Advancements in Isolator Technology

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Agenda

- Gloveless/Robotic Isolators
- RFID Technology
- Biological Indicator Alternatives
- Polypropylene construction
- Particle monitoring
- Ingress/Penetration testing

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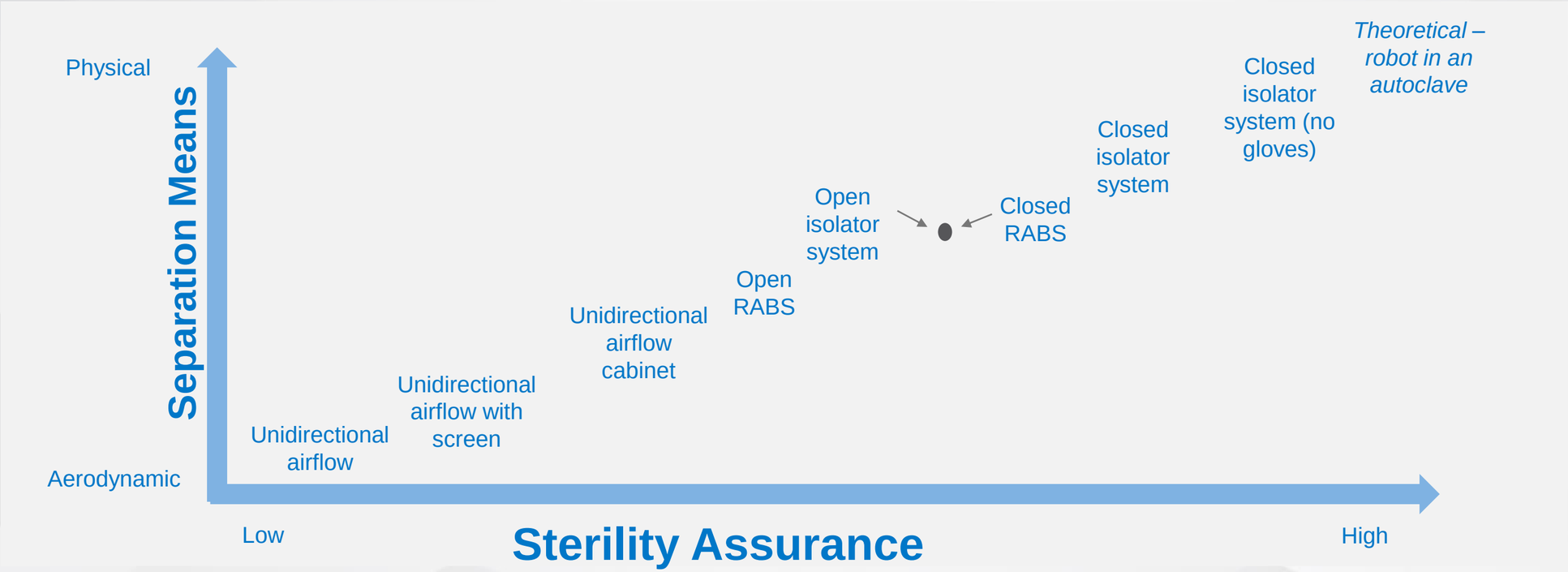
Gloveless/Robotic Isolator Systems

Challenges with gloved or open isolators

- Biggest risk to an aseptic process is… the human!
- Standard isolators carry a risk of gloves rupturing, contaminating the process
- Routine glove testing is required which takes time

Separation Assurance Continuum

Increasing separation increases assurance of sterility in process



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Increased efficiency

- Can perform a repetitive process quicker than a human, increasing capacity
- Can reduce human mistakes in critical processes e.g. fill/finish
- But are still prone to breakdowns and process mistakes
- Robotic isolators eliminate the **human** operator from the process, minimising risk
- Contamination risk still remains from interventions i.e. loading of materials
- Robotic loading of isolator is the next step to further remove risk from process

Example – Aseptic Technologies Crystal L1 robot inside a stainless steel isolator

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Industry Uptake

- Five contract manufacturing organisations (CMOs) have publicly announced their use of Vanrx's SA25 Aseptic Filling Workcell.
  - AB Biotechnologies
  - Fujifilm Diosynth
  - Patheon (Thermofisher)
  - Singota Solutions
  - Wuxi Biologics

Vanrx aseptic filling workcell

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RFID Technology

Radio Frequency Identification Technology

- Digital data encoded in tags on H_2O_2 bottles captured by a reader on isolator

Isolator bottle module

- Benefits include:
  - Prevents bio-decontamination cycle from starting without a sufficient quantity of H_2O_2 solution
  - Prevents expired peroxide from being used
  - Traceability by printing batch number on cycle report
  - Prevents other potentially dangerous chemicals from being accidentally vaporised
  - Ensures only **approved** peroxide is used…

```
************************
******* L-4 Opti *******
************************

11/12/2020 09:52:02

PLC VERSION: V1.08
HMI VERSION: V2.02

SERIAL NUMBER: 201601L44172
CYCLE COUNT: 1
CALIBRATION DUE DATE: 09/12/2021

------------------------------------------------
EQUIPMENT REFERENCE: ABF0950110111091

H2O2 LOT NUMBER: AAA0000000000000
------------------------------------------------
CYCLE NAME: Training test cycle


3.PRESSURE TEST ENABLED
4.TEST PRESSURE 100 Pa
5.TEST TIME 180 s
6.TEST DECAY 50 Pa
8.AIRFLOW SETPOINT 20 m^3/h
9.DELIVERY TEMPERATURE 60°c
10.PRESSURE CONTROL ENABLED
11.PRESSURE SETPOINT 40 Pa
12.PRESSURE LOW ALARM 30 Pa
13.PRESSURE HIGH ALARM 50 Pa
16.CONDITIONING TIME 300 s
17.GASSING INJECTION RATE 2.0 g/m
18.GASSING TIME 180 s
19.DWELL INJECTION RATE 1.5 g/m
20.DWELL TIME 180 s
21.H2O2 ALERT LEVEL     0.0 ppm
24.AERATION VFC DELAY 300 s
25.AERATION PARAMETRIC ENABLED
26.AERATION TIME 600 s


------------------------------------------------

USER: Engineer


SIGNATURE:_____


################################################
 09:52:14 PRESSURISING 3 Pa
################################################
 10:05:53 TEST START 100 Pa
################################################
 10:08:53 TEST PASSED 89 Pa
################################################
 10:08:54 CONDITIONING
  89Pa  0.0m^3/hr  21.9°c  53%    0.0ppm
################################################
 10:14:04 PRE-GASSING
  37Pa  6.1m^3/hr  59.0°c  50%    0.0ppm
################################################
 10:14:30 GASSING
  41Pa 20.9m^3/hr  57.5°c  49%    0.0ppm
total  6.0 g
peak concentration    0.0 ppm
################################################
 10:17:30 GASSING DWELL
  39Pa 20.0m^3/hr  61.1°c  85%    0.0ppm
```

Example report

Regulatory requirements - BPR

- EU regulation 528/2012 Biocidal Products Regulation (**BPR**) came into force in Europe in September 2013 and applies to all biocidal products used in Europe
- The regulation concerns both the sale and **use** of biocidal products in Europe and involves:
  - The analysis of a product's performance (efficacy)
  - Toxicity
  - Environmental fate and risk during use
- Registrations include not only the biocide, but the **method** in which it is introduced to the enclosure
- Therefore RFID technology ensures that only the registered **biocide** is used in combination with the registered **equipment/bio-decontamination method**

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Biological Indicators Alternatives

Chemical Indicators

Why do we use chemical indicators?

Their use is recommended in regulations

FDA Guidance for Industry states:

"An appropriate, quantified Biological Indicator (BI) challenge should be placed on various materials"

*"**Chemical indicators** may also be useful as a qualitative tool to show that the decontaminating agent reached a given location. "*

Calibrated Chemical Indicators are a new technology which are a **quantitative** tool...

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Calibrated Chemical Indicators

- Consist of a card indicator containing a chemical strip impregnated with ink
- Ink reacts to hydrogen peroxide vapour and changes colour to indicate the efficacy of the bio-decontamination cycle.
- Provides **instant** indication of the bio-decontamination process efficacy
- Results are calibrated against biological indicators

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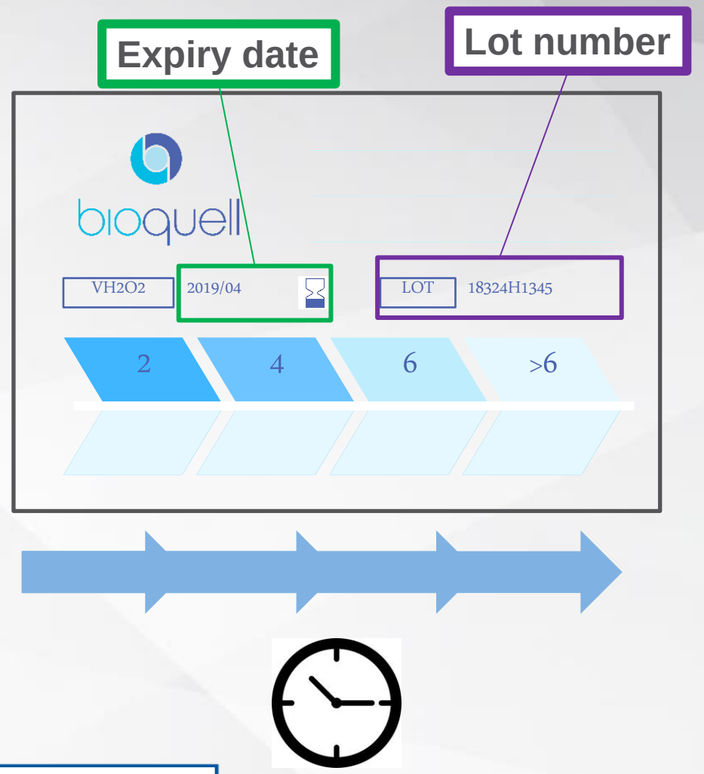
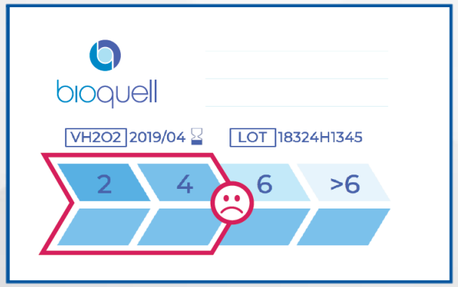
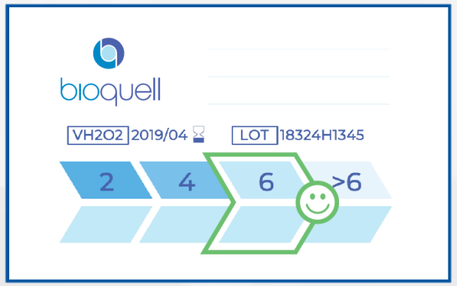
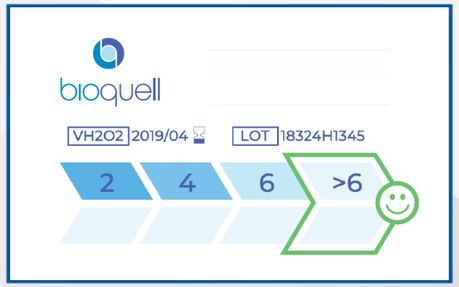
How do they work?

- Reactive ink
  - The reactive ink portion changes colour
  - It will all change to the same colour at the end
- Reference colours
  - The reference colours do not change colour
  - ✓ The number “6” indicates log 6
  - ✓ The number “>6” indicates beyond log 6 was reached
  - ✘ The numbers “2” and “4” indicate log 6 is not reached









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Chemical indicator reader

- A handheld device which enables customers to quickly and easily obtain a real-time, **quantifiable** log reduction indication from a bio-decontamination cycle
- Scans reactive ink and uses software to calculate equivalent BI log
- Provides a PDF report of the results including:
  - Equivalent log reduction
  - Date
  - User login
  - A copy of the instrument calibration certificate

CI reader

Example report

Bioquell CI Report

User name: Doe, John
Device Calibration due: 26/04/2023

Report Date: 03/02/2022
Device S/N: 2010006614

Bioquell Room CI
Lot number: 12345L1234

Expiry date: 25/11/2022

Name	Date	Time	dE	Log reduction	Result
Sample 1	08/04/2019	15:23	10.18	7.27	PASS
Sample 2	08/04/2019	15:23	8.98	7.46	PASS
Sample 3	08/04/2019	15:24	9.43	7.39	PASS
Sample 4	08/04/2019	15:24	9.47	7.38	PASS
Sample 5	08/04/2019	15:24	7.60	7.69	PASS
Sample 6	08/04/2019	15:24	8.21	7.59	PASS
Sample 7	08/04/2019	15:25	8.82	7.49	PASS

Enzymatic Indicators

- Based on the inactivation of a tAK (thermostable Adenylate Kinase) enzyme
- Enzyme catalyses a reaction that produces light and the amount of light produced is directly comparable to the amount of remaining tAK activity on the indicator.
- Light output is measured using a luminometer and provides a quantifiable numerical value
- Results are outputted to a computer which correlates light units to the log reduction of a BI

Comparison between indicators

Category	BI	Calibrated CI	EI
Mode of activity	Inactivation of biological spore	Breakdown of chemical dye	Inactivation of enzyme
Time to result	7 days	Instant Read	Minutes (after 30 min test prep)
Read method	By eye after incubation in TSB at 57°C	By eye or by light reader	React with Luciferin and read with luminometer
Quantifiable result	No	Yes (vs. BI)	Yes
Shelf Life	12 months	12 months	6 months
Use supported by Regulations?	Yes	No	No
Cost per indicator	$10	$2	$25 (plus reader @ $20k)

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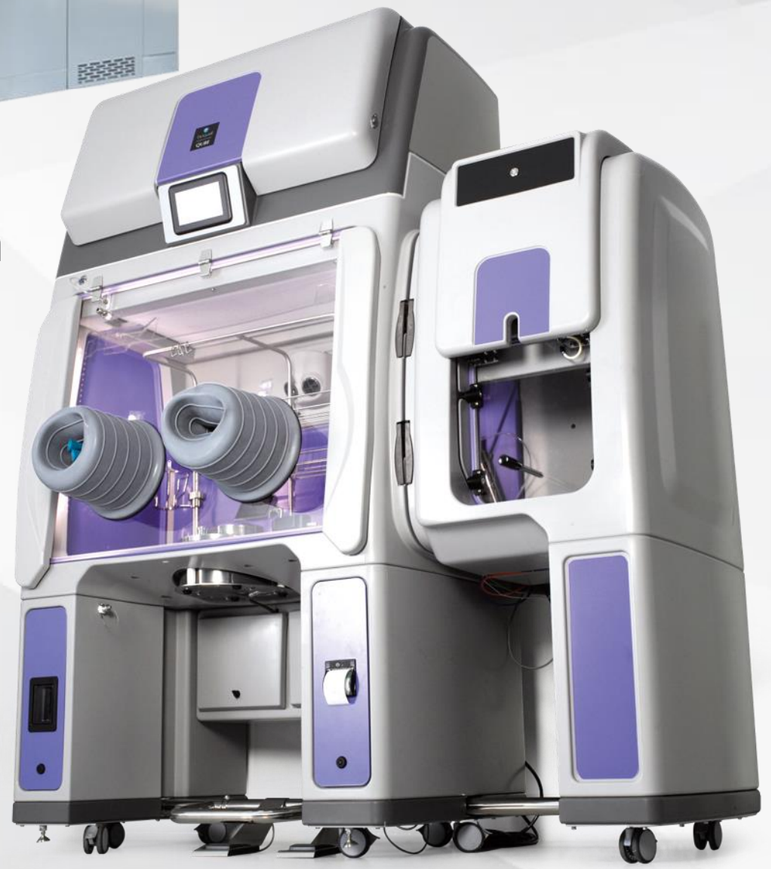
Polypropylene construction

Background

- Traditionally, all isolator systems were made of stainless steel
- Developments in technology have led some companies to develop isolators from a unique polypropylene construction
- This has several advantages over stainless steel…

Stainless steel isolator system



Polypropylene isolator system

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Stainless Steel vs Polypropylene comparison

Stainless Steel	Polypropylene
Manufacturing process	
Fabricated isolators will all be slightly different even if manufactured to the same design as they are 'handmade' – cut, bent, welded, polished etc, which can result in inconsistent fit and variation between each unit	Polypropylene isolators are manufactured from the same mould, therefore, the final product is consistent and correct every time. However, this means the dimensions will be standard, and customization is more complex
Manufacturing time	
Stainless Steel isolators require significant lead times based on the production/fabrication process. Fabrication alone can take up to 6 weeks	Polypropylene isolators can be manufactured in as little as one day allowing delivery in as little as 6 weeks from the time of order through validation

Stainless Steel vs Polypropylene comparison

Stainless Steel	Polypropylene
Weight	
Stainless steel is extremely heavy putting significant load on floor	Polypropylene has a density 8x less than stainless steel, so is optimal for stainless steel, so is optimal for minimal floor loads loads
Ergonomics	
Standard box shapes mean corners can be sharp and can allow for trapped and can allow for trapped dirt.	The moulding process allows smooth corners, which makes cleaning easier which makes cleaning easier (GMP compliant)
Leak tightness	
Each weld, joint and gasket can lead to a potential risk of leaks	A single-piece moulded chamber shell means there are fewer penetrations, so risk of leaks is drastically reduced

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Particle monitoring

Particle Monitoring – Regulatory changes

Updated Annex 1 section 5.9 states sampling head must be “as close as possible to critical location”

5.9 Particle counters, including sampling tubing, should be qualified. The manufacturer’s recommended specifications should be considered for tube diameter and bend radii. Tube length should typically be no longer than 1m unless justified and the number of bends should be minimized. Portable particle counters with a short length of sample tubing should be used for classification purposes. Isokinetic sampling heads should be used in unidirectional airflow systems. They should be oriented appropriately and positioned as close as possible to the critical location to ensure that samples are representative.

However, Annex 1 section 4.19 also states isolators should ensure “first air protection in the critical zone”

4.19 The design of the technology and processes used should ensure appropriate conditions are maintained in the critical zone to protect the exposed product during operations.

i. Isolators:

a. The design of open isolators should ensure grade A conditions with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing.

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Centrally Located Isokinetic Cone

- To comply with 4.19 and 5.9 of Annex 1, some isolator manufacturers have developed a centrally located iso cone position
- Consists of a sampling pipe with bends
- Position can be adjusted during install/OQ to allow operators to define sampling location, but must be fixed during operation.
- Location should be a compromise between being as close as possible to ‘critical zone’ without compromising ‘first air’

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Ingress/Penetration testing

Background

- EU GMP Annex 1 section 4.22 requires customers to demonstrate that bio-decontamination agents do not **impact** the medicinal **product** i.e. ingress into packaging

> 4.22 Decontamination methods (cleaning and bio-decontamination, and where applicable inactivation for biological materials) should be appropriately defined and controlled. The cleaning process prior to the bio-decontamination step is essential; any residues that remain may inhibit the effectiveness of the decontamination process. Evidence should also be available to demonstrate that the cleaning and bio-decontamination agents used do not have adverse impact on the product produced within the RABS or isolator.

- H_2O_2 vapour is the most common bio-decontamination agent used in isolators
- Industry requires an H_2O_2 vapour penetration testing service…

Hydrogen Peroxide Vapor Ingress Testing

Determines concentration of H_2O_2 (down to ppb) which may permeate into critical samples i.e. vials and bags, which are decontaminated with H_2O_2 vapor

Sample is subjected to H_2O_2 vapor bio-decontamination and a horseradish peroxidase assay is performed to determine the levels of H_2O_2 present inside sample

Example bio-decontamination load

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Hydrogen Peroxide Vapor Ingress Testing

Report is provided to summarize what parameters were used in the bio-decontamination cycle, and what concentration of H_2O_2 (if any) was measured inside the sample tested

Customers then decide whether the exposure level of H_2O_2 is acceptable

Test required	H_2O_2 Amplex red assay test on sample following HPV gassing cycle (developed) on sample within Walk-in-Chamber (WiC)
Sample Extract Reading (ppm)	**5ml Ampoule:** Test 1, 25-June-2013; Gassed; 0.043, 0.039, 0.040 (ppm) (average of 0.041ppm) Un-gassed; 0.010, 0.010, 0.009 (ppm) Test 2, 27-June-2013; Gassed; 0.031, 0.031, 0.031 (ppm) (average of 0.031ppm) Un-gassed; 0.007, 0.007, 0.007 (ppm) Test 3, 1-July-2013; Gassed; 0.041, 0.047, 0.043 (ppm) (average of 0.044ppm) Un-gassed; 0.005, 0.004, 0.005 (ppm) Notes: Overall average of gassed samples = **0.039ppm** All un-gassed samples have a reading below the lower detectable limit (0.015ppm) Assay detection limits = 0.015 – 0.189 ppm.

Example report

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Thank you and
any questions?