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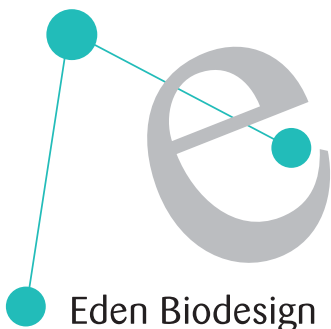


Designing for Flexibility: a Case Study of the National Biomanufacturing Centre

How would you design a biopharmaceutical facility which is capable of the development and early clinical manufacture of 95% of the products and processes coming through the biopharmaceutical pipeline in the next 5-10 years? This was what Eden set out to achieve when it was selected to operate the UK National Biomanufacturing Centre (NBC). The NBC is a government funded initiative set to become Europe's leading biopharmaceutical design centre, capable of developing a wide variety of novel biopharmaceutical medicines from proof of concept through to GMP manufacture for clinical trials. The NBC project also includes an access fund (of

approximately £3 million) to assist qualifying Merseyside and UK Biotech SMEs to purchase services from the Centre.

Eden already has a successful international consultancy business in biopharmaceutical development. Its consultants all have experience of developing proprietary products within biopharma companies and know what is important to get right. Eden has previously grown a successful business out of helping biopharma companies to choose the right contract manufacturer to outsource their products to, and also manages the resulting projects. Eden has also been employed by CMOs to help them improve their facilities and



BEGIN WITH THE END IN MIND

client services. So the Eden Team knows the difficulties in product development, what clients want from a contract manufacturer and what the common gripes are. All in all an ideal position from which to begin specifying the NBC.

Eden's expertise however is not in designing and project managing capital projects, so one of their first steps was to hire consultants of their own; industry professionals of international repute to assist and guide with the process design, layout, regulatory trends and the overall project process. With their help, Eden approached the project by:

- being very clear about what it wanted from the facility
- communicating that to a team of designers so that those needs could be successfully translated into a design
- ensuring that the design intent would be maintained as the facility moved from paper to construction on site
- continuing with the flexible approach into operation to ensure that all of the benefits which were designed in, would be realised in practice.

Being clear about what you want: Beginning with the end in mind

Before you set a design team running, you need to put down very clearly what you want from the finished facility. As the saying goes "if you don't know where you're going, any road will get you there"! How it gets delivered is down to the design team to develop in line with the project cost/time/quality objectives.

Eden developed a User Requirement Specification (URS) for the NBC, which stated very clearly and without too much

jargon what Eden needs the facility to be capable of. Some of the key elements of this URS are explained below.

1. Overall Requirement

Eden's high level requirement for the NBC is to create value for clients by the development of robust products and processes, efficient production of clinical trial material and sound documentation, advice and regulatory support.

In order to achieve this there needed to be separate GMP manufacturing suites for Clinical Trials, and non-GMP areas for process development and scale-up, with as much focus on the labs as on the production areas. Consideration should be given to minimal down time in the labs and GMP suites including low/off-line maintenance, fast change-over between products and low exposure to equipment failures. Automation should be simple but compliant with current GAMP regulations. The overall facility should be capable of running the maximum number of processes, products and technologies simultaneously without any chance of cross contamination. The layout should promote fast and efficient technology transfer and engender team work and the cross over of skills between the laboratory areas and the GMP manufacturing suites. The rooms need to be designed with future flexibility in mind so that equipment is installed for current needs but has the ability to change this in the future to accept other equipment or be used for another purpose.

The design should give attention to the overall security of the site and the building, safety within the labs and GMP suites such that a person can work on their own safely, and to encouraging

teamwork and communications between employees working in different areas. The design also needs to allow for easy future expansion.



2. GMP Area Requirements

The GMP suites are the hub of the facility where the clinical trial manufacture takes place. They should therefore allow multiple products to be handled concurrently and have the capability to simultaneously process mammalian cell, microbial/yeast and viral technologies. Within each suite there should be separate upstream and downstream processing areas which include inoculum preparation and cell banking, scale-up and cell growth, primary separations and secondary purification to a bulk active liquid.

In order to guide the designers, Eden set down 10 Candidate Processes containing the range of technologies, unit operations, scales and biological containment levels that the facility should be capable of running. The products range from cell therapy to E.coli fermentation products and everything in between and include the

following characteristics

- Small scale viral/mammalian processes: cell growth in monolayer or suspension, with and without live virus infection, intracellular and extracellular products. Bioreactors capable of batch, fed-batch and perfusion operation. Products capable of being cooled during purification
- Microbial processes: Smaller and larger scale intracellular and extracellular products, whole cells (live or inactivated). Fermenters can be run in batch or fed-batch mode and purification streams can be cooled
- Candidate Mammalian: Smaller and larger scale, intracellular and extracellular products. Bioreactors capable of running in batch, fed-batch and perfusion mode.

3. Process Development Labs Requirement

The process development labs will be critical to the overall facility, handling the upstream and downstream development of biopharmaceutical processes including comprehensive cell biology studies, process derivation, design, optimisation, scale-up and modelling. In addition they should produce pilot scale pre-clinical material to GDP quality standards.

Like the GMP suites, these labs should handle a variety of pre-clinical development campaigns efficiently with minimal downtime (for changeover or maintenance), process multiple products concurrently and handle exactly the same processes, products and technologies as the GMP Suites involving mammalian cells, microbial cells and viruses. In summary, the process development labs should be a scale-down version of the GMP suites to facilitate fast and efficient process scale-up and technology transfer.

4. Analytical and QC Labs Requirement

The analytical and QC labs will provide a valuable product testing facility for the products generated and developed by the GMP and Process Development areas as well as providing QC release testing and facility monitoring functions. All product testing will be to a high quality and QC functions will be conducted to cGMP. The analytical laboratories will provide technical support to all other areas of the NBC when required and may interact directly with clients for provision of stand alone analytical services, working through the appropriate project manager. The area should include microbiology, immunochemistry, biochemistry and molecular biology labs and a Category 3 room. The labs will be supported by areas for wash, prep, stores, cold storage, ultracentrifuges, fine balances and booking in.

5. Regulatory Requirements

There are two main regulatory requirements which relate to product quality and operator safety. Relevant parts of the facility must comply with the current Good Manufacturing Practices of the US and EU for the production of biopharmaceutical medicines up to clinical trials Phase 2. In live areas, the operator must be protected according to guidelines on the handling of genetically modified organisms and dangerous pathogens.

6. Support Area Requirements

Like all biopharma facilities, the labs, offices and GMP suites need support in the form of: utilities, waste treatment, storage, media and buffer prep, cleaning

and sterilisation and maintenance & workshop facilities. These should all be designed to complement the main operations.

Cleaning & Sterilisation should have special attention since the performance and verification of clean down and disinfection/sterilisation of facility and equipment will be a main contributor to downtime. The following requirements should be designed in:

- Minimisation of cleaning/sterilisation validation
- Ability to commence turnaround of USP and DSP suites independently of each other
- Robust and rapid cleaning methodologies (for suite and equipment)
- Robust and rapid sterilisation methodologies (for suite and equipment)
- Ability to demonstrate successful cleaning between campaigns.

So between Eden and its consultants, the requirements were discussed, agreed and documented and Eden was ready to begin discussions with the design team.

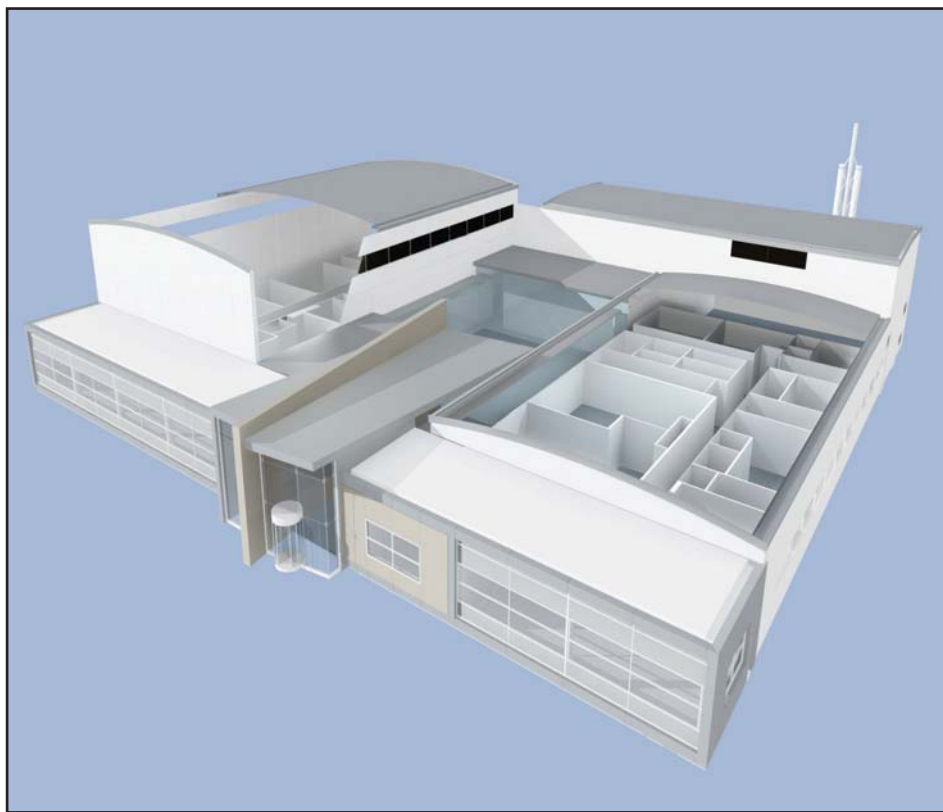
Getting it down on paper: Turning the User Requirement into a Design

The most critical part of the project is the Conceptual Design. It is relatively low cost and takes a relatively short time but it sets the scene for the whole project. Skimping here is paid for later (in spades!!). Understanding this, Eden, although a busy company, dedicated half of its team to working with the designers during the Concept phase.

The Team (Eden, consultants, designers) researched the market, benchmarked against other similar facilities, and captured best practice in key areas to be assimilated into the design.

So the design developed and the facility began to take shape. The main entrance to the facility is via a reception area where visitors can be taken to a meeting room for a virtual tour of the facility. Access to the labs and GMP suites requires higher security access and can only be achieved with an Eden employee. The main working areas (approx 4100m²) are all on the one level to encourage communication; and between the labs and the GMP suites there are meeting rooms and an informal interaction area, again to encourage teamwork and communication.

The GMP manufacturing area was divided into 3 independent suites each containing separate upstream and downstream rooms which can run different products and be turned around independently ie a maximum of six different products at one time is possible. One suite contains small scale equipment and is suitable for viral processing and speciality products. A second suite is designed specifically for microbial products and the third suite for mammalian products. The live areas are designed for large scale category II containment as defined by the Advisory Committee on Genetic Modification (ACGM) and the Advisory Committee on Dangerous Pathogens (ACDP). The suites each have their own air handling systems. These suites will be capable of handling viral, mammalian cell and microbial products simultaneously. The equipment within the suites is largely skid mounted and



connects to the utilities via standard wall plates – in popular jargon the equipment is “plug ‘n play”. This improves flexibility and makes it easy to move the equipment in and out of suites or make substitutions for unusual processes.

The design uses mainly disposable technology for media, product and buffers. This facilitates minimal down time and minimal space for the wash and prep area, allowing the space to be focused where it is needed – in the operating suites.

Running around the outside of the suites is a viewing corridor which allows visitors to gain a good understanding of the facility without the need for gowning or compromising product quality.

The non-GMP process development and scale-up areas are scale-down versions of the GMP block with three

independent suites containing separate upstream and downstream areas. The same (but smaller) equipment will be found in the labs as in the GMP areas which will enable rapid transfer from the lab to production and less time spent in the GMP suites.

The analytical and QC labs contain separate testing areas for microbiology, molecular biology, immunochemistry and biochemistry.

The layout has considered the need for fast and efficient transfer of samples from the GMP production area to the testing labs.

People and material flows achieve the requirements of clear uni-directional flow with no cross-overs in the GMP suites and minimal cross-overs in the process development labs. Direct personnel access from upstream to downstream rooms within a GMP suite

is not allowed without circulating round and going through the main change room again. Material access between rooms of a suite is via material air-locks and pass-through hatches.

Operator protection has been considered at 2 levels: primary protection within contained equipment has been used where possible; where the equipment is not contained primary protection is via isolators or Class II Biosafety cabinets; Secondary protection in the event of an unexpected release of contaminated material is provided by the kill tanks, decontamination autoclave and the room pressure cascade with interlocked lobbies to contain any gaseous material within the facility. Product Protection has also been considered at 2 levels: Primary protection through the use of contained process equipment where possible and via Laminar Flow cabinets for areas where the equipment is not fully contained; Secondary protection by maintaining a positive pressure with interlocked lobbies within the clean area. Preliminary meetings have been held with the regulatory authorities to ensure that the design is in line with current and proposed guidelines.

The operating areas are supported by Central Facilities which contains all of the utilities to run the plant. Redundancy of key equipment is provided so that any failure will not disrupt operations and maintenance can be carried out off-line.

A lot of thought has been given to the way in which utilities are supplied to, and waste is removed from each suite to avoid cross contamination, and a robust solution has been found in each different case for example:

- The risk of cross-contamination from the viral suite is mitigated by transporting WFI in bottles/bags

instead of piped supply. The scale here is small so this solution fits well.

- There are no floor drainage gullies in any GMP areas. All GMP drains are piped connections on wall plates within the room.
- Pipework to the kill tank system is fully sealed with filtered air vents on the vessels and kill tank, to ensure no pressurisation and therefore no backflow.

In each area, the concept design addressed the user requirement and found a design solution to achieve it.

Maintaining Design Intent: Turning the design in to reality

The NBC facility is currently entering this stage of moving from design to reality.

Nearing the completion of detailed design, the design group carried out a gap analysis to ensure that the design still met the URS. Where the design has diverged from the URS, it was noted and a decision taken with Eden present on whether this caused a problem and needed to be changed, or whether it could be accepted. This was a critical activity to complete before the design moved in to construction.

Eden's main concern during this next phase of the project will be that the design intent is maintained and that the final facility still meets the URS. The Project Team has nominated an individual to be responsible for Design Intent Maintenance. This is an experienced team member who has been involved since the beginning of the project, understands the URS and the concept design. This person will regularly audit sub-contractor and vendor drawings and information for

continued compliance with the URS, and will be present on site endeavouring to ensure that no site decisions are made to compromise the URS.

Eden's other main involvement during this phase of the project is to prepare for validation and beneficial operation, ready to receive its first clients of the NBC in 2006.

The proof of the pudding: Operating for Flexibility

A short section as this is all still in the planning stage! Once operational, the flexibility designed in to the facility will be measured by Eden's ability to compete in the commercial market place through its range of services, efficiency, speed of response and bottom line price.

However not only is the facility designed to be flexible but so is Eden's approach to helping its clients in the NBC.

Each Client project will be assigned a team. The project teams will be led by a project manager who will be the main interface with the client during the project and will ensure that knowledge is transferred back to the client at the end of the project. He/she will also be available to continue working with the client after the project has left the NBC to ensure continuity. The teams will be small and consist of multi-skilled individuals who will move with the project from the development labs into the GMP manufacturing suites.

A key feature of Eden's culture is to help and guide its clients. Whether you are a university spin-out finding your way or a big biopharma company requiring a specific service, Eden philosophy is to work with you to make sure you get exactly what you want.