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Sustainability in the biopharmaceutical industry: seeking a holistic perspective

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Abstract

Biopharmaceuticals manufacturing is a critical component of the modern healthcare system, with emerging new treatments composed of increasingly complex biomolecules offering solutions to chronic and debilitating disorders. While this sector continues to grow, it strongly exhibits "boom-to-bust" performance which threatens its long-term viability. Future trends within the industry indicate a shift towards continuous production systems using single use technologies that raises sustainability issues, yet research in this area is sparse and lacks consideration of the complex interactions between environmental, social and economic concerns. The authors outline a sustainability-focused vision and propose opportunities for research to aid the development of a more integrated approach that would enhance the sustainability of the industry.

Keywords

Biopharmaceuticals

Sustainability

Integrated perspective

Industrial ecology

Holistic approach

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1. Introduction

Biopharmaceuticals, pharmaceutical treatments produced from biological sources, are an important and evolving component of the modern healthcare system. Table 1 details a variety of biologically sourced pharmaceuticals and their therapeutic indications.

The first biopharmaceutical treatments can be considered to have developed in the late 19th century, with the development of the first vaccines and the proliferation of safe, repeatable blood transfusions. The early 20th century then saw the discovery and application of products such as insulin, derived from animal sources (and with concomitant risk of adverse allergic reaction to treatment), and penicillin, the industrial scale production of which was developed during the second world war. A paradigm shift occurred in 1973 with the discovery of recombinant DNA technology by Cohen and Boyer, and the fruits of this discovery were realised in 1982, with the regulatory approval of recombinant human insulin (Humulin: Eli Lilly & Co, 1982) produced by the genetic engineering of *E. coli*. The ensuing decades have seen the expanded application of recombinant DNA technology to develop treatments for a wide variety of conditions, many of which are chronic, debilitating disorders with significant impacts on quality of life and life expectancy. The 21st century has brought about the commercial approval by the US Food & Drug Administration (FDA) of the first gene therapy (Luxturna: Spark Therapeutics, 2017) treating congenital blindness. Successful commercialisation of gene therapy represents another paradigm shift in biopharmaceutical development, with the prospect of advanced treatments for a large variety of disorders such as haemophilia and mucopolysaccharidosis providing therapeutic benefit (favourable response to treatment) with a single dose, in comparison to the prolonged use required for contemporary treatments.

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Table 1: Examples of biologically derived pharmaceutical products

Era	Description	Examples	Therapeutic Indications
19th Century – Present	"Conventional" biotech products Isolated from animals or humans	Blood and blood components e.g. blood plasma	Blood transfusions
		Stem cell therapies e.g. bone marrow transplants	Leukaemia
		Immunoglobulins	Inducing immunity for diseases such as tetanus following exposure or in high-risk individuals
19th Century – Present	Vaccines Provides immunity to certain diseases	Inactivated Attenuated Toxoid Subunit Conjugate	Measles Influenza Tetanus Human papilloma virus Hepatitis
1982 – Present	Recombinant biopharmaceuticals Produced using recombinant DNA technologies	Blood factors e.g. Factor VIII and Factor IX	Haemophilia
		Growth factors e.g. human growth hormone, gonadotrophins	Growth hormone deficiencies Breast cancer Prostate cancer Endometriosis
		Cytokines e.g. interferons,	Anaemia

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Era	Description	Examples	Therapeutic Indications
		interleukins, erythropoietin	Bone cancer Hepatitis Multiple sclerosis
		Enzyme replacement therapies	Lysosomal storage disorders e.g. mucopolysaccharidosis
		Monoclonal antibodies	Cancers Autoimmune disorders
2017 – Present	Gene Therapies Introduction of foreign nucleic acid into cells to induce therapeutic effects	Somatic cell gene therapy	Haemophilia Congenital blindness Leukaemia

Biopharmaceutical drugs may be categorised based on their source and therapeutic indication, as described in Table 1, or based on other factors. Table 2 describes three categories of biopharmaceuticals.

Table 2: Terms used to describe treatments

Type	Description	Examples
Blockbuster	Drug with revenues exceeding $1 billion in a given year.	Humira Enbrel

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Type	Description	Examples
		Remicade
		Rituxan
Biosimilar	*Similar biotherapeutic products,* or biosimilars, are drugs which are "similar" to existing products in terms of therapeutic efficacy (the benefit to the patient from the treatment), safety (avoidance of adverse effects) and structure. Due to the immensely complex nature of biologic molecules, it is prohibitively expensive and scientifically difficult to characterise molecules. Therefore, development of *similar biotherapeutic products* to established drugs upon patent expiration relies on proving equivalency of therapeutic benefit, manufacturing process and safety. The result are molecules which are not *identical* to established drugs, but exhibit *similar* therapeutic benefits and safety as established drugs.	Inflectra Ixifi Amjevita Mvasi
Orphan	Orphan drugs are developed for treatment of conditions with small patient populations, defined by the European Medical Agency (EMA) as being: life-threatening or chronically debilitating; having a prevalence of less than 5 in 10,000; and, having a lack of treatments delivering significant benefit to patients. Regulatory agencies offer market exclusivity, tax incentives and/or other financial incentives to promote orphan drug development, as otherwise it would be prohibitively expensive to do so.	Revlimid Rituxan Soliris Pomalyst

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In this review, a thorough examination of the biopharmaceuticals manufacturing industry is conducted from a sustainability viewpoint. First, the economic and technological state-of-the-art of biopharmaceuticals manufacture is detailed. Identification of the key trends in the industry is subsequently explored, namely the pursuit of integrated, continuous manufacturing utilising perfusion cell cultures and continuous downstream processing, along with the proliferation of single use technology and the advent of new modalities of biopharmaceuticals such as gene therapies. The established research in the area of sustainability applied to the biopharmaceuticals manufacturing industry is then assessed, and opportunities for further research highlighted. Finally, a vision of a sustainability-focused biopharmaceuticals manufacturing industry is outlined.

2. Economic and technological state-of-the art of biopharmaceutical manufacture

2.1 The biopharmaceutical industry through an economic lens

The manufacture of substances of therapeutic value from biological sources has evolved since the regulatory approval in 1982 of recombinant human insulin (Humulin; Eli Lilly & Company) to a behemoth industry almost four decades later, projected to be worth $445 billion by 2019 (Deloitte, 2016). Despite a lag in regulatory approvals following the initial breakthrough by Humulin, there has been a near-constant rate of drug approvals since 1995, with 45 new substances approved in the period 2010-2014 (Walsh, 2014) and a near-record 56 approvals by FDA in 2017 (DeFrancesco, 2018). That year also saw the FDA approval of the first gene therapy (Luxturna: Spark Therapeutics, 2017) for congenital blindness, a significant milestone (DeFrancesco, 2018). A significant portion of these approvals were for orphan drugs, which, due to their small patient populations, can require

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significant compensatory pricing to recoup research and development costs (Love et al., 2013). In addition, biosimilars are now achieving regulatory approval, providing alternatives to established blockbusters. 28 biosimilars had been approved in Europe as of June 2017 (Moorkens et al., 2017) and it is anticipated that biosimilars will earn a market value of up to $35 billion by 2020 (Deloitte, 2016), providing potential savings of up to $100 billion (Moorkens et al. 2017). With reports of as many as 671 potential first-in-class drugs in development pipelines (PhRMA, 2018), many of which exist in the gene therapy and orphan spaces, the biopharmaceutical sector appears set to continue to grow as more and more innovative treatments gain regulatory approval.

The biopharmaceutical industry is not without its risks, however. While drug development pipelines appear healthy, the cost of bringing a drug to market continues to rise, now exceeding $2.5 billion (pre-approval cost estimate; DiMasi et al., 2016). This contributes greatly to the exorbitant pricing of biopharmaceuticals with the cost of actual drug manufacture estimated to be as low as 5% of total price (Love et al., 2013). Indeed, biopharmaceuticals are estimated to cost on average $45 per day in comparison to $2 a day for small-molecule treatments (Walsh, 2014). Competition from biosimilars may drive a decline in price disparity of circa 10-30%, though this still falls short of established pricing for small-molecule products (Love et al., 2013). The advent of gene therapy requires additional considerations due to the nature of treatment. Gene therapies may offer a “cure”, that is, a single treatment may provide clinical benefit for long periods, potentially indefinitely (Brennan and Wilson, 2013). As a result, where conventional treatments provide steady income streams for biopharmaceutical manufacturers over a patient’s lifetime, gene therapies may require a single payment for a lifetime benefit (Brennan and Wilson, 2013). In order to recoup the huge clinical development costs, prices in excess of $1 million upfront could be warranted, risking public outcry (Brennan and Wilson, 2013). While this may be ameliorated by utilising novel policies including performance related pricing and annual payments (Brennan and Wilson, 2013), a historical assessment of the financial performance of biotechnology companies (Thakor et al., 2017) with this conundrum in mind proves foreboding. As evidenced by Thakor et al., biotechnology companies

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have consistently underperformed in the market and shown propensity for unprofitability (Thakor et al., 2017). A large part of this is a result of scientific challenges in drug development, multiple contenders for treatment of the same illness facing approval at once, and the falling-off of financing during periods of economic downturn (Thakor et al., 2017). Should gene therapies lead to large initial uptake and subsequent decline, investors may baulk at the risk of a "boom-and-bust" scenario, of the sort that the industry has historically demonstrated, and financing of future treatments may be critically compromised.

2.2 Technological considerations for biopharmaceuticals manufacturing

2.2.1 Biopharmaceutical drug structure

In contrast to chemically synthesised drugs, the structures of which are known and whose molecular mass does not often exceed about one kilodalton (kDa), biopharmaceutical drugs are often complex proteins, with molecular masses orders of magnitude greater. As a result of this molecular size and complexity, additional considerations are required of biopharmaceuticals compared to chemically synthesised drugs, including immunogenicity (provocation of immune response on introduction to body), folding and modification of molecules, and sensitivity of molecules to temperature, pH, enzymatic degradation and other conditions encountered during manufacturing.

The simplest biopharmaceuticals are proteins such as insulin (molecular weight about 5 kDa), a hormone which regulates metabolism in the human body, and somatotropin, or human growth hormone (molecular weight about 22 kDa), which stimulates cell reproduction, regeneration and growth in the human body. Such (relatively) simple proteins are biologically active in the human body following protein biosynthesis in the host cell without need for further chemical modification

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following translation of messenger RNA in the ribosome. Simple proteins such as these composed approximately 7.5% (48 of 640) of all EMA approved drugs in 2012 (Kyriakopoulos and Kontoravdi, 2013).

Increasing complexity of biopharmaceutical proteins is due to the requirements of post-translational modification by the host cell following the protein's manufacture in the ribosome of the host cell. Post-translational modification refers to the modification, often by enzymatic reactions, of proteins following translation of messenger RNA in the ribosome to generate the initial polypeptide chain, and is present in many biopharmaceutical proteins in the form of glycosylation, which is the modification of the protein by addition of a carbohydrate molecule to the protein structure. Glycosylation results in positive consequences for protein folding and stability, and is a vital component of the manufacturing process as glycosylated proteins have lower immunogenicity and increased therapeutic efficacy and stability in the body. Such proteins may be referred to as glycoproteins, and constituted 12.5% (78 of 640) of all EMA approved drugs in 2012, the most common of all biologically-derived drugs (Kyriakopoulos and Kontoravdi, 2013). A large proportion of glycoproteins are therapeutic enzymes, which are administered as enzyme replacement therapies (ERT) to patients which lack or have low levels of specific enzymes. Another prominent category of glycoproteins are monoclonal antibodies (mAbs), which are used to bind to targeted cells or proteins in the human body in order to identify and/or destroy them, and are used in the treatment of cancer and autoimmune disorders. Glycoproteins have molecular weights ranging from about 30 kDa for erythropoietin (EPO), a cytokine which stimulates red blood cell production, to in excess of 100 kDa, with monoclonal antibodies having molecular weight of the order of about 150 kDa.

The most complex biopharmaceutical products are those produced by viral propagation, with viral vectors for gene therapy of particular note. These treatments utilise relatively colossal molecules such as viral capsids, with the adeno-associated virus capsid having a molecular weight in excess of about 1 MDa. The mechanism of action of gene therapy differs from that of existing

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biopharmaceutical treatments. Currently, many biopharmaceuticals are designed to replace or supplement substances in the body that are not naturally produced, often due to a defective or missing gene. As such, ongoing administration of manufactured versions of these substances is required to provide ongoing therapeutic benefit. In the case of gene therapy, the defective or missing gene is replaced with a correctly functioning gene, allowing for the body to produce the previously absent substance over a longer, and potentially indefinite, period of time. The introduction of this correctly functioning gene is accomplished primarily through the use of viral vectors, viruses which have been modified to suppress possible pathogenic activity and transduce the target gene into the human body's cells. This process is complex, and requires introduction of the gene to specific cells to ensure sufficient uptake to allow for prolonged production of the target substance.

2.2.2 The biopharmaceuticals manufacturing process – current state

Contemporary production of biopharmaceutical substances is accomplished through the use of large-volume stainless-steel vessels in which a cell culture ferments a growth medium to produce the target substance, often a protein or, in the case of certain vaccines or gene therapies, a virus. This substance is then separated from the cell supernatant in a series of purification stages employing variously: centrifugation, depth filtration, tangential flow filtration, homogenisation and chromatography to achieve high levels of purity and identity of the target substance. The majority of biopharmaceuticals are administered parenterally. To ensure patient safety, there is thus a requirement for microbiological controls including micro- and nanofiltration stages to remove pathogenic bacteria and viruses, while Water for Injection (WFI) is utilised for product and cleaning waters. Figure 1 shows an overview of a typical biopharmaceutical manufacturing process.

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Here: **Figure 1: Overview of a typical biopharmaceutical manufacturing process, encompassing cell culture by fed-batch or perfusion; clarification of cell culture fluid by centrifugation, depth filtration and/or homogenisation; purification to drug substance by chromatography and tangential flow filtration, with added steps to inactivate and remove micro-organisms; and sterile filling of the drug substance to final drug product**

There are numerous options of cell lines which have been adapted for use in biopharmaceutical manufacture. Cell cultures often used include bacterial cultures such as *E. coli*, mammalian cultures such as Chinese hamster ovary (CHO), baby hamster kidney (BHK) and human embryonic kidney 293 (HEK 293), plant cultures and insect cultures. The selection of cell culture is determined during process development and is influenced by the type of substance being produced. For example, glycoproteins are produced primarily by mammalian cell culture as mammalian cells can perform post-translational modifications similar to those provided by human cells (Kyriakopoulos and Kontoravdi, 2013). Proteins which do not require significant post-translational modification may be produced in bacterial or yeast cell cultures such as *E. coli* or *S. cerevisiae* which are simpler and more productive than mammalian cells. For the production of viral vectors for gene therapy, mammalian cell culture is most popular (Emmerling et al., 2016). The production of adenovirus and adeno-associated virus is documented extensively in HEK 293 cell culture (Robert et al., 2017; Grieger et al., 2016; Cortin et al., 2004; Chahal et al., 2014; Kamen and Henry, 2004) as the HEK 293 cell culture expresses certain proteins required for adenovirus and adeno-associated virus propagation.

Cell culture fermentation is accomplished usually either on a fed-batch or perfusion basis. Fed-batch cell culture is composed of scale-up stages through a number of bioreactors of increasing volume until the culture reaches maximum cell density in the production bioreactor, the volume of which can exceed 40,000 litres. The cell culture is terminated prior to its death phase, and the bioreactor contents are harvested. In contrast, perfusion cell-culture operates at pseudo-steady-state. The cell culture is scaled up to an optimum cell density and inoculated in the production bioreactor. Fresh growth medium is added continuously, and cell culture fluid is harvested at the same rate. Cell

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retention devices are utilised to maintain the cell density in the bioreactor, and constant cell bleeds may also utilised to prevent densities reaching unsustainable levels.

Purification is carried out generally in a batchwise manner. Harvested cell culture fluid is clarified by centrifugation or depth filtration to remove cellular debris. If the target substance is produced intracellularly, as in the case of many bacterial cultures, homogenisation may be required to lyse cells and release the substance. Tangential flow filtration may be utilised to concentrate the cell culture fluid and exchange the depleted growth medium with purification buffers. Chromatography is then utilised, with three chromatography stages generally utilised: capture, intermediate and polishing. The target substance is separated from the cell culture fluid by charge (ion exchange), hydrophobicity or hydrophilicity (hydrophobic/hydrophilic interaction), affinity (immobilised metal or Protein A) or by size (size exclusion) to name but a few. The solution is treated to inactivate enveloped viruses which may be present, and tangential flow filtration is applied to exchange process buffers with drug formulation substance to stabilise substance for storage. The final solution may then be filtered to remove non-enveloped viruses and other micro-organisms prior to filling.

3. Future trends in biopharmaceutical manufacture

3.1 Fed-batch or perfusion?

The choice of fed-batch or perfusion cell cultures under current manufacturing technology is typically a function of product stability and titre. Studies documented in the literature identify an association of extended cell culture residence times with impacts to glycosylation profile (Pacis et al., 2011), heterogeneity (Liu et al., 2016) and on aggregation (Joshi et al., 2014), with the cause of these impacts linked to exposure of the product to specific enzyme activity within the cell culture. These can significantly impact critical quality attributes of the product such as biological activity and immunogenicity (Costa et al., 2012; Liu et al., 2016) and concomitant risks to therapeutic efficacy and patient safety. Monoclonal antibodies, which make up a significant portion of approved biopharmaceuticals (Walsh, 2014), are stable proteins, and can withstand extended durations under

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the operating conditions of the bioreactor (Konstantinov, 2006). Thus, they are predominantly produced using the fed-batch cell culture mode, in which residence times may exceed 14 days. In contrast, many other recombinant glycoproteins are unstable, prone to formation of dimers or aggregates, and therefore must be produced in perfusion cell cultures to prevent degradation (Konstantinov, 2006; Meuwly et al., 2006). The residence time in perfusion cell culture mode is much shorter than fed-batch mode, with residence times exceeding 1 day unusual. In many cases, the target substance falls somewhere between these scenarios and the choice may be determined by factors such as established facility infrastructure (Konstantinov, 2006). Table 3 details a comparison of fed-batch and perfusion cell cultures.

Table 3: Comparison of fed-batch and perfusion cell cultures

Fed-batch culture	**Perfusion culture**
High protein/glycoprotein titres – >1 g/L	Low protein/glycoprotein titres – 10-100 mg/L
Low viral genome titres – ~$1x10^{12}$ vg/L	High viral genome titres – ~$5x10^{12}$ vg/L
Higher volumetric scalability	Increased versatility
Requires stable substances	Higher cost-of-goods (growth medium dependent)
Lag phase upon inoculation	Consistent product quality
Downstream bottlenecks	

For the production of viral vectors for gene therapy, the required viral genome (vg) titres for therapeutic dosage are documented for adenovirus and adeno-associated virus as being higher for perfusion systems over batch and fed-batch systems (Kamen and Henry, 2004; Cortin et al., 2004; Grieger et al., 2016). This is due to the "cell-density effect" (Kamen and Henry, 2004) whereby a limit in viral genome cell-specific production at high cell densities is reached due to growth medium limitations. This is analogous to challenges facing the adoption of perfusion technology for the

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production of proteins and glycoproteins, however, interestingly, in this case the reduction in titre is instead observed in batch and fed-batch modes.

Industry trends indicate a move toward the implementation of perfusion cell cultures, resulting from three main drivers:

1. Increased product quality – operating at pseudo-steady-state contributes to improved product quality (Konstantinov, 2006; Meuwly et al., 2006). Additionally, significant portions of development drugs in pipelines are heavily glycosylated glycoproteins (Walsh, 2014), which may require a perfusion cell culture to maintain acceptable levels of product quality.

2. Increased versatility – fed-batch cultures typically operate at levels exceeding 10,000 litres. Facing pressure from biosimilars, facilities which once produced large volumes of blockbuster drugs may now be retasked to produce multiple products. Similarly, the explosion of the orphan drugs market may warrant small-volume campaigns as opposed to lengthy production of single products. Implementing a perfusion cell culture may remove requirements for facility redesign and capital expenditure at the cost of reduced titres (Pohlscheidt et al., 2013).

3. Lower volumetric requirements – the commercialisation of gene therapy providing indefinite therapeutic benefit from a single-dose may impact the volumetric production capacities required for treatment of even large patient populations. While initial uptake following approval may require large volumes, a drop-off is likely as no further dosages are required over long periods. This may impact the likelihood of any company constructing large-volume manufacturing facilities requiring large capital expenditures. Furthermore, with the potential for gene therapies to target existing conditions treated by proteins or glycoproteins on an

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on-going basis, there is potential for large reduction in demand for existing treatments, making existing manufacturing strategies relying on large-volume production redundant.

A number of studies document comparisons of fed-batch and perfusion cell cultures from an economic and product quality perspective (Meuwly et al., 2006; Yang et al., 2014; Klutz et al., 2016). The outcome of these studies indicates higher productivity from fed-batch cultures (Meuwly et al., 2006), while the application of perfusion cell cultures exhibits improved product quality (Yang et al 2014). Fed-batch cell cultures proved more economically viable (Meuwly et al., 2006; Klutz et al., 2016). In order to achieve parity with fed-batch cultures, titres of perfusion cell cultures must improve to match those of fed-batch cultures, using a move known as "push-to-low" (Konstantinov, 2006). The "push-to-low" method refers to the iterative reduction in perfusion rate, the rate at which fresh growth medium is supplied and harvested product removed. By reducing the perfusion rate, a greater residence time is achieved and increased utilisation of growth medium is seen, yielding higher titres of product. Barriers to reducing the perfusion rate include product stability under increasing residence times, the quality of growth medium, maximum cell density achievable and the capacity of the cell retention device implemented (Konstantinov et al., 2006).

3.2 Single-use technology

Single-use technology has emerged as an alternative to contemporary stainless-steel manufacturing technologies. Composed primarily of plastics, single-use technology offers the prospect of flexible, multi-product facilities by elimination of the risk of product carry-over, which is of major regulatory concern (EudraLex, 2015). Additional benefits in the form of reduced capital costs and potential for debottlenecking during facility changeover make single-use technologies an attractive proposition (Shukla and Gottschalk, 2012). Table 4 describes the benefits and challenges of single-use technology.

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Table 4: Single-Use Technology – Benefits and Challenges

Benefits	Challenges
Elimination of CIP and SIP requirements	Potential for leachables and extractables
Reduced facility footprint	Limited scalability
Increased flexibility for changeover	Increased supply-chain risk
	Not fully realised for all unit operations
	Increased operating costs
	Single-use instrument calibration and reliability
	Increased potential for human error
	Robustness of materials of construction
	Potential increased contamination risk during perfusion campaign
	Increased/ongoing material consumption and waste disposal of non-recyclable single use equipment waste

Challenges to the uptake of single-use technology include the risk to patient safety from potential leachables and extractables, the volumetric limit of about 2000L and the additional supply-chain risk due to the limited number of suppliers (Shukla and Gottschalk, 2012). A paucity of literature exists concerning the operation of perfusion cell cultures over long periods in single-use bioreactors, with a duration of 28 days documented by Klutz et al (2015), while periods of up to 200 days are utilised in the industry (Pohlscheidt et al., 2013). Extended operation of perfusion campaigns poses risks from contamination, due to additional operator interactions, and potential for increase in leachables and extractables due to exposure of the bioreactor container for extended periods at elevated

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temperatures to the cell culture. While single-use technology is available for all unit operations, the capital costs associated with some equipment, such as TFF cassettes (~$10,000/$m^2$) and chromatography resins (~$5000/L), limits any justification for the use of such equipment in a truly single-use fashion. Finally, utilising single-use technologies poses significant economic and environmental challenges due to the increased volumes of solid waste requiring disposal. Much of this is composed of plastics which are not readily recyclable, and so are removed to landfill or incineration at end of life, which poses sustainability challenges.

3.3 Continuous Downstream Processing

While continuous cell culture processing in the form of perfusion cell culture is well-established in the biopharmaceutical manufacturing sphere, continuous downstream purification processes are uncommon, with few documented in literature. While the current paradigm is for large, fed-batch cell cultures feeding similarly large batch purification trains, the previously mentioned economic risks to the industry from biosimilars and unsustainable treatment costs has led to a desire for increased volumetric productivity, reduced capital expenditures and an overall reduction in cost of goods (Klutz et al., 2015b). While single-use technology satisfies this in part, by reducing facility footprint and capital expenditures, it does not impact the issue of volumetric productivity (Klutz et al., 2015b). As a result, the adoption of continuous manufacturing becomes attractive. This can be accomplished by employing perfusion cell culture in tandem with continuous purification unit operations such as tangential flow filtration and chromatography. Fully continuous processes have been documented in the literature (Klutz et al., 2015a; Klutz et al., 2015b; Walther et al., 2015) and continuous chromatography operation also has been documented (Steinebach et al., 2016). Table 5 describes the benefits and challenges of implementing continuous purification.

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Table 5: Continuous downstream purification: benefits and challenges

Benefits	Challenges
Increased volumetric productivity	Potential economic benefits may not be realised
Increased separation efficiencies	Regulatory challenges from product licence changes
Increased product quality	Development of reliable methods for all unit operations
Reduced capital expenditures	Increased complexity
Debottlenecking the process	

Continuous purification processing is plausible utilising current technologies (Jungbauer, 2013). Significant challenges exist to its implementation at a commercial scale, ranging from technical issues including the development of a reliable method of incubation for steps such as viral inactivation and diafiltration (Przybycien and Titchener-Hooker, 2015) to uncertainties surrounding the predicted economic benefits being realised at commercial scale (Jungbauer, 2013) and, perh aps most significantly, the regulatory requirements to change product registrations (Przybycien and Titchener-Hooker, 2015). Until commercial scale applications of continuous purification processing are implemented and analysed, its development and uptake may remain inhibited by established attitudes within the industry.

3.4 Drug discovery and optimisation

From a new drug discovery perspective, of particular promise is gene therapy, the first of which obtained approval by FDA in 2017 following an estimated 1,992 gene therapy clinical trials worldwide in the period 1989-2013 (Walsh, 2014). While gene therapies offer breakthrough

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treatments, they may be beset by economic issues, as noted in previous sections, and by previous challenges to patient safety, which culminated in the death of a patient during clinical research in 1999 (Wirth et al, 2013) and which stymied efforts to implement the technology. It remains to be seen whether gene therapies can be realised on a grand scale.

For existing drugs, challenges exist from therapeutic efficacy and the rise of biosimilars. Currently, many approved drugs require significant doses (>1 mg/kg) to deliver therapeutic effects, resulting in patients requiring annual doses in gram-quantities (Love et al., 2013). Potency and efficacy of these drugs is affected by variations in glycosylation profile, heterogeneity and aggregation (Costa et al., 2012; Liu et al., 2016) which contribute to the necessity for high dosages to be delivered. Improvement of the therapeutic efficacy by increased uniformity of product and concomitant reduction in required therapeutic dosage is essential to enable greater access and reduction in price of established products (Love et al., 2013). The challenge of this may be solved by increasing process understanding from current manufacturing processes, or by discovery and approval of biosimilars exhibiting greater therapeutic benefit. These needs may place pressure on companies to improve current approved products, or face competition from biosimilars with lower-costs and/or improved therapeutic benefits.

In summary, the future of biopharmaceuticals manufacturing is tending towards small-volume, high-potency treatments produced in flexible, multi-product facilities utilising continuous manufacturing and single-use technologies, as illustrated in Figure 2.

Here: **Figure 2: Overall trend in biopharmaceutical research and innovation indicating a move towards high-potency, novel treatments; production using single-use technology; and realisation of continuous manufacturing throughout the manufacturing process**

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4. Sustainability considerations and research in the biopharmaceutical industry

4.1 Reflections on sustainability for the biopharmaceutical industry

It has been suggested that sustainability, as a concept, entails facilitating the potential for life to flourish on this planet over a prolonged period of time, that is, for many generations to come (Ehrenfeld, 2009). While there are many ways of representing sustainability, the concentric model shown in Figure 3 reminds us that economic activity is embedded within human society, which in turn exists within the parameters of the physical environment.

Here: **Figure 3: Concentric circle model of sustainability which shows the economy existing within society, which exists within the environment (Adapted from Lozano, 2008)**

One of the key aspects of sustainability thinking is to enable an "integrational perspective" (Lozano, 2008) or an "integrative approach" (Hedlund-de Witt, 2013, 2014; Byrne, 2016); that is, one which recognises the influence and impact of disparate (though ultimately interconnected) elements within the operation of a larger complex system. Under the prevailing market-based socio-economic paradigm that shapes our world, microeconomic benefit-risk evaluation is the usually singular factor in decision-making (with the question of how and to whom the benefits and risks are allocated being a contested matter). Frequently, therefore, the societal and environmental impacts of human activities are absent from decision-making or represent marginal considerations compared to those of investors' financial "bottom line". The consequences of 'business-as-usual' economic practices have been sharply highlighted at the time of writing by reports on the pace and implications of climate change (IPCC, 2018); the extraordinary loss of biodiversity (WWF, 2018); and on emerging threats to global freshwater availability (Rodell et al., 2018). Consequentially, given increasing recognition of such existential threats, many businesses are now seriously examining their production systems in order to minimise environmental damage arising from their practices.

How, then, can sustainability thinking make itself felt in biopharmaceuticals manufacturing? By their very nature, biopharmaceuticals are intended to bring about improved quality of life and life

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expectancy, often for debilitating diseases in vulnerable patients such as children. However, many existing business and scientific practices within the pharmaceutical industry as a whole, and including the biopharmaceutical sector, have served to degrade the environment and erode public trust in pursuit of profitability. There are a number of examples of such practices, some of them deliberate, others a consequence of unforeseen outcomes. For example, the increase in pharmaceutical uptake and subsequent excretion by patients to wastewater has resulted in unintended consequences for the aquatic environment through disruption of biological processes resulting in damage to some aquatic species (Fabbri, 2014). Additionally, pharmaceutical effluents have been implicated in the development and proliferation of antimicrobial-resistant strains of micro-organisms (Milmo, 2017). A key obstacle to proposed remedies of the latter practice is the additional costs associated with achieving environmentally benign manufacturing processes, which could impact access to generic forms of established drugs, particularly antibiotics (Milmo, 2017). Pharmaceutical pricing is a universal problem with impacts on access across high-income and low-income countries alike (Hurst, 2017). Accusations of price-gouging are rife, with the case of Turing Pharmaceuticals' 5000% increase in pricing of pyrimethamine (Daraprim; Turing Pharmaceuticals, 2017) making headlines worldwide due to the apparently exploitative practices it embodied (Saltiel and Finnefrock, 2018). While there may be a variety of reasons for pharmaceutical pricing, such as market size, recoup of development costs and supply chain problems, the conflation of any and all pricing strategies with more infamous examples has led to a reduction in public trust in pharmaceutical producers applying fair costs on their products. Furthermore, transparency regarding the treatments provided by pharmaceutical companies is controversial, with suggestions by some authors that clinical trial details are often published only if positive, accusations that clinical trial data published has been cherry-picked to strengthen arguments for approval, and that patient safety is compromised by a lack of public availability of regulatory hearings, investigations and approvals (Löfstedt and Way, 2016). From an environmental perspective, growth in the number and volume of biopharmaceuticals requiring manufacturing and transport globally increases the cradle-

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to-grave impact through increased emissions to land, air and water and greater usage of natural resources. The aforementioned issues combine to impair the sustainability of the pharmaceutical sector as a whole, driven by environmental degradation and poor socio-economic relationships, the former of which leads to the destruction of the natural ecosystem humanity relies on to survive and thrive, and the latter of which corrodes societal trust and reduces and removes safe, equitable access to treatment worldwide.

Away from nefarious practices, the "business-as-usual" approach to biopharmaceutical innovation and manufacture also contribute to increased sectoral fragility. The rate of approval of biopharmaceuticals has maintained a constant trajectory since the approval of Humulin in 1982, with FDA approvals in 2017 reaching a near-record high (DeFrancesco, 2017). While each approval is a milestone in the treatment of disease, there are corresponding impacts to the environment and society. As previously discussed, the financial success of biopharmaceutical manufacturers is contingent on strong pipelines and gaining regulatory approval for new products on a consistent basis (Thakor et al., 2017). This has resulted in spiralling development costs at greater than the rate of inflation (DiMasi et al., 2016) and resultant increased pricing to recoup these costs, requiring greater investment from governments and impinging on access to treatments.

Overall, in order to promote a more sustainable sectoral model, the manifestation and application of sustainability thinking (economically, socially, environmentally and ethically) in the biopharmaceuticals manufacturing sphere is required to address the socio-economic and ethical-environmental challenges posed by contemporary manufacturing, innovation and economic philosophies in order to develop and deliver accessible treatments to those afflicted by disease globally.

4.2 Established research

Research in the area of biopharmaceuticals regarding the environmental impacts resulting from their manufacture is not well-documented, as is evidenced by scant coverage of this in the literature.

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Pollock et al. (2013) compared fed-batch and perfusion cell culture processes under environmental uncertainty, determining that the fed-batch cell culture scenario performed better from an environmental perspective as a result of reduced water consumption and consumable usage. Pietrzykowski et al. (2015) conducted a detailed life cycle assessment of the production by fed-batch cell culture of a monoclonal antibody under single-use and conventional stainless-steel modes of operation. The result of this analysis indicated reduced environmental burden from the single-use process across a variety of operating scales due to the reduced need for water and steam utilities associated with the elimination of cleaning and sterilisation procedures, which outweighed the increased solid waste disposal requirements associated with the increased use of single-use technologies. Bunnak et al. (2016) performed a life cycle assessment of the production of a monoclonal antibody under fed-batch and perfusion modes of operation, drawing the conclusion that the fed-batch process was more environmentally friendly when the perfusion process pooling duration, the interval at which harvested material was combined and sent for purification, was four days, but became less environmentally friendly when extended to eight days. Finally, Conley et al. (2017) conducted an evaluation of eco-friendly detergents for enveloped virus inactivation. Triton X-100 is used by many biopharmaceuticals manufacturers in conjunction with an organic solvent to inactivate enveloped viruses by disrupting their lipid membranes and rendering them inert. Triton X-100 may degrade to an alkylphenol upon discharge to aquatic environments, with resultant impacts as an endocrine disruptor on aquatic species and the wider environment. Conley et al. (2017) conducted a study to determine whether an eco-friendly detergent could be implemented to replace Triton X-100, and determined that lauryldimethylamine-N-oxide (LDAO) could be substituted for Triton X-100 due to its comparative ability to inactivate enveloped viruses and low ecotoxicity. While this was not a quantitative study as per Bunnak et al. (2016) or Pietrzykowski et al. (2015), it is noteworthy due to its potential to eliminate toxic substances from the biopharmaceutical manufacturing process.

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To summarise, the major conclusions stemming from the established research in the area indicate that fed-batch cell culture processes have reduced environmental impacts than perfusion cell culture processes (under certain conditions), primarily due to the increased water consumption associated with perfusion cell cultures, and also that single-use technologies are more environmentally benign than conventional stainless steel, with the increased solid waste generated offset by a reduction in energy usage associated with cleaning and sterilisation processes. Additionally, consideration for eliminating toxic substances has been documented, in the case of a particularly hazardous substance (Triton X-100), however investigation of other pollutants is not present in the literature.

5. Next steps for sustainability thinking in the biopharmaceutical industry

While established research in the area provides some conclusions with regard to the environmental implications of biopharmaceutical manufacture under diverse modes, there is scant research informing stakeholders of the preferable manufacturing modes from an integrated perspective incorporating the three core facets of sustainability thinking: economy, society and the environment. By contrast, investment decisions in biopharmaceutical production are to date guided almost exclusively across the industry by financial cost benefit analysis and do not even take into account broader environmental issues such as around water or material consumption. As described by Ramasamy et al. (2015), there does not exist a decision-making framework within the biopharmaceutical industry which incorporates environmental concerns, with few life cycle assessment studies completed for the biopharmaceutical industry in comparison to industries such as the energy sector for which more than five hundred exist. From a societal viewpoint, impacts from the biopharmaceutical manufacturing life-cycle have not yet been comprehensively documented, but rather tackled on a piece-meal basis through the use of process-level tools such as life-cycle costing for economic sustainability (Bunnak et al., 2016) and at patient level, through well-documented concerns over drug pricing and availability (Love et al., 2013; Garattini and Padula,

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2018). It is clear, then, that integrated, system-wide evaluation is required to determine the impact of biopharmaceutical manufacture from an integrative sustainability viewpoint.

Of interest for this evaluation are industrial ecology models proposed by Allenby and Graedel (Allenby and Graedel, 2010). Industrial ecology is defined as the study of material and energy flows through industrial systems, and can be understood as the interaction between the biosphere, the environment on which all life depends to survive, and the technosphere, the sphere of technological development on which humanity depends to transform raw materials from the biosphere into useful goods and services, with concomitant wastes released to the biosphere as a result. Modelling of the relationship through an industrial ecology lens may be achieved through use of the following (Allenby and Graedel, 2010):

- Class 1 model - Model incorporating the technological, environmental or human aspect singularly (Examples include economic evaluations, process modelling and environmental impact assessments).
- Class 2 model - Model incorporating two of the technological, environmental or human aspects (Examples include life cycle assessment, life cycle costing and eco-design).
- Class 3 model - Model incorporating technological, environmental and human aspects in a holistic fashion

The endeavour of developing a Class 3 model for biopharmaceutical manufacture could be pursued to determine the cradle-to-grave impacts holistically, beginning with the following:

- ❖ Further documentation of the environmental impacts of diverse modes of operation including perfusion and fed-batch cell cultures, batch and continuous purification, and single-use and conventional technologies, and possible applications of design-for-environment principles
- ❖ Evaluation of the trends in biopharmaceutical manufacture and development of holistic decision-making tools incorporating the environmental and societal aspects of manufacture,

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along with the technological and microeconomic considerations which currently govern decision-making

- Identification and prioritisation of the development of novel technologies with potential to ameliorate the environmental impacts of biopharmaceutical manufacture
- Continued macroeconomic assessment of biopharmaceutical manufacture, approval and sale and incorporation of technological and environmental models within these assessments

Here: **Figure 4: A vision of sustainable biopharmaceutical manufacture, achieved by embracing sustainability principles in the technological, environmental and societal paradigms.**

Figure 4 is intended to show a sustainable vision of biopharmaceuticals manufacture, driven by technological, environmental and societal consideration and innovation of the product lifecycle, from discovery through manufacture to the patient level. Initially, the development of new drugs and optimisation of existing drugs to achieve equitable or superior therapeutic benefits under lower dosages is important to reduce volumes of drugs required to be manufactured, with positive impacts on environmental emissions and operational expenditures as a result. Additionally, the pursuit of novel therapeutics such as gene therapies with potential for single doses providing life-changing results could also yield environmental benefits, potential for adverse societal impacts (such as those described by Brennan and Wilson (2014)) notwithstanding.

Continuing through the product life-cycle, the manufacturing processes utilised require exploration and assessment to inform decision-making. Under current regulatory framework, changes to product registrations incur additional time and expense of the regulator and the manufacturer , and are generally only made if absolutely necessary. Therefore, it is important that consideration of environmental and societal impacts is made prior to regulatory submissions and capital expenditure. To this end, the documentation of life-cycle assessment and life-cycle costing must be completed to develop an economic and environmental framework that can inform decision-making at the earliest possible stages of the product life-cycle. Additionally, novel amelioration technologies may influence

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manufacturing processes through discovery and development of environmentally and economically superior technologies.

Finally, at a socioeconomic level, several topics require attention. From a microeconomic perspective, a more transparent life-cycle costing of drug discovery and manufacture should be provided. Current estimates of the cost of drug discovery fluctuate wildly, while cost of drug development has increased above the level of inflation (DiMasi et al., 2016). The cost of manufacture can often be a relatively minor part of drug pricing, which may render any economic gains in the manufacturing process of negligible benefit to the end user. Increased transparency in this area would enable health authorities to understand the primary costs associated with each treatment and could lead to positive-regulating of certain technologies, in order to prevent excessive treatment costs.

A more holistic approach taken by drugs manufacturers could also involve more explicit support for reducing drug requirements societally through, for example, supporting the development of public health initiatives such as cycle to work greenways and public recreational spaces, as well as policy measures to promote healthy eating, etc.

Macroeconomically speaking, the provision of biopharmaceuticals for treatment of all manner of illnesses is widely-documented and can be the source of dispute globally. Accusations of price-gouging are often levied at biopharmaceutical manufacturers, and the price of biopharmaceuticals has been documented as 20 times higher on average compared to small-molecule treatments (Walsh, 2014). Pressure is thus placed on governments to provide treatments to its citizens in a prudent manner, while remaining often at the mercy of drug manufacturers, a combination which can result in inequalities of access. While there is no easy remedy to this situation, the continued development of informed policies incorporating the product life-cycle costs, including the environmental costs, in addition to increased transparency of drug pricing, will lead to maximisation of drug access.

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6. Conclusions

Biopharmaceuticals continue to gain approval in significant numbers, and provide real societal benefit from treatment of hitherto untreated illnesses and malaises. The advent of breakthrough gene therapies could herald the dawn of a golden age in biopharmaceutical development, yet the risks posed from historical economic difficulties, competition from biosimilars and accusations of unfair pricing may cause turbulence in the coming years. On a larger scale, humanity faces challenges from ecosystem degradation, anthropogenic climate change and rising levels of economic inequality. Sustainability principles can be applied to the biopharmaceutical industry in order to understand the overall impact of biopharmaceuticals manufacturing on the economy, society and environment, and to facilitate meaningful continued contributions to human flourishing.

Trends in the biopharmaceutical industry indicate a move towards fully continuous manufacturing processes utilising single-use technologies to produce multiple high-potency treatments in flexible manufacturing facilities. Challenges existing to this vision include economic feasibility concerns over single-use technologies and continuous manufacturing, scientific challenges from product quality and societal apprehension over existing product availability and new product pricing.

Established research in the area indicates environmental benefits from utilisation of fed-batch cell culture in tandem with single-use technology; however, limited information is available, providing minimal direction to policy- and decision-makers in the way of environmentally benign manufacturing routes. Similarly, macroeconomic policies such as inequality of access and unfair pricing are examined in isolation from the technological and environmental aspects of product manufacture. Integrated perspectives are required to analyse sustainability of existing practices and identify areas for improvement. One such method proposed is the application of industrial ecology models to the biopharmaceutical manufacturing life-cycle, in an effort to ensure continued innovation, reduced emissions to air, land and water, fair, equal access to biopharmaceutical treatments over the coming generations, and ultimately, human flourishing.

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Figure 1

Figure 2

Figure 3

Figure 4

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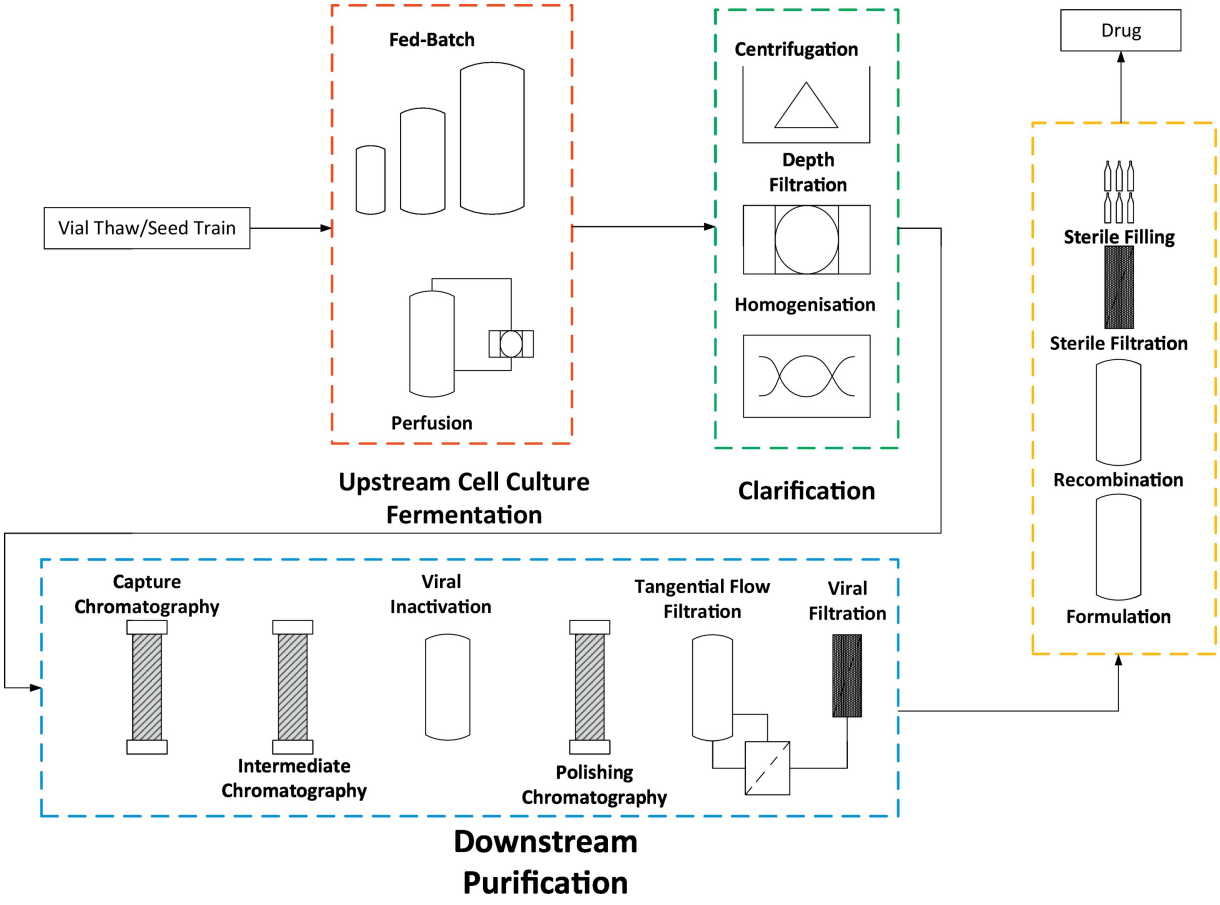

Fed-Batch
Vial Thaw/Seed Train
Perfusion
Upstream Cell Culture
Fermentation
Centrifugation
Depth
Filtration
Homogenisation
Clarification
Drug
Sterile Filling
Sterile Filtration
Recombination
Formulation
Capture
Chromatography
Intermediate
Chromatography
Viral
Inactivation
Polishing
Chromatography
Tangential Flow
Filtration
Viral
Filtration
Downstream
Purification

Figure 1

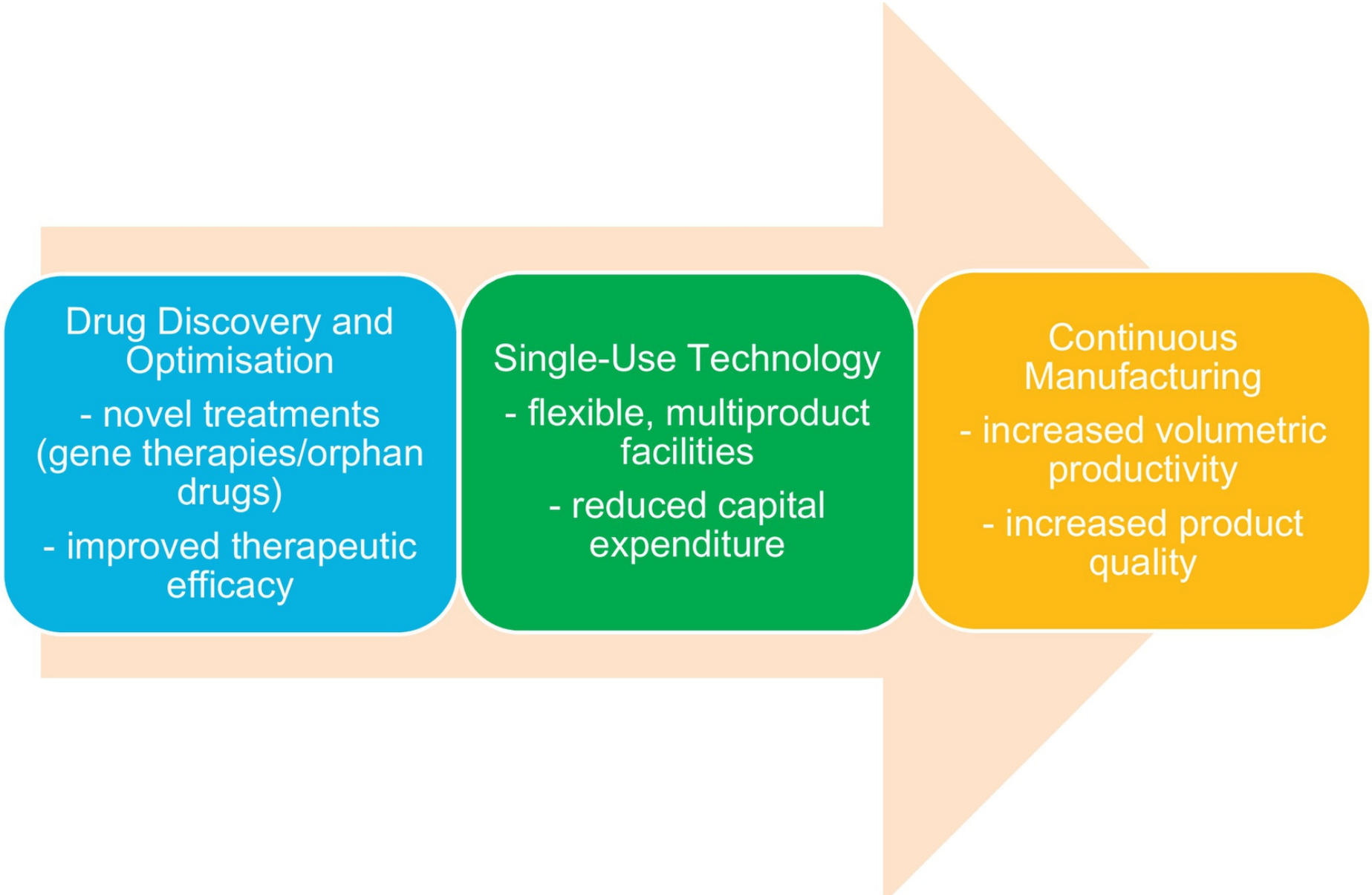

Drug Discovery and Optimisation
- novel treatments (gene therapies/orphan drugs)
- improved therapeutic efficacy
Single-Use Technology
- flexible, multiproduct facilities
- reduced capital expenditure
Continuous Manufacturing
- increased volumetric productivity
- increased product quality

Figure 2

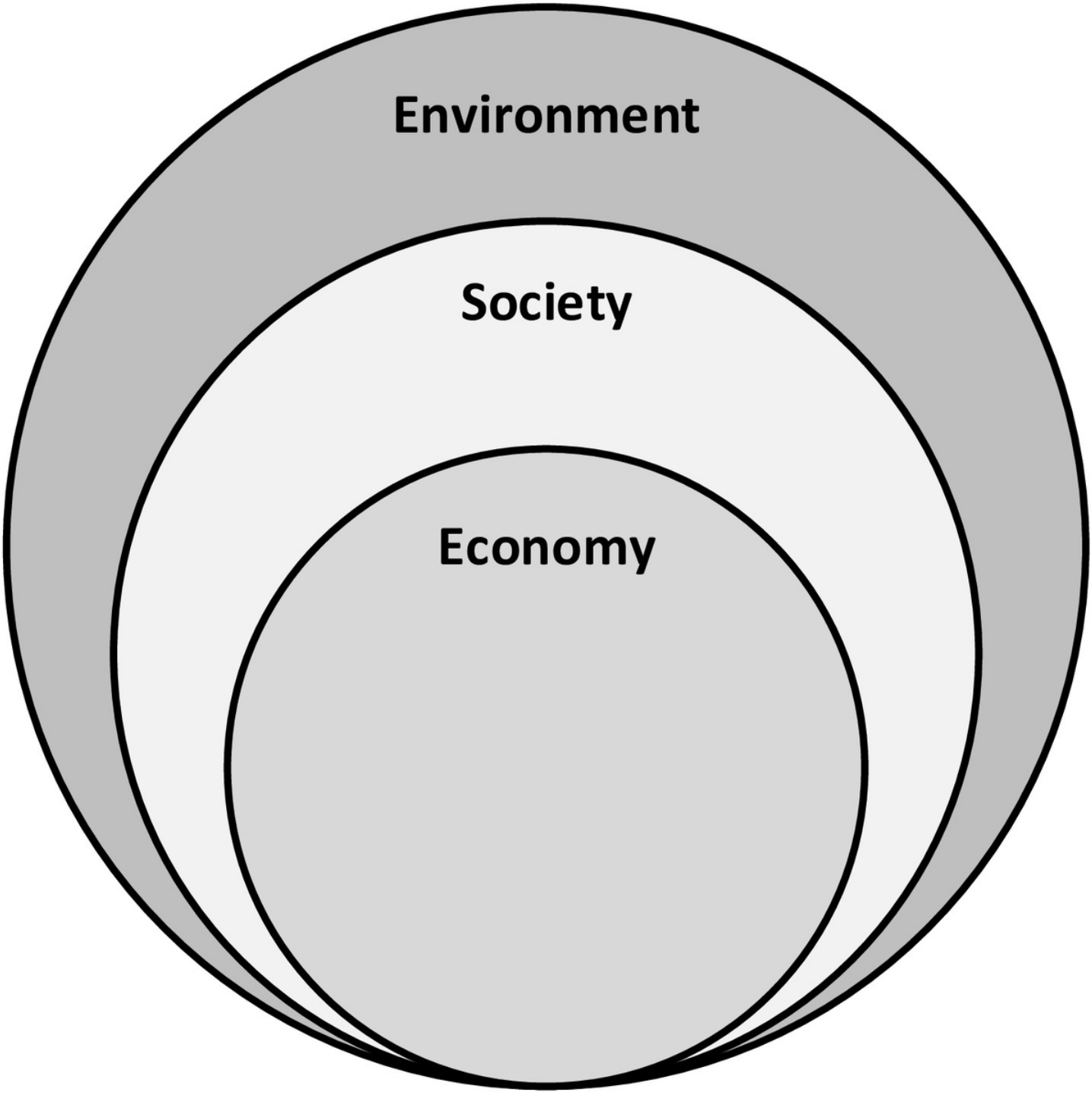


Figure 3

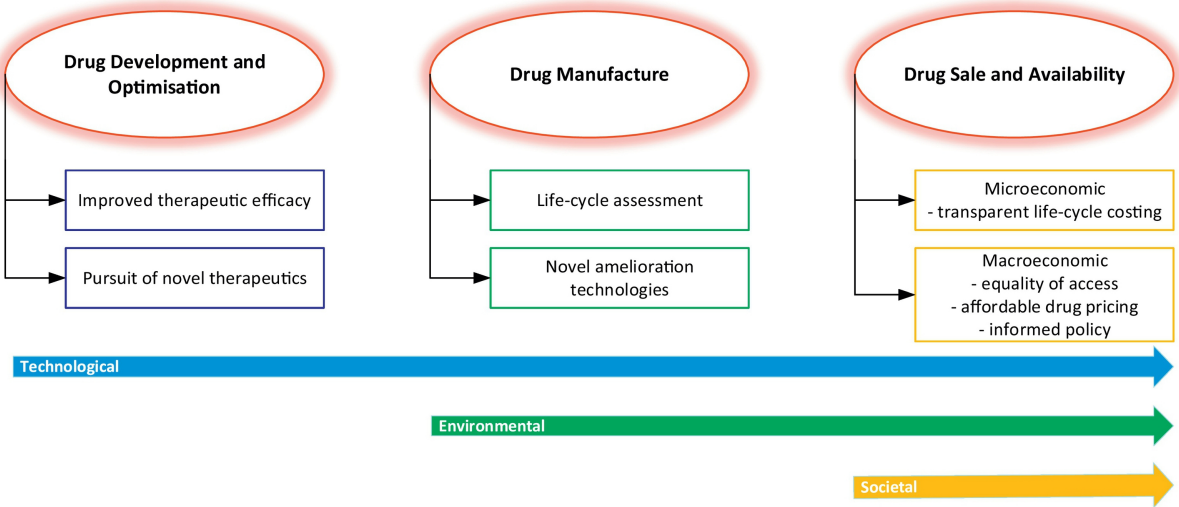

Drug Development and Optimisation
Improved therapeutic efficacy
Pursuit of novel therapeutics
Drug Manufacture
Life-cycle assessment
Novel amelioration technologies
Drug Sale and Availability
Microeconomic
- transparent life-cycle costing
Macroeconomic
- equality of access
- affordable drug pricing
- informed policy
Technological
Environmental
Societal

Figure 4