

Vaccine Production Systems

Principles of Vaccine Production (I)

Pathogen (seed = clinical isolate)

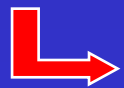


Culture → Inactivation → Vaccine (wP, HAV)



Purification → Vaccine (Rab, Flu)

Ag purification



Inactivation → Vaccine (aP)

Principles of Vaccine Production (II)

Pathogen (clinical isolate)



Attenuation



Seed (live attenuated)



Culture → Vaccine (MMR, OPV, aP?)



Passages

Site-directed mutagenesis

Principles of Vaccine Production (III)

Pathogen (clinical isolate)



Cloning, GMO (*E. coli*, *S. cerevisiae*, baculovirus...)



Seed



Culture → Purification → Vaccine (*HBV*, *HPV*)

Futuristic Vaccines (I)

Pathogen (clinical isolate)



Cloning, GMO (*E. coli* + plasmid)



Seed



Culture → DNA purif. → Vaccine (???)

Futuristic Vaccines (II)

Pathogen (clinical isolate)



Cloning, GMO (live vector: vaccinia, adenovirus...)



Seed



Culture → Vaccine (???)

Vaccine Production: Processes

Biomass production

Inactivation

Purification

Formulation

Vaccine Production Facilities

Vaccine Production: Requirements

Protect the product

Protect the environment

Protect both

Vaccine Production: Requirements

Protect the product

Avoid air- /water- / human-borne contamination

Protect the environment

Large scale cultivation of pathogens, GMO's

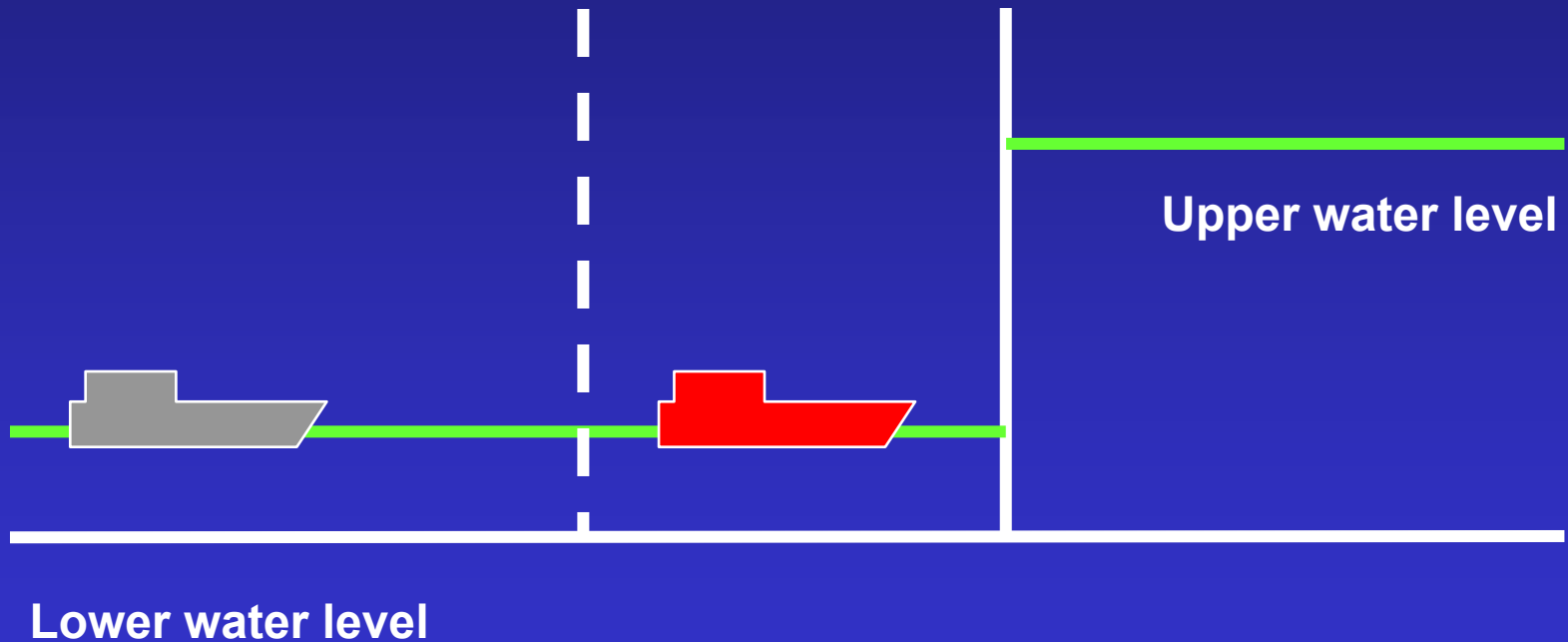
Protect both

In large scale operations, measures to protect the environment also result in protecting the product

Air

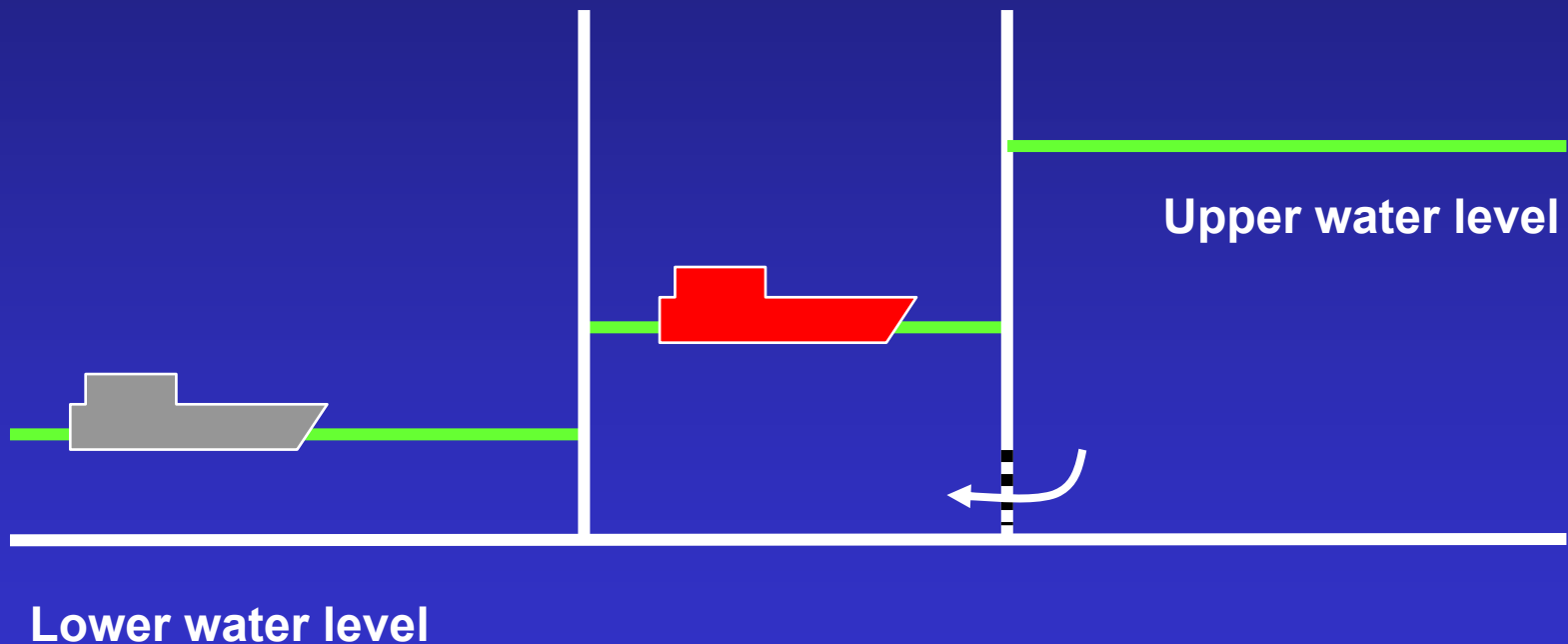
Air Protection Principles

Lock, Ecluse, Sluis, Sas... (river navigation)



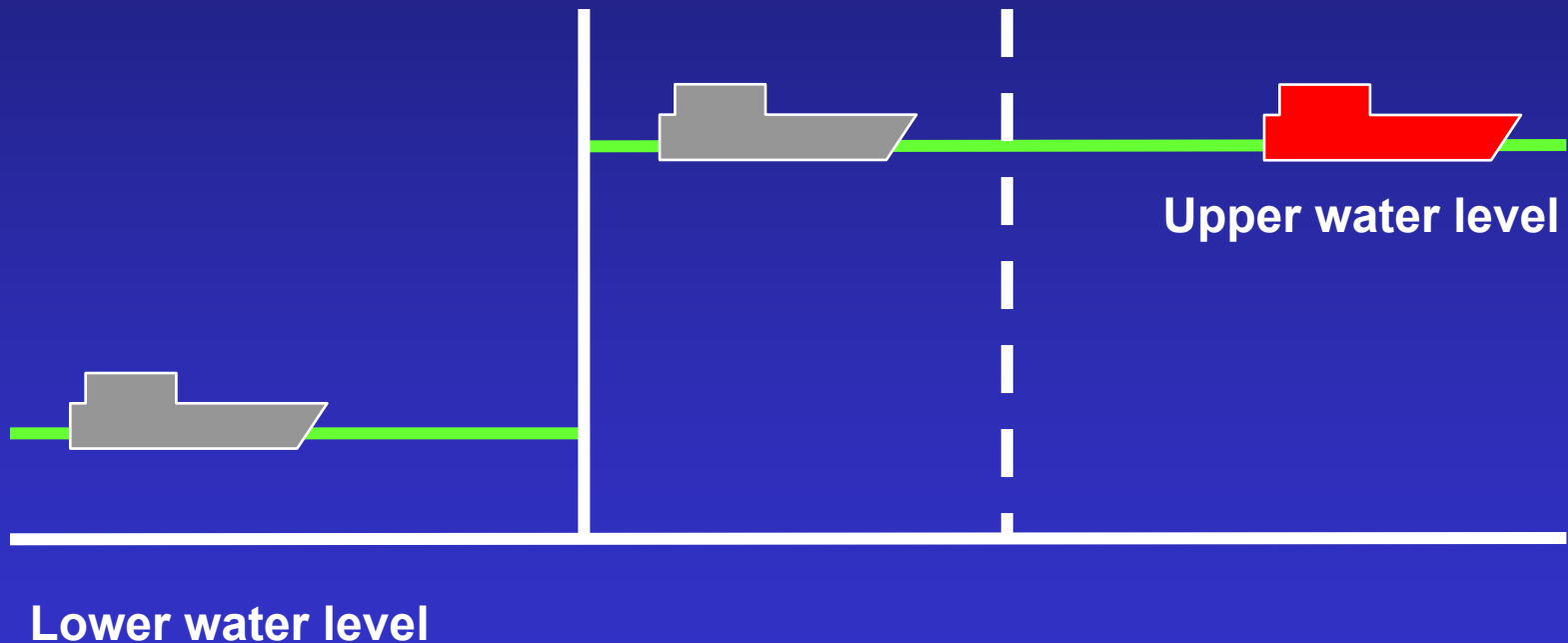
Air Protection Principles

Lock, Ecluse, Sluis, Sas... (river navigation)



Air Protection Principles

Lock, Ecluse, Sluis, Sas... (river navigation)

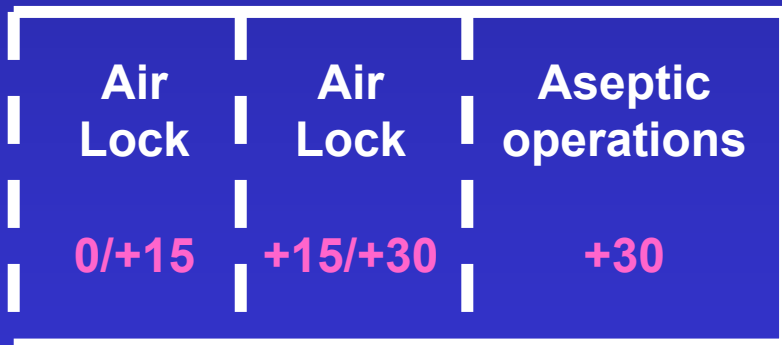


Air Locks

Protect the product



Protect the environment



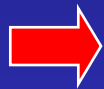
Protecting Product and Environment

Air Lock	Air Lock	Air Lock	Contained & clean operations
0/+15	+15	+15/0/-15	-15

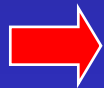
Reasonable Protection Compromise

The Solution of Bionet Asia Ltd.

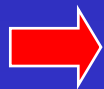
Large scale = closed equipment & systems



no open air operation



the product is by definition protected

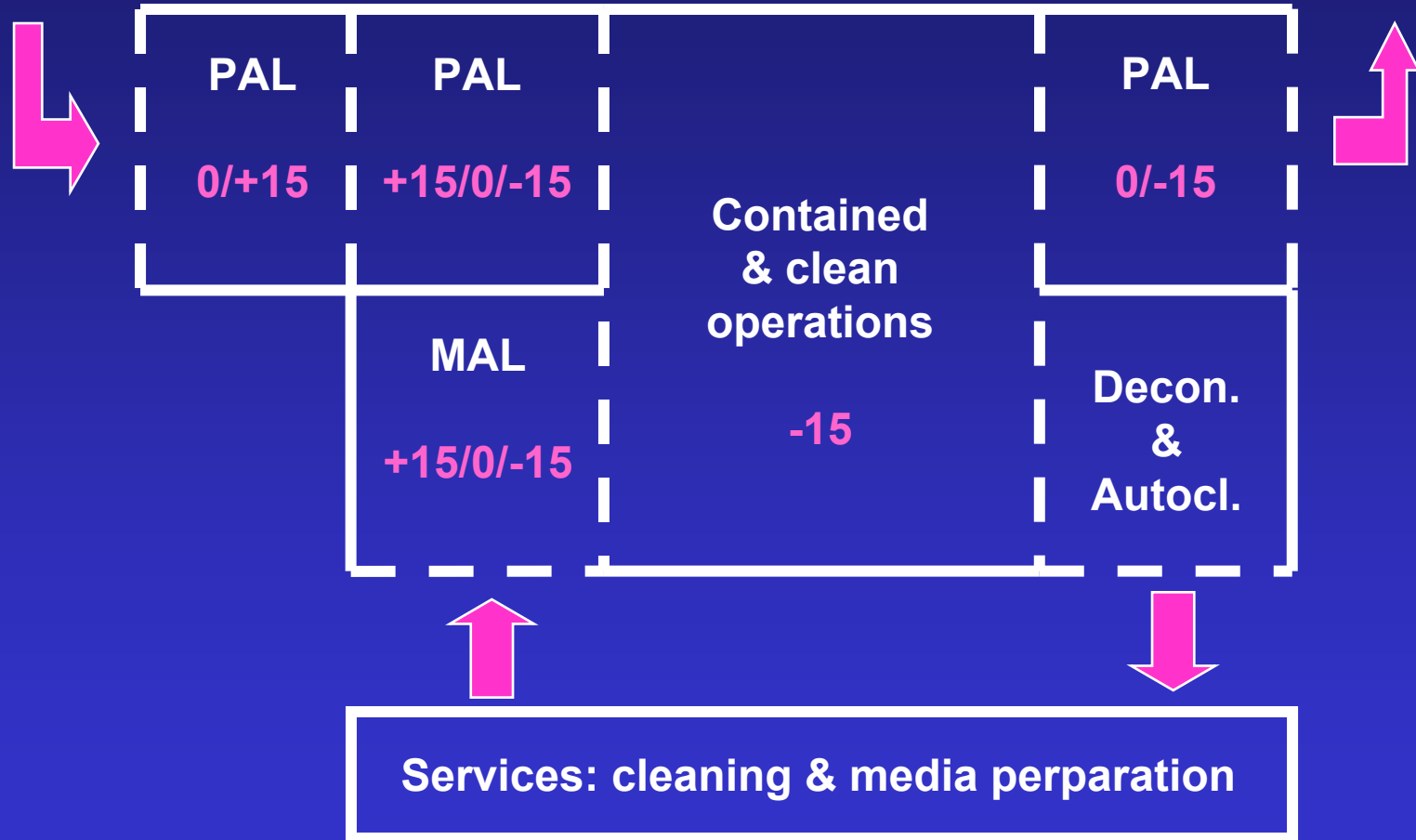


priority on containment

BSL2 Operations at BNA

People in

People out



Clean Operations

- **Grade D**

- Closed system operations (fermentor...)

- **Grade C**

- Clean operations (purification...)

- **Grade B**

- Background for aseptic operations

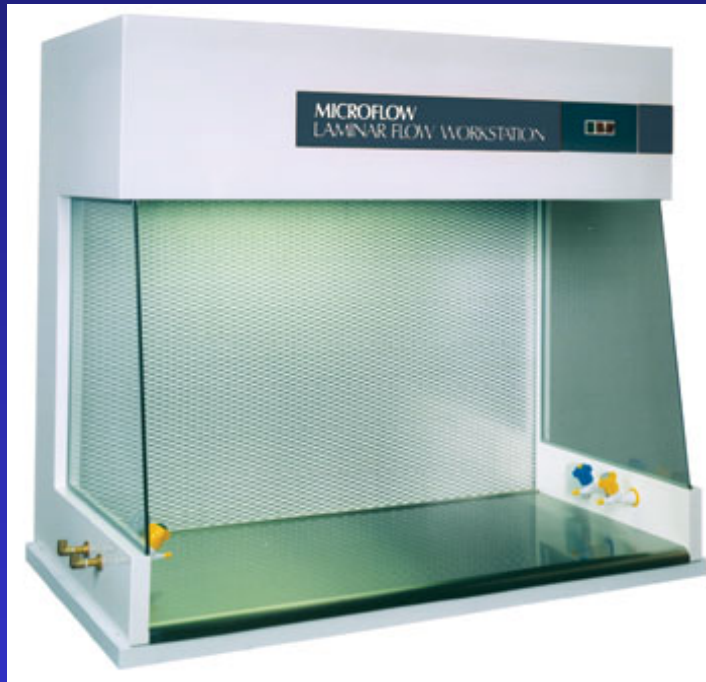
- **Grade A**

- Aseptic operations (sterile filtration, final bulk formulation, vial filling)

Clean Air Specifications

Maximum permitted number of particles/m ³				
Grade	At rest		In operation	
	0.5 µm	5 µm	0.5 µm	5 µm
A	3,500	0	3,500	0
B	3,500	0	350,000	2,000
C	350,000	2,000	3,500,000	20,000
D	3,500,000	20,000	Not defined	Not defined

Clean Air Cabinets



Protect the product:
Class A
horizontal flow cabinet



Protect the product and the environment:
Cat. II biosafety cabinet
(pathogens cat. I to III)

Air Ducts Above Clean Rooms



Water

Water Specifications

- **CW (city water)**
 - General, non-pharma operations
- **PW (purified water)**
 - IEX or other suitable process
- **HPW (highly purified water)**
 - 2-stage reverse osmosis → EDI (optional)
 - Chemical quality = distilled water
 - Cooled loop (<20°C)
- **WFI (water for injections)**
 - Distilled HPW (EU); HPW (US)
 - Hot loop, ≥80°C (Eur. Ph.) / loop (USP)

Water Specifications: PW

Parameter	Units	USP	Eur. Ph.
TOC	ppm C	0.50	0.50
Conductivity	$\mu\text{S/cm}$	$\leq 1.3 @ 25^\circ\text{C}$	$\leq 4.3 @ 20^\circ$
Nitrate (NO_3)	ppm	-	≤ 0.2
Heavy metals	ppm as Pb	-	≤ 0.1
Bacteria	CFU/ml	≤ 100	≤ 100

Water Specifications: HPW

Parameter	Units	USP	Eur. Ph.
TOC	ppm C	n. c. st.	0.50
Conductivity	$\mu\text{S/cm}$	n. c. st.	$\leq 1.1 @ 20^\circ$
Nitrate (NO_3)	ppm	n. c. st.	≤ 0.2
Heavy metals	ppm as Pb	n. c. st.	≤ 0.1
Bacteria	CFU/100 ml	n. c. st.	≤ 10
Endotoxin	EU/ml	n. c. st.	≤ 0.25

n. c. st. = no comparable standard

Water Specifications: WFI

Parameter	Units	USP	Eur. Ph.
TOC	ppm C	0.50	0.50
Conductivity	$\mu\text{S/cm}$	$\leq 1.3 @ 25^\circ$	$\leq 1.1 @ 20^\circ$
Nitrate (NO_3)	ppm	-	≤ 0.2
Heavy metals	ppm as Pb	-	≤ 0.1
Bacteria	CFU/100 ml	≤ 10	≤ 10
Endotoxin	EU/ml	≤ 0.25	≤ 0.25

Water Production Systems

Water Quality	Produced by (USP)	Produced by (Eur. Ph.)	How distributed
PW	Suitable Process	IEX, other process	One way pipework
HPW	n. c. st	RO/UF, EDI Distillation	Loop RT or cooled
WFI	RO or distillation	Distillation only	Loop $\geq 80^{\circ}\text{C}$ (Eur. Ph.)

n. c. st. = no comparable standard

In practice: HPW (Eur. Ph.) = WFI (USP)

Water Requirements for Production

● PW

- Fermentation / cell culture
 - Extraction, primary recovery
- } Unless more stringent technical requirement

● HPW

- Extraction
- Purification (except last step)

● WFI

- Last purification step, formulation, filling

● Cleaning / washing / rinsing

- Final rinse with same water quality as required by operations

Lab Water System



HPW System



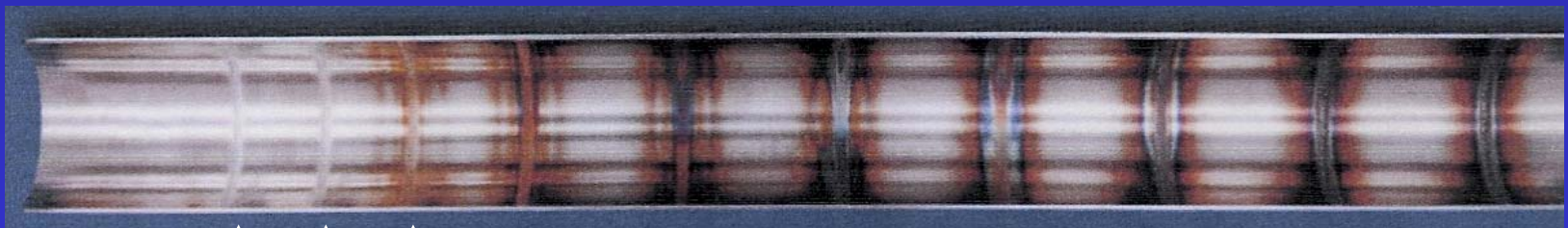
Water Pipework

- **Requirement**

- Avoid bacterial bio-film formation

- **Solution**

- Stainless steel, 316L with additional specs.
- Internally electro-polished tubes
- Orbital (TIG) welding under argon flux (≤ 25 ppm O_2)



↑ ↑ ↑
10 25 50 ppm O_2

Orbital Welding Coupons



Each day, a test weld is prepared with the batch of tube to be used that day. The tube is then cut next to the weld to inspect the interior of the weld. If OK, welding parameters are stored in the system and applied throughout the day. Coupons are numbered and archived as part of the system's documentation.

People

Gowns



**Women at work
Baxter Laboratories, 1942**

**Disposable, non-woven
Isolation gown, 2008**

