE CONTROLE INSPECTION NOTES NSCA 161/31		VALIDATION MANAGER	
			N°	Page	Name	Date & Visa
			4.0	HAZOP and Socotec check	NSCA 161/16	N/A
5.0	Electrical installation check					
	5.1 Electrical cabinet component check	Electrical file	N/A	N/A	J. NOTTINGHAM	
	5.2 Cabling check	Electrical file	N/A	N/A	J. NOTTINGHAM	
	5.3 Valve and blower operation	NTA 3014/2	4 (1/2 to 2/2)	23 to 24	J. NOTTINGHAM	
	5.4 Munters	NSCA 161/16	N/A	N/A	J. NOTTINGHAM	
6.0	Mechanical installation check					
	6.1 Isolator transfer systems	NTA 3014/2	5 (1/1)	25	J. NOTTINGHAM	
	6.2 Access windows and doors	NSCA 161/16	N/A	N/A	J. NOTTINGHAM	

INSPECTIONS / TESTS	LA CALHENE		CUSTOMER	
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# INSTALLATION QUALIFICATION (3)



## ETUDES & DEVELOPPEMENT VALIDATION

C	3/4	TESTS GUIDE	NSCA 161/16		LC reference :	37K53E
	IQ		Page	Rev. Page	Customer reference :	45382135/392
			10/49	C	Customer :	MSD

N°	TESTS	REFERENCE DOCUMENT	FICHES DE CONTROLE INSPECTION NOTES NSCA 161/31		VALIDATION MANAGER	
			N°	Page	Name	Date & Visa
7.0	Calibration check					
	7.1 Relative humidity sensors	NSCA 161/16	6	26	J. NOTTINGHAM	
	7.2 Differential pressure switches	NSCA 161/16	7	27	J. NOTTINGHAM	
	7.3 Differential pressure sensors	NSCA 161/16	8	28	J. NOTTINGHAM	
	7.4 Air velocity sensor	NSCA 161/16	9	29	J. NOTTINGHAM	
	7.5 Temperature sensors	NSCA 161/16	10	30	J. NOTTINGHAM	
	7.6 Thermometers	NSCA 161/16	11	31	J. NOTTINGHAM	
	7.7 Temperature switches (heat tape control)	NSCA 161/16	12	32	J. NOTTINGHAM	
	7.8 Converters	NSCA 161/16	13	33	J. NOTTINGHAM	
	7.9 Loop test	NSCA 161/16	14	34	J. NOTTINGHAM	
	7.10 Pressure gauges	NSCA 161/16	15	35	J. NOTTINGHAM	

INSPECTIONS / TESTS	LA CALHENE		CUSTOMER	
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## ETUDES & DEVELOPPEMENT VALIDATION





# INSTALLATION QUALIFICATION (4)


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## ETUDES & DEVELOPPEMENT VALIDATION

C	4/4	TESTS GUIDE	NSCA 161/16		LC reference :	37K53E
	IQ		Page	Rev. Page	Customer reference :	45382135/392
			11/49	C	Customer :	MSD

N°	TESTS	REFERENCE DOCUMENT	FICHES DE CONTROLE INSPECTION NOTES NSCA 161/31		VALIDATION MANAGER	
			N°	Page	Name	Date & Visa
			8.0	Functional testing of control hardware and software		
8.1	Hardware check	NSCA 161/25	N/A	N/A	J. NOTTINGHAM	
8.2	Backup and restore test	NSCA 161/25			J. NOTTINGHAM	
8.3	Loader and application verification	NSCA 161/25			J. NOTTINGHAM	
8.4	Input/output tests	NSCA 161/25			J. NOTTINGHAM	
8.5	Unitary tests (functional block)	NSCA 161/25			J. NOTTINGHAM	
8.6	Transition tests	NSCA 161/25			J. NOTTINGHAM	
8.7	Sequencing tests	NSCA 161/25			J. NOTTINGHAM	
8.8	Phase tests	NSCA 161/25			J. NOTTINGHAM	
8.9	Default testing – secondary network	NSCA 161/25			J. NOTTINGHAM	
8.10	Phase view tests	N/A			J. NOTTINGHAM	

INSPECTIONS / TESTS	LA CALHENE		CUSTOMER	
	NAME	DATE & VISA	NAME	DATE & VISA
Executed by				
Verified by				



# OPERATIONAL QUALIFICATION (1)



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## ETUDES & DEVELOPPEMENT VALIDATION

C	1/2	TESTS GUIDE	Doc N° : NSCA 161/17		LC reference :	37K53E
	OQ		Page	Rev. Page	Customer reference :	45382135/392
			7/28	B	Customer :	MSD

N°	TESTS	TEST PROCEDURE	FICHES DE CONTROLE INSPECTION NOTES NSCA 161/32		VALIDATION MANAGER	
			N°	Page	Name	Date & Visa
1.0	Check of IQ priority 1 punchlist completion	NSCA 161/17	N/A	N/A	J. NOTTINGHAM	
2.0	Filter integrity testing	NTA 3014/10	1 (1/13 to 13/13)	3 to 15	J. NOTTINGHAM	
3.0	Leak testing	NTA 3014/6	2 (1/1)	16	J. NOTTINGHAM	
4.0	VHP® 1001 functional check	NTA 3018/1	3 (1/2 to 2/2)	17 to 18	J. NOTTINGHAM	
5.0	Sterilization phase test	NSCA 161/21	4 (1/4 to 4/4)	19 to 22	J. NOTTINGHAM	
6.0	Air distribution					
	1.1. Pressure differential in production phase	NSCA 161/10	5 (1/2 to 2/2)	23 to 24	J. NOTTINGHAM	
	1.2. Recirculation rate in production phase	NSCA 161/10	6 (1/14 to 14/14)	25 to 38	J. NOTTINGHAM	
	1.3. Air change rate in aeration step of sterilization phase	NSCA 161/10	7 (1/3 to 3/3)	39 to 41	J. NOTTINGHAM	
	1.4. Air speed map, uniformity of airflow and smoke test in production phase	NTA 3014/11	8 (1/8 to 8/8)	42 to 49	J. NOTTINGHAM	

INSPECTIONS / TESTS	LA CALHENE		CUSTOMER	
	NAME	DATE & VISA	NAME	DATE & VISA
Verified by				



# OPERATIONAL QUALIFICATION (2)



## ETUDES & DEVELOPPEMENT VALIDATION

C	2/2	TESTS GUIDE	Doc N° : NSCA 161/17		LC reference :	37K53E
			Page	Rev. Page	Customer reference :	45382135/392
OQ			8/28	B	Customer :	MSD

N°	TESTS	TEST PROCEDURE	FICHES DE CONTROLE INSPECTION NOTES NSCA 161/32		VALIDATION MANAGER	
			N°	Page	Name	Date & Visa
7.0	Particle count	NTA 3014/12	9 (1/7 to 7/7)	50 to 56	J. NOTTINGHAM	
8.0	Noise level check	NTA 3014/17	10 (1/2 to 2/2)	57 to 58	J. NOTTINGHAM	
9.0	Light level check	NTA 3014/13	11 (1/2 to 2/2)	59 to 60	J. NOTTINGHAM	
10.0	Manual phase test	NSCA 161/25	N/A	N/A	J. NOTTINGHAM	
11.0	Emergency phase test	NSCA 161/25	N/A	N/A	J. NOTTINGHAM	
12.0	Cleaning phase test	NSCA 161/25	N/A	N/A	J. NOTTINGHAM	
13.0	Testing phase test	NSCA 161/25	N/A	N/A	J. NOTTINGHAM	
14.0	Production phase test	NSCA 161/25	N/A	N/A	J. NOTTINGHAM	

INSPECTIONS / TESTS	LA CALHENE		CUSTOMER	
	NAME	DATE & VISA	NAME	DATE & VISA
Verified by				



# CYCLE DEVELOPMENT PROGRAMME (1)


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## ETUDES & DEVELOPPEMENT VALIDATION

<b>C</b>	<b>TEST GUIDE</b>	Doc N° : NSCA 161/37		Project :	<b>MK 0826</b>
		Page	Rev. Page	Reference LC :	<b>37 K 53 E</b>
<b>CD</b>		8/30	B	Client :	<b>MSD</b>

N°	CONTROLS TESTS	TEST PROCEDURE	INSPECTION NOTES NSCA 161/38		VALIDATION MANAGER LA CALHENE	
			N°	Page	Nom	Date & Visa
1.0	Prerequisites check	N/A	N/A	N/A	J. NOTTINGHAM	
2.0	Isolators / VHP® generators OQ completion check	N/A	N/A	N/A	J. NOTTINGHAM	
3.0	Check of IQ priority 1 punchlist for equipment completion	N/A	N/A	N/A	J. NOTTINGHAM	
4.0	Isolator preparation					
	4.1. Initial positioning of temporary distribution fans	N/A	N/A	N/A	J. NOTTINGHAM	
	4.2. VHP inlet flow, uni-directional flow air speed and distribution fan flow checks	NSCA 161/10, NTA 3014/9	1 (1/2 to 2/2)	3 to 4	J. NOTTINGHAM	
	4.3. Pre sterilization checks	NTA 3022/1, NTA 3022/4, NTA 3022/6, NTA 3022/7	2 (1/1)	5	J. NOTTINGHAM	
	4.4. VHP programming and isolators sterilization recipe checks	N/A	3 (1/1)	6	J. NOTTINGHAM	
5.0	Verification of data acquisition system and calibration of thermocouples	N/A	4 (5/14 to 6/14)	10 to 12	J. NOTTINGHAM	
6.0	Temperature mapping and gaz distribution using chemical indicators	NTA 3014/18	4 (1/14 to 14/14)	7 to 20	J. NOTTINGHAM	

INSPECTIONS / TESTS Verified by	LA CALHENE		CLIENT	
	NAME	DATE & VISA	NAME	DATE & VISA



# CYCLE DEVELOPMENT PROGRAMME (2)


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## ETUDES & DEVELOPPEMENT VALIDATION

C CD	TEST GUIDE	Doc N° : NSCA 161/37		Project :	MK 0826
		Page	Rev. Page	Reference LC :	37 K 53 E
		9/30	A	Client :	MSD

N°	CONTROLS TESTS	TEST PROCEDURE	INSPECTION NOTES NSCA 161/38		VALIDATION MANAGER LA CALHENE	
			N°	Page	Nom	Date & Visa
7.0	Base cycle verification and isolator reconfiguration	N/A	5 (1/2 to 2/2)	21 to 22	J. NOTTINGHAM	
8.0	Verification of biological indicators	NTA 3022/6	6 (1/1)	23	J. NOTTINGHAM	
9.0	Bio-decontamination capability using Bis	NSCA 161/08	7 (1/24 to 24/24)	24 to 47	J. NOTTINGHAM	
10.0	Aeration testing	NSCA 161/08	8 (1/1)	48	J. NOTTINGHAM	
11.0	Final cycle parameters	N/A	9 (1/1)	49	J. NOTTINGHAM	
12.0	Definition of final distribution fan positioning	N/A	N/A	N/A	J. NOTTINGHAM	

INSPECTIONS / TESTS Verified by	LA CALHENE		CLIENT	
	NAME	DATE & VISA	NAME	DATE & VISA



# *EXAMPLE OF A RECENT PROJECT (1) - Pre sterilisation checks*



**Do's - Prepare the isolator and the room,  
Limit access to test personnel only,  
Check that other project activities will not interfere,  
Hold daily progress meetings to keep all parties informed.**

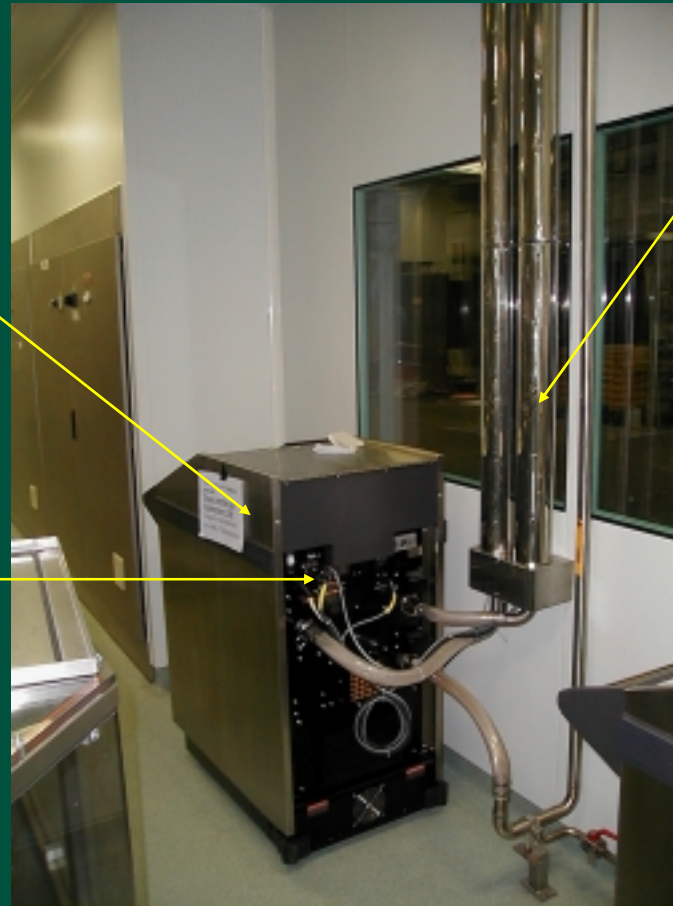
**Don'ts -Start with an element  
missing or faulty - compromises  
can bite back later on**



# *EXAMPLE OF A RECENT PROJECT (2) -VHP generator qualification*

Calibration - do before starting cycle development tests

Pressure reference point - don't forget possibility of pressure variations



Supply pipe work - don't forget the risk of condensation





# *EXAMPLE OF A RECENT PROJECT (3) - verification of data collection system and thermocouples*



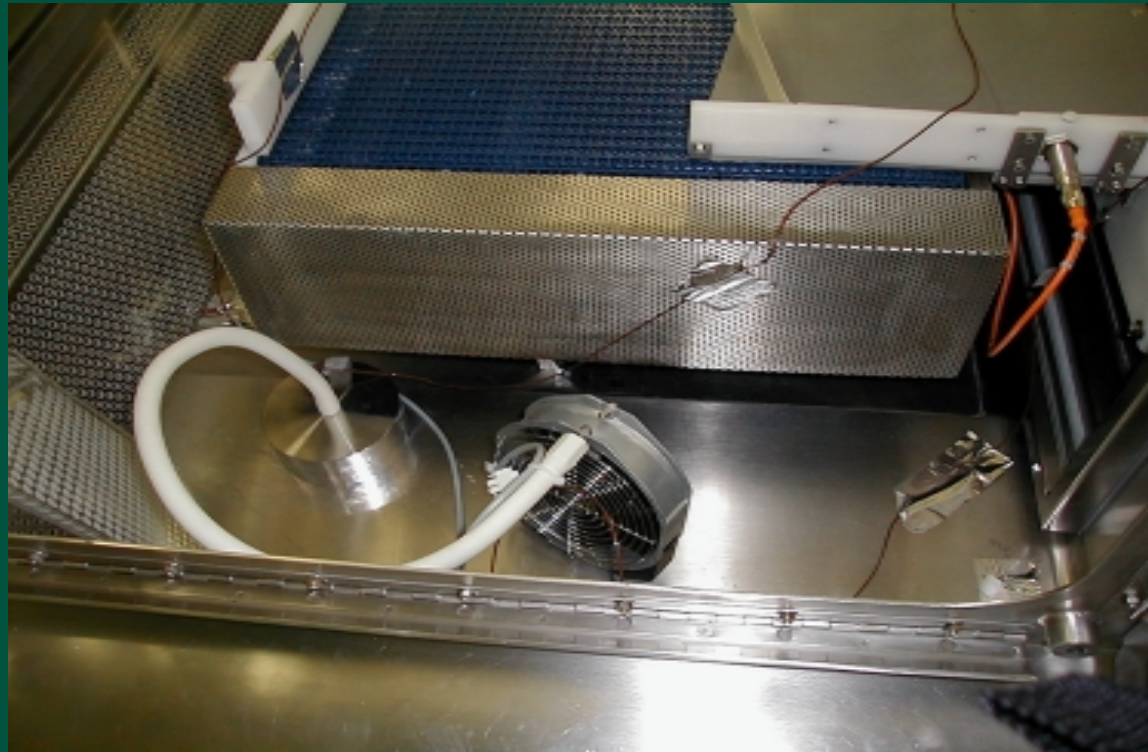
**Do's** - Calibrate thermocouples in advance,  
Make accurate and detailed records of the  
cable routings,  
Synchronise clocks on all test equipment,  
the VHP and isolator PLC

**Don'ts** - Don'ts forget to check that thermocouples  
will not catch in moving parts





# *EXAMPLE OF A RECENT PROJECT (4) - initial positioning of distribution fans*



**Do's - Define N° of fans during design**  
**Check for interference with other elements**  
**Check where supply cable will pass**

**Don'ts - Forget to accurately record position in three dimensions before and after testing,**



# EXAMPLE OF A RECENT PROJECT (5) - Gas distribution studies



**Do's** -Prepare a « CI team ». It is best to have 3 people per team - 2 to read CIs and one to record the results,  
Train each member to recognise the same colour change,  
Split the isolator into sections,  
Use a gas concentration monitor (UOP).

**Don'ts** - Don't ask someone to read CIs unless they are perfectly familiar with each location - looking for the CIs affects the results,  
Do not carry out test without a « map » for each tester



# EXAMPLE OF A RECENT PROJECT (6) - BI tests



**Do's - Work under controlled conditions and use « aseptic » techniques,  
Know the D value,  
Record any handling errors,  
Place BIs in « representative » areas only.**

**Don'ts - Use too many locations,  
Use BIs without removing the packaging (some are supplied in paper/tyvek bags).**



# *NOTES ON STERILISATION CYCLE TESTING (1)*

*↳ GOOD PREPARATION AND GOOD CONTROL ARE  
OF UPMOST IMPORTANCE*

*↳ CYCLE DEVELOPMENT FOR A SPECIAL  
PRODUCT SUCH AS A FILLING LINE SHOULD BE  
REGARDED AS A SEPERATE STAGE IN THE  
VALIDATION PROCESS POSITIONED BETWEEN  
OQ AND PQ*





# *EXAMPLE OF A RECENT PROJECT (7) - Sterility test suite*



PLC controlled transfer  
and workstation isolators

VHP gas generator



# *EXAMPLE OF A RECENT PROJECT (8) - Sterility test suite qualification*

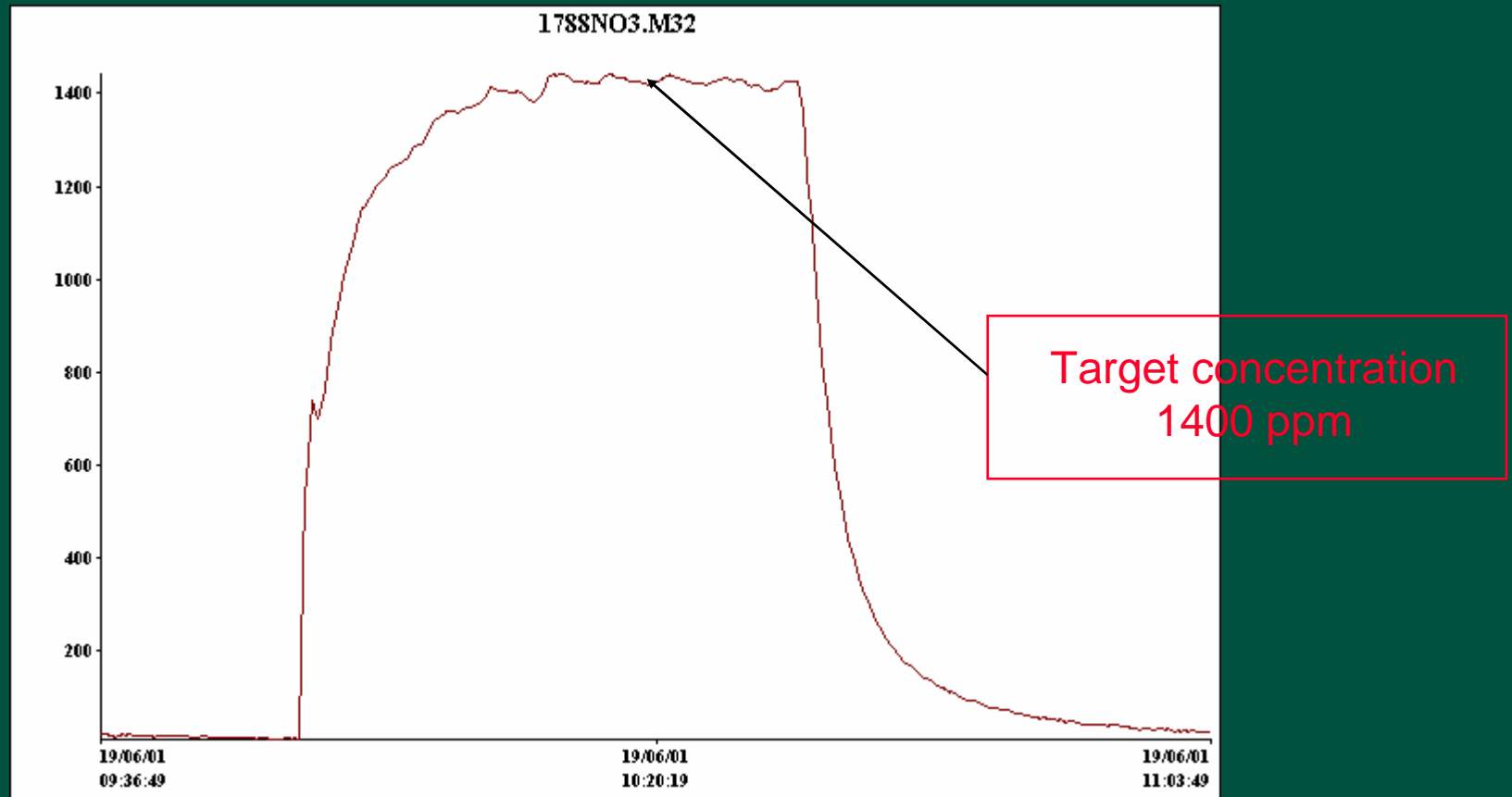


Operational  
Qualification  
ends with  
sterilisation  
tests using Bis

3 types of test:  
temperature  
mapping, CI  
tests and BI  
tests



# EXAMPLE OF A RECENT PROJECT (9) - gas concentration transfer isolator using Polytron HC sensor





# *EXAMPLE OF A RECENT PROJECT (10) - Technical support for PQ*



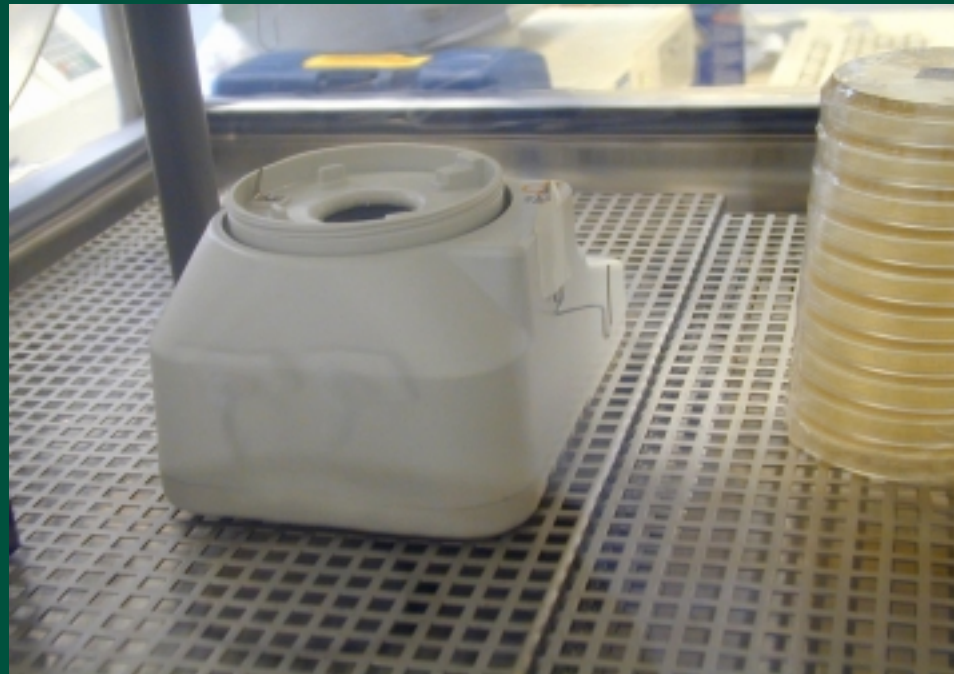
Sterilisation tests at end of OQ with isolator load

A typical isolator load - must be evenly distributed for good gas distribution





# *EXAMPLE OF A RECENT PROJECT (11) - Technical support for PQ*



Advice on the use and positioning of environmental monitoring equipment

Advice on isolator cleaning procedures and material compatibility



## *Conclusion*

- **Isolator technology is one solution to perform aseptic processing**
- **The validation and the periodic re-validation is one important part to assure the profile of quality of the production**
- **The time dedicated to the validation and re-validation has to be taken in account for the production planning**
- **The reproducibility in the use of Isolation Technology brings an important safety factor when compared with manned Aseptic Processing Area**