

Alternative monitoring approaches for new aseptic fill technologies for individualized therapies: Closed gloveless filling isolators.

Dynamic Viable Environmental Monitoring (dVEM)

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Cell & Gene Therapy Products (CGTP)

Ice breaker - Application of modern technology to eliminate risk



How to avoid
infection in meetings

Risk-Mitigation → Face masks



Routine monitoring needed



Risk-Elimination → Remote work



All good !



Presentation Outline - Application of modern technology to eliminate risk

Risk-Mitigation → Gloves, etc



Routine environmental monitoring needed



How to avoid bioburden
in our drugs

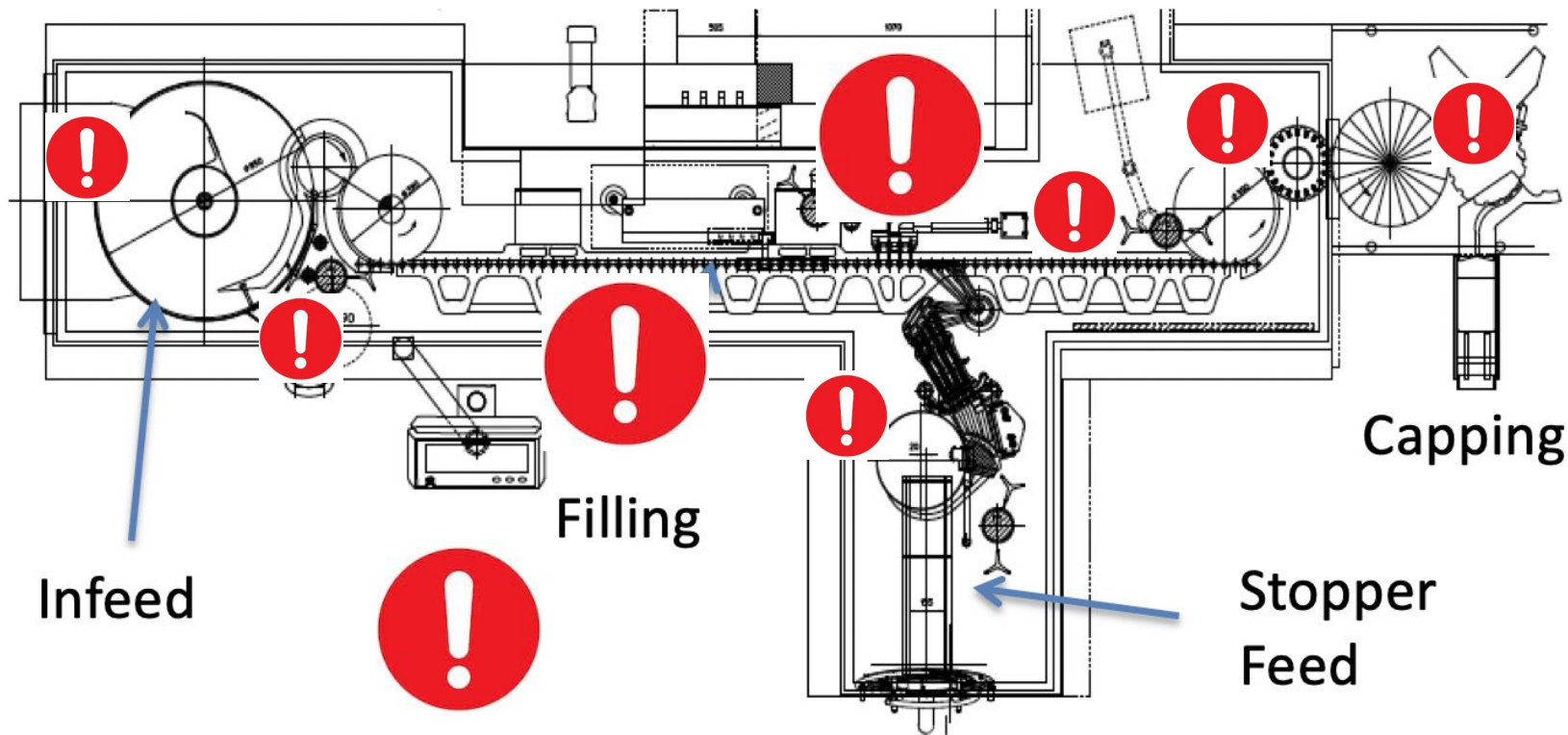
Risk-Elimination → Gloveless



Conventional Isolator; outside and inside view



Conventional Filling Isolators; potential viable contamination risk areas*

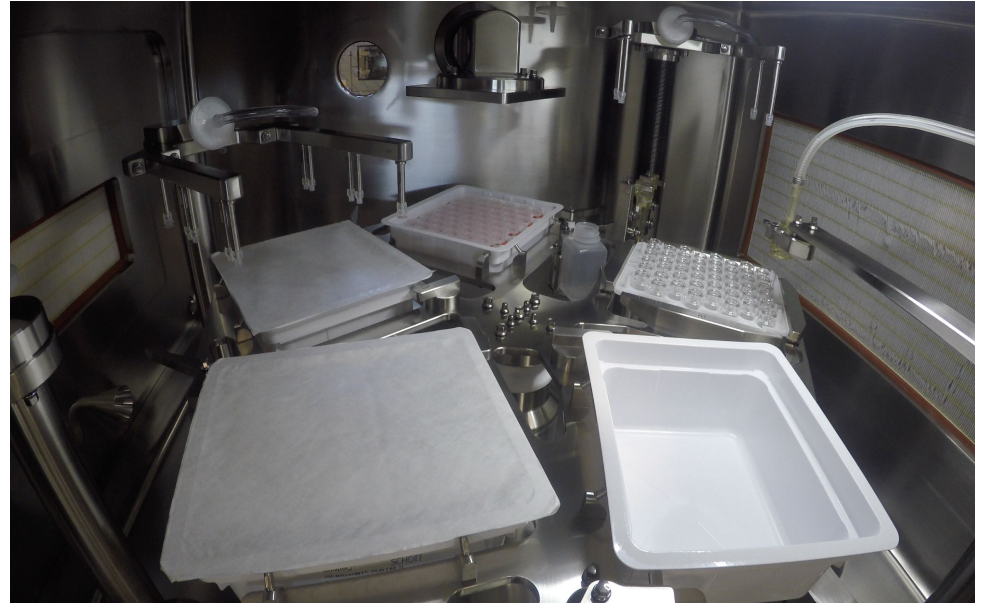


Next Generation Gloveless Filling Isolator; Vanrx® (Microcell)

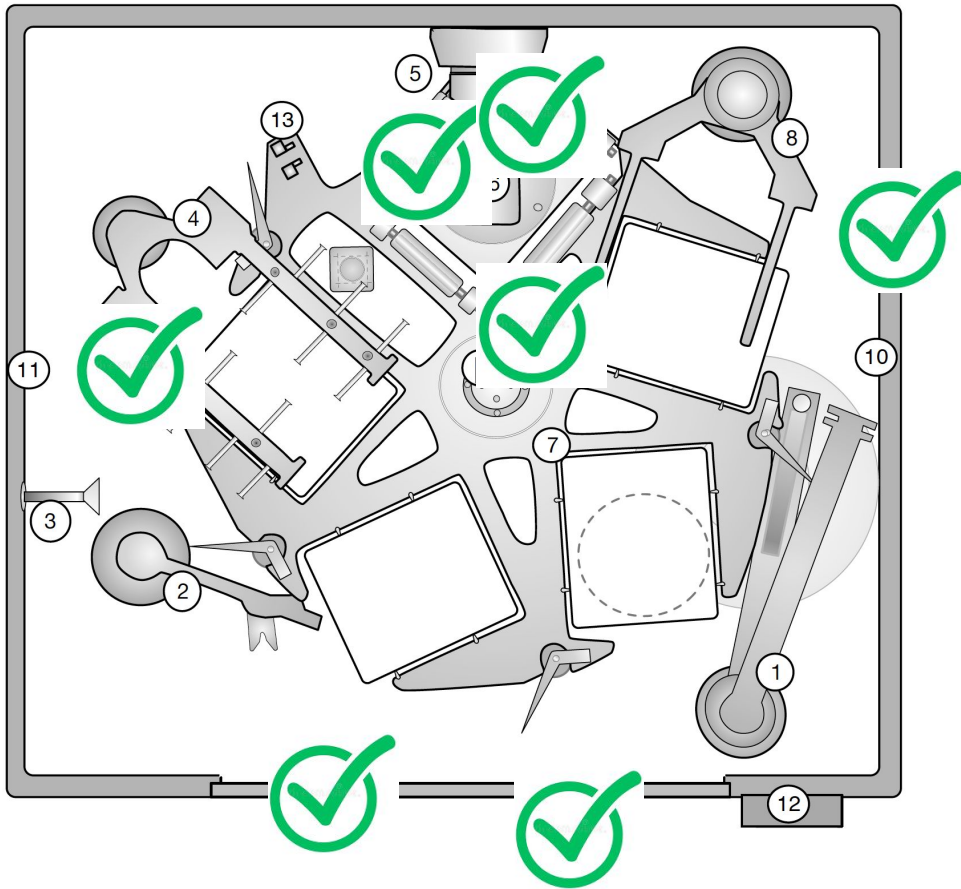
- Single unit for small and mid size batches (Off the shelf concept)
- 3 nested vial-tubs per load
- Isolator technology, gloveless fill-stoppering-capping system
- Ready-to-use (RTU) components (vials, stoppers, caps)
- No glass to glass contact
- Single needle fill assembly
- VPHP decontamination
- Horizontal unidirectional air flow
- Significantly reduces mechanical complexity of traditional filling (conveyors, transition points...)



Vanrx® Microcell outside and inside view




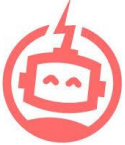


Gloveless Filling Isolator; Vanrx® (Microcell); elimination of potential viable contamination risks



- Load/unload pre-/post filling; isolator fully closed
- No material transfer ports
- No indirect product contacting equipment
- Easy to clean
- Capping inside isolator
- No isolator gloves
- No manual interventions (no VEM handling during routine production)



Aseptic Advantages of Microcell to Traditional Isolators

	Feature	Advantage
	No gloves on isolator	Risk of introducing bioburden into isolator due to manual interventions eliminated.
	No transfer ports on isolator	Risk of introducing bioburden into isolator due to introduction of material after decontamination of system eliminated.
	Standardized, pre-sterilized primary packaging material (PPM)	Risk of introducing bioburden through isolator openings (mouse holes), PPM transfer/handling, and capping outside isolator eliminated
	No indirect product contacting surfaces in isolator	Risk of contact contamination with non-sterilized surfaces and material eliminated

The VEM-Conundrum

Improving aseptic processing using next generation gloveless isolators:

- Developing a fully automated system without manual intervention
- Highest possible containment of the aseptic boundary after decontamination cycle
- Elimination of gloves and aseptic ports to avoid potential introduction of bioburden



Maintaining the current regulatory EM requirements:

- Viable environmental monitoring during routine production required based on risk measures of conventional isolators
- Current established monitoring methods need manual interventions using isolator gloves and aseptic ports
- Detectability of current VEM methods compare to the theoretical residual risk is low
- Alternative solutions not yet developed and tested to be used as adequate alternative

Problem statement:

The VEM methods currently available which are generally expected for routine GMP production have now become the highest risk of introducing bioburden into the aseptic process.

Dynamic Viable Environmental Monitoring (dVEM)

We developed an enhanced media simulation that includes the essential elements of a conventional VEM, and tailored it to a more holistic method that we refer to as “***Dynamic viable environmental monitoring (dVEM)***”.

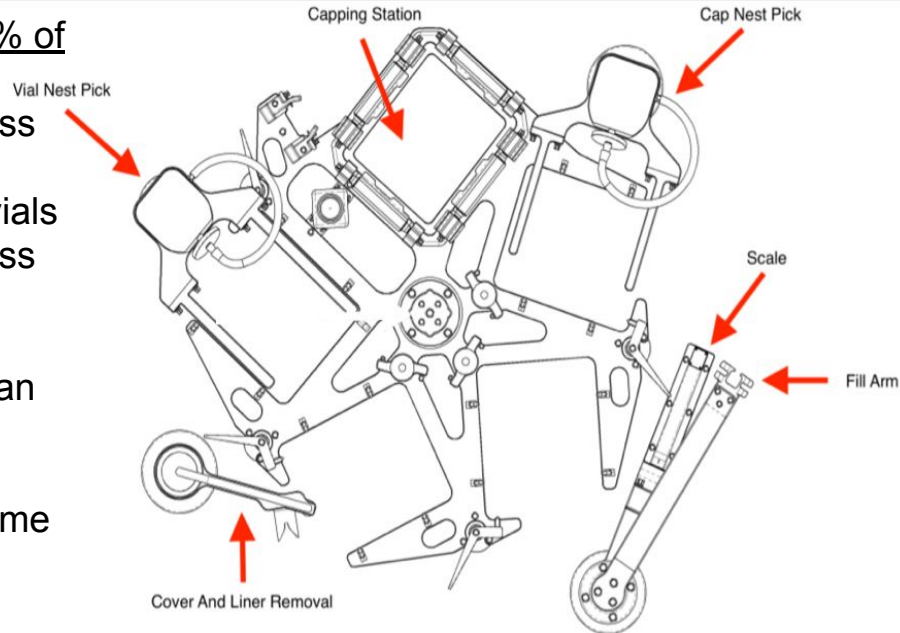
- Simulation beyond worst-case scenario of the routine production process
- Part of the initial qualification of the system in addition to an extensive media fill program
- More sensitive and increased detectability than currently used VEM methods
- Generate extensive VEM-data to challenge if the system and the automated process is in control and aseptic
- No process or IPC handling errors compared to conventional VEM methods



→ **Alternative VEM-Program to create VEM-data during Qualification**

dVEM method

- Tryptic Soy Broth (TSB) in a bag is connected to the decontaminated isolator, simulating the same process steps as in a routine production.
- TSB is filled into the vials of the first nest using 25% of the target fill volume
- Robot moves the nested vials to all possible process position within the machine
- Next 25% of the target fill volume is filled into the vials
- Robot moves the nested vials to all possible process position within the machine
- Cycle repeated two additional times
- Hold steps in between the cycles and positions to an overall time >2hours
- Capping of the first nest
- The second and third vial nest is processed the same way
- Total processing time > 6 hours
- Incubation and analysis of filled vials using standard media fill read out procedure



Advantages of dVEM to Conventional VEM

Monitoring surface area:

Reference: Exposed media area of a standard settling plate is approximately 63.6 cm²



- DVEM covers a surface area range from approximately 84 cm² to 179.7cm²
- Split filling process (4x25% fill volume for each cycle) increases the exposed surface area due to the liquid stream droplets in the air
- TSB is actively passing through all the different process steps of aseptic filling
- TSB in direct contact with all product contacting surfaces
- TBS is incubated in the respective drug product containers (vials)
- Sampling errors (often the case with settling plates) after process completion is eliminated; sample is closed in isolator

Exposure time:

Reference: Overall exposure time of settling plate would be between 25 and 120 minutes.

- The dVEM qualification run for all vials (3 nests) takes a total of > 360 minutes
- Exposure of TSB to the isolator environment is 3-14 times longer than the product would be exposed in a routine filling process

Advantages of dVEM to Conventional VEM (cont.)



Location:

Reference: Settling plates should be placed close to the aseptic process. Ideal position is often difficult to find and compromises often need to be made. This method only provides a static monitoring in one location in the isolator

- dVEM is a versatile monitoring method
- TSB replacing the product moving through the entire process
- All process positions, including peel off position, nest removal, and presenting position, are included in the simulation

Data points:

Reference: Conventional VEM provides one data point per settling plate over a period of one batch

- dVEM creates 144 or 300 data points per test run (depending on the vial format used)
- Data points can be traced back to a certain process time



Conclusion and outlook

The dVEM approach as a VEM alternative during Qualification of the Microcell should increase detectability of potential environmental contaminants in the process in comparison to the conventional VEM approach. Using proven and reliable elements of qualification and GMP-monitoring practices, we will use dVEM during the initial qualification as a suitable alternative to conventional VEM methods of new gloveless isolator filling lines.

Next steps:

- Continuation of constructive discussions with health authorities about dVEM as alternative method to sunset conventional viable environmental monitoring during routine production.
- Perform qualification, dVEM tests and extensive media fills
- Analyze data and include respective reports to the health authorities/inspectors



***Doing now what patients
need next***

