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Transferring a Genetically Engineered Biopharmaceutical from Research to Clinical Development - Impact on Facility Design and Build Projects

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To overcome inherent difficulties with biopharmaceutical technology transfer, the approach to cGMP facility design and build must be integrated and flexible. Areas of change and risk must be identified, highlighted, communicated, addressed, monitored, and controlled using a skilled project team.

Introduction

Development of biopharmaceuticals, derived from the manipulation of biological systems, has progressed rapidly in recent years. Improved forms of insulin, new vaccines against Hepatitis B, and a whole generation of monoclonal antibodies for the treatment of cancer are among the first wave of new products. Our knowledge on the molecular biology of diseases, gained from the Human Genome Project, has led many analysts to predict a billion-dollar market for gene therapy products within the next five years.

New advances in the development of viral vectors, that is, viruses which have been genetically modified to carry therapeutic genes into the body, has moved such products closer to the marketplace. These products are being targeted against diseases such as cancer and heart disease by a number of biotech companies.

Many products are now moving from research into clinical development. This technology transfer brings with it a whole new raft of questions and uncertainties. Is the process ready to move into clinical production? Will perceived gains now cause greater and more costly delays later? How will this move be financed? What is the required scale of operation to satisfy demand? What resources will be required? Should manufacturing take place in-house or should it be contracted out? Biotech companies, for example, are often faced with the decision to manufacture clinical material outside their own domestic territories.

The provision of suitable cGMP facilities, in a timely and cost effective manner, can be complicated by many specific technology-transfer issues. Such issues result from: (a) interpretation of regulations and regulatory pressure, (b) health, safety, environmental, and social concerns, (c) competence of the supply chain, (d) inter-organizational differences in culture, (d) shortfall in manufacturing capacity (e) skills shortage, (f) budgetary and cashflow concerns, and (g) complexity of product analysis.

Of particular importance is the commercial need for biotech companies to transfer their products out of research into clinical development as soon as possible. This, and subsequent steps, are often linked to milestone payments from investors and therefore to the very survival of the company.

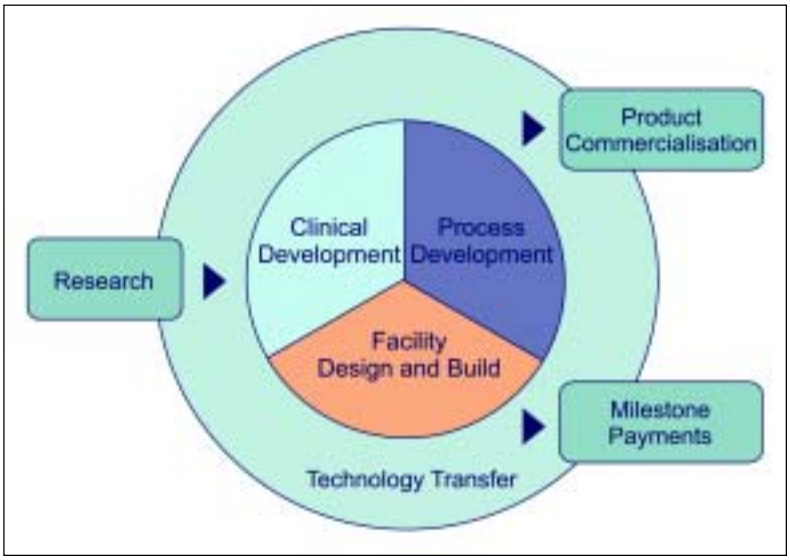

Figure 1. Moving a biotech product from research toward commercialization.

Logic would dictate that one should understand fully the production process prior to the design and construction of a facility. However, the 'dash for cash' often means that this logic must be ignored and biotech companies must progress on all fronts as shown in Figure 1. Key

External Influences		Potential Impact on facility design
Cause	**Influencing Factor**	
Interpretation of pharmaceutical regulations and regulatory pressure[1-2]	- Facilities for all phases of clinical manufacture can be subjected to FDA inspection - Pressure to produce Phase III clinical material in commercial facility - Regulations constantly evolving	- Increase in cost of production and capital costs for early stage clinical production - Changes in facility design to accommodate regulatory changes
Health, Safety, Environmental and Social concerns[3,4,5]	- License may be required for the handling of organisms. - Level of containment to be defined using detailed scientific justification	- Containment level may change - Pressure groups may slow down progress - Design will be subject to HSE/EPA scrutiny - Changing requirements may force design change
Competence of the supply chain/Service Providers	- Production equipment often lab-based and not cGMP compliant.	- Lab equipment may not be scalable, or suitable especially in relation to cGMP and HSE requirements - Equipment Vendors may not be able to supply cGMP compliant equipment or understand the requirements
Inter-organizational differences in culture	- Technology transfer between small biotech companies and medium to large pharmaceutical companies can be difficult due to cultural differences. - Equipment and methodology used in R&D may not be suitable for production	- Difficult to control the R&D wish list for the facility - Lack of understanding on the need to 'freeze the process' - Big pharma companies often lack biotech experience resulting in sub-optimal design - Scale-up may involve some process change which can be difficult to evaluate and therefore slow down facility design
Shortfall in manufacturing capacity	- Few companies involved in the contract manufacture of viral vectors and other GMOs.	- Manufacturing strategy must be developed early. High initial outlay of capital required and high risk if decision taken to manufacture in-house. Facility design occurs prior to process definition.
Skills shortage	- Difficult to resource projects	- Poor preparation and review of key documents - Poor evaluation of cGMP and HSE requirements
Budgetary and Cashflow concerns	- Project 'fast-tracked'	- Process still evolving therefore facility design initiated prior to process definition
Complexity of product analysis	- Difficult to evaluate yield, level of purity, level of contaminants etc.	- Process changes to accommodate new information from analytical studies may impact facility design.

Table A. External causes and influencing factors relating to technology transfer and their subsequent impact on facility design.

decisions relating to process and facility design are therefore often taken very early in the project so that the product can get to the marketplace in the shortest possible time. Such decisions are made in the absence of development data and manufacturing process definition and can carry significant risks.

The aim of this article is to give the reader an appreciation of the issues and difficulties associated with the provision of a production facility to accommodate the transfer of a biopharmaceutical product from research into clinical development. Changes occurring within the transfer process and their impact on facility-related projects will be discussed. Ways to minimize this impact will be addressed, in particular, how to ensure that the approach to facility design and build reflects the inherent difficulties with the technology transfer of a biotech product. A case study will be used to illustrate these project-related issues and difficulties.

Issues Related to Technology Transfer

Biotech companies face many difficulties as their product makes that great leap forward from research into clinical manufacture, and service providers must respond to these challenges. Difficulties and uncertainty within the technology transfer process can lead to similar difficulties and uncertainty with respect to facility design. It is often the case that many aspects of the production process are still unknown during the design phase of the facility. An evolving production process can lead to a never-ending cycle of design changes and subsequently higher costs. Project teams must be able to recognize this uncertainty early in the project, know what the causes are, and know how to control it.

Table A lists some of the external influences relating to technology transfer and their subsequent impact on facility design projects. This article will discuss those factors that result in facility design changes, that is, factors which slow down the project and/or increase capital costs. In the following section, a case study will be used to illustrate these issues and subsequent learning points.

Case Study

This case study is based on the transfer of a biopharmaceutical product, from Research and Development into Phase I clinical production. New cGMP compliant facilities were required for clinical production, and issues related to the provision of this facility will be discussed below.

Process Description

Figure 2 shows that the production of this biopharmaceutical involved the use of a genetically modified virus and a genetically modified human cell line. The following paragraphs describe this particular process; however, there are a variety of techniques used to reach the same end-point, i.e. purified viral material.

Once removed from cold storage, cells were initially expanded in tissue culture flasks, roller bottles, small (seed) bioreactors, and subsequently used to inoculate the production

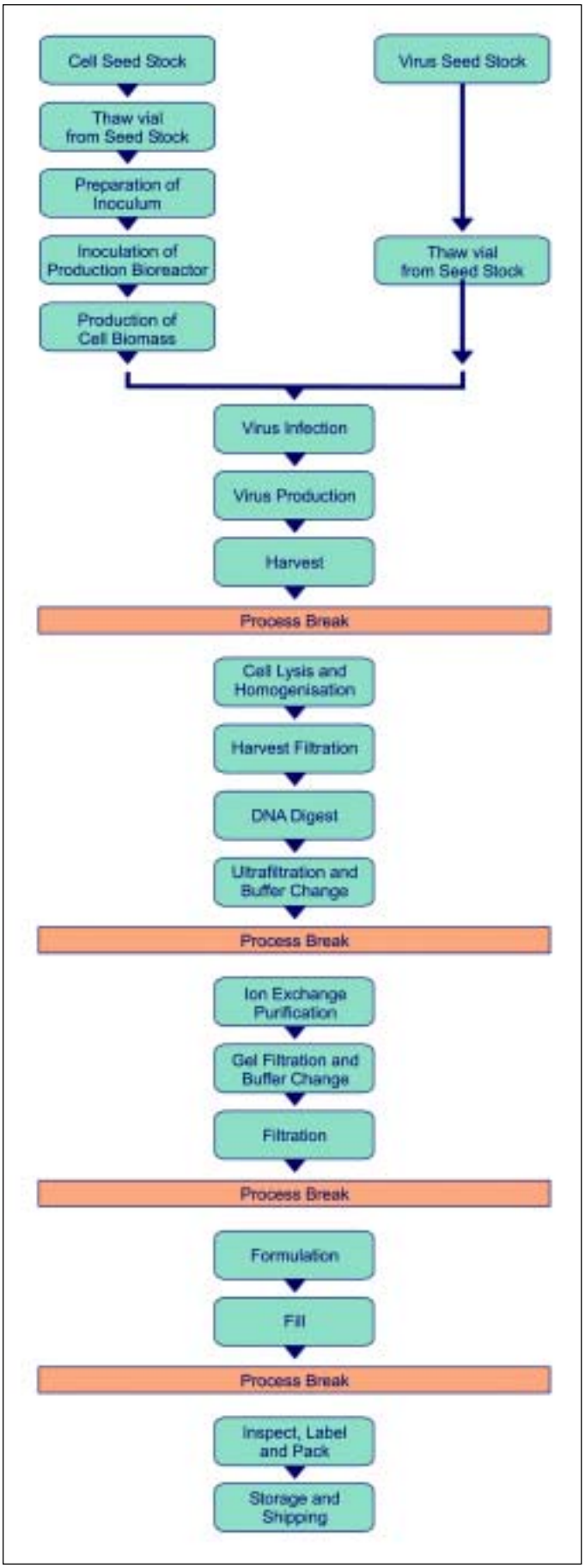

Figure 2. Process flow diagram for ViraVac.

bioreactor. When the cells reached the appropriate concentration, they were infected with virus. At peak virus production, the bioreactor material was harvested.

The harvested material was homogenized to release virus material contained within the cell. Once ruptured, cell fragments were separated from the viral product by using filtration. Cellular DNA was digested using endonucleases. Further processing involved ultrafiltration to remove contaminating macro-molecules and to carry out a buffer change. Finally, the bulk material was filtered to remove smaller particles prior to purification.

Purification was carried out using anion and cation exchange columns, followed by Gel Filtration (Size Exclusion). Formulation consisted of preparing the product in a physiological solution at the correct concentration. A stabilizer also was added to improve product shelf life without resorting to freeze-drying. Finally, the formulated bulk was sterile filtered and filled into vials under aseptic conditions in a class 100 environment.[6]

Case Study Evaluation

A decision was made to provide a new facility for this process because of the shortfall in contract manufacturing capacity. Due to tight time constraints, facility design commenced long before the process was defined and many of the technology transfer issues listed in Table A were faced by this project. These external influences impacted the technology transfer process and in turn the facility-related aspects of the project as shown in Figure 3.

The case study will be evaluated and learning points discussed in the following sections. Primary areas for discussion are:

a) approach to facility design and project organization
b) handling risk and change
c) supply chain selection and integration into the project process

The following secondary issues also will be discussed:

d) specialist skills requirements
e) regulatory and social pressures
f) utilities
g) refurbishment of existing facilities

Evaluation of Primary Issues

a) Approach to Facility Design and Project Organization

The approach to this project, as shown in Figure 4, was conventional, highly structured, and did provide a firm foundation for the project. However, this approach meant that the project team could not respond to (or were not aware of) changes that were occurring in the technology transfer process, in particular, development of the production process. There was an over-dependence on the contractor and because of resource limitations there were insufficient documentation reviews. A detailed project URS was not developed and the Front End Engineering Study was completed prior to having many key production process details. The project subsequently moved into its next phase, Detailed Design, without first identifying and understanding gaps in information. Delays to design freeze were not reflected in the project plan which meant that timelines became unrealistic. It was assumed that time lost early in the project could be recovered later.

There was a high level of control systems and mechanical integration of process equipment. This had the tendency to reduce flexibility and resulted in high costs related to design change. Qualification of the systems also proved to be difficult and resulted in time delays.

In summary, the approach used resulted in project delays and increased costs. Furthermore, the facility was difficult to operate, resulting in process inefficiencies and higher staffing levels. Further modifications were required to the facility and equipment during the Qualification phases.

b) Risk and Change

Table B and Figure 5 show the results of an analysis that was conducted. It lists the main categories of change, the number of changes, which were authorized within each category, and the cost of those changes.

The Front End Engineering Study estimated, supposedly within a 15% level of accuracy, that the new facility would cost $17.92 million (approx. £11.2 million) to the end of OQ. The actual cost of the project was $24.96 million (approx. £15.6 million), an increase of $7.04 million (approx. £4.4 million). This increase can be directly attributed to the cost of change during detailed design, construction, and qualification.

Facility and equipment design changes constituted some 50% of the total number of changes, which formed 31% of the total cost of change - *Figure 5*. This was a direct result of poor process definition and was the accepted consequence of moving forward with facility design prior to completing process development.

Of equal, or even greater, significance was the project management category, which constituted 40% ($ 2.81 million) of the total cost of change. Changes in this category were mainly due to extensions to time required by the contractor to execute the project. These time extensions are directly attributable to changes in the other categories.

c) Supply Chain Selection and Integration of the Project Team

Vendor selection and pre-qualification was generally poor and audits were not sufficiently thorough. Process changes resulted in equipment modifications causing project delays and increased expenditure. External consultants were used to determine many aspects of equipment and facility design. There was insufficient dialogue between operators and equipment vendors, which meant that the latter were not incorporated into the project process.

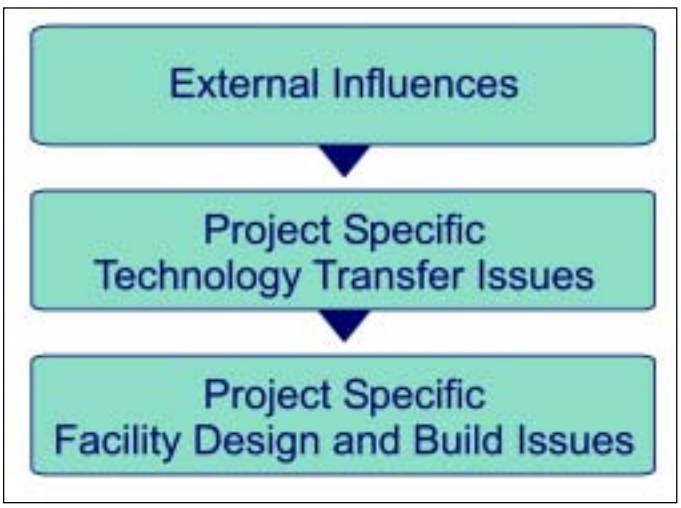

Figure 3. Impact of external influences on facility design.

Many critical requirements, especially with respect to scale, were not identified in the feasibility or front-end engineering studies; therefore, the basis for design and philosophy documents were not developed sufficiently early in the project. Preparation of URS documents also was hampered by poor process definition and resources were not available to support this activity.

The scale of manufacture required for the provision of clinical material was only two-fold greater than the scale developed in the R&D laboratory. This meant that much equipment could, in theory, simply be duplicated, thus reducing technology transfer complications. However, it transpired that many equipment suppliers were not familiar with cGMP requirements, which resulted in lengthy delays and sub-optimal equipment. Finally, airflow patterns, pressure regimes, and containment systems were not properly defined due to a lack of understanding of virus-based processes.

Evaluation of Secondary Issues

d) Key Resources

Recruitment of some key resources for the project was difficult and the recruitment activity itself was initiated very late in the project. There were inadequate resources to support the project; therefore, detailed reviews of drawings were not carried out. External consultants were used, but their scope of work was not properly defined. Such consultants often made decisions without referring back to the project team.

e) cGMP and HSE Regulatory Requirements

A number of assumptions were made early in the project with respect to cGMP and HSE regulatory requirements. Decisions based on these assumptions were made in the absence of (a) a detailed risk assessment of the biological systems used, (b) detailed discussions with the FDA and MCA, (c) accurate analytical techniques, and (d) a detailed evaluation of the existing production process. These assumptions had to be modified late in detailed design as new information emerged. This led to costly design changes and further delays. It also took longer than expected to obtain a facility license for the handling of GMOs due to the weight of public concern that needed to be taken into account.

f) Utilities

It was decided early in the project that the new production facility would draw on existing utilities such as WFI, steam, and compressed air. Utility capacity requirements for the project were calculated based on inaccurate data with respect to existing usage and future site needs. Changes in site usage over the lifetime of the project meant that there was insufficient capacity to run all facilities simultaneously.

Linking to the existing utilities ('tie-ins') caused unexpected project delays for two reasons: (a) the change control procedure required very detailed information before any engineering work could be authorized. It took longer than expected to collect this information, (b) the tie-in required a partial site shutdown, due to production pressures on site. It was difficult to schedule this, which resulted in further delays.

g) Facility Refurbishment

The provision of facilities involved the refurbishment of an existing redundant suite of cleanrooms. Assumptions made with respect to the validation status and quality of engineering for this suite proved to be incorrect. A detailed assessment and

subsequent remedial work was initiated very late in the project again resulting in unexpected costs and time delays.

Learning Points from the Case Study

Learning Point 1: Approach to Facility Design and Project Organization

It is vital for all key players from both the Steering Group and Project Team to align their objectives for the project during the initial design studies. This should be done in the form of a workshop where each person is encouraged to voice his or her opinions and concerns.[7] If objectives are not prioritized early, individual differences may occur later resulting in project delays or additional costs. Decisions made as part of the workshop should form a sound basis for later stages of the project. All main departments must be represented in both the Steering Group and Project Team, and these representatives must be empowered to make decisions. It is equally important that the 'wish list' of each individual is checked such that cost and timelines can be controlled. It is vital that (a) lines of communication are established, (b) the decision making process is clear, and (c) ownership of different aspects of the project is assigned. This will reduce the level of uncontrolled decisions and information flow.

Poor process definition means that the supporting studies, which include the Feasibility, Conceptual, and Front End engineering studies, can underestimate the capacities required for major equipment. The Front End Engineering study should herald the facility design freeze and allow detailed design to commence. Any slippage in freezing the design and any subsequent changes must be reflected in the overall program.

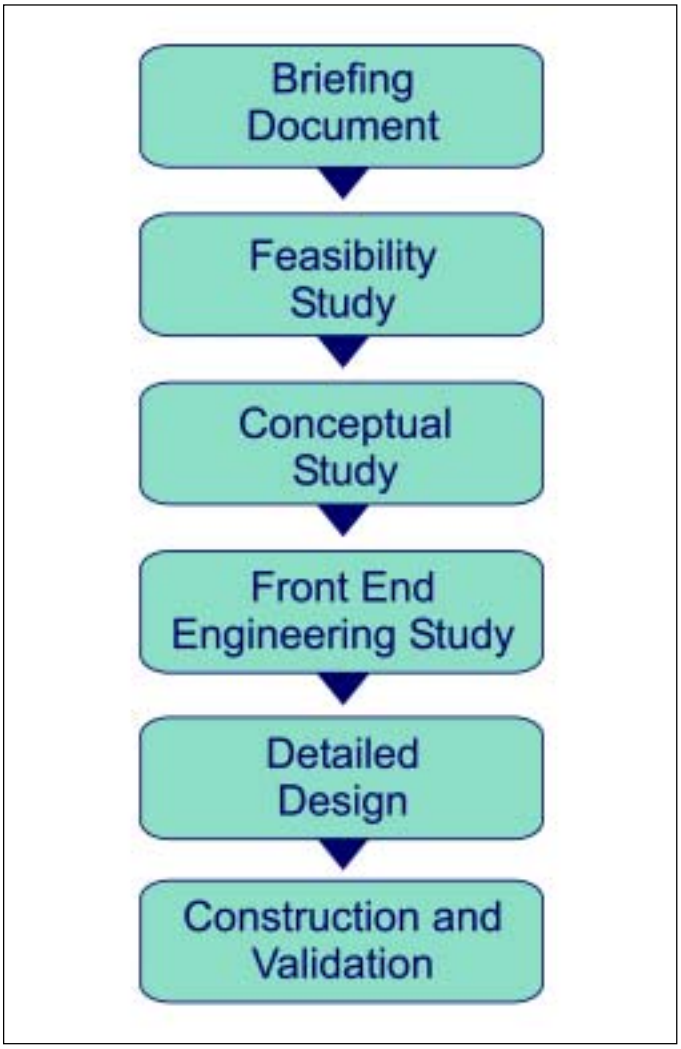

Figure 4. Approach to the project.

Project Parameter	*No of changes	*Cost of change
Facility Refurbishment	8%	3%
Facility and Equipment Design	50%	31%
cGMP and Regulatory	3%	14%
Documentation	5%	4%
Utilities	16%	5%
Project Management	7%	40%
Miscellaneous	11%	3%
*Percentage of the total of change		

Table B. Project changes within the project.

Table C shows how project-related documentation could be developed and reviewed. This structure should be suitable for any biopharmaceutical facility design project; however, what will vary is the integrity of the process detail at each stage. (Note: the feasibility study is not included in this table).

Where possible, facility design should be kept as simple and as flexible as possible. Increasing the level of process equipment and control system integration will inevitably increase facility complexity. When process parameters are well known, this can be managed satisfactorily. If process development has not sufficiently evolved and process parameters are changing, integration can be very difficult and may result in numerous design changes late in the project. In these cases, 'simple is best' to ensure maximum ability to respond to change.

Learning Point 2: Handling Risk and Change

There must be an effective and efficient review mechanism available to the project team to assess both (a) the impact of potentially high risk areas or areas which are prone to change, and (b) progress in these areas. This is shown in Figure 6.

High Risk Areas are those which have the potential to impact timelines, budget, and quality of the facility (i.e., the facility may not be fit for purpose). The Risk Analysis, through a scoring process, should measure (a) the likelihood of a specific issue occurring, and (b) the likely magnitude of impact the issue could have on the project. For example, lack of key

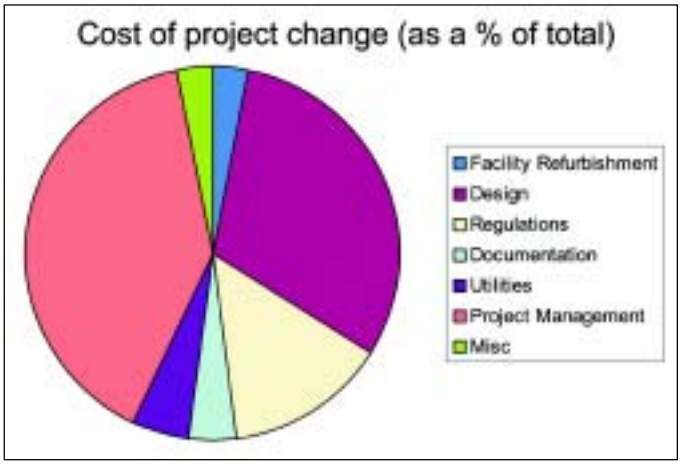

Figure 5. Cost of project change (as a % of total).

resource could be raised as an issue which (a) was likely to occur, and (b) would have a significant impact on the project. This issue, on a scale of 1 to 3, would score '3' in both cases, with a combined score of 9, moving it into the high-risk bracket.

Once selected, special attention should be given to each of the high-risk areas. Progress should be measured periodically by calculating both the percentage actions/decisions that have been carried over since the previous meeting and the percentage completed against schedule. The impact of delays should be reflected in a simplified project plan that would highlight clearly the urgency of critical decisions. It should never be assumed that time lost during one part of the project can be recovered later…this simply will not work.

Detailed project plans are not generally user friendly and top-level project plans cannot highlight individual problem areas. Most decision-makers on project teams have other responsibilities and are not dedicated to the project; therefore, problem areas and hold-ups must be presented clearly, concisely, and accurately.

In a similar way, **all** changes or proposed changes within each of the selected high-risk areas should be collated and quantified. Development scientists, in particular, must be fully aware that changes to the process at lab or pilot scale can have a significant impact on facility design. The level of change within each parameter should be presented visually and action taken if the level of change is excessive. This system will avoid incremental sometimes-uncontrolled change, which bedevils many projects. Using the Change Control procedure, changes should be monitored against the User Requirement Specification and the Front-End Engineering study. As part of this review, each change and key decision should be assessed for its likely impact on time and cost, the risks associated and the likelihood of adverse impact.

Learning Point 3: Supply Chain Selection and Integration of the Project Team

To ensure a successful outcome, the expertise and experience of contractors, equipment suppliers, and consultants involved must be clearly evident. It is important to know the combined limitations of the project team members and the supply chain. The latter must be audited so that their competencies are understood. In this way, skills can be aligned to ensure that the project process is integrated and efficient.[8]

Therefore, it should not be assumed that all vendors understand what is required from them with respect to surface finishes, testing, documentation, etc. Time should be spent upfront to ensure that all requirements are documented, talked through and agreed upon prior to placing a purchase order. Equipment vendors need to be carefully selected and monitored for any pharmaceutical project. Audits must be carried out to ensure that vendors are capable of supplying equipment to the required standard, and they should be carefully monitored during the fabrication and testing phases. URS documents must be carefully detailed especially in relation to cGMP and HSE requirements

To reduce the impact of project change means that the project structure must be adapted to suit. An integrated approach to design, build, and validation is required, and biopharmaceutical companies need to work closely with contractors and vendors. Additional resource is required to manage, monitor, and review all aspects of the project. The impact of key decisions and change requests needs to be evaluated fully using this integrated approach, and all parties involved in the project should participate in interactive planning sessions. Interactive planning sessions are excellent communication tools, and if facilitated properly, highlight all planning constraints thus avoiding unrealistic timescales.

Learning Point 4: Resources

As stated above, sufficient resources must be in place to review project documentation and decisions. It is vital that the recruitment strategy must be developed early in the project life cycle.

The project team must be comprised of a cross-section of people across the company, and all major departments must be represented. These should include Quality, Regulatory, Engineering, HS and E, Production, and R&D. The team members must be dedicated to the project and empowered to make decisions.

Apart from the normal project activities, special attention should be given to ensure that:

a) there is specialist resource available to deal with cGMP, Regulatory, and HSE requirements
b) all project documentation, including drawings, are prepared and thoroughly reviewed in a timely fashion
c) equipment suppliers are selected and monitored carefully

Process requirements	Project Stage	Review activities
Outline manufacturing specification	Briefing Document	Workshop 1 to align project objectives and goals
Manufacturing Specification: (Draft)	Conceptual Study, Basis of Design, outline URS and outline VMP	Review against the Briefing document. Workshop 2 to select best option. cGMP and HAZOP reviews
Detailed Manufacturing Specification: First Issue	Front End Engineering Study Detailed Basis of Design, URS and VMP documents	Review against outline URS. Basis of design and draft VMP. cGMP and HAZOP reviews
Detailed Manfacturing Specification: Second Issue	Detailed Design	Review against the detailed URS. cGMP and HAZOP reviews
Development of Qualification test functions	Construction	Ongoing reviews against detailed design documents
Development and execution of Qualification test functions	Commissioning and Qualification	Ongoing reviews against detailed design and construction documents

Table C. Project stages showing review stages and supporting activities.

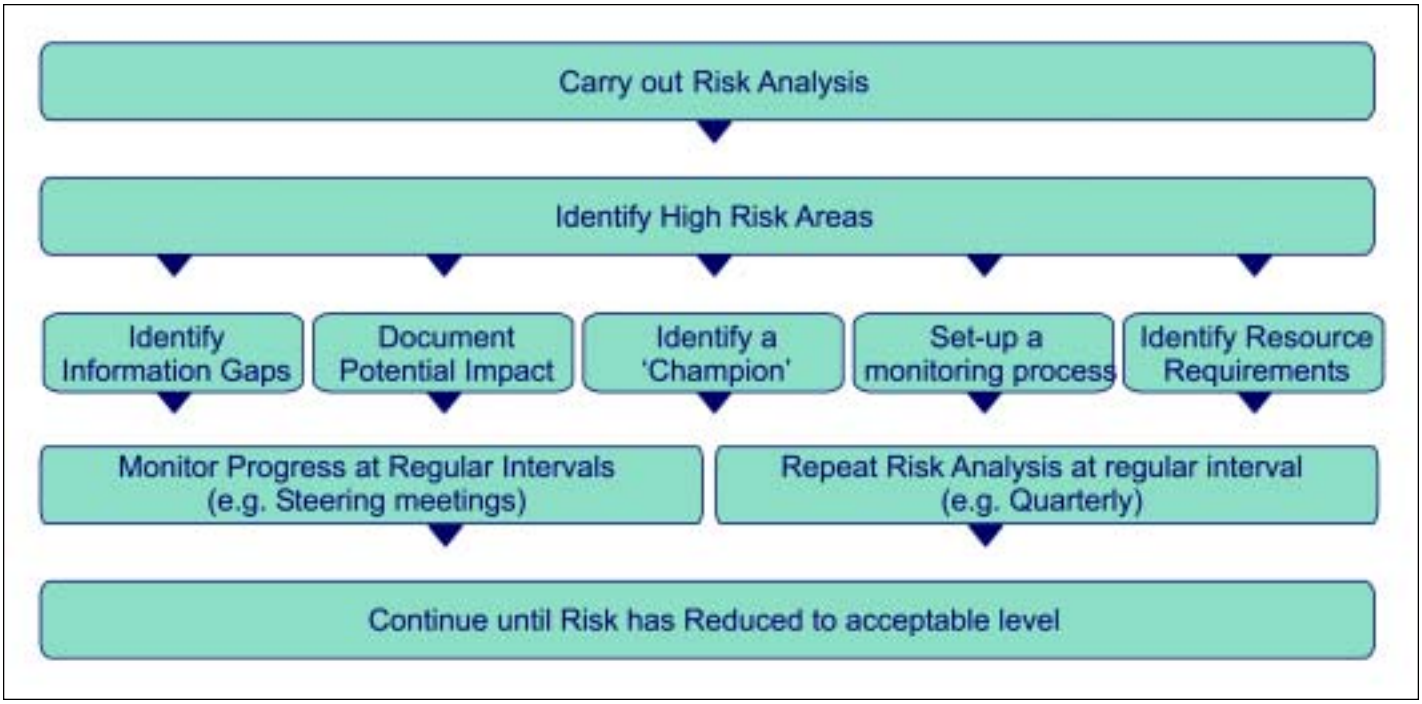

Figure 6. Handling risk.

d) changes resulting from process development and other technology transfer activities are carefully evaluated for their impact on facility design

The additional resources described will increase some aspects of the project costs; however, this must be balanced against a reduced scope of work for contractors and external consultants.

Learning Point 5: cGMP and HSE Regulatory Requirements

Moving from R&D into Clinical Development means that biotechnology companies need to source production facilities that will comply with regulatory requirements. Today, material for all clinical phases is produced in such facilities and production strategy must be developed early in the product lifecycle. Generally, there are three options open to biotech companies:

a) contract out
b) manufacture in-house using purpose built facilities
c) collaborate with a large pharmaceutical company. Manufacture using purpose built facilities within licensed premises.

Option 'b' is generally avoided, but in all cases, expert advice is required early in the project. It must be recognized that facility design may be subject to change due to emerging regulations; therefore, as far as is practicable, potential future regulatory requirements must be taken into account and dialogue with regulatory authorities must be initiated as soon as possible.

The use of GMOs is still in its infancy and while there are numerous laboratories handling genetically modified material, there are very few large-scale facilities involved in their manufacture. Detailed risk assessments on the organisms and expert scientific input is required to determine risk to Health, Safety, and the Environment. Research scientists, for very good reasons, are often reluctant to hand over detailed descriptions of the GMOs that they have developed, but this is a barrier which must be overcome so that a valid risk assessment can be carried out and to obtain a HSE/EPA license.

As with cGMP requirements, it must be recognized that expert advice is required for facility design to ensure that the correct containment requirements are part of the design. For example, many companies use modelling of air flow patterns to facilitate HVAC design. Waste handling also needs to be carefully considered to ensure that there is sufficient capacity for inactivation of effluent streams.

Society in general is still wary of any activities concerning genetically modified organisms. Publicity and staff-related issues must be carefully handled and additional security measures may be required. Staff will need to be assured that (a) they will not be exposed to dangerous biological material, (b) the facility has adequate safety measures built-in, (c) that the highest level of training will be provided, and (d) there are no potential ethical issues.

Learning Point 6: Utilities

Time should be spent weighing the choice of either a link up to existing utilities or making the facility self-sufficient. If calculations are not carried out properly, linking in to existing utilities may stress the system thus reducing quality. Process simulation tools should be used to help determine generation capacity required.[9]

Linking to site utilities also can be difficult to schedule, especially if it entails a partial site shutdown. This factor alone has the potential to delay a project significantly. Many tie-ins will result in the need to re-validate the existing system, and in some cases, prior acceptance of the change from regulatory authorities will be required. Therefore, it is vital that all prework documentation is in place and correct. The change control procedure should (a) trigger a detailed check of this documentation, (b) ensure that the work will be carried out properly *via* detailed method statements, and (c) ensure that the system is properly re-validated once the engineering work has been executed.

Learning Point 7: Facility Refurbishment

Refurbishment of facilities is difficult and can cost more than a total re-build. Assumptions are often made regarding the quality of existing documentation and engineering. These assumptions sometimes prove to be incorrect, and an in-depth study of the facility and its associated documentation must be carried out early in the project. This will enable the project team to (a) determine how much remedial work (including re-validation) is required, (b) how much it will cost, and (c) compare these costs against a total re-build. It is often the case that no matter how much money is spent on rectification work, the facility does not operate as required.

Conclusion

The transfer of any pharmaceutical product from research to clinical development is difficult. The transfer of biopharmaceuticals, in particular genetically engineered products, is further complicated due to many external influences such as those listed in Table A. These complications result in incremental facility design changes, which in turn lead to increased facility costs and program extensions. To overcome these difficulties, an integrated and flexible approach to design and build is required using a skilled project team.

Risk areas must be identified, highlighted, communicated, addressed, monitored, and controlled. The potential impact of change also must be fully evaluated to minimize the overall risk to the project. The adoption of a change control process early in the project life-cycle is essential and sufficient resources must be in place to manage and review all aspects of the project documentation.

Glossary

CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
DNA	Deoxyribonucleic Acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GMOs	Genetically Modified Organisms
HAZOP	Hazardous Operations
HS and E	Health Safety and Environment
HSE	Health and Safety Executive
HVAC	Heating, Ventilation and Air Conditioning
IQ	Installation Qualification
MCA	Medicines Controls Agency
OQ	Operational Qualification
PEAT MSc	Pharmaceutical Engineering Advanced Training Master of Science Degree at UMIST
R&D	Research and Development
US	United States
UMIST	University of Manchester Institute of Science and Technology
URS	User Requirement Specification
WFI	Water for Injections

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Rodger Edwards graduated with a BSc (Honors) in metallurgy and materials science from the joint UMIST/University of Manchester Department of Metallurgy in 1979 and then spent three years as a research student in the same department, researching thermophysical properties of liquid metals. He joined the Department of Building Engineering at UMIST as a research assistant in 1983 with his main research areas being the measurement of ventilation rates using tracer gases and the computer simulation of hot water systems. He finally obtained his PhD from UMIST in 1986. In 1987, he was appointed as a lecturer in the Department of Building Engineering at UMIST, and in 1997 was promoted to Senior Lecturer. He was elected to membership of the Chartered Institution of Building Services Engineers (CIBSE) in the same year. Edwards has been the Director of the Pharmaceutical Engineering Advanced Training (PEAT) program since December 1996, and has supervised more than 40 successful MSc graduates through their dissertations. He is also a Tutor to the UMIST Graduate School, and serves on the Merseyside and North Wales Regional Committee of the CIBSE. He has been an ISPE member since 1996.

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