Manufacturing Strategy, Facility Design, and Manufacturing Operations
July 19, 2023

Q: As CGT manufacturing is moving towards automated, closed system processes, do you see a shift in how people are thinking about facility design with this shift in manufacturing paradigm?

A: The industry shift towards fully closed and higher automated manufacturing technologies has dramatically changed cell therapy facility design. Closed systems reduce the risk to and from the surrounding cleanroom environment and enables you to utilize lower classifications and dramatically simplify airlocking and corridor schemes. Use of fully automated small-footprint systems which can be surrounded by an equipment-based classified environment can result in dramatically reduced facility classifications such as grade D or even CNC, assuming your equipment is properly closed, and you have a supporting QRM assessment.

Q: To understand the trade-offs between in-house manufacturing, outsourcing and hybrid facilities- what does this decision matrix look like?

A: Often the choice between Make vs Buy is made considering a number of different factors, but mostly comes down to ability, cost and control. It should be noted too that this debate extends beyond just manufacturing and into all product lifecycle aspects including product and assay development, quality testing, supply chain, etc.

Are there vendors out there who have the technology and competence that you feel secure outsourcing activities to? Do they offer the range of services that your company requires in order to meet your business needs and delivery strategy? Do they have availability in their schedule to take on the tech transfer and handling of your needs?

For cost concerns you should weigh how costly are the facility spaces, equipment, labor, performance and maintenance of these activities vs how costly is it to outsource. How frequently are you planning on performing these activities? High cost to own and low frequency activities may be easy opportunities to outsource.

How much control do you want, or need to have, over the development, schedule, execution and delivery of those activities? There may be key, highly critical aspects of your business that you want to maintain direct control of as of means of securing your business strategy or company culture.

Q: Is there a standard outside of meeting the minimum number of air changes per hour when thinking about single-pass versus recirculated air? As an example, is 100% single-pass air superior to 50% recirculated even though both meet the same minimum air change standards?

A: In general, the use of air recirculation is for creating a more energy efficient HVAC system. Running 100% outside, single-pass airflow requires your equipment and facility to filter, temper and treat all incoming air at the extremes of your outdoor environment. Recycling already treated air back into your

system reduces the overall workload of the system, which in turn reduces the sizing, count and loading on your systems, as well as ongoing energy use (and cost).

Air change rates, on the other hand, are designed for driving and sweeping particles (from personnel, activities, equipment, etc.) and heat loads in the airspace out of the cleanroom, and are a function of meeting the air classification and temperature requirements of the space. The formula for calculating air change rates doesn't change based on the percentage of recirculated or outside air.

How much air you can recirculate (maximum), assuming there are no manufacturing drivers for exhausting the air, is typically determined by building code (refer to ASHRAE standard 62 for indoor air quality) and is based on the size of the space and how many people occupy the room. It would also be driven by factors that will exhaust air from the room outside of the HVAC system, such as fume hoods or exhausted Class II Type B2 biosafety cabinets, because this air will need to be replenished within the HVAC circuit with outside air.

Use of single-pass air can also be a risk mitigation measure for GMP operations, however. This is typically where we see 100% single-pass air requirements. If there are process activities performed within the space that may impact the airspace, for which (even with HEPA filtration) there is concern about cross contamination across different process steps, 100% single-pass air can be used as a strategy to support segregation and managing processing risk.

Q: Are there any guidelines which define number of personnel allowed in the cleanroom?

A: In general, the number of personnel validated to be allowed within your cleanroom at any single given time would be bracketed by the maximum number of people performing operations (as defined during EMPQ) before their combined particle shedding causes the air quality to become dirtier than the threshold requirements for the room classification. You can (and should) test this threshold during the classification and HVAC commissioning process for the rooms by loading personnel performing routine activities and monitor the air quality to ensure that the personnel level is safe to operate within.

Specific maximal personnel counts per room will depend on a number of different factors including the size of the space, the number of air changes per hour, the location of the HEPA filters and return ducts, and not least of all the cleanroom classification required for the space.

Of course, personnel loading within a GMP operations space should account for the activities and equipment required to be performed, and the space should be designed large enough to accommodate the number of equipment and personnel to meet the manufacturing need without overcrowding the room.

Q: How do you segregate areas working on virus (either used in manufacturing or in QC lab) from non-viral areas in the same facility?

A: Whenever you are trying to co-locate two different processes within the same facility, you need to evaluate the risk of cross contamination between said processes. What are the materials and equipment used, what are the scale of operations, what is the degree of process closure and containment, how are they handled and what are the chances that materials from one stream are going to find their way to the other. As an example (biosafety considerations aside), propagating large volumes of replication

competent virus in open systems is going to pose a much higher risk for impacting adjacent operations than say handling a fixed quantity of replication incompetent viral material within a closed system or within a biosafety cabinet.

The most conservative solution is generally to have separate and dedicated GMP spaces, with separate access, HVAC and flows. This approach will typically require the largest footprint and therefore be the most expensive, but will also require the fewest questions to be answered to justify the segregation scheme. The closer mixed operations become (across a shared corridor, in adjacent rooms, campaigned within the same space, sharing the same equipment), the more risk for cross-contamination you are generally undertaking, and thus the more robust your risk management plan will need to be to support your proposed operations. For example, based on your specific risk assessment, it may be deemed acceptable to work with viral material in an adjacent suite with a dedicated HVAC and unidirectional personnel and material flows, supported by appropriate gowning and waste handling SOPs to promote containment and segregation.

Every operation is going to have its own inherent risk profile, and it is important to have a corresponding Quality Risk Management plan in place to justify and support your approach for facility design, containment equipment, GMP flows and operations and handling procedures.