Pharmaceutical
BIOPROCESSING

Biopharmaceutical factory of the future

The growth in stratified medicine and the economic pressures to reduce capital investment, cost of development and cost of goods are forcing a change in how biopharmaceutical manufacturing plants are designed, built and operated. It is likely that future manufacturing facilities will be built on the principle of flexibility and make even greater use of single use technology, continuous manufacturing and alternative expression systems. Large scale production will in many cases be achieved by the 'scale out' of multiple smaller facilities rather than the 'scale up' to large capacity plants. Some of the core technology required to achieve this vision is already available though further development is required in many areas.

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There has been much recent discussion on the nature of the biopharmaceutical manufacturing factory in the future. The traditional model of large scale, stainless steel facilities with high capital costs, high requirements for purified water and other services, operated in fed batch mode has served the industry well but many factors are forcing a rethink about biopharmaceutical manufacture and the design of manufacturing facilities.

The factors forcing change are both economic and technical. Economic factors include the need to reduce capital investment required for new manufacturing facilities and the need to reduce cost of goods for biopharmaceutical therapies, technical drivers of change include the move toward novel types of molecule and the rise of stratified and ultimately personalized medicines.

Given these pressures, the improvements in the productivity of bioprocesses and the availability of new process technology solutions, it is likely that future biopharmaceutical manufacturing plants will look considerably different from those we have become used to. In particular there is a significant gulf between current biopharmaceutical manufacturing facilities and the needs of stratified and personalized medicines.

The biopharmaceutical industry, from drug discovery through to manufacturing, process technology developers and suppliers to healthcare providers and regulators, are actively seeking better ways of discovering, developing and manufacturing drugs. The opportunities for innovators that take up the challenge are significant with a growing, worldwide market for successful solutions. This article aims to summarize the main drivers of change and what their impacts will be on manufacturing facilities.

Current state of biopharmaceutical manufacturing

From the launch of the first recombinant biopharmaceutical product in 1982 (Humulin Insulin, Eli Lilly), the market has grown to one of global importance. It is estimated that the value (net sales) of therapeutic proteins produced in mammalian cell culture alone was US$120 billion in 2013 and growth at 6–8% per annum is predicted [1]. Biopharmaceuticals represent one of the fastest growing, if not the fastest growing segments of the entire pharmaceutical industry.

From being a niche part of the pharmaceutical industry in the 1980s, biopharmaceuticals are increasingly seen as a

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Key terms

Personalized medicine: A treatment designed for an individual patient.

Stratified medicine: A therapy that is designed to be used on a subset of the patient population based on certain patient biological markers.

mainstream element in the future plans of all major pharmaceutical companies. This is demonstrated by the emergence of the biopharmaceutical blockbuster drug, it is estimated that of the total revenue generated by blockbuster drugs, the share taken by biopharmaceuticals increased from just over 10% in 2000 to nearly 35% in 2010 [2]. In 2012, seven of the top ten prescription drugs worldwide were recombinant proteins of which 6 are made in mammalian cells [3].

Most manufacturing processes use batch or fed-batch culture techniques. In fed-batch processes, small volumes of key nutrients are added during the fermentation with the aim of increasing the biomass in the reactor. Alongside improved expression systems the development of feeding strategies has been a highly important contributor to the improvements seen in productivity for processes making recombinant proteins, in the case of monoclonal antibodies, titres of up to 10 g/l can now be achieved even at the largest operating scales [4].

The therapeutic success of biopharmaceuticals and the demand for large amounts of the leading drugs – particularly driven by monoclonal antibodies which are often required in high doses, has shaped the design of biopharmaceutical production facilities. These facilities typically are based on large stainless steel bioreactor vessels with downstream capabilities scaled accordingly, being based on fixed equipment these facilities also have a high requirement for clean and sterilize in place technology. To meet the demand for the required amount of product, facilities have been developed with bioreactor volumes of up to 20,000 l for mammalian cell systems and even larger in some cases for microbial systems, the largest capacity facilities having multiple reactors of this size.

Traditional facilities as described require extremely high levels of capital investment to develop and have high running costs; typically they operate as centralized facilities where the therapeutic is bulk produced for worldwide distribution. While facilities of this nature may continue to be the best option for supplying drugs that have achieved blockbuster status and have stable and predictable markets, for a new generation of therapies this manufacturing model may not fit and therefore a rethink in the type of production facility best suited to meeting their needs is required.

Drivers of change: diversification & stratification

Stratified & personalized medicine

Traditionally drug discovery has involved screening the effects of many potential drugs against diseased cells to enable the selection of promising candidates intended to be used on any individual displaying a certain range of symptoms and without necessarily having a good understanding of the causative mechanisms of the disease, the empirical medicine approach. Some such medicines work for almost all relevant patients whereas others may only work for a subset of patients, and indeed may even be harmful to some patients.

Recent advances in genomics and the understanding of the biological basis of disease have enabled new classes of therapies to be designed and developed; in many cases, these therapies have smaller target patient groups than the traditional blockbuster. This move toward smaller volume, more directed therapies is supported by pressure from medicine reimbursement strategies whereby the emphasis is on paying pharmaceutical companies for positive health outcomes rather than for doses supplied. Taken together these factors are forcing an increasing move toward the development of stratified and personalized medicines [5].

With stratified medicine, patient characteristics such as age, sex, genotypic and phenotypic biomarkers can be used to identify cohorts that are more or less likely to respond to a particular treatment. Personalized medicine represents the ultimate form of stratification whereby treatment is customized according to patients' individual characteristics, for example, production of a cancer vaccine from patient's own cells.

The human genome project together with other advances in biological knowledge and improvements in DNA sequencing technologies has provided the basis for a much deeper understanding of the causes of disease and the best form of treatment for a particular individual. Specific dysfunctions can be linked to variations in DNA sequences and their resulting proteins. The DNA of an individual patient can be analyzed to ascertain the exact molecular basis for their condition and the best course of treatment chosen based on this knowledge [6].

This approach is starting to enable medical research to re-categorize diseases, for example, breast cancer has multiple underlying gene mutations leading to the disease [7], with different types responding to the available treatments in different ways. Knowledge of the exact cause of an individual's condition can therefore enable the most effective treatment to be selected; this has an obvious benefit for the patient but also an economic benefit as expensive drugs are directed only to those who will benefit. Similar approaches are also

enabling rare diseases with poorly met clinical needs to be addressed.

The end result of these changes to the way drugs are developed and treatments selected is that it is likely that there will be a multifold increase in the range of therapies available. However, these therapies will have specific indications against patients with specific biological markers, based on genotypic or phenotypic analysis. Disease diagnosis will enable determination of these markers, and selection of the most effective therapy. For patients and healthcare providers the benefits will be significant, it will offer better health outcomes, less side effects attributed to administration of suboptimal therapies and a more cost effective approach, all of this against a backdrop of growing global demand for innovative medicines.

It is likely that this move toward patient stratification will become one of the most important trends in healthcare over the next few decades and will perhaps be the major influence on how future manufacturing facilities will be configured and operated.

While the drug discovery sector is rapidly investing in this new approach, there is a 'market failure' starting to emerge. Pharmaceutical supply chains are geared toward the manufacture and supply of a relatively small number of therapies for specific diseases; in particular the large pharmaceutical companies have become focused on a small number of blockbuster status drugs. As stratified medicine becomes more widespread the diversity of therapies required will increase while the size of patient cohorts receiving them will reduce. Hence large scale manufacture of a relatively limited range of therapies will need to transform to smaller scale manufacture of a diverse range of therapies. Furthermore, given the need to target the underlying molecular basis of the disease via genetic and protein targets, an ever increasing number of therapies will contain biopharmaceutical – protein or nucleic acid – components.

Economic impacts of stratification

If as suggested stratified and personalized therapies are likely to be a major trend within the biopharmaceutical industry and drive the adoption of new types of manufacturing facility then some consideration should be given to how this will affect healthcare economics [8]. For the healthcare provider, the economic benefits seem clear – less money is spent on drugs that are ineffective for many patients resulting in an obvious cost saving, equally for the patient there is the clear benefit of an improved therapeutic outcome. For the drug developers the issues are less clear, stratified approaches can be seen as a disincentive as their drugs are used in reduced amounts, furthermore there may be an onus on the drug developers to provide a companion diagnostic which will absorb further development costs and likely command lower margins [9]. It is likely that in time a good part of this 'lost' revenue can be recovered as the increased certainty of a beneficial effect promotes increased uptake of the drug amongst responders and increased patient compliance. The added certainty of positive effects may also enable the price per dose to be increased based on overall cost/benefit analysis. Also while current stratified approaches rely on specific diagnostic tests it is likely that in the future there will be more use of equipment 'platforms' (such as whole genome sequencing), this will diminish part of the disincentive, in that a new diagnostic may not need to be developed for every new drug [10,11].

Ultimately the financial pressures on healthcare providers, whether public or private, their demands on the Pharmaceutical industry and the needs of society for more effective medicines will decide the success of stratified approaches. Given this it is difficult to see a future global healthcare industry where patient stratification does not play a large role, the only question then is how the pharmaceutical industry will respond; adopting a streamlined, predictive approach to drug and process development is likely to be one such response [12] and a rapidly scaled, flexible and cheaper approach to manufacturing is likely to be another.

Diversification of therapy type

Alongside the impact of patient stratification leading to an increase in the number of drug candidates that will need to be manufactured there is also an expanding range of molecule types, both natural and engineered that are being used as therapeutics.

Early biotherapeutics were largely naturally occurring molecules or very slightly modified molecules. Following the advent of monoclonal antibody based therapies it began to be realized that for many modes of treatment it was not necessary to have a complete antibody molecule and therefore simpler, engineered forms could be used such as Fabs and single chain variable region fragments (scFvs). These forms retained the binding specificity of full antibodies but lacked the biological effector functions and were often easier to manufacture due to their simplified structure, in many cases they could be manufactured in microbial rather than mammalian systems.

More recently a whole range of engineered molecules are being explored for therapeutic use ranging from further antibody based formats – single domains, bi- and tri-specifics and antibody drug conjugates (ADCs) [13], to new protein scaffolds such as DARPins and anti-calins [14,15]. Also becoming important are large complexes such as virus like particles (VLPs)

Key terms

Scale up: addition of manufacturing capacity by increasing the size of the production units.

Scale out: addition of manufacturing capacity by building additional production units.

and a range of peptides, DNA and RNA based molecules, some of which blur the boundaries between traditional biological and chemical approaches. These molecules are likely to stimulate interest in new types of manufacturing facility for a number of reasons:

- They are engineered to increase potency and therefore are required in smaller doses than conventional therapeutics, particularly mAbs. Combined with stratification leading to smaller patient cohorts the batch sizes required may be much smaller than current therapies;
- The sequence of unit operations required for the manufacture of these new therapies is likely to vary from molecule to molecule; investment in a fixed facility therefore becomes risky as it is unlikely to be capable of manufacturing other molecules without extensive and expensive refitting;
- For molecules such as ADCs, the biologically manufactured component is just one part of a more complex molecule that combines biologic and chemical entities, the full supply chain must include components and operations not normally found in a biologics facility.

Antibody drug conjugates: challenges of a mixed supply chain

Perhaps the challenges posed by antibody drug conjugates best exemplify how the pharmaceutical supply chain and manufacturing systems will need to adapt to new types of therapeutic molecules. Essentially ADCs consist of three components – an antibody or fragment of – for targeting within the body, a cytotoxic payload to act on a diseased cell and a linker to join the cytotoxic payload to the antibody. This results in a high COGs for the complete molecule along with an extended supply chain as in some cases the required manufacturing steps are geographically distant due to a reliance on existing facilities and multiple partners involved in the manufacturing of the complete drug. The high potency, high level of containment required, often limited target population and in some cases lack of stability of the complete molecule also result in a poor fit with current facilities.

The ideal manufacturing facility for an ADC could be as follows:

- Contained and based on single use technology – to prevent contamination and accidental release of highly potent components;
- Rapidly configured with a range of unit operations – including biological production, chemical synthesis and a variety of purification steps;
- Incorporates all necessary analytics – for process monitoring and batch release;
- Scaled to produce small batch sizes – to match demand and reduce the potential for problems during scale up of a diverse set of unit operations;
- Modular in construction – to enable production facilities to be located close to treatment centers;
- Quick and cheap to build – enable scale out to meet increase in demand.

In many ways, the concept of small, flexible and self-contained manufacturing units is ideally suited to ADC production.

Geographic expansion: the pull of emerging markets

As new biopharmaceutical markets have emerged for that were formerly difficult or uneconomic for large pharmaceutical companies to access and as biopharmaceuticals have increased in worldwide importance there has been a demand to widen the geographic base of manufacture, indeed in some new territories there are strong pressures to manufacture locally for the local market. Even the largest multinational pharmaceutical companies are unlikely to have the time, desire or finances to invest in multiple large-scale traditional facilities in these territories, therefore to access these markets a new type of facility is required that can be built quickly, cheaply and have the flexibility to manufacture alternative therapies if required.

Economic pressures on biopharmaceutical manufacture

Cost of goods

Historically the cost of goods of biopharmaceutical products was thought to represent between 10 and 25% of the sales price of the drug. For monoclonal antibodies, rising productivities have seen this figure fall significantly such that the cost of production is now less than 5% of the selling price in some cases. For mainstream, high-volume monoclonal antibody therapies this has reduced the pressure on cost of goods for the time being at least. However, future mAbs are likely to face more reimbursement barriers than the first generation mAbs [16] and hence this is likely to result in an increase

in the pressures on the manufacturing cost of goods. For biopharmaceuticals other than monoclonal antibodies cost of goods is and will remain an important issue, largely due to the typically lower productivities and reduced scales of manufacture as compared with mAbs.

The development of biosimilars also adds a new dimension to the pressures on biopharmaceutical manufacturing costs. Biosimilars are likely to be much more price sensitive than current innovator molecules and therefore new, lower cost manufacturing routes will be sought. While in many cases traditional large scale facilities may provide the cheapest route of manufacture, particularly for high-volume products and where an existing facility has spare capacity; there is also likely to be an interest in exploring lower cost manufacturing operations that can be rapidly scaled to match demand, particularly for supply in emerging territories.

While reducing cost of goods for biopharmaceuticals will require technological advancements in many areas, the method of manufacture is likely to play its part. By switching to more flexible and rapidly scalable methods of manufacture it is possible that many biopharmaceuticals could be produced more cheaply, due to lower operating costs and a reduced cost contribution from the capital cost.

Capital investment

The cost of constructing a traditional biopharmaceutical plant is in the order of tens of millions (US$) for medium sized (1000–5000 l) facilities to hundreds of millions for large facilities (10,000–200,000 l) facilities [17]. Alongside the high build cost, the timelines required to construct and bring into operation are long, typically it will take between 3 and 5 years for construction and commissioning. In order for a new plant to be ready for initial market supply following drug approval construction must begin during the clinical trials process; therefore, large amounts of capital must be invested in plant construction while significant risks of drug failure in the clinic and the market still exists; however, the financial penalties of delays and interruptions to market supply are also potentially very large. Given these risks it is usual for companies to commit to building capacity as late as possible in the development of the drug. Outsourcing to contract manufacturing organizations and sharing capacity with partners [18,19] are often used as strategies to manage this risk and ensure that initial market supply needs can be met following successful approval. Obviously a new type of manufacturing facility that is cheaper to build and importantly, very fast to bring on line would be extremely helpful to minimizing risk.

While the economic case for investment in new manufacturing plants is a complex equation and the process type, productivity and scale all have a major impact on the optimum solution, it has been suggested that for monoclonal antibody producing facilities at scales ranging from 200 to 2000 l and cell line titers of between 0.5 and 5 g/l switching from a largely fixed, stainless steel method of construction to a facility using disposable, single-use technologies wherever possible can reduce capital investment requirements by 30–40% and ultimately cost of goods by 20–30% [20–22]. While this adoption of single use technology can be seen as one step toward a more flexible manufacturing approach the adoption of a fully modular configuration holds the potential for further reductions in the capital barriers and in particular could link the required capital investment to demand for the therapeutic, thus reducing risk.

Timeline & risk management

From identification of a therapeutic candidate it takes a minimum of 1 year and sometimes much longer for cell line/strain development, process development and early stage manufacture before clinical trials can begin. The clinical trial process then takes typically several years before a new drug can be approved for the market. This all represents lost time to the industry, particularly given the limited length of patent protection.

While the scale up of the manufacturing process is not usually a major limiting factor in the timeline it can cause problems. The transfer to the final manufacturing scale can be unpredictable and introduce delays during the clinical trial process and as mentioned above, the decision to add manufacturing capacity and the high costs involved must be balanced against the risk of failure of the drug. A more flexible, modular manufacturing approach based on the principles of scale out rather than scale up would to a large extent mitigate many of these risks, allowing rapid addition of capacity without the risks of process scale up.

The future state of biopharmaceutical manufacture

As described above there are multiple factors that are stimulating a change in thinking of how biopharmaceuticals will be manufactured, these factors being both technical – patient stratification and increasing number of molecule types, and economic – the increasing pressures on cost of goods and capital investment, to summarize:

- Biopharmaceutical manufacturing will need to serve an increasing range of needs across the healthcare sector;

- There will be the need to manufacture an increasing range of molecule types, many of which do not fit into current platforms;
- There will be a need for cost effective manufacture of multiple small lots of stratified and personalized therapies;
- Cost pressures, driven by reimbursement strategies will increase, even on traditionally high margin innovator products.

How this changing environment will be translated into the design and operation of future manufacturing facilities is therefore a topic of much discussion, in practice the pharmaceutical industry will adapt to these pressures in a number of ways across the entire supply chain; an adoption of a cheaper, flexible and rapidly constructed manufacturing facility is likely to be one of these adaptations.

In principal, the future supply chain for a new generation of stratified therapies could look as follows:

- A patient presents to clinic with symptoms, diagnostics are performed to categorize the disease and determine the most effective therapeutic from a range of possible treatments;
- Manufacture of the biopharmaceutical is performed according to demand in a small scale modular manufacturing unit located either remotely or close to patient;
- Central manufacturing facilities consist of multiple modular units which can be reconfigured to rapidly change to manufacture different therapeutic forms;
- The therapeutic manufactured could have been developed to effectively treat a small cohort of patients with similar biological characteristics or it could be a bespoke treatment developed for an individual patient.

Schematically this concept is shown in Figure 1.

Many of the components required to make this concept a reality already exist, while in other areas further innovation and technology development is required. For many diseases further understanding of the biological basis of the disease is required together with the identification of suitable biological markers to enable accurate diagnosis and development of stratified approaches.

One particular issue that will need to be addressed is how clinical trials for stratified therapies are designed and conducted. For a stratified therapy, the requirement for large-scale clinical trials for each version is likely to be prohibitively expensive even if it were possible to find sufficient trial patients. A new approach will be needed, possibly based on multiple smaller trial patient cohorts or the trial of an exemplar therapy from which the stratified versions are derived. Adaptive licensing [23] approaches may become the norm whereby drugs are licensed in a stepwise fashion based on continual data gathering and rigorous risk assessment. These changes to the way clinical trials are conducted will have implications for manufacturing plants though overall will largely reinforce the need for smaller, flexible methods of production.

In terms of the process equipment and technology needed, a key enabler is the wide range of single use, disposable equipment that is now available in a presterilized, ready to use form. Further development is needed to integrate different pieces of equipment into fully modular manufacturing units but the basic components are already in existence.

Single use process technology

Over the past 10 years, the availability of single-use technologies has moved beyond single use bags for product hold, media and buffer preparation to viable upstream and downstream single use processing options.

One of the most important developments in biopharmaceutical production over recent years has been the availability of an increasing range of single-use, disposable bioreactor equipment and a tendency for the single use approach to be applied at ever increasing process scales. Even in traditional, large scale and largely fixed stainless steel based plants single use technologies are having an impact.

While single-use bioreactors have found ready acceptance in mammalian cell-based processes, further development is required to improve their performance and use in microbial processes. Compared with fixed systems the maximum gas transfer rates achievable in single use equipment are limited; while generally sufficient for mammalian cell processes, the higher transfer rates required for microbial growth currently limit applicability [24].

As with single use bioreactor technology there has been a rapid increase in the availability and applicability of single use downstream equipment. Adoption of single-use technologies in downstream processing includes the use of depth filters for primary recovery, viral reduction filters and numerous types of self-contained membrane chromatography units of various chemistries and suitable for a range of production scales. Again these technologies are finding increasing use within traditional manufacturing facilities but more importantly are key enablers to developing a different way of manufacturing, particularly when pro-

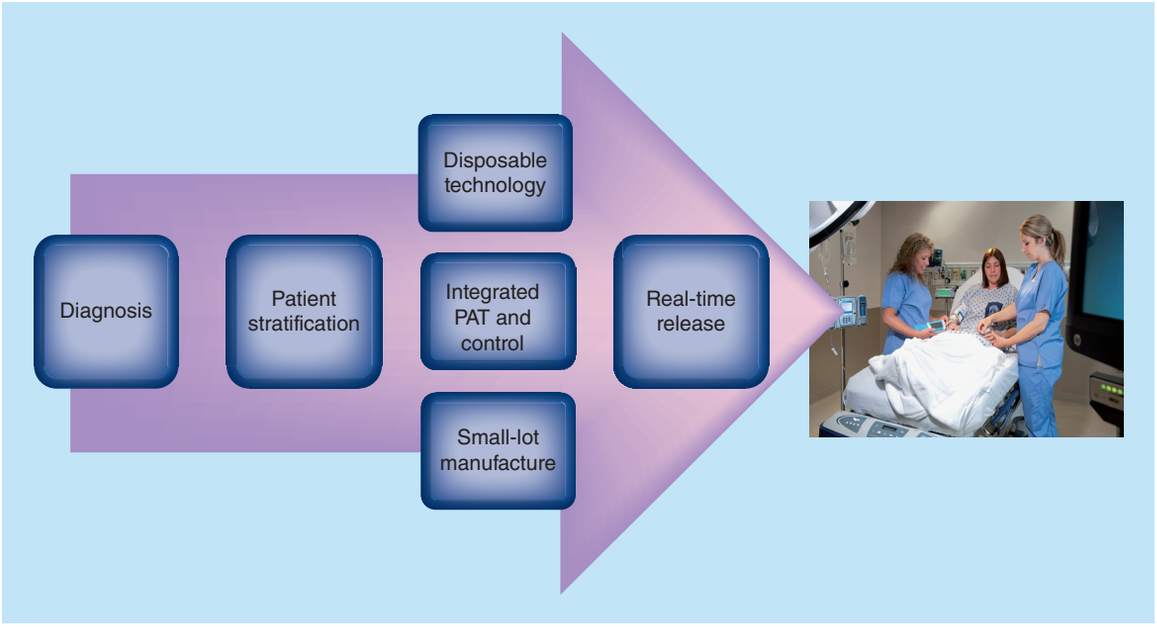

Figure 1. Basic supply chain concept for stratified therapies: disease will be diagnosed and patients stratified based on genotypic and phenotypic markers, appropriate treatment will be selected from a range of therapies each manufactured in small batch sizes.

cesses are designed to take advantage of these technologies, for instance chromatography steps designed to operate in flow through rather than bind/elute mode.

Further developments are required in downstream processing, many processes and products are still reliant on packed bed chromatography operated in bind/elute mode which adds complexity to the process, and many chromatography matrices are too expensive to be regarded as suitable for a single use format. Alternatives are therefore desirable, both new chromatography formats and nonchromatographic alternatives.

Current examples of single use technologies are shown in Figure 2. These are from the Sartorius FlexAct® system (Sartorius AG, Goettingen, Germany) which is a series of single-use solutions for individual unit operations that can be combined for entire bioprocesses.

The main advantages of a single use process equipment can be summarized as follows:

- Reduced capital investment compared with fixed asset stainless steel facilities;
- Reduced clean in place (CIP) and sterilize in place (SIP) demands;
- Reduced qualification and validation demands;
- Reduced risk of product cross-contamination;
- Increased flexibility from 'plug and play' reconfigurable unit operations.

The ongoing improvements and range expansion of single use technology coupled with increases in cell line and process productivity will underpin manufacturing facility change over the coming years.

Continuous manufacture

One area of technology with the potential to bring about major change in manufacturing is the adoption of continuous manufacturing for the production of biopharmaceuticals. Even though there is a shift toward lower volumes of any single product continuous processing has a major role to play in future manufacturing strategies. Continuous manufacture has the potential to enable the production of relatively large amounts of product from a small manufacturing footprint, thus facilitating the scale out strategy for commercial supply. Continuous manufacturing also has the potential to offer better process control opportunities, thus better meeting the needs of Quality by Design strategies for biopharmaceutical manufacture, another important trend that is bringing about change in the way biopharmaceuticals are developed and manufactured [25].

Continuous upstream processes are generally based on perfusion cultures, generally involving the use of filtration to retain cells in the culture vessel while harvesting the old culture media containing product and feeding with fresh media, thus the productive life of the culture can be extended compared with current batch or fed batch strategies. Perfusion culture is in itself not new, being used for the production of 5 out of the 30 or

Figure 2. Single-use equipement examples. **(A)** Sartorius FlexAct® UD system for single-use ultrafiltration processing. **(B)** Sartorius FlexAct CH disposable cell harvesting Biopharmaceutical processing modules: suitable for incorporation into a flexible, single use manufacturing module.
Courtesy of Sartorius AG.

so commercial monoclonal antibodies currently manufactured [26]; however, there has been a resurgence of interest in the potential of perfusion culture due to the availability of new equipment and the possibilities for process intensification, particularly when coupled with continuous downstream approaches.

The downstream options for continuous manufacturing are currently based on existing chromatography techniques but operated in a multicolumn set up, the simulated moving bed approach. The basis of this is the use of multiple smaller columns operated cyclically such that there is always a column available for loading with product. Again this is a technology that is likely to have a place in more traditional types of plant, particularly considering the downstream bottlenecks that often exist, particularly for monoclonal antibody manufacturing. However, the greatest impact will be from the process intensification possible from combining continuous up and downstream technologies. Future innovations are likely to lead to commercial, non-

chromatographic separation technologies; these will have great potential to improve process efficiency in both continuous and traditional batch manufacturing modes.

Traditionally the main issues with continuous technologies have been the increased complexity of the apparatus required along with sterility and contamination concerns. Significant progress has been made in addressing these through development of fully automated control systems and fully disposable flow paths; however, further development, both of equipment and process techniques is still required. It is likely that there will be some crossover of technology from industries where continuous processing is standard, for example, food processing, small molecule pharma, in fact simulated moving bed chromatography is routinely used in other industries at a wide range of scales and only now being incorporated into biopharmaceutical manufacturing.

Alternative expression technology

Traditionally the biopharmaceutical industry has relied on the development and use of stable, continually expressing cell lines and microbial strains to produce the protein of interest. However, the creation of stable mammalian cell lines in particular is a time consuming process on the critical path to clinical manufacture. It is also a heavy resource requirement and therefore expensive, especially so if future scenarios of multiple personalized or stratified therapies are needed. The development of a multiplicity of stable cell lines will be problematic to say the least.

One solution being proposed is the use of transient expression systems for clinical supply. Such systems use a single stock of cells which can be transfected with a range of expression vectors each producing a particular form of the therapy. The transfected cells only produce product for a limited amount of time but the productivities available from such systems are now at a level where this approach can be considered for the production of small batch sizes.

A logical extension of the transient expression approach would be the use of cell-free expression systems. Here an extract prepared from previously grown cells is used to express a protein from an added gene; the removal of the cell from the final production step potentially removes a significant source of risk and variability while allowing greater control and potentially manipulation of protein synthesis. Cell-free expression may find a particular use in processes and products combining biotechnology with chemistry. While cell-free systems have been developed to the point at which they can be considered as potential production systems for nonglycosylated proteins, further improvements to productivity and product quality are undoubtedly required before they are a mainstream option [27].

Process analytical technology

The development and incorporation of suitable process analytical technology is an area that requires much further work if multiple small modular manufacturing units are to become a reality. While the options available for on line process monitoring have expanded greatly in recent years, there is still room for the development of new sensors that can be incorporated into small scale, single use systems without compromising sterility. Obviously when incorporated into a single use process unit, sensors must be cheap, robust enough to withstand the manufacturing and sterilization process while having sufficient accuracy and precision for their intended use.

A major focus of development is likely to be the development of on line batch release testing, indeed this is necessary if truly flexible manufacturing methods are to be implemented. Of course this will require both technology development and regulatory changes and is an area where close interaction with relevant licensing authorities is required.

Perhaps a further innovation to come will be the centralized on line monitoring, collation and analysis of process data from multiple manufacturing units, perhaps widely spread geographically. Such models exist in other industries and would reduce the cost of operation of individual manufacturing units while enabling larger scale data trends to be identified.

Batch release testing & regulatory Implications

If biopharmaceuticals are to be manufactured in small batches, perhaps from production units spread over a wide geographic area then it is likely that the way in which batch release testing is approached will need to be modified. The current system works well where batch sizes are large and sufficient stocks of released product are available while newly manufactured batches undergo testing, but where a small batch of product is manufactured in response to an immediate patient demand the system becomes too slow and expensive. Ultimately the answer to this will come from better process analytical technologies and true quality by design strategies, thus by measuring critical process parameters known to influence the critical quality attributes of the molecule being produced a measure of real-time batch release can be achieved. Before this can happen however there will need to be further technology development of process analytical technologies and improved understanding of the relationship between process parameters and the critical quality attributes of the molecule. Only then can we

expect a change in the regulatory environment that will allow real-time release.

A vision of the factory of the future

What might the factory of the future look like? On the basis of the demands of future manufacturing needs, as described above, it is possible to formulate a view of the physical form of a future processing unit.

The process technologies necessary to manufacture a product, from upstream to downstream, will be integrated into a small format unit, that ideally will be self-contained and therefore not require the levels of physical containment currently achieved in clean rooms. Operation of the unit will rely on automation in the main with very little human intervention.

The earliest forms of the unit will include small scale disposable versions of current technologies, such as bioreactors, chromatography columns and membrane filtration units. A current realization of this concept by GE Healthcare (Buckinghamshire, UK) is shown in Figure 3. However, existing technologies have limitations and there is likely to be more emphasis on the development of new technologies that are more compatible with the new process schemes and end user demands.

One of the key attributes of the factory of the future will be its ability to provide real time measurement and control which will enable real time release of products. This represents one of the greatest development challenges, in that there are few if any technologies that are available off the shelf to facilitate this currently.

Conclusion & future perspective

Biopharmaceutical manufacturing has developed from small beginnings to its current status as a multibillion dollar business behind some of the most advanced therapeutics available, integral to the plans of the largest pharmaceutical companies. To achieve this has required enormous advances in the science and engineering that underpin the manufacture of complex biopharmaceuticals.

Despite the successes we are at a point where numerous pressures are forcing a rethink of how we manufacture biopharmaceuticals, the pressures that will force further change within the industry can be summarized below.

Stratification & diversification of therapies

As the biopharmaceutical industry matures there is an ever increasing range of molecule types in development, not just a variety of natural and engineered proteins but also DNA-based drugs, viral therapies and drugs that combine biological and chemical approaches. While there is much commonality in the range of unit operations required to produce these molecules the complete processes will be very different. There is therefore a need to develop a means of manufacture that makes use of standardized unit operations and can be put

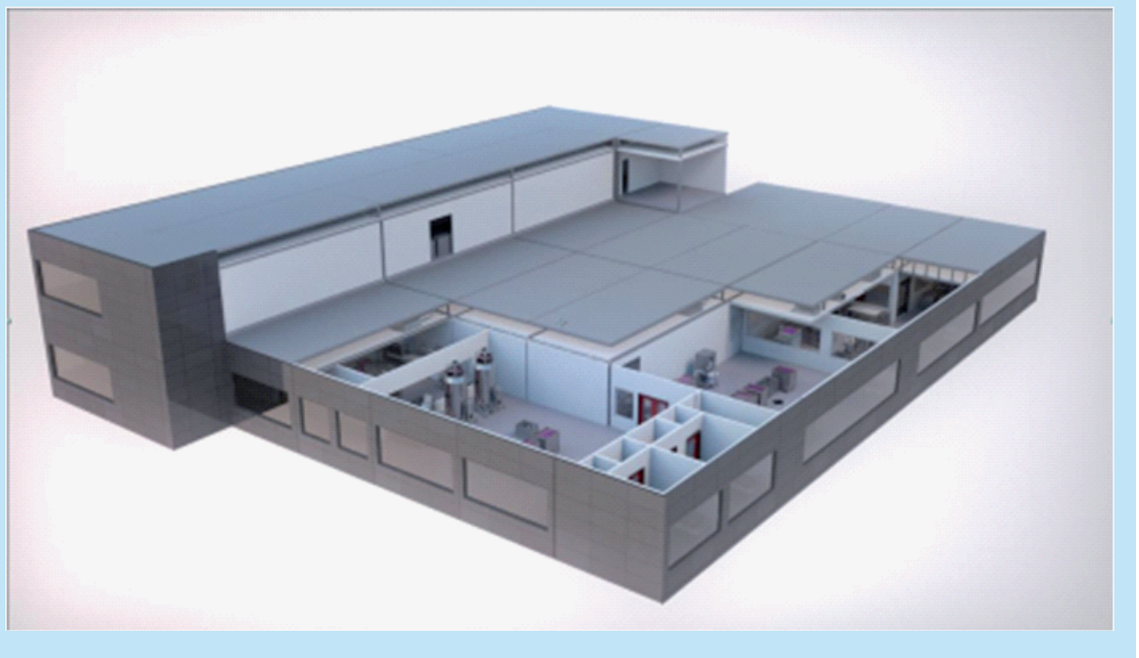

Figure 3. Modular interior of GE's KUBio Single Purpose Biopharmaceutical Factory:GE will prebuild the modules under cGMP specifications and deliver to the site of manufacture.
Image courtesy of GE Healthcare.

together in a flexible manner with additional capacity capable of being rapidly developed. This is in direct contrast to current production facilities which are still largely based on fixed equipment, have highly defined throughputs and are expensive and time consuming to commission. Also adding pressure for change here is the fact that many of this new generation of therapies have been designed to be highly potent and therefore potentially required in smaller batch sizes than those current plants are designed to manufacture.

A further factor is that as our knowledge of how an individual's genome interacts with disease progression and a biopharmaceutical treatment there will be an increase in stratified and even personalized therapies. This is likely to result in the requirement for multiple smaller batches of a range of treatments. Again this is not a model that fits with current manufacturing facilities designed as they are for the manufacture of large batches of a single product. Finding an economically viable way of meeting these manufacturing needs will be essential if the biopharmaceutical industry is to maintain its position.

Finally as new territories and markets open up for biopharmaceuticals there will be a need to broaden the geographical manufacturing base. The high levels of capital investment required for traditional facilities is likely to mean that an alternative type of facility will be required to fill this need.

Economic & timeline pressures

Biopharmaceuticals are generally expensive products for healthcare systems to provide. Though there are many contributory factors to the high cost it is undoubtedly the case that there is a significant contribution from the capital investment required to build manufacturing plants, the development costs of the therapy and the cost of goods to manufacture.

Traditionally plants have been large, fixed facilities based on fixed, largely stainless steel equipment. The cost to build and operate these facilities is high and the timeline required to bring them into market supply is long. A further problem is balancing the construction of a plant against the risks associated with drug development, risk of failure being significant up until and sometimes even after market approval. A type of manufacturing facility that is faster and cheaper to build and the components of which can be rapidly reconfigured to manufacture a different product is therefore highly desirable.

A final risk factor to be considered is that of encountering problems during the scale up process. Typically this process runs in parallel to the clinical trial process and is not necessarily on the critical path, problems can and do occur which cause delays to the supply of material for trials or market launch. An alternative manufacturing scenario using a scale out rather than scale up approach is therefore attractive as a means of mitigating these risks.

Given the factors outlined in this article, it is likely that over the next 10 years we will see a fundamental shift in the way we manufacture biopharmaceutical products. While current manufacturing plants will remain in operation for some time to come and there will always be a number of products for which large,

Executive summary

- Economic and technical challenges are forcing a rethink of how biopharmaceuticals are manufactured.

Current state of biopharmaceutical manufacturing

- Current biopharmaceutical manufacturing plants are largely based on large scale stainless steel 'fixed' technology and operate in batch mode. They are reliant on clean and steam in place technology and are expensive to build and operate.

Drivers of change

- Factors forcing a change in how biopharmaceutical plants are built and operated are:
  - The rise of stratified medicine and a new generation of engineered biopharmaceuticals – these factors will reduce batch sizes required and so be difficult to produce from current plants;
  - Geographic expansion of the industry and emerging markets – manufacturing plants will be required in new territories.

Economic pressures

- The biopharmaceutical industry is facing renewed economic pressure; there is a need to reduce cost of goods, capital investment costs and cost of development.
- The addition of manufacturing capacity has to be balanced against the clinical and commercial risks of failure of a new therapy.

Future state of biopharmaceutical manufacturing

- Future manufacturing plants are likely to consist of smaller, modular units that can be rapidly configured to the unit operations required for a particular drug. Units will be based on single use technology with more emphasis on continuous manufacturing.
- Production units may well be built centrally and then shipped to the site of production ready for operation.

stainless steel based facilities will be appropriate, for a new generation of products a different manufacturing paradigm will need to be found.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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