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Lessons Learned in the Ballroom

by David A. Wolton and Andy Rayner

This article presents an alternative approach to the ballroom concept. It studies the lessons learned from the operation of recently commissioned facilities to predict what the next generation of disposables plant could look like. Will the "Dance Floor" concept be the next step in the evolution of fully disposable facilities?

Previous articles and seminars[1] have discussed the advantages of using the "ballroom concept" for the layout of biopharmaceutical bulk biologics production facility design, using both stainless steel and single use equipment. This article will evaluate the strengths and weaknesses of this approach with regard to single-use equipment based facilities now that the concept has been used to a greater and lesser extent in recently commissioned facilities. It also will seek to learn from these experiences and propose an alternative dance floor concept; that could result in a leaner, smaller, standardized facility, more suited to repeatable, reliable, high performance manufacturing.

Advantages of the Ballroom Concept

Definition of the ballroom concept is:

> *"A large manufacturing area that has no fixed equipment and minimal segregation due to the use of functionally closed systems."*[2]

Ideally, using the ballroom concept would result in a totally open production space where media preparation, buffer preparation, cell culture, purification and final filtration would all take place in the same room. However, most "ballroom" type facilities built recently have stopped short of the full implementation of the concept - *Figure 1*.

These improvements have the following advantages:

- **HVAC Cost Saving** – by containing the equipment, the surrounding area can be reclassified. This has a significant impact upon HVAC annual running costs as the higher the classification the greater the energy usage. (33% reduction in air supply for the classified space).[3]
- **Open Area** – *a large open area where all skids are on wheels allows for rapid reconfiguration of the facility, easy cleaning and fast construction.*

All of these advantages have made the construction of ballroom style facilities increasingly popular, especially

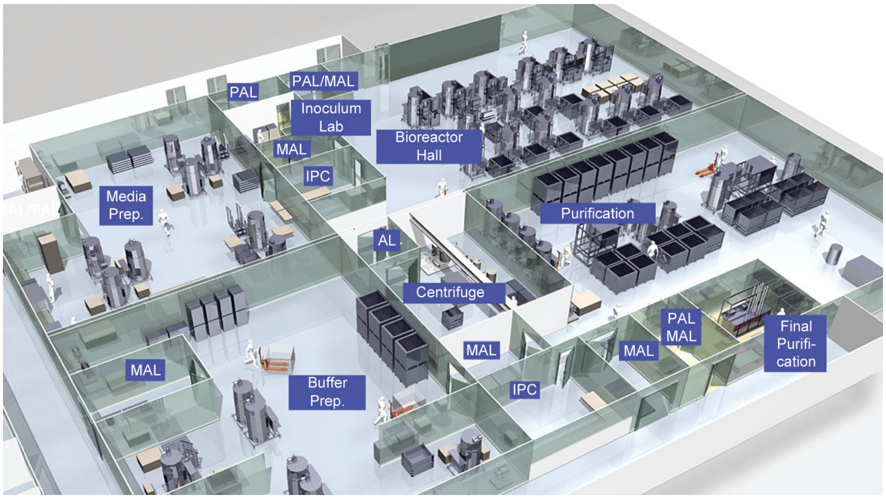

Figure 1. 3D model of a ballroom type facility.

when coupled with disposable technology. Recently however drawbacks have started to surface as a result of operational reviews (such as those undertaken using lean six sigma).[4] For in-market supply, where reliability and repeatability are key, another approach may be preferable.

…the dance floor concept (a smaller and more defined space) is being considered as an alternative to the ballroom concept…

Lessons Learned From Implementation of the Ballroom Concept

Movement of Totes

In the last 5 years, plant designs have shown significant decreases in facility footprint compared to traditional plants. These designs have incorporated many of the ballroom concepts including functionally contained systems. These facility designs also have relied (in most cases) on the physical movement of totes from the media preparation areas to point of use. It is now being realized that this movement is:

- A "non-value add" operation and is in effect Muda (wasted effort).
- Moving hundreds of pounds of weight can often be challenging and require special safety accommodations

Use of Mobile Totes for Transport of Bags

When it was first introduced, one of the big advantages of disposable bag technology was its mobility. Processes could be changed without the need for expensive modifications of the facility. The disadvantages of this mobility were seen as irrelevant until operations personnel in commercial production facilities started to focus on reliability and repeatability (typically using operational excellence approaches, such as lean six sigma), this resulted in the following disadvantages coming to light:

- Increased possibility of mix-up
  - By taking away the fixed pipework normally associated with stainless facilities, the disposable facilities have removed a physical "layer of defence."[5]
- Large tote storage areas and wider walkways
- Potential for tubing on the floor/trip hazards

Customization of Disposables

In the beginning, the end user really appreciated the ability to customize their equipment; however, as the use of disposables has become mainstream, this customization has started to cause problems; especially for the supply chain. It is known that the customization of parts results in:

- Increases risk of stock-out
  - Stock-outs can be mitigated in many ways; however, if parts become an "off the shelf" item in the future, all end users will benefit.
- Larger volumes of inventory
- Higher cost

Has Flexibility Gone Too Far?

There has now become a realization that market supply/ phase III a more reliable, effective and efficient production operation is required and some of the "fully" flexible ap-

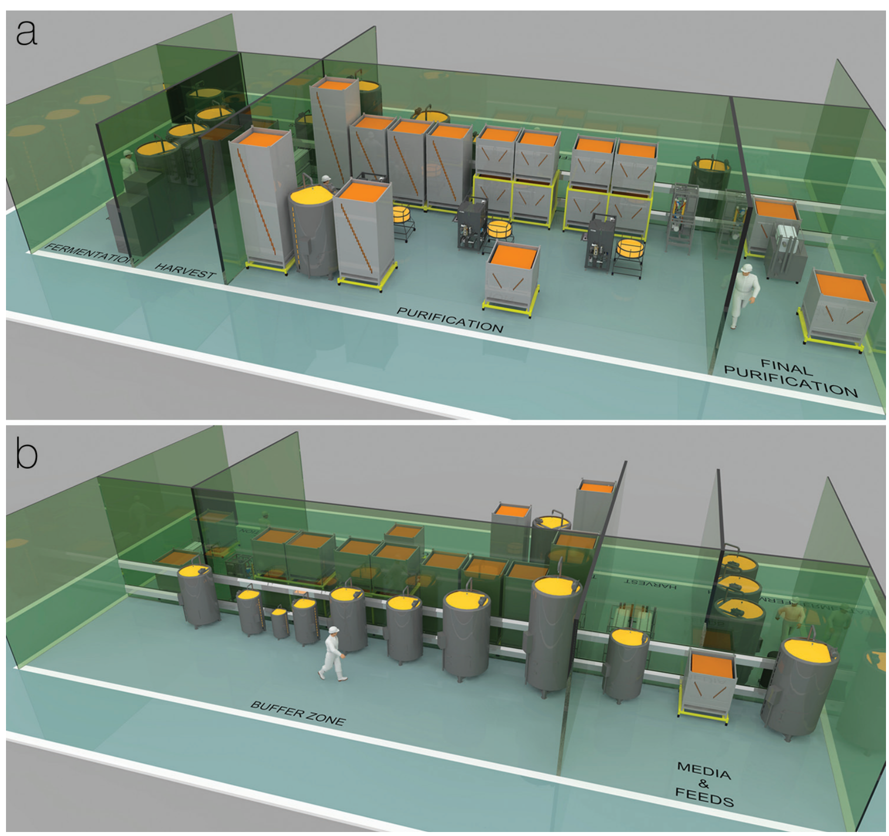

Figure 2a. View of the dance floor (3 × 2,000 L bioreactor) from the reactor hall areas.
Figure 2b. View of the dance floor from the buffer/media preparation areas.

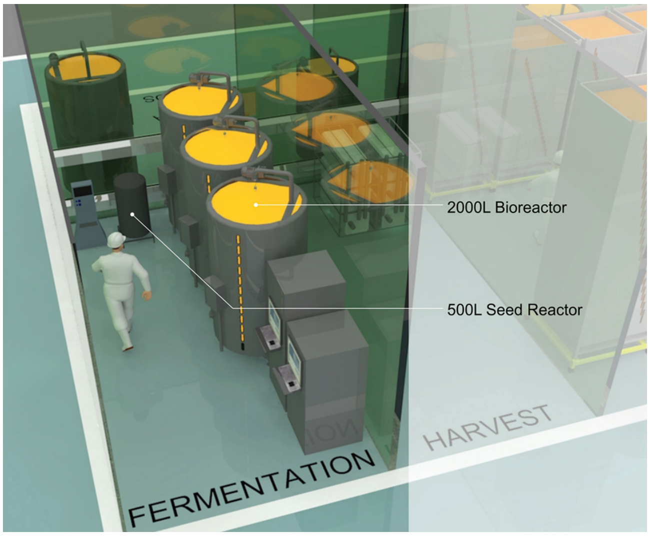

Figure 3. Three 2,000 L bioreactors with associated seed reactor.

proaches may need to be revisited. In exploring the potential for a more optimal approach, the dance floor concept (a smaller and more defined space) is being considered as an alternative to the ballroom concept and this alternative is described below.

The Dance Floor Concept

It is important to note that disposable mammalian cell culture facilities are limited in size to ~2 to 4 kg per batch. If quantities greater than 4 kg per batch are required, a stainless steel facility may be chosen. Modelling during the concept design phase will help the client make these decisions. Recent plant designs have positioned the media and buffer preparation facilities adjacent to the manufacturing operations - *Figures 2a and 2b*. This allows direct transfer through the wall to the production equipment and avoids movement of totes. This concept has developed into the philosophy of the 3m rule.

Definition of the 3m Rule

"Wherever possible, equipment should be static (in use) and situated no greater than 3m from its associated equipment."

The 3m rule has had a number of beneficial knock on effects:

- Reduction in operator error
- Reduction in tubing length/waste
- Storage vs just in time
- Fitting the facility around the equipment rather than the equipment around the facility

Figure 3 shows a close up of the three 2,000 L bioreactors. The bioreactors are clustered together to minimize tubing length and provide routed tubing paths. Note: the 2,000 L reactors can be clustered close together because there is not the need for the maintenance access of the equivalent stainless systems, also the equipment can be moved periodically (when empty) to facilitate cleaning.

Reduction in Operator Error (Poka-Yoke)

With some production steps, for example Protein A, there are a significant number of sequential additions. When mobile totes are used, it increases the risk of a mix up. Manual checks are often put in place to mitigate this, for example, conductivity checks; however, sometimes these systems fail. There are other ways of avoiding mix-ups:

- Color coding
- Defined tubing routes
- Automation

By making the systems static, all three of these mitigating measures become available. A 3D interpretation of the defined tubing routes concept is shown in Figure 4 (along with a "draw bridge" which swings into place when totes are in use).

Automation

The level of automation is dependent upon the end users requirements. If the plant needs to be very flexible, automation may not be desirable; therefore, color coding and defined routes used instead. However, if repeatability is key (i.e., in market supply), automation could be desirable. In stainless steel facilities, it is normal to link skids (e.g., Protein A chromatography controller skids) to systems like:

- Distributed Control Systems (DCS)
- Manufacturing Execution Systems (MES)
- Supervisory Control and Data Acquisition Systems (SCADA)

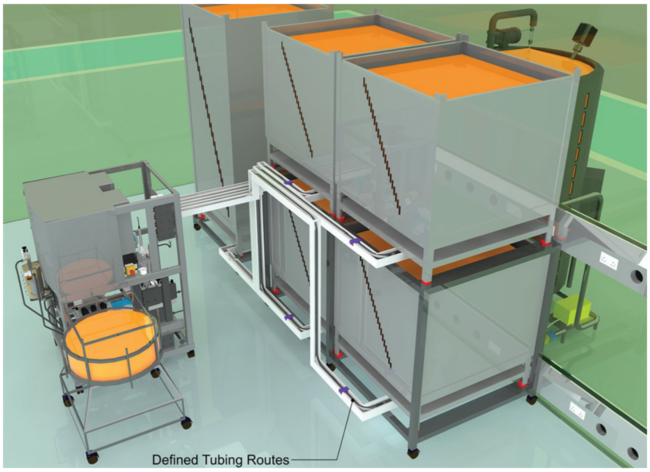

Figure 4. Defined tubing routes and the "drawbridge" used to connect to the chromatography control skid.

These computer control systems control the whole process and data within the facility. This is not normally done in disposable facilities, mainly due to the mobile/simple nature of the equipment. If the equipment becomes static, this can change.

Figure 5 shows a pinch valve next to an Iris valve (the Iris valve closes around the tube as it passes through the wall between buffer and purification). By defining the tubing route from the buffer preparation system to the pinch valve, the computer then knows what buffer is being made (using an MES system), what tank it is being made in (via the load cells on the buffer preparation skid), what route it is taking (via the peristaltic pump and the pinch valve), and what bag/tote it is filling (via the routed tube). As the tube from the buffer tote is routed to a specific port on the chromatography skid as seen in Figure 4, the computer then controls when that buffer is added to the process.

Reduction in Tubing Length

By changing the way the facility is designed (see section on fitting the facility around the equipment), engineers can focus on minimizing tubing length, thus reducing waste in the design phase.

Storage vs. Just-in-Time

By implementing the 3m rule, space around the production skids (e.g., Protein A) is at a premium. This can be solved in a number of ways.

Storage

- Racking is used to use all available vertical height - *Figure 4.*
- Multiple batch buffers – specific buffers can be chosen which have a long shelf life, these buffers are stored in tall containers that will last for a number of batches, the buffer is filtered in with a large filter and filtered out with a small filter. One outlet filter is used per batch to ensure the bag contents do not become contaminated. This approach not only reduces the amount of plastic waste, but also reduces cost, due to reduced preparation time, paperwork, dispensing and number of bags needed.
- If all avenues are exhausted, the buffer is stored in a mobile tote and wheeled to the skid.

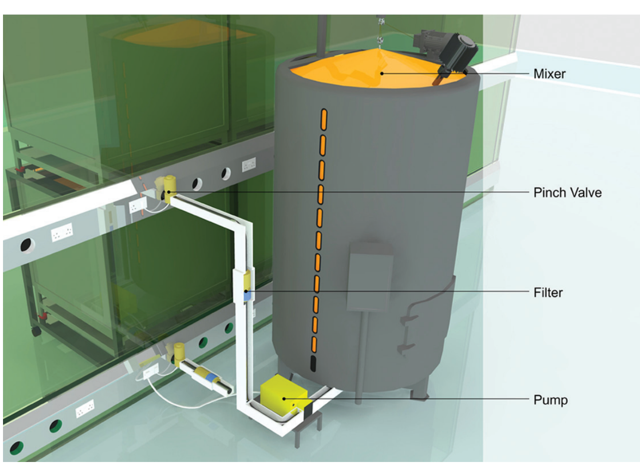

Figure 5. Use of pinch valves and defined tubing routes to control transfers through the wall.

Just-in-Time

- With most Mab processes, 2 to 6 buffers per batch can be made just-in-time and fed directly from the buffer preparation area to the chromatography skid. This reduces plastic waste by cutting out the need for a storage bag as well as the saving footprint needed for the storage tote.

Note: bioreactors can be filled directly from the media mixing systems and the media held in them prior to use, again negating the need for a media storage bag.

Fitting the Facility around the Equipment, Not the Equipment into the Facility

The introduction of standard disposable parts[6] has a positive impact upon defining the distance between equipment. It is now possible to put standard disposable parts on order while locking down the process flow diagrams. This allows the potential for early prototyping of the process, which in turn allows for resolution of ergonomic/lean/Poka Yoke issues earlier in the design lifecycle.

During prototyping, the final positioning of the internal walls between areas can be positioned for optimal use of space. The decisions here will be based on level of containment and client preference. Regarding client preference; having no walls between areas will normally be preferred by operations personnel (one team and easier communication); however, this approach is not widely seen in the industry to date. Note: it has been found that the use of glass significantly improves the communication between the areas, and is highly recommended.

The above can be coupled with 3D modelling to give a high degree of assurance that the facility will be both lean and ergonomic.

The Wheels Are Not Removed

Although there are defined paths for the tubing and ergonomic clustering of equipment, it is not envisaged that the equipment would become fixed. It is more akin to the super skid where if necessary, the equipment can be changed or relocated. Product change-over times will be increased (slightly) compared with the current highly flexible units; however, this will be outweighed by increased reliability and reduced size (and therefore running costs) needed for phase III and in-market supply. In effect the room will still be like a ballroom; just smaller.

Summary

- Leaner: minimal movement of totes, just in time production of media and buffer.
- Smaller: only space provided for ergonomic access, close proximity of all associated equipment, vertical height utilized.
- Standardized: use of standardized disposables where possible, only one way of assembling disposables, consistency of operation and simpler training requirements.
- Reliable: defined tubing routes, static equipment, recipe driven automation, central data gathering.

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