

Jan Mottlau

Senior Specialist

Utility and process design
NIRAS

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Compagny

- Engineer in NIRAS since 2014
- Professional bear taster ISO9001, certified since 2016

Experience

Been working with classified facility area since 1994

- Client advice, Project management - and specialist functions
- Technical adviser for Hospitals, pharma, lifescience, Cleanroom, datacenters, Containment Facilities as BSL2-3 (Ag),

Hospitals Design, programming:

- **OR**-departments,
- **HLIU** facility, (High Level Insulation Units)
- **PCR**, (Polymerase Chain Reaction)
- **CGT** (Cell and gene therapy)
- **BSL3**, (Biosafety level 3) Pharmacy,

Jan Mottlau



Certificate

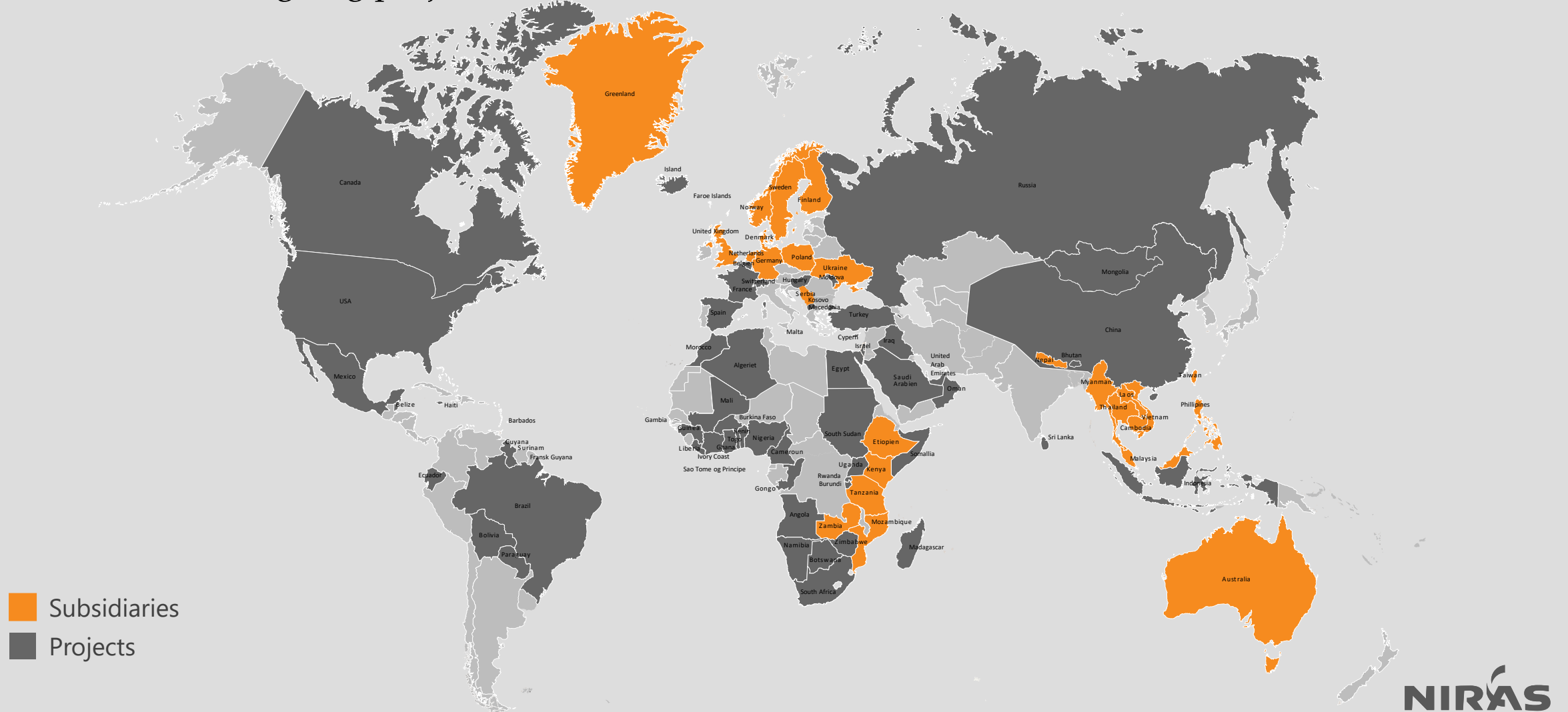
- CTCB-i Certified cleanroom tester

Committees:

- **R3-Nordic** (Hospital Symposium 23/24-5, Elsinore in Denmark)
- **ISPE** (International Society for Pharmaceutical Engineering)
- **FSTA** (Danish Union for Hospital, Technical & Architecture)
- **Danish Standard** DS/ S-438 - Cleanroom technology
- **ISO** TC209 WG 3, 5, 15. (ISO 14644)

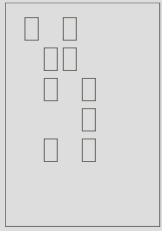
Global Footprint

Over 7,000 ongoing projects in more than 30 countries



Broad range of services

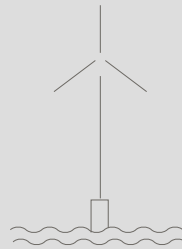
Across the NIRAS Group



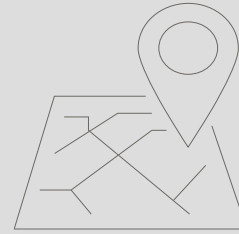
Building



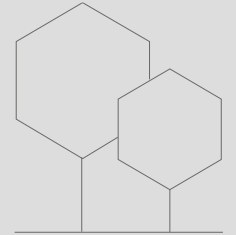
Process Industry



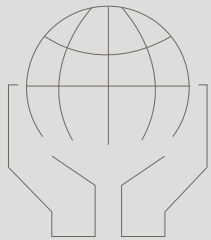
Energy



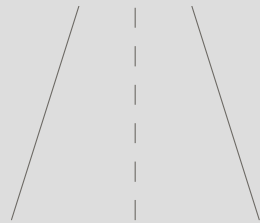
GIS, Geodata & Automation



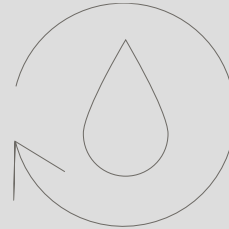
Environment & Nature



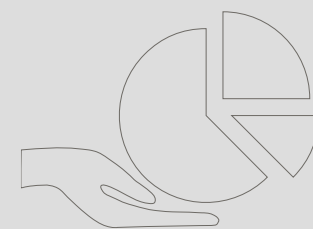
Development Consulting



Infrastructure



Water & Utilities

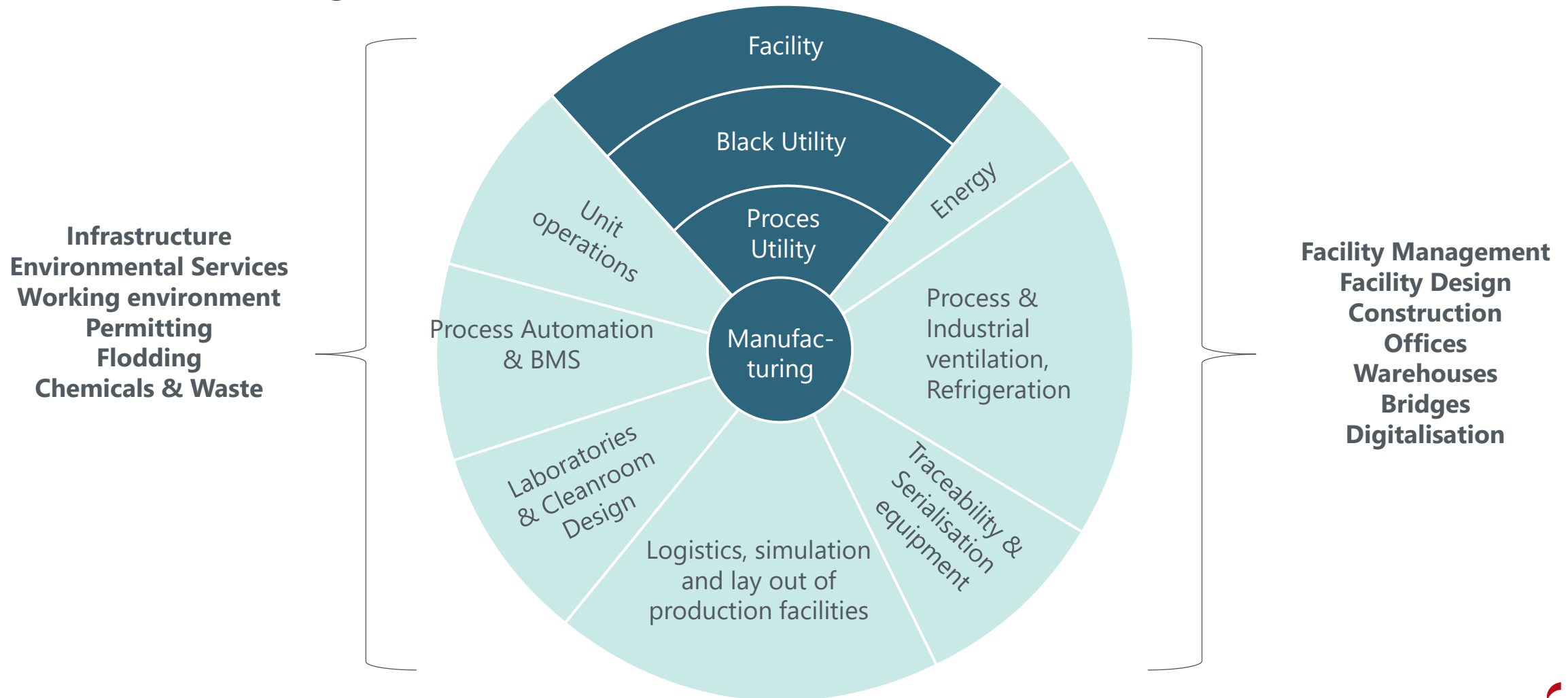


Analysis & Planning

We strive to move towards an enhanced sustainable future



Integration of the manufacturing in a quality demanding Life Science (GMP) market



Project and Consultancy

Carefully designed project steps keep things in control

GMP services to ensure compliance

Front load project	Conceptual Brief / Conceptual Design	Basic Design / Detail Design	On site
<ul style="list-style-type: none"> • Integration of User Demands • Organization / Resource load • Financial requirements • GAP Analyze/Audits • Logistics • Development of master plan • Business Cases • Supply Chain • Due Diligence 	<ul style="list-style-type: none"> • Total Cost of Estimate • Lay outs • Master Planning • Logistic, Manflows, • Facility planning & Design • Modular Engineering • URS • Overall Time Schedule • Project execution plan • ATEX & EX, • Long lead items 	<ul style="list-style-type: none"> • Vendor selection & Tendering services • Review and Design qualification • Process Simulation, Virtual Reality • URS Review • Sparring in choice of technologies. • Sanity Check of TIC. • Process Flow Diagrams, PI&D • Automation Process & BMS 	<ul style="list-style-type: none"> • Process Project Management • Vendor Coordination • Construction Management • Punch list management • Cost control • Scope control • FAT/ SAT, IQ, OQ, PQ • Training • Material Control • Approval of deliverables • Hand Over

Decision gateway

Decision gateway

Validatation master plan, Qauality plan, Consultancy, Advisory

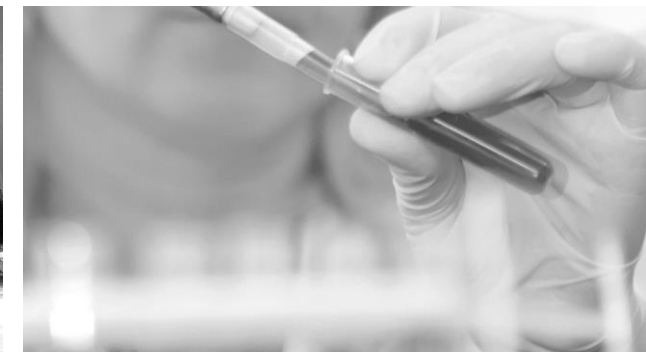
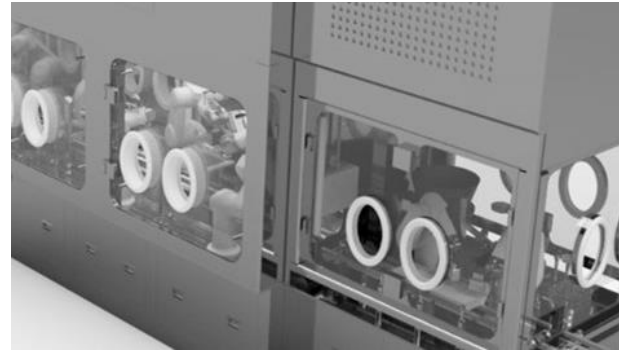
Project execution plan, Procurement startegy, **Project Management**, Time Schedule, Financial reporting




Lesson learned

During design and cleanroom testing

2023



A photograph of a blue house with a dark roof, tilted at a steep angle. The house is oriented upside down, with the roof at the top and the ground at the bottom. The tilt is significant, and the house appears to be leaning precariously. The background shows a clear sky and some greenery. A white text box is overlaid on the center of the image.

**Always to remember:
Instructions, prescriptions and guidance is a delicate matter.
Simple small details gone wrong, can make everything go wrong.**

What didn't work

It works !!!

Quality assurance in several steps.



Requirements and facility -Do they match

Material in cleanroom, use of cleanroom

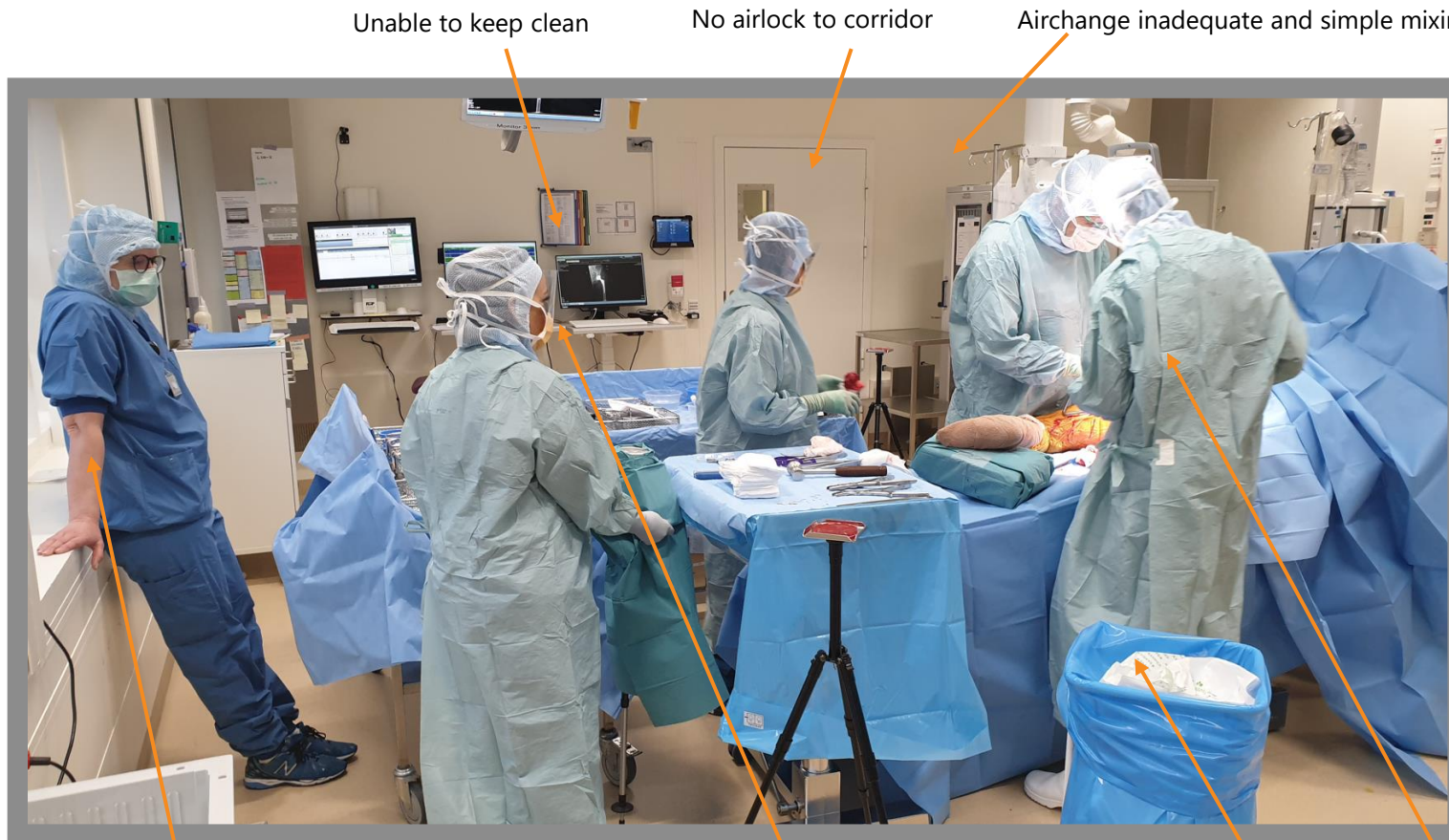


- Grade B cleanroom
- <10 CFU
- 5-10 persons
- Mixing ventilation
- 10 ACH
- No airlock
- Iso 7(5) – non classified

Oviously here is several things gone very wrong. Find easily 5 mistakes. - RIP

2: Requirements and facility -Do they match

Fast overview - faults



Unable to keep clean

No airlock to corridor

Airchange inadequate and simple mixing principle in Grade B facility, it's a no go.

- When operating in bones, the body can not recover from bacteria in the bone part, as no blood flow is present.
- Normally a totally different OR suite set up is necessary. To avoid Hospital acquired sickness.

Alternative

An optimised OR suite cost, extra Once: 140.000 EUR
Reoperation is approx. 90.000 EUR

Suite last 20 years.

One incident a week in 20 years = 1040 incidents.

If you want to save money, please make facility right first time.

How to start improving:

Start learning from: ISO14644- 1, 2, 3, 4, 5. ☺

Un covered arms in turbulent airflow

Use of cosmetic

Open dust spin and no protection zone to patient

Too low grade cleanliness clothing

Energy optimization – How far can you go ?

what can go wrong ?

“why can't we just stop the HVAC unit, when we don't work in the cleanroom”

I often get the question, “why can't we stop the HVAC unit when we don't work in the cleanroom”

Issues is compliance “in Control” definition pressure and cleanliness must be obtained. Standard for setback there is none. But ISO 14644-4 describes to do a risk based analysis using:

- HACCP (hazard analysis Critical Control point),
- FMEA (Failure Mode Effects Analysis) or
- FTA (Fault Tree Analysis)

And set back is very relevant as people are the polluter in the room, and when they are not there, the source strength is much lower. And airchange needed to keep cleanliness is therefor much reduced. (cleanliness and pressure shall be obtained at all times, in order to be in control.

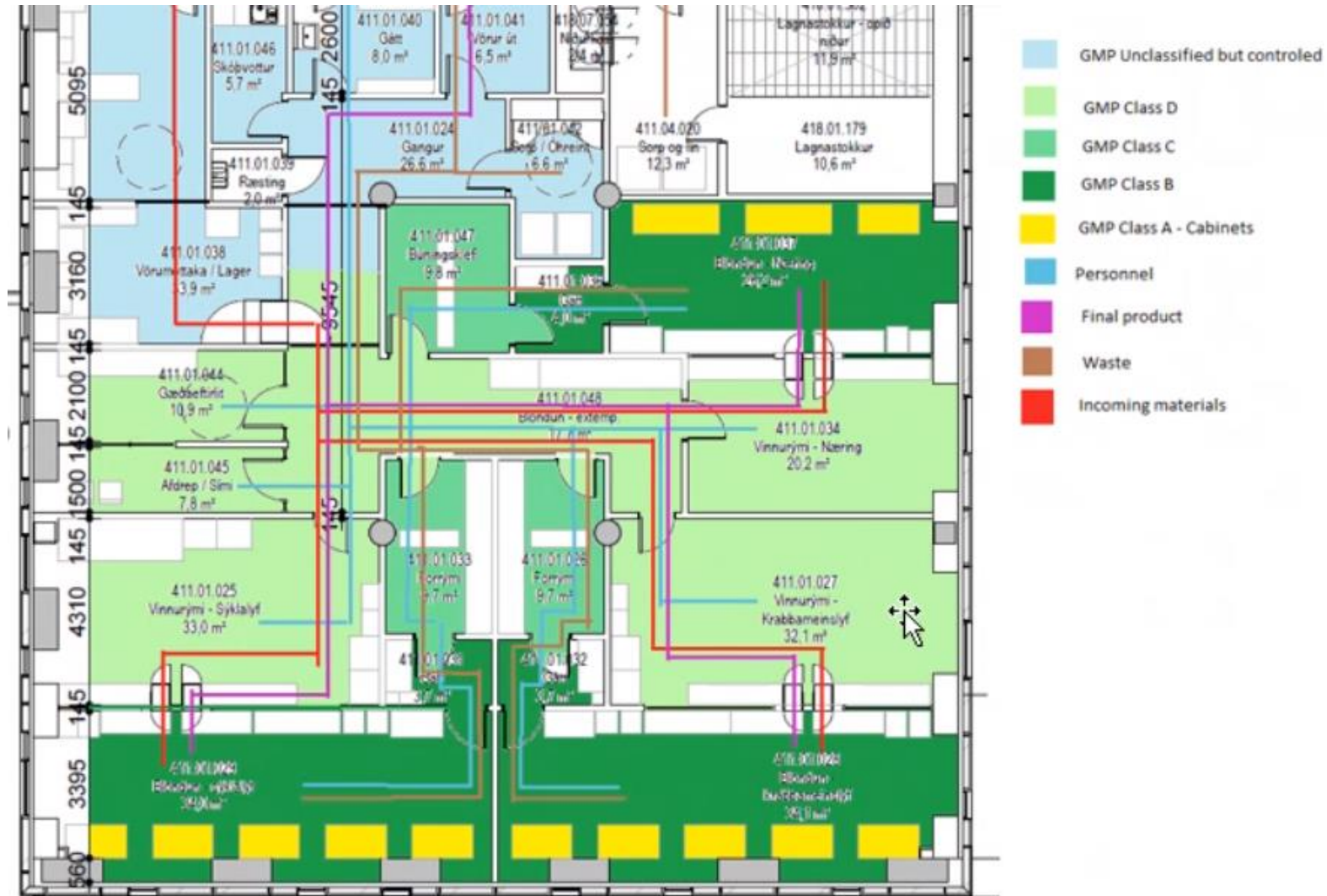
If you stop the ventilation, a full cleaning procedure and change of HEPA filters, shall be carried out, before next operation, in order to be “in Control”

Ultra clean OR room in Denmark, is Iso Class 7 “in operation” and ISO class 5 “at rest” this is grade B.



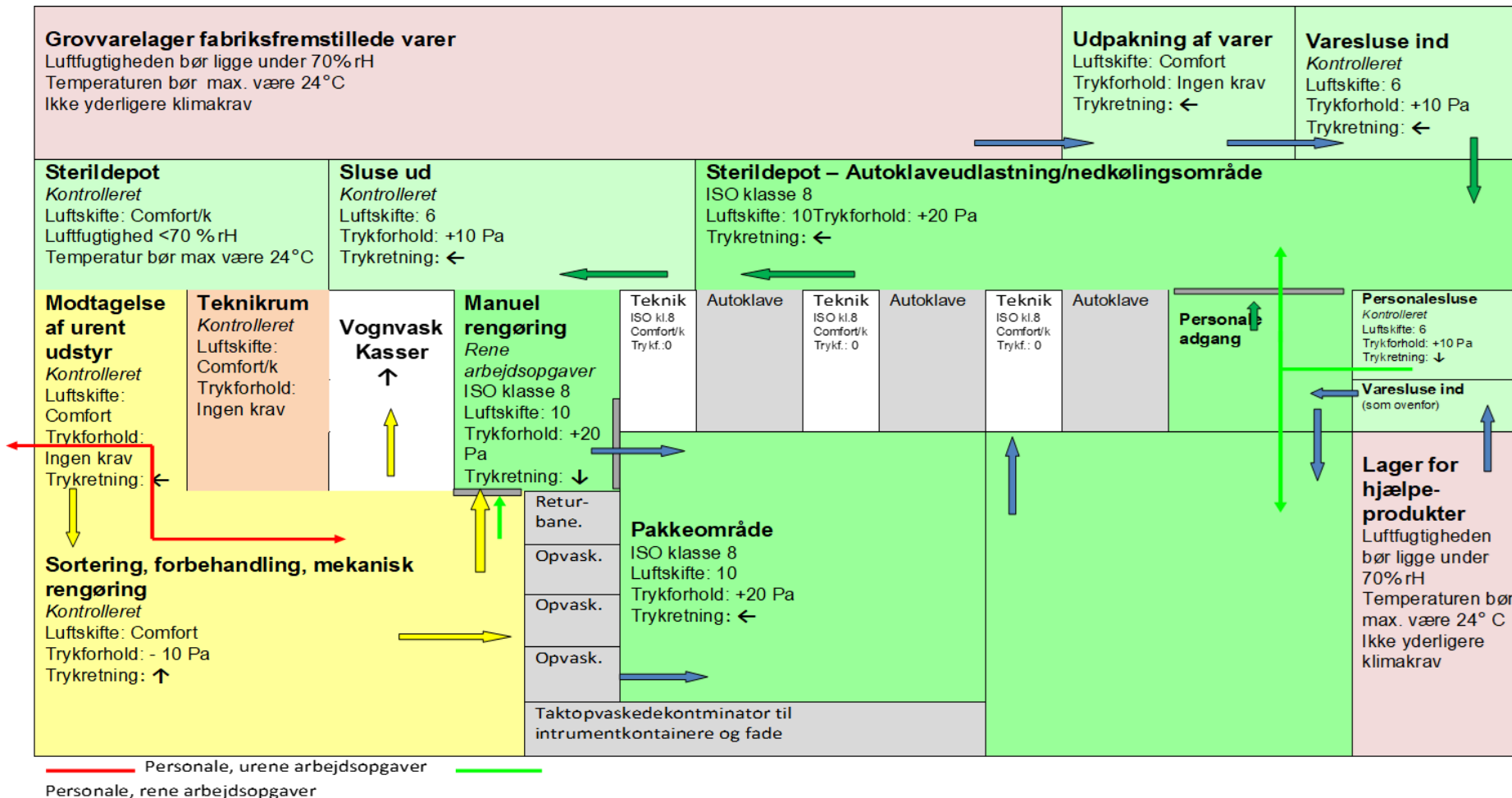
Flow diagram for different processes

Basic flow – no timing.



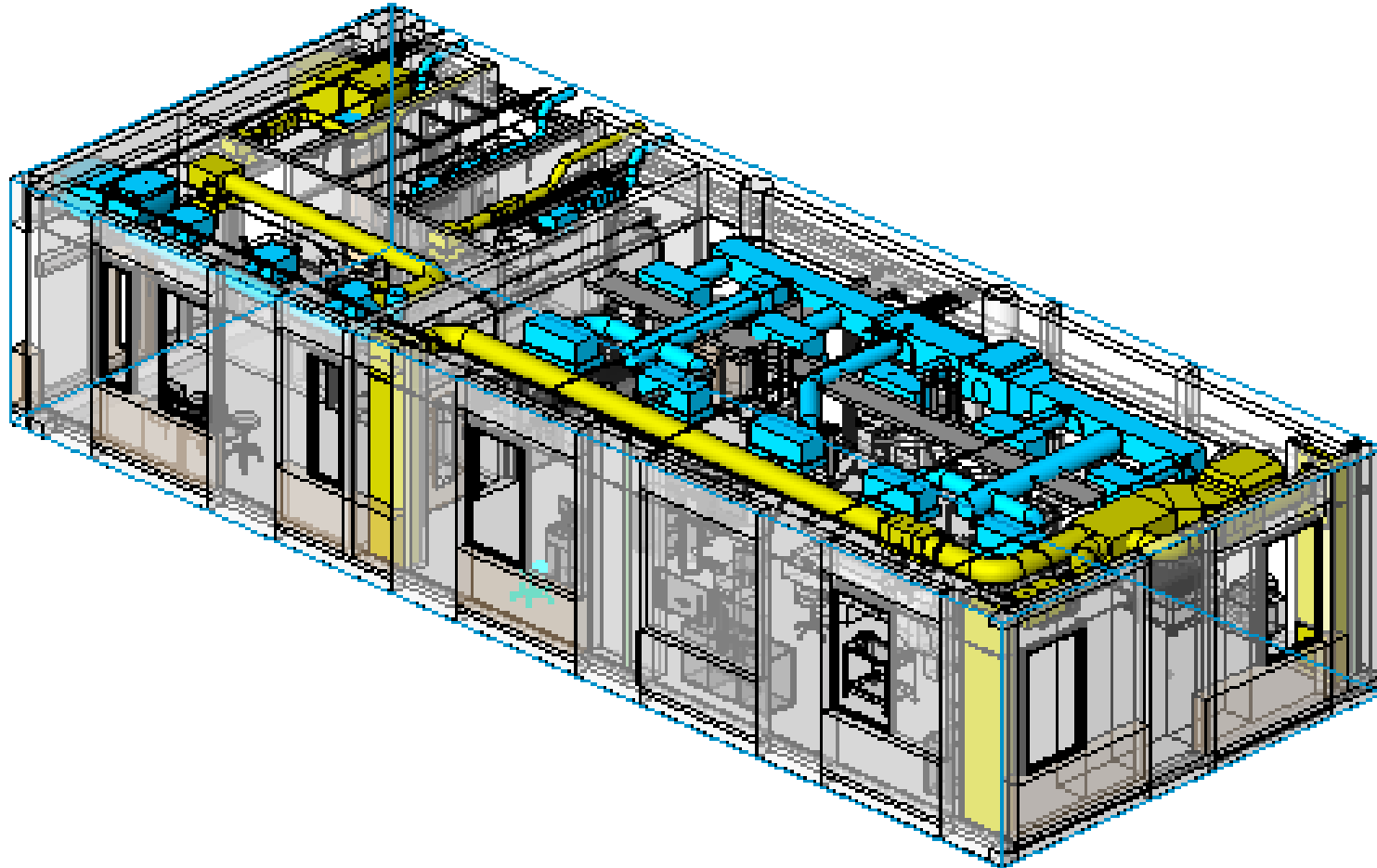
Design Sterilisation site

standard DS 2451-13 (NIR)



Service friendly installations

Is service possible ?



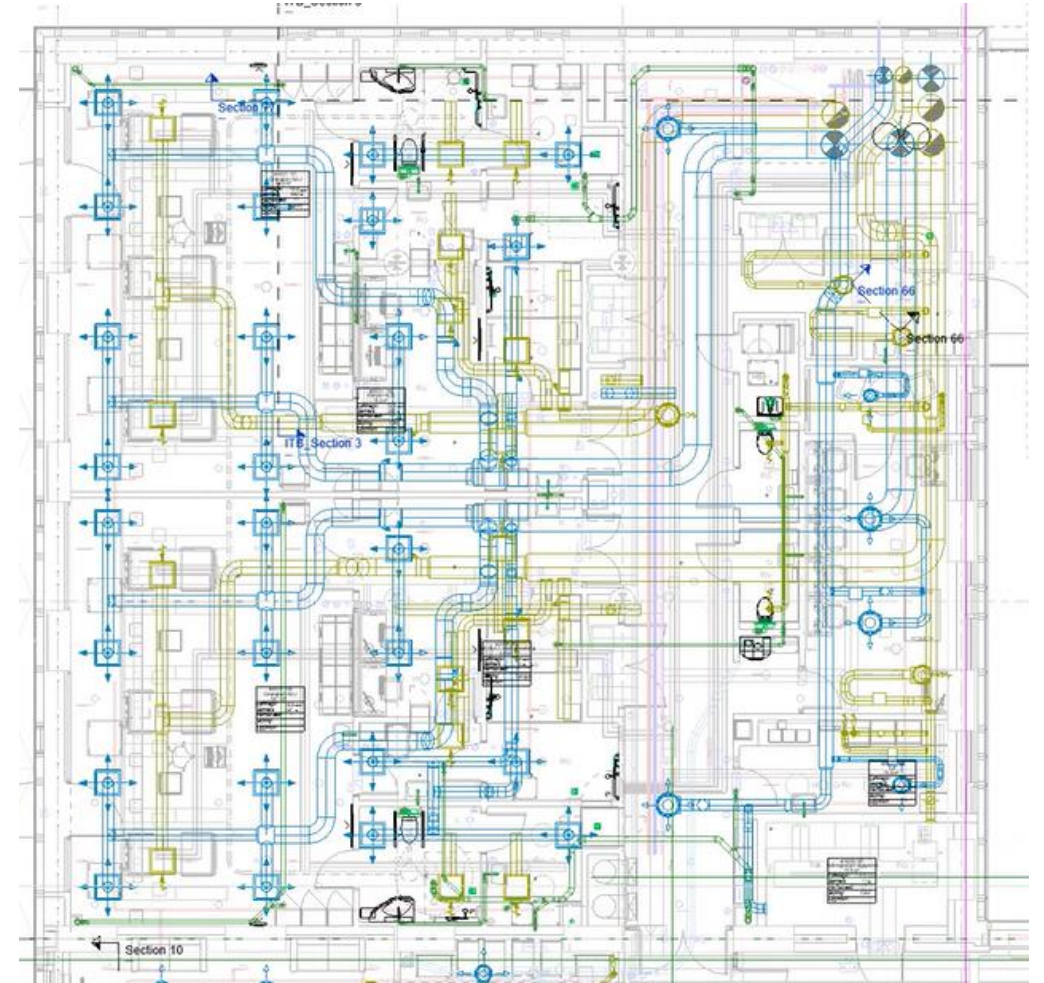
- Is service only possible in summer and Winter close down period ?
- Or accessible also in between ?
- Service demanding gear smart placed in the corridor
- Hatches were needed
- Space so normal persons can do the job.
- Build safe work environment for maintainers

Accessibility

After handover, how to ensure accessibility and service on all components

Example Containment areas as:

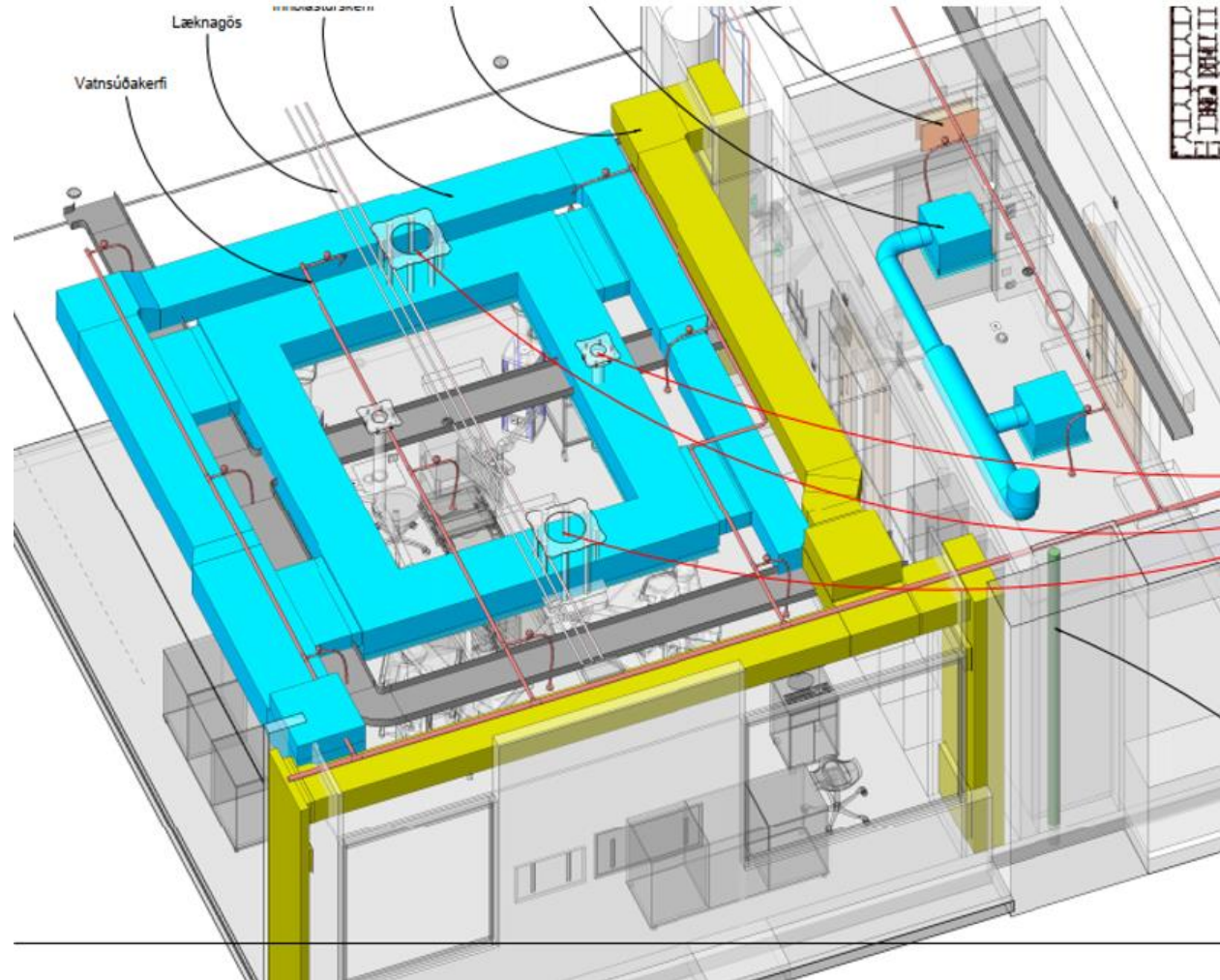
- BLS3 or
- HLIU High Level insulation Rooms



Collisions on drawings when installer work

What will happend ☺

During installation, if nothing is updated.

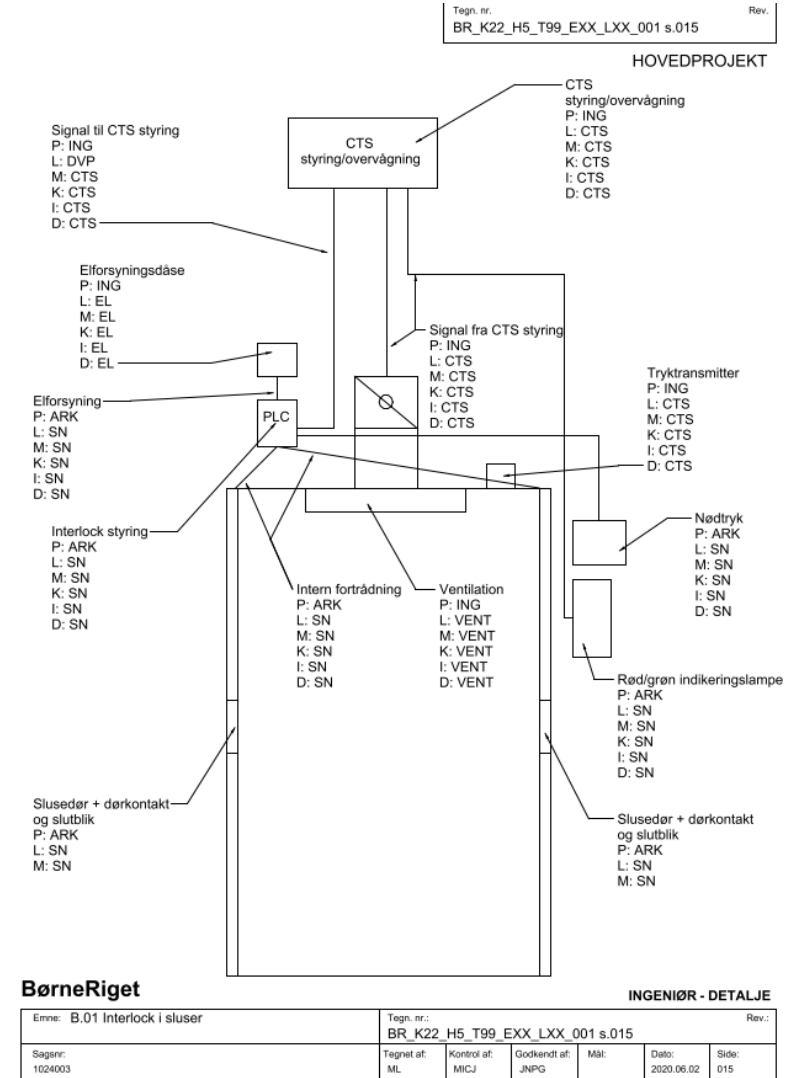


Borders, Equipment

Who do what, and when

During design, and construction need for Clear border lines, for the entrepreneur and engineers

Limits; gaps and doubt.

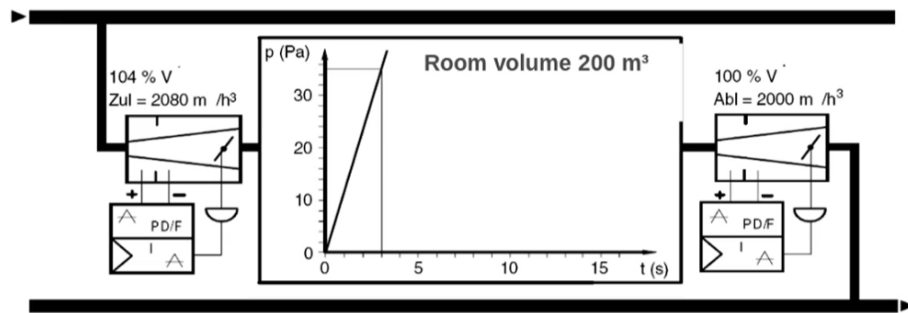


Examples: on Borders for a interlock

Pressurisation - Tight room

Small air changes make pressure jump the tighter the worse

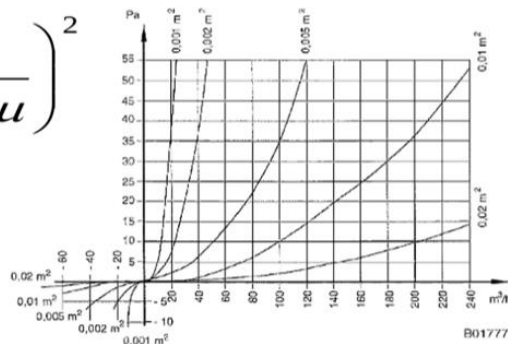
RELATION BETWEEN LEAKAGE, FLOW AND RESULTING NEGATIVE PRESSURE



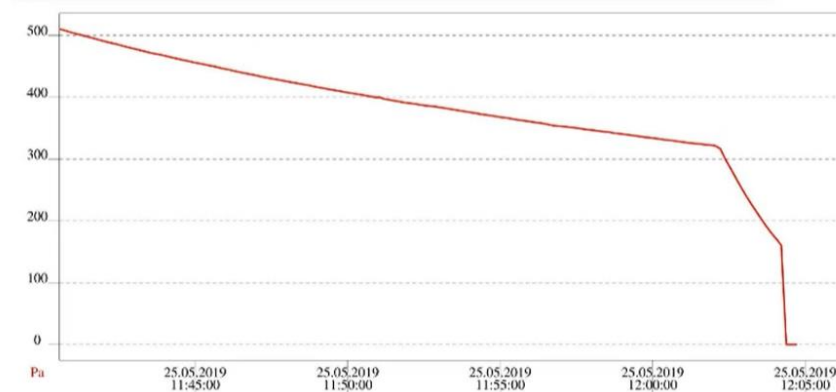
3 second = + 35 pa

RELATION BETWEEN LEAKAGE, FLOW AND RESULTING NEGATIVE PRESSURE

$$\Delta p = \frac{\rho}{2} \cdot \left(\frac{\dot{V}}{A \cdot \mu} \right)^2$$



TIGHTNESS TEST BY PRESSURE DECAY METHOD



TIGHTNESS TEST BY PRESSURE DECAY METHOD

V [m³] : Inner Volume of Test Object

P_i [Pa (abs)] : Initial Pressure

T_i [K] : Initial Temperature

t [min] : measuring time

P_f [Pa (abs)] : final Pressure

T_f [K] : final Temperature

Q [l/sec] : Leakage Air Flow

$$Q = \left(\frac{P_i}{T_i} - \frac{P_f}{T_f} \right) \cdot \left(\frac{V}{R \cdot \Delta t \cdot 60 \cdot 1.201} \right)$$

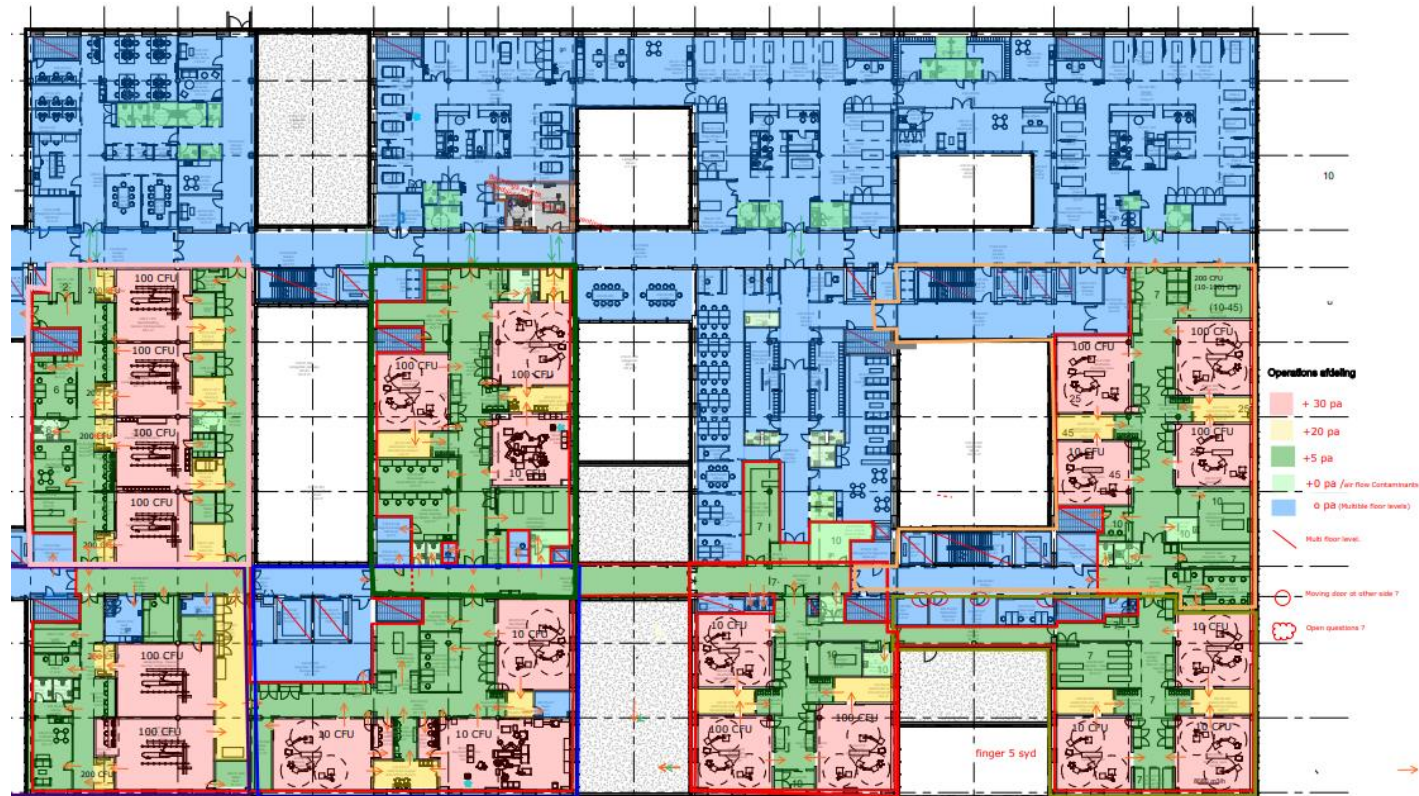
Pressure cascades - how to

Pressure and flow must be combined in order to keep pressure cascades right

What will happen if all light-red rooms opens up to green corridor ?

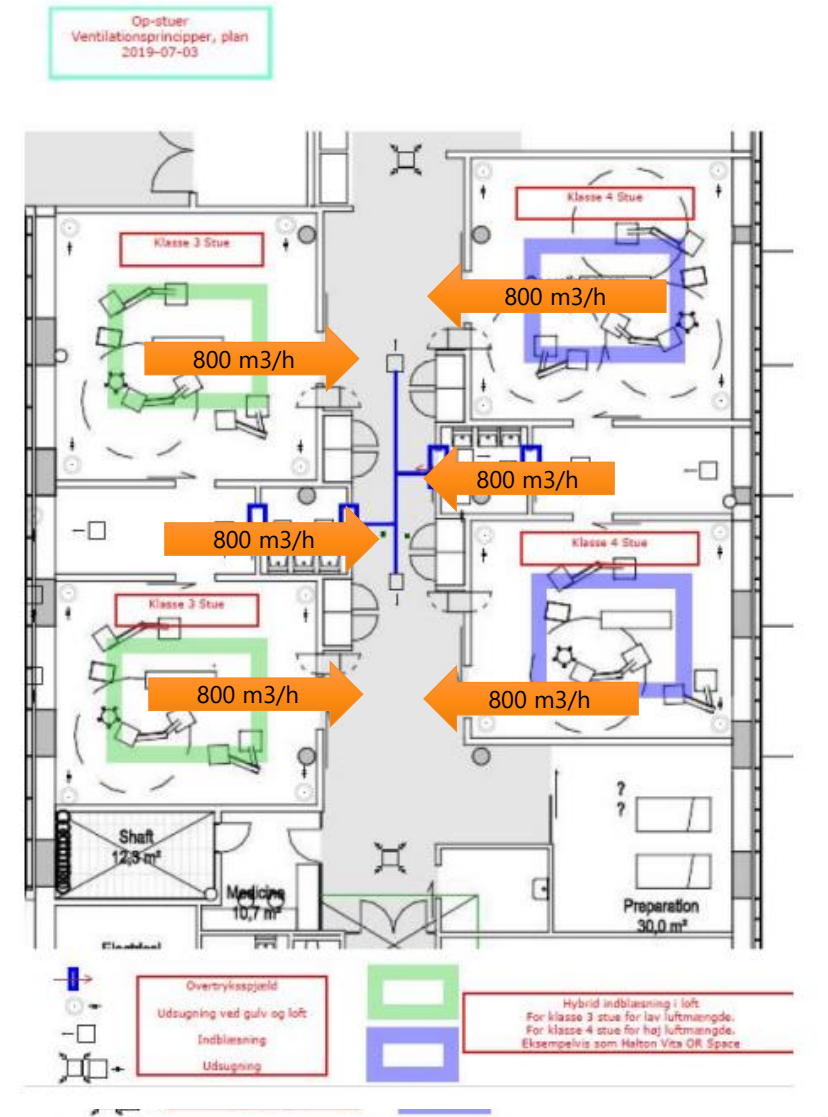
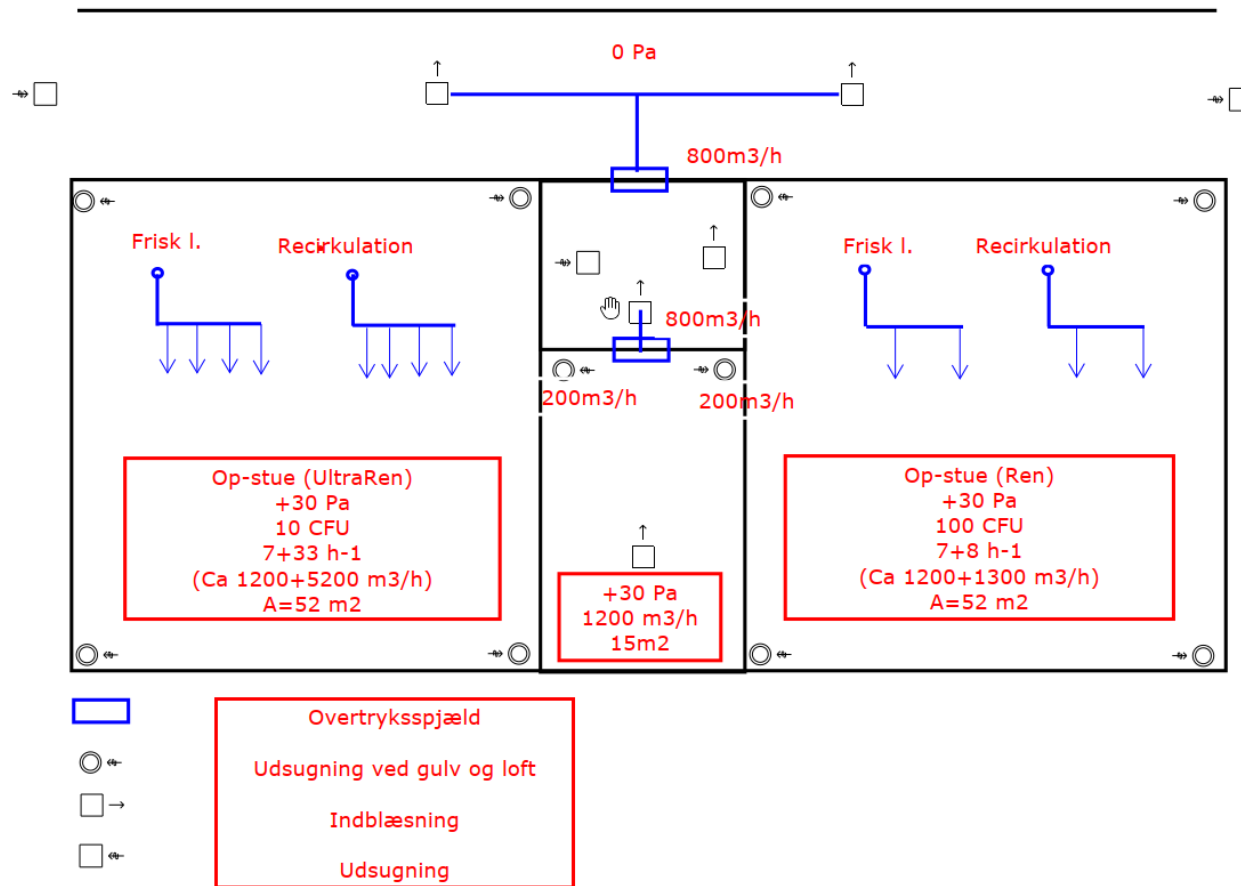
Pressure !

-Flow is faster than pressure to adjust.



Pressure - flow - control

Example on how to keep differential flow in cascade



Tight room – hard to pressure control

Small air change make pressure jump the tighter the worse

One way to reduce the sensibility for pressure "jumps"
-is to install controlled stable leaks.

- Holes with HEPA filter in,
- Appreco balance pressure damper (picture)
- Faster loop for BMS
- Air consuming equipment is better synchronised
- With inlet. "Open Gap" stabilises a workbench.
- Etc.



Airlock as clean barrier.

How to design.

Capacity in airlocks by design.

Higher airchange =>

Lower particle concentration =>

Faster pass-through of personnel.

Concider if waiting time is only needed one way, the other no waiting time is needed.
(how to control interlock?)

Pressure cascades – and outdoor pressure

Room in room classified rooms – Here BSL3 facility.

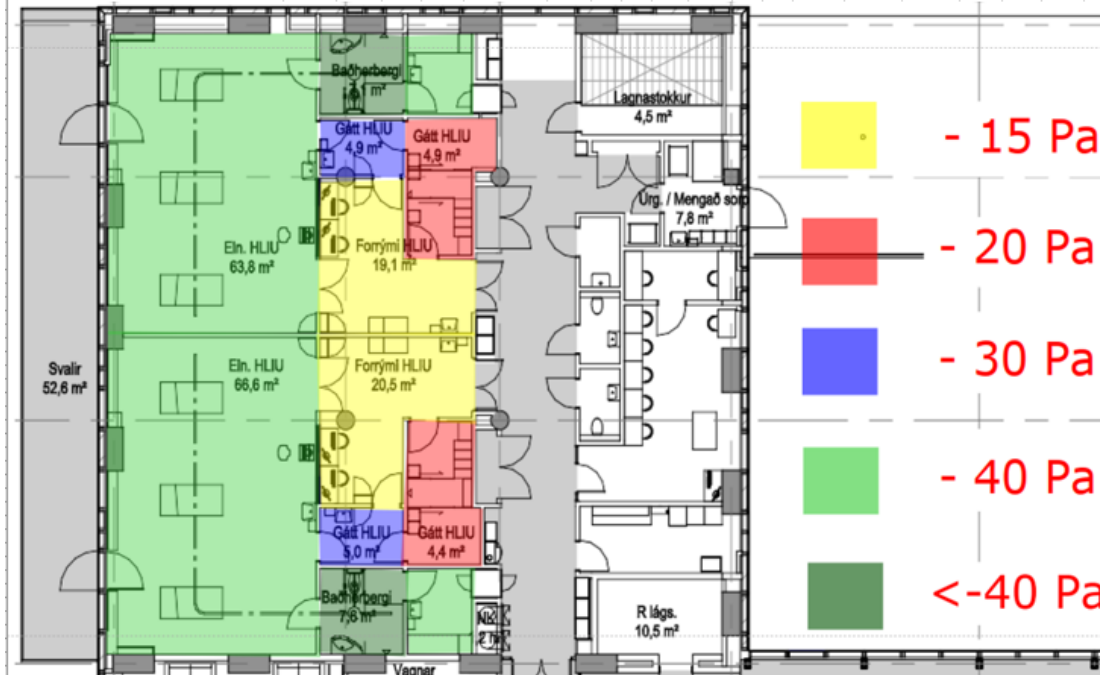


In / Ex Filtration

Leaks have great impact on the HVAC and the pressure.

- Leak must be taken into account while designing cleanroom facilities.
- A scheme as above can be used to describe the level of leaks.

AHU nr.	Plantroom AHU	Room nr.	Level	Status/used e noteflag	Room name	Hygiene requirement (e.g., ISO, etc.)	Area	Room height	Room volume	Room temperature (°C)	Room humidity (g/kg)	Room air pressure	Air change		Airflow		Process extraction	Process extraction 2	Process extraction 3	In and out air	Room outlet	Total outlet air	Note
													h-1	m³/h	l/s	m³/h							
Call 1																							
		TBD	2H		Patient room	1.1	64	2,7	173	20-26	<70	-40	25	4.320	1.200	-	-	-	-	-	*****	4.300	
		TBD	2H		Clean air-lack, Working space	1.2	22	2,7	58	20-26	<70	-15	12	697	194	-	-	-	-	-	*****	700	
		TBD	2H		Dirty Air-lack	1.4	9	2,7	15	20-26	<70	-30	46	671	186	-	-	-	-	-	*****	700	
		TBD	2H		Staff, derinf., zhasuer, changing	1.3	10	2,7	26	20-26	<70	-20	46	1.205	335	-	-	-	-	-	*****	1.200	
		TBD	2H		Patient bath room wash, autoclaving	1.5	14	2,7	38	20-26	<70	-40	10	360	100	-	-	-	-	-	*****	400	
Call 2																							
		TBD	2H		Patient room	2.1	65	2,7	176	20-26	<70	-40	25	4.320	1.200	-	-	-	-	-	*****	4.300	
		TBD	2H		Clean air-lack, Working space	2.2	21	2,7	57	20-26	<70	-15	12	680	189	-	-	-	-	-	*****	700	
		TBD	2H		Dirty Air-lack	2.4	9	2,7	15	20-26	<70	-30	46	671	186	-	-	-	-	-	*****	700	
		TBD	2H		Staff, derinf., zhasuer, changing	2.3	10	2,7	26	20-26	<70	-20	46	1.205	335	-	-	-	-	-	*****	1.200	
		TBD	2H		Patient bath room wash, autoclaving	2.5	14	2,7	38	20-26	<70	-40	10	360	100	-	-	-	-	-	*****	400	



Leak level, in a facility before handover .

Example is from a contamination facility.

Different ways to test and find leaks is normally by smoke and blowerdoor testing .



TIGHTNESS TEST BY CONSTANT PRESSURE METHOD

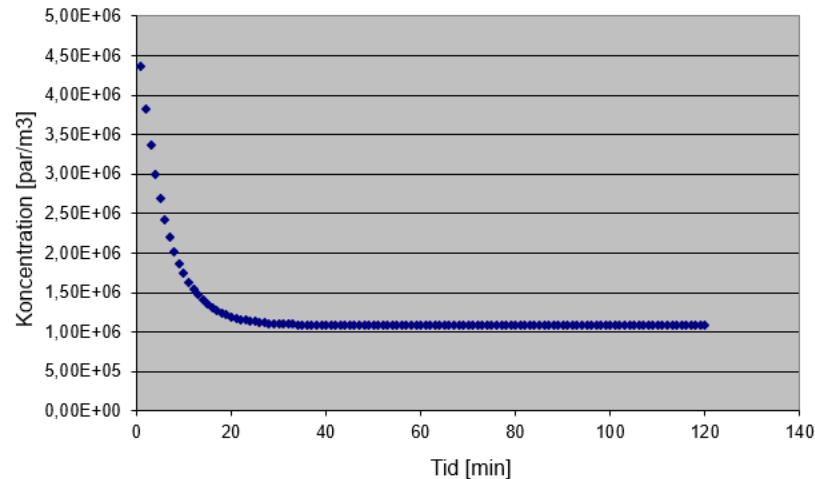
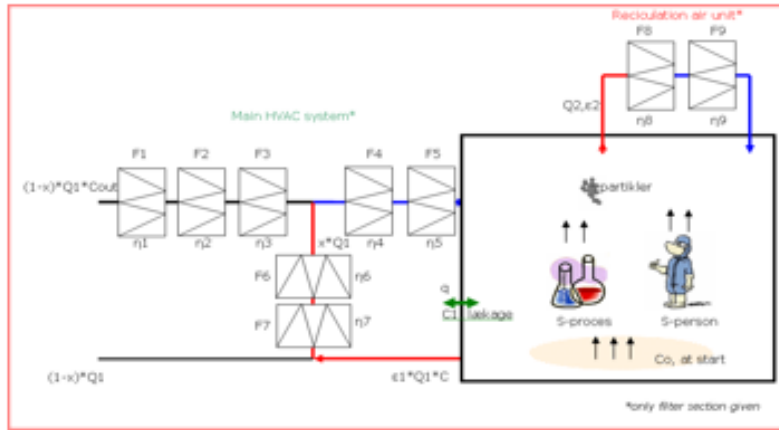


LEAK DETECTION BY ULTRASONIC



Cleanliness calculation

Example on how to calculate different scenarios to a cleanroom ISO14644-1



Renrumsberegning ISO

Kunde:
 Projekt:
 Fase:

Projektør:
 Fagansvarlig:
 KS

Angiv Rumnr. eller navn: **2.24.0**

Partikel størrelse
 Partikel størrelse større end: **0,5** µm

Udendørs Kilder
 Udendørs koncentration større end: **0,5** µm **30.000.000** partikler/m³ **3,00E+07**

Indendørs Kilder
 Person: Partikler udvikling, større end: **0,5** µm **10.000** partikler/sek*person **1,00E+04**
 Proce: Partikler udvikling, større end: **0,5** µm **10.000** partikler/sek **1,00E+04**
 Person & Proce: Partikler udvikling, større end: **0,5** µm **50.000** partikler/sek **5,00E+04**
 Kilder ved start: Koncentration af størrelse større end: **0,5** µm **5.000.000** partikler/m³ **5,00E+06**
 Lækage: Koncentration af størrelse større end: **0,5** µm **30.000.000** partikler/m³ **3,00E+07**

Rum
 Længde: **12** m
 Bredde: **4** m
 Højde: **3** m
 Areal: **48** m²
 Volumen: **144** m³
 Luft skifte, system (1): **30** h⁻¹
 Luft skifte, system (2): **30** h⁻¹
 Luft skifte, system (1)+(2): **60** h⁻¹
 Ventilation effektivitet, system (1): **0,7**
 Ventilation effektivitet, system (2): **0,7**
 Recirkulations luft, system (1): **80** %
 Personer: **4** pcs.
 Areal/person: **12** m²/person
 Luft mængde, system (1): **4320** m³/h **1,20** m³/s
 Luft mængde, system (2): **4320** m³/h **1,20** m³/s
 Lækage i rum: **50** m³/h **0,01** m³/s

Filter
 Pre-filter 1, type: **F5** partikel størrelse større end: **0,5** µm ffektivitet: **0** %
 Pre-filter 2, type: **F6** partikel størrelse større end: **0,5** µm ffektivitet: **0** %
 Pre-filter 3, type: **F1** partikel størrelse større end: **0,5** µm ffektivitet: **64** % **3,60E-01** (1-rec1)
 Ende-filter 4, type: **F3** partikel størrelse større end: **0,5** µm ffektivitet: **92** % **8,00E-08** (1-rec3)
 Ende-filter 5, type: **H14** partikel størrelse større end: **0,5** µm ffektivitet: **39.3939** % **1,00E+00** (1-rec2)
 Recirkulation filter 6, type: **N/A** partikel størrelse større end: **0,5** µm ffektivitet: **0** % **1,00E-06** (1-rec4)
 Recirkulation filter 7, type: **N/A** partikel størrelse større end: **0,5** µm ffektivitet: **0** %
 System (2) filter 8, type: **H14** partikel størrelse større end: **0,5** µm ffektivitet: **39.3939** %
 System (2) filter 9, type: **N/A** partikel størrelse større end: **0,5** µm ffektivitet: **0** %

konstant **k1** **1,63**
 konstant **k2** **4.1666666,814**
 Rum koncentration efter 1 min: **2612477** partikler/m³ **2,61E+06**
 Rum koncentration efter 5 min: **415367** partikler/m³ **4,16E+05**
 Rum koncentration efter 10 min: **280316** partikler/m³ **2,80E+05**
 Rum koncentration efter 15 min: **276302** partikler/m³ **2,76E+05**
 Rum koncentration efter 20 min: **276183** partikler/m³ **2,76E+05**
 Rum koncentration efter 60 min: **276180** partikler/m³ **2,76E+05**
 Koncentration efter min: **277192** partikler/m³ **2,77E+05**
 Koncentration i steady-state: **276180** partikler/m³ **2,76E+05**

Ren klassen efter ISO 14644-1: **6,3** ISO
 Ren klassen efter Fed Std 205E: **5,4** M, informativ
 Reduktion opretnings 20 min: **9**

filter 1 eff.: **10** %
 filter 2 eff.: **30** %
 filter 3 eff.: **0** %
 result. off.: **37** %

Potens beregner
 basis: **10** **6** **1000000**
 potens:
 værdi:
 C-out
 S-person/person
 S-kilde
 Co
 C-lækage
 L
 W
 H
 A
 V
 ACH1
 ACH2
 ACH
 ε1
 ε2
 x
 N
 N/m2
 Q1
 Q2
 q
 η1-out EUT (F1) 50%; EU8 (F8) 65 %; 0,1mm
 η2-out
 η3-out
 η4
 η5
 η6-rec
 η7-rec
 η8
 η9
 k1=1*Q1+1*q+2*Q2+1*Q1*x*(1-rec2)*(1-rec3)+2*Q2*(1-rec4) [m3/s]
 k2=(1-x)*(1-rec1)*(1-rec3)*Q1*Co+q*Clækage [par/m3]
 c=(Co-S/k1-k2/k1)*eksp(-k1*60/V)+S/k1+k2/k1, t [min]=1
 C-st
 C-steady-state

Page 1

I flere pre-filter, ende-filter or recirkulation filter, kan man beregne resultende effektivitet:

Recovery time - calculation

Example on calculation on recover time

Renrumsberegning ISO

Kunde
Projekt
Fase

Projektnr.
Fagansvarlig
KS

Beregning af oprensningstid på baggrund af DS 14644-3 - B4 recovery test

Recovery rate

Rate	konstant	Tidskonstant	
1:10	0,1	-2,30	4 min
1:100	0,01	-4,61	4 min

Inddata fra cleanroom beregning

Total luftskifte (1+2)		15,0 h ⁻¹
Ventilationseffektivitet		0,7
Tidskonstanten	T	4 min

Oprensningstid 1:10

Faktisk oprensningstid 1:10

-9,2 min

-13,2 min

Oprensningstid 1:100

Faktisk oprensningstid 1:100

-18,4 min

-26,3 min

Note:

Opretningsstiden er under forudsætning af, at der ikke tilføres infiltration
infiltration forlænger oprensningstiden

Recovery time

Number of people, gowning type, and cleanliness level required.

Rensrumsberegning ISO	
Kunde	Projekt nr.
Projekt	Fagansvarlig
Dato	KS

Beregning af nødvendig luftmængde ift. CFU

$$Q_v = S/c$$

Q_v = required air flow rate, m³/s
 S = total contaminat source strenght, CFU/s
 c = allowed CFU concentration in the space, CFU/m³

$$S = n \cdot q_s$$

n = number of persons in the operation room

q_s = source strenght of one person, value depends on what kind of clothing system is used by the personnel, see values (* below)

- surgical clothing system, cleanroom quality, 99 % polyester, 1 % carbon fibre => $q_s = 0,7$ CFU/s
- single-use surgical clothing system, 100 % polypropylene => $q_s = 1,15$ CFU/s
- common surgical clothing system, 50 % cotton, 50 % polyester => $q_s = 1,9$ CFU/s
- surgical clothing system, 99 % polyester, 1 % carbon fibre => $q_s = 2,9$ CFU/s
- common surgical clothing system, 69 % cotton, 30 % polyester, 1 % carbon fibre => $q_s = 5,0$ CFU/s

*) Values are from Practical Safety Ventilation in Operating Rooms- An Introduction, Ljungqvist & Reinmuller, 2013, Chalmers University of Tehnology

c = allowed number of colony forming unit in m³ of air (*)

- $c = 10$ CFU/m³ for ultra clean air
- $c = 100$ CFU/m³ for clean air

*) Values based on CEN TC 15/6 WG 18 - standardisation work (not yet published)

Required air flow rate based on allowed contaminent concentration (=cleanliness):

$Q_v = 0,56$ m³/s

NB! Enter values to yellow cells below to re-calculate

- 8 Number of persons
- 0,7 q_s value, clothing type, see above
- 10 Allowed number of CFU/m³, see above
- 100 Volume of the operation room, m³

Recovery time:

= 13,7 min

According to CEN TC 15/6 WG 18 - Recovery time should be < 15 min at high risk operation

Huge difference in particle emission of particles.

Requerments is in ISO14644-3 for recovery time

New equipment solves problems and gives new problems

Instrumentcontainer

How to make it safe

When they turn they rip up the floor if not extremely stable.

Smart new technology



Questions



A simulation by

NIRAS

www.niras.com

Simulering

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