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Sustainability Analysis of Biopharmaceuticals Manufacturing

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Thesis submitted for the degree of Doctor of Philosophy

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I, Fergal Lalor, certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.

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Fergal Lalor

Abstract

The production of biopharmaceutical treatments is increasing globally at a rapid pace, leading to the treatment of more and more disorders, many of which historically were untreatable and debilitating. This increase in production poses sustainability concerns, with economic unsustainability from erratic returns on investment, societal concerns around treatment cost and access, and a dearth of published research on pathways to environmentally sustainable production methods.

Recombinant protein production by perfusion cell culture under stainless-steel and single-use technologies was investigated using life cycle assessment (LCA) to determine the impact on environmental factors. The ReCiPe for LCA method was utilised, and the single-use scenario was found to result in 40% impacts than stainless-steel alternative across all production volumes. Factors influencing the difference in environmental impacts include infrastructural variables, such as the electricity source to the facility, and process variables, such as the interval between ultrafiltration/diafiltration batches.

The feasibility of environmentally sustainable manufacturing processes were investigated, with novel technologies such as water-for-injection (WFI) production by reverse osmosis, the use of biologically-sourced polymeric materials for single-use items and the benefits of increased containment using single-use equipment on cleanroom maintenance evaluated. The results of this analysis indicate reductions in environmental impacts across both single-use and stainless-steel scenarios of 60%, but with further research required to fully understand the process impacts resulting from adopting these technologies.

A multiple-criteria decision-making framework was developed to evaluate the economic, environmental and social sustainability of biopharmaceutical manufacturing processes under varying value orientations, enabling the comparison of treatments produced under different modalities. This framework may be utilised to assess treatments for regulatory approval and governmental reimbursement in a holistic manner, as opposed to a reductionist economic standpoint. Further research is required to account for greater complexities in the biopharmaceutical industrial system such as feedback loops between various stakeholders and to provide and document indices from existing processes to be used for evaluation of prospective treatments.

Acknowledgements and Foreword

"But he had gone his way, the grass all mown
And I must be, as he had been, - alone
….
Men work together, I told him from the heart
Whether they work together or apart"
The Tuft of Flowers, Robert Frost (*A Boy's Will,* 1913)

Emulating the words of my favourite poet, Robert Frost, this piece of work has been an effort of collaboration and independence, ranging from robust, engaging discussion to long, lonely evenings of writing, and everything in-between. It is something I could never have achieved without spending hours alone in thought and at work, and yet without the support of so many, I would never have made it through those times, or produced a work of which I am so proud.

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Finally, to my family, my parents, Martin and Angela, and my brother, Eoghan. You are my support structure, where I go when I am elated and when I am despondent, and without your wisdom, encouragement and love, I could not have enjoyed this journey as much as I have, much less made my way to its' end. Know that this work is dedicated to you all.

List of Publications

Peer reviewed journal publications proceeding from this work

- Lalor F, Fitzpatrick J, Sage C, & Byrne E. Sustainability in the biopharmaceutical industry: Seeking a holistic perspective. Biotechnology Advances, Volume 37, Issue 5, 2019, Pages 698-707, ISSN 0734-9750, https://doi.org/10.1016/j.biotechadv.2019.03.015.

Part I: Sustainability in the biopharmaceutical sector: seeking a holistic perspective

Chapter 1: Introduction to biopharmaceuticals: chemistry, manufacturing and control

1.1.The developmental history of biopharmaceuticals

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.

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, interleukins, erythropoietin	Anaemia 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 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

1.2.The nature of biopharmaceutical molecules

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 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 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.

1.3.The biopharmaceutical manufacturing process

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.

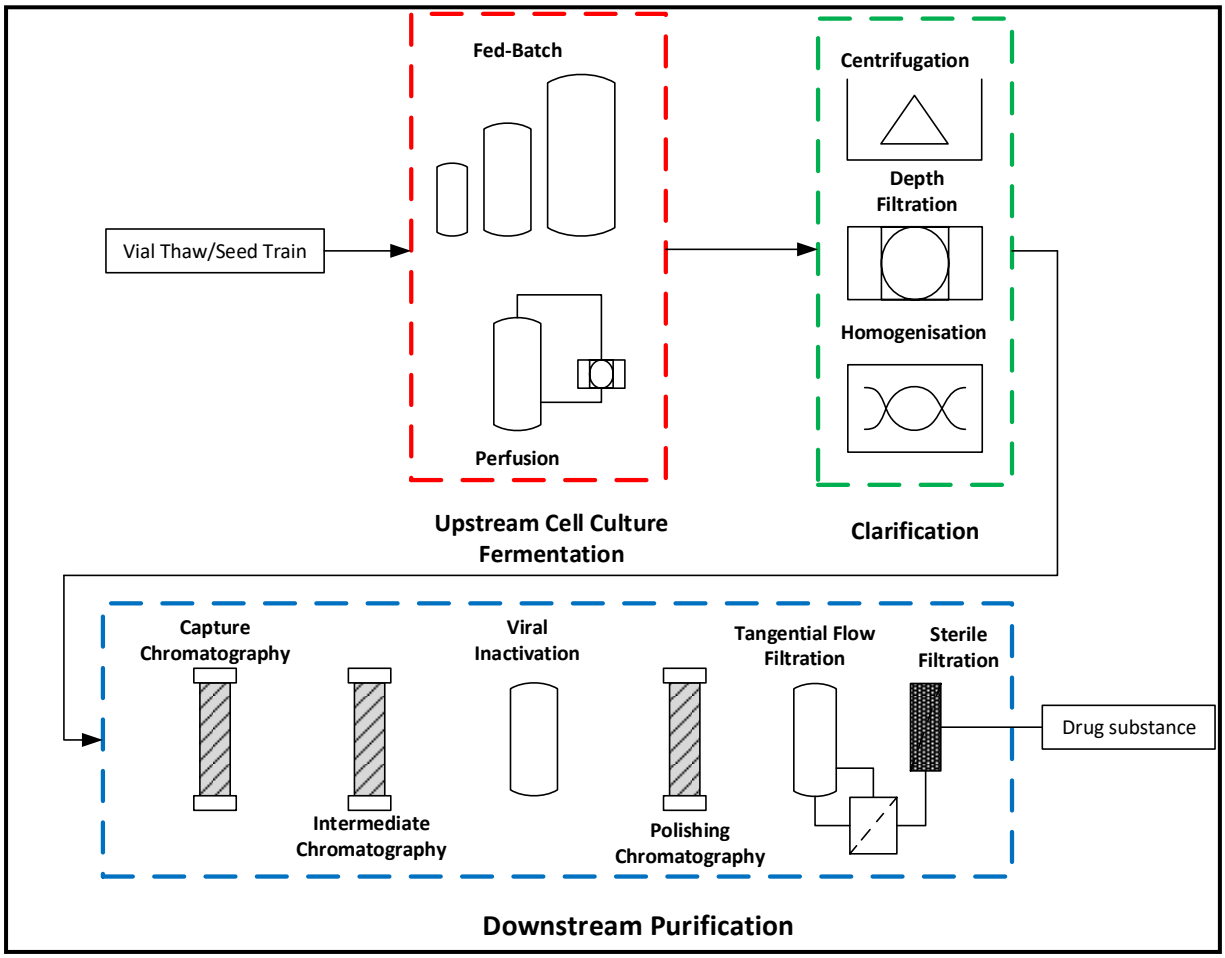


Figure 1: Overview of a typical biopharmaceutical manufacturing process

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 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 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.

1.4.Future trends in biopharmaceutical manufacture

1.4.1. 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 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 growth media (mAbs) Low viral genome titres – ~$1x10^{12}$ vg/L	Low protein/glycoprotein titres – 100-500 mg/L growth media (mAbs) 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 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 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).

1.4.2. 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.

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 4000L for bioreactors and 5000L for storage vessels, 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 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.

1.4.3. 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.

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, perhaps 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.

1.4.4. 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

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.

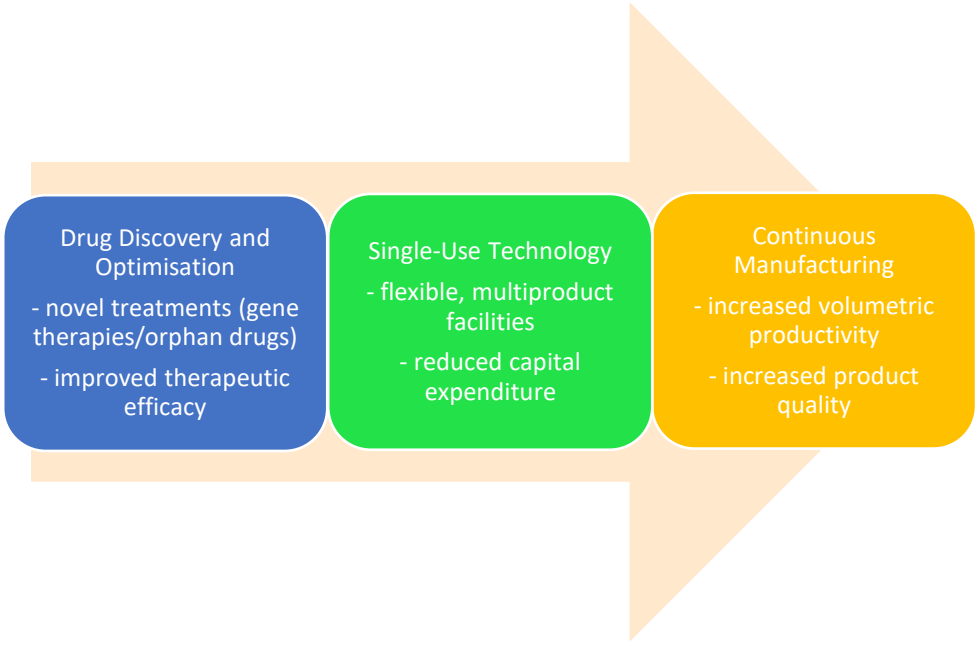


Figure 2: Overall trend in biopharmaceutical research and innovation

1.5.Control of biopharmaceuticals manufacturing: patient safety and regulation considerations

Owing to the typical poor health of recipients and intrusive delivery methods such as intravenous or intrathecal, biopharmaceuticals are subject to stringent controls on manufacture, sale and supply. Governed by regulatory bodies such as the European Medicines Agency (EMA) (and its member agencies) and the US Food and Drug Administration (FDA), the manufacture, sale and supply of biopharmaceutical treatments require a marketing authorisation granted on condition of adhering to good manufacturing practices (GMP) and being subjected to surveillance audits of facilities and operations to verify rules and guidelines are met. Through the use of a science-based dialogue and principles of quality management, organisations are required to demonstrate that the potency, safety and efficacy of treatments is built in throughout the manufacturing process and the supply chain. While this is critical to provide patients with assurance of a safe and efficacious treatment, perceptions that over-engineering and inefficiencies perpetuate both within and without the industry.

1.6.Research Motivation

From this chapter, it can be seen that biopharmaceutical treatments form an important component of the modern healthcare system, with positive health outcomes demonstrated for sufferers of ailments hitherto untreatable. The manufacturing of biopharmaceuticals involves a

number of complex fermentation and purification stages, and is subject to strict controls from governmental agencies to maintain patient safety and ensure efficacy of treatments which are commercialised for market sales. Recent trends have indicated a movement towards the development of novel therapeutics such as gene therapies using manufacturing processes consisting of continuous operations utilising single-use technologies, although this shift presents challenges to mainstream implementation.

These changes to the dominant paradigms of discovery, manufacturing and sale offer opportunities for an extension of positive patient outcomes observed over the past four decades. However, these trends also pose sustainability challenges, with a number of unanswered questions regarding the potential for environmental, economic and social impacts from these new therapeutics and technologies. In addition, the aggressive expansion in the biopharmaceuticals market further endangers these existing positive patient outcomes, should they be delivered in ways causing harm to other facets of society or the organisms with which humanity shares the Earth. The purpose of this thesis is therefore:

- To evaluate the biopharmaceuticals manufacturing industry through a sustainability lens and sustainability considerations for the industrial system
- To determine the potential impacts of certain trends in the manufacturing process, namely the adoption of single-use technologies, on existing perfusion cell culture manufacturing processes, through the use of life cycle assessment
- To assess the feasibility of moving towards an environmentally sustainable perfusion cell culture manufacturing process using existing stainless-steel and single-use technologies
- To propose a conceptual model of sustainability for biopharmaceuticals manufacturing, incorporating economic, social and environmental indicators
- To conduct an analysis of the economic, social and environmental flows in the biopharmaceuticals manufacturing system, and evaluate the relationships between these flows in the context of creating sustainability

Chapter 2: Sustainability as a concept and its' application to biopharmaceuticals manufacturing

2.1. Introduction to sustainability

What is sustainability? An often asked question, one which does not have a straightforward answer and is frequently answered incorrectly. Contemporary definitions often suggest sustainability is something which can be quantitatively analysed by reductions in negative impacts, often in the environmental sphere. Some definitions consider sustainability as an attractive economic proposition, particularly when it contributes to growth, be it in revenues, sales, or the global economy as a whole. Comparing these two statements, it could be construed that sustainability involves reducing bad things from happening, while ensuring more good things happen, and frequently. To an extent this is true, based on the dominant paradigm in which society exists. However, a better explanation of sustainability is that it is the possibility that human and other life will flourish on the planet forever (Ehrenfeld, 2009). Instead of reflecting on negatives in order to eliminate them, there should be focus on nurturing possibilities and creating prosperity in the present without damaging future generations' ability to survive and thrive. Sustainability is therefore not isolated to the environment, with which it is most often associated, but with the other two pillars, economy and society, which form the basis for human survival.

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.

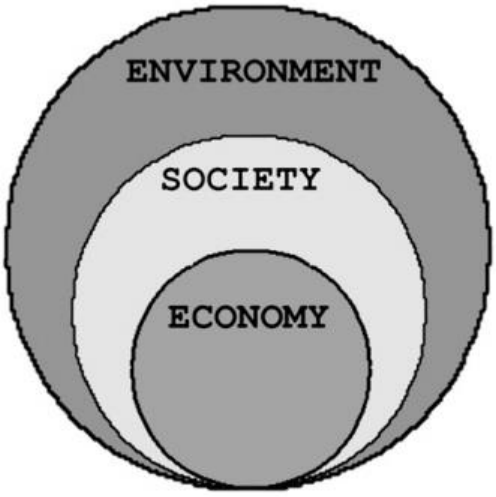


Figure 3: Concentric circle model of sustainability (Adapted from Lozano, 2008)

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.

2.2. The many faces of sustainability

Efforts to create sustainability can be directed towards a single pillar, or a combination of pillars in tandem. Creating sustainability is most often associated with the environmental pillar due to the expanding awareness of the impacts of climate change and ecosystem degradation on the flourishing of future generations. Environmental sustainability manifests in initiatives such as the creation of a circular economy; eliminating the use of harmful chemicals using green chemistry; moving towards low-carbon energy sources; reducing environmental impacts through lifestyle changes such as utilisation of public transport and dietary choices such as veganism; and management of the biosphere in an effort to maintain biodiversity and prevent ecosystem degradation caused by human activities. However, efforts at environmental sustainability often require radical rethinking of activities enveloped by other pillars of sustainability, such as ecological economics, and the economics of "degrowth". These stand apart from traditional economic thinking, which focuses on the financial sustainability both of individuals and companies, but also on a macroeconomic scale on the maintenance of a global economy free of recession, which can cause negative societal impacts, and solutions to challenge the growing trend towards economic inequality. These efforts move towards social sustainability as efforts to enable individuals and communities globally to live and prosper free from conflict, discrimination or other suffering. As can be seen from these examples, creating

sustainability requires an acceptance and appreciation for the complex web of relationships underpinning the flourishing of life of all types on Earth, and the diverse wants and needs required by these organisms to survive and thrive for generations to come.

2.3. Reflections on sustainability for the biopharmaceutical industry

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 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-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.

2.4. The economics of biopharmaceuticals manufacturing

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 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 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.

2.5. Environmental impacts of biopharmaceuticals manufacturing

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. A review indicated two works on life-cycle assessment from cradle-to-grave, one evaluating fed-batch production under stainless-steel and single-use technology paradigms, with the other investigating the use of fed-batch and perfusion production using stainless-steel technology. In addition, two papers were identified which documented the operation of fed-batch and perfusion technologies, and batch and continuous downstream technologies, using the E-factor and process mass intensity methods. Finally, a paper on the positive environmental impact of eliminating a toxic substance from the biopharmaceuticals manufacturing process was also reviewed.

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. Pollock et al. (2017) conducted an evaluation of fed-batch and perfusion technologies and batch and integrated continuous downstream trains, concluding that from an environmental perspective, hybrid strategies employing semi-continuous manufacturing yielded positive results. 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.

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.

2.6. 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, 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, 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

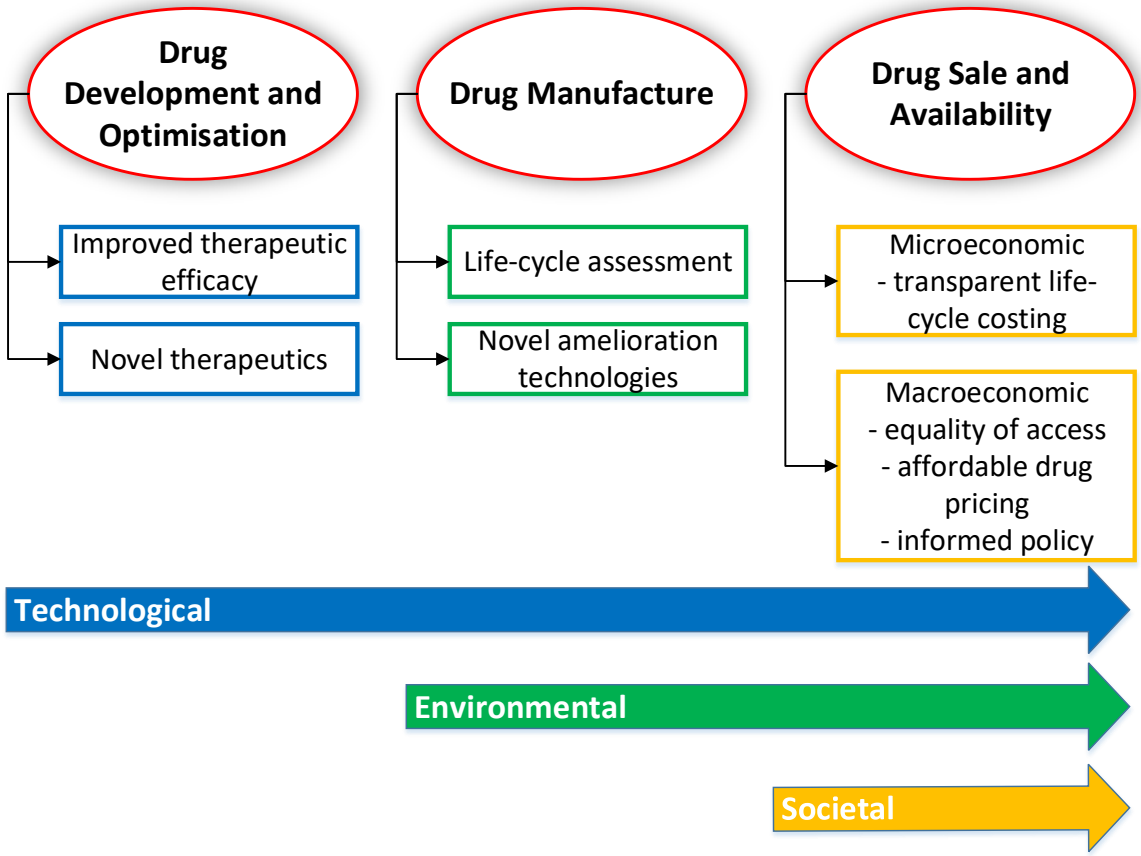


Figure 4: A vision of sustainable biopharmaceutical manufacture

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 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.

Part II: Comparison of the life cycle environmental impacts of single-use and stainless-steel technology for the production of a recombinant protein by perfusion cell culture

Chapter 3: Life Cycle Assessment Introduction and Methodology

3.1.Introduction

The purpose of this chapter is to investigate and compare the environmental consequences of the production by perfusion cell culture of a recombinant protein using stainless-steel and single-use technology. The objectives are:

- Identify major environmental impacts and their causes
- Identify which technology is more environmentally benign
- Investigate the impact of process variables on disparities between the technologies and between unit operations

The outcome of this study could then be used in conjunction with previously completed LCA of biopharmaceuticals to inform the decision-making process for development and design of manufacturing processes.

3.2.Methodology

A variety of methods exist for evaluating the environmental impacts of an industrial process. From a qualitative perspective, environmental impact assessment is a widely-used tool to identify and assess environmental impacts from a process or project, and is employed by state and European agencies in a multitude of applications, from roadway and railway evaluations to the granting of planning permission for public- and private-housing developments. While elements of the environmental impact assessment may be quantitative in nature, it tends to be a qualitative tool, while from a scope perspective, it is limited to the project in question and may not consider long term impacts of supply chain or end-of-life activities.

Beyond environmental impact assessment, a number of quantitative tools may be used to evaluate the environmental inputs and outputs of an industrial process. Process mass intensity (PMI) is an evaluation method whereby the mass of the required inputs, such as raw materials and facilities, is calculated as a function of the finished product. Typically processes such as fossil fuel production have a low process intensity, with little mass inputs required to generate finished product, while processes such as pharmaceuticals and biopharmaceuticals are highly intensive. Related to process mass intensity is E-factor, which is a calculation of the total waste generated by mass in the production of the finished product. A combination of process mass intensity and E-factor may be used in environmental assessment, depending on the complexity required.

Of greater sophistication is life cycle assessment (LCA), which is the assessment of the environmental impacts of a product throughout its life cycle. There may be some variation in scope and system boundaries: for example, an LCA may focus on the full cradle-to-grave impacts of a specific product, or alternatively could be a gate-to-gate assessment of the environmental impacts associated with a specific unit operation or process. Similarly, an LCA may have a broad system boundary whereby the impacts of raw materials production is included, or a narrow system boundary focusing only on the direct impacts of the process or product under investigation. The scope and system boundaries must be clearly stated to ensure equivalency when comparing multiple LCAs or other environmental assessments and avoid the drawing of incorrect conclusions.

For the purposes of this assessment, the evaluation method selected was life cycle assessment as defined in ISO 14044 (ISO, 2018). Life cycle assessment utilises four components; goal and scope definition; inventory analysis; life cycle impact assessment; and interpretation of findings.

3.2.1. Goal and Scope Definition

3.2.1.1.Scope of the LCA

The scope of the LCA was cradle-to-grave production of a functional unit of therapeutic protein over a defined time period. Figure 5 shows the scope of the LCA, which is composed of three distinct temporal phases:

- Supply-chain phase - the extraction, manufacturing and transport of materials used in the process including the equipment materials of construction (stainless-steel/polymeric), and process reagents
- Use phase – the utilities used in support of the manufacturing process including water (reduced ion water (RIW), water for injection (WFI)), plant and pure steam, electricity for HVAC supply to cleanrooms and equipment, and cleaning agents
- End-of-life phase – the transport and disposal methods of used materials including non-hazardous liquid waste for standard waste-water treatment, hazardous liquid waste requiring decontamination by heat sterilisation or transport for offsite recycling, waste stainless-steel for landfill or recycling, and waste polymeric components for landfill, recycling or incineration

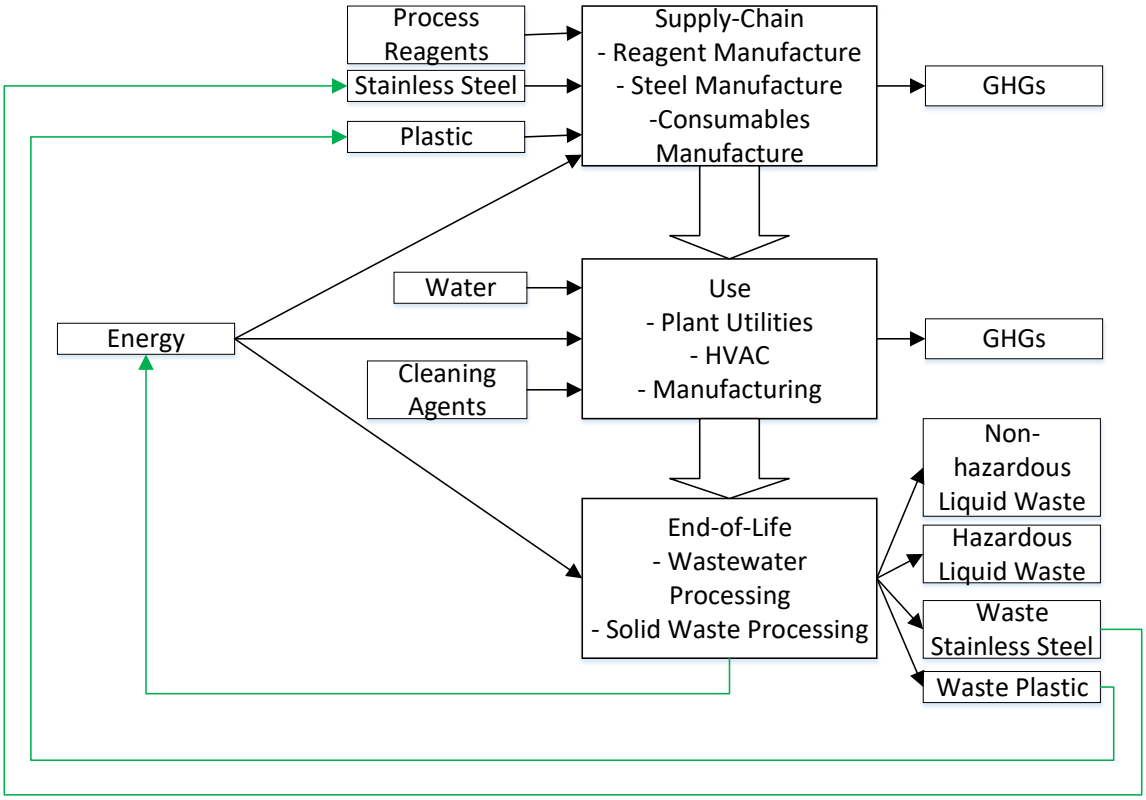


Figure 5: Scope of the life cycle assessment, showing the three phases investigated and the associated inputs and outputs**.**

The manufacturing process was composed of cell culture fermentation by perfusion culturing of Chinese Hamster Ovary (CHO) cells, harvest and clarification of the cell culture fluid by depth filtration and tangential flow filtration (UFDF) and purification using chromatography, solvent viral inactivation, UFDF and virus removal stages to produce bulk drug substance.

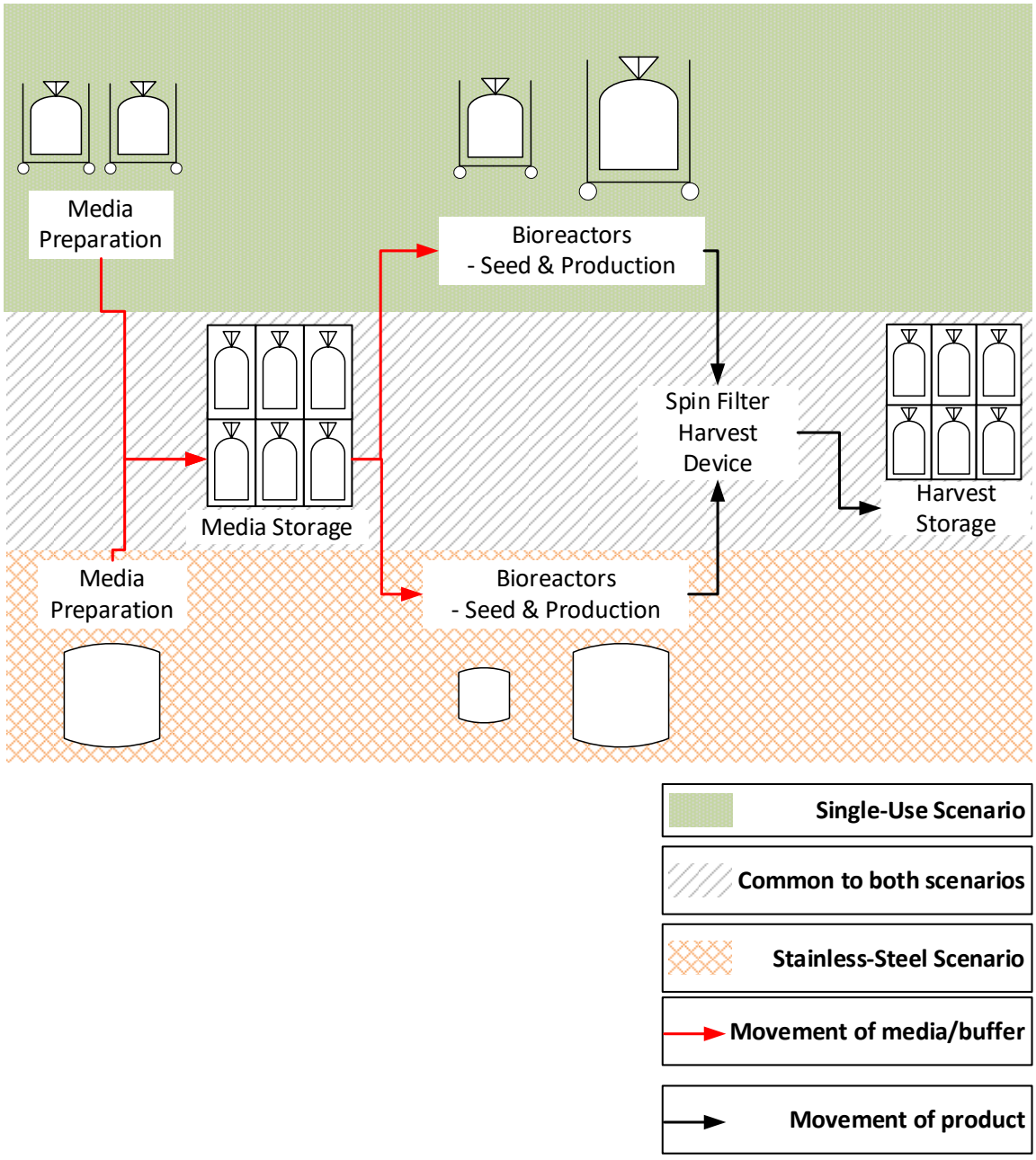


Figure 6: Process flow diagram for the cell culture fermentation of the process under study encompassing growth media preparation, perfusion bioreactor scale up and operation, and harvest collection and storage.

All process equipment was not investigated under both single-use and stainless-steel scenarios; growth medium and buffer storage was assumed to utilise single-use bags in both scenarios and depth filtration in both cases was assumed to be single-use. Figures 6, 7 and 8 show the process flow diagram for the manufacturing process. The difference in HVAC requirements for both scenarios was explicitly addressed, assuming that both scenarios were to be developed

from greenfield sites, and not from retrofitting of established facilities. The difference in labour requirements was not evaluated as part of this study.

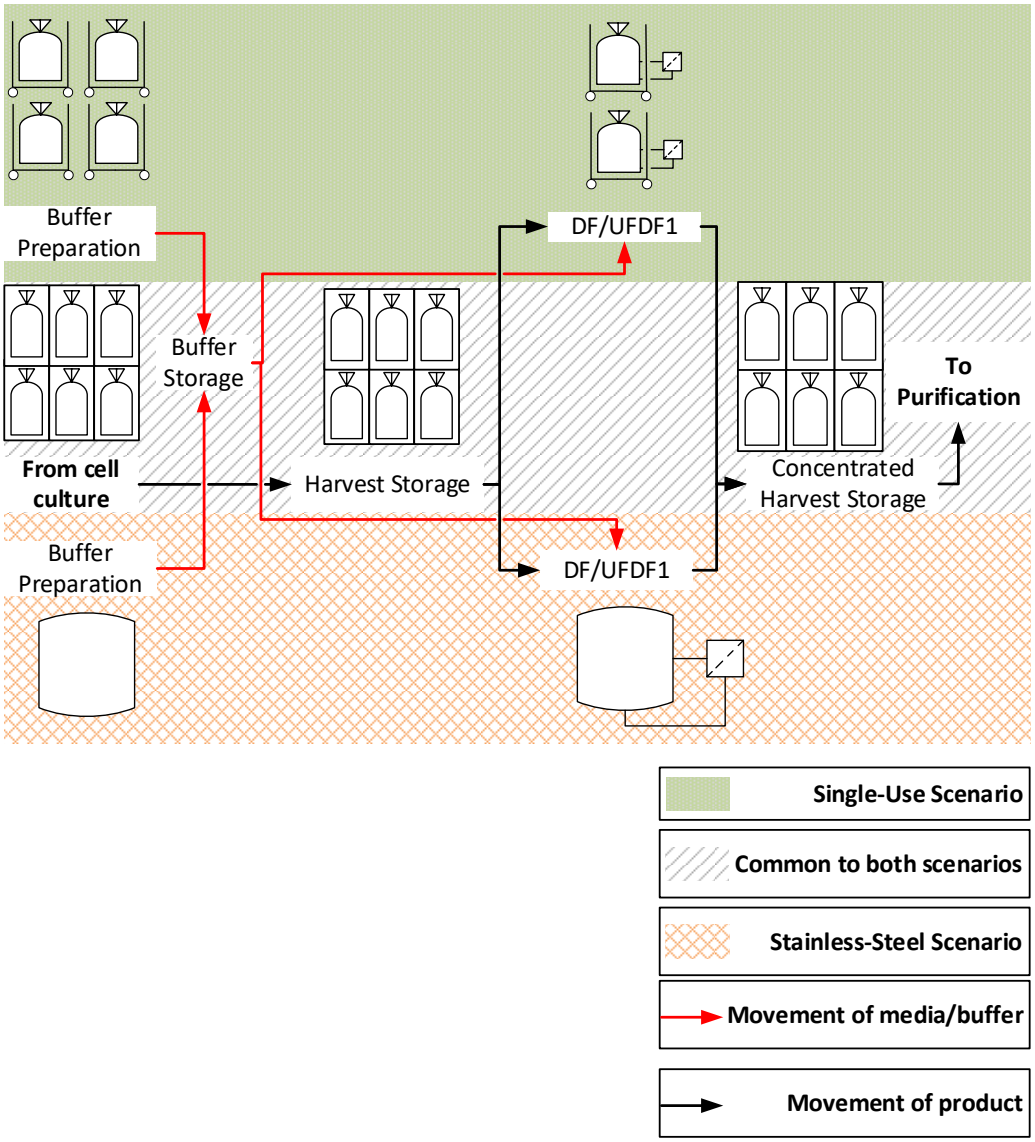


Figure 7: Process flow diagram for the harvest component of the process under study, consisting of a depth filtration (DF) and ultrafiltration/diafiltration (UFDF1) stage to concentrate the cell culture harvest and exchange buffer to prepare for purification stage. Also displayed is the buffer preparation and storage operation, which is utilised throughout the harvest and purification process stages.

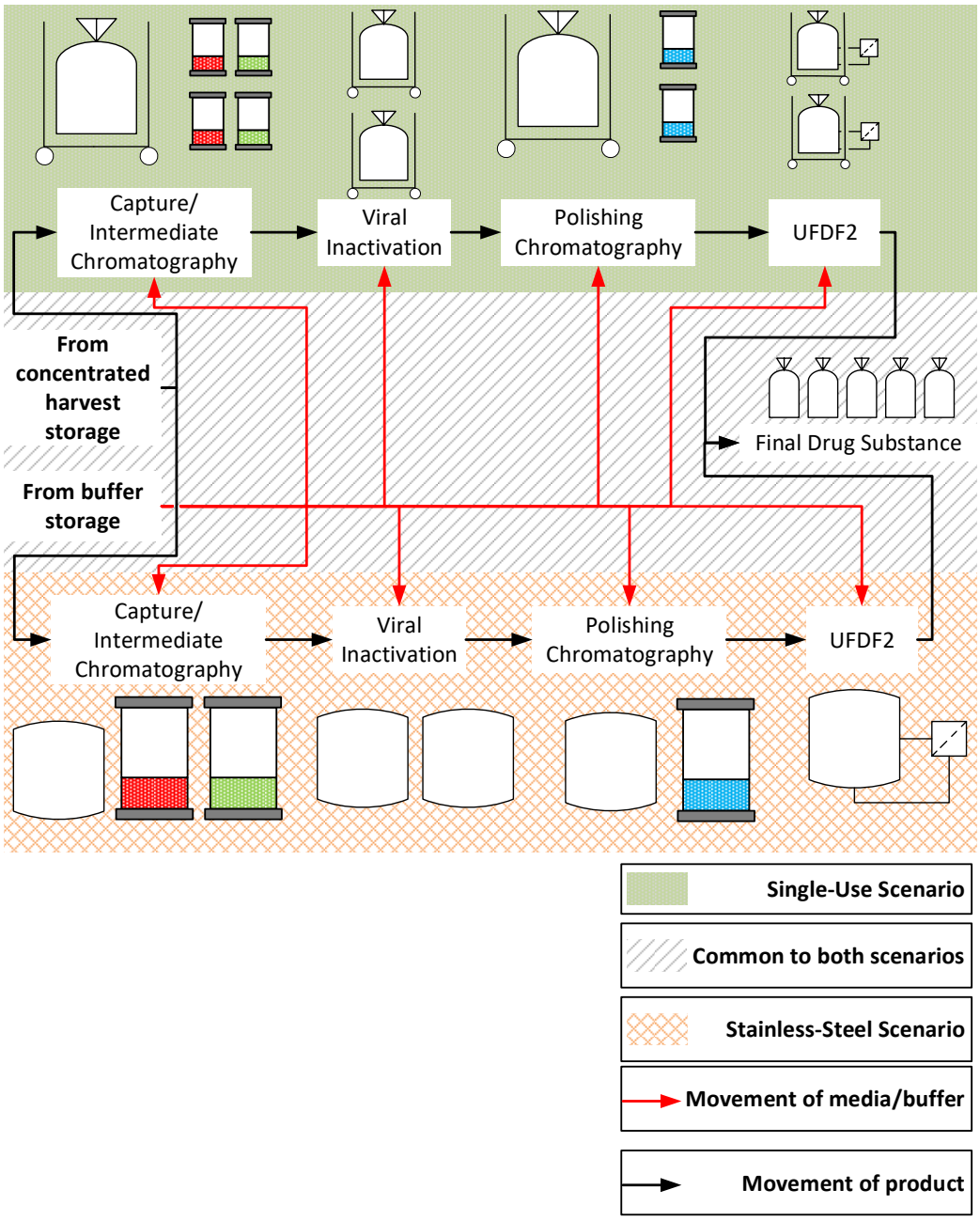


Figure 8: Process flow diagram for the purification component of the process under study, encompassing three chromatography separation processes, a solvent/detergent viral inactivation and a final ultrafiltration/diafiltration (UFDF2) with final bulk drug substance being stored in bags prior to further manufacturing to drug product

3.2.1.2.Determination of the Functional Unit

The functional unit of the study was determined as a function of patient population and typical therapeutic dosage regimen. By review of existing therapies, a therapeutic dosage of 1mg therapeutic protein per kilogram patient body mass was selected, which is equivalent to 3.64g therapeutic protein per patient per annum, assuming an average patient weight of 70kg. Patient populations of 1,000, 5,000 and 10,000 were selected to reflect production of orphan drugs and for large scale manufacturing. A time period of 10 years was selected, as this is the typical patent lifetime. Table 6 details the functional units under study.

Table 6: Functional units to be assessed, reflecting production volumes for orphan drugs, intermediate scale and large scale manufacturing.

Average Dosage	Patient Population	Time Period	Functional Unit
3.64 g/patient/annum	1,000	10 years	3.64kg per annum
	5,000		18.2kg per annum
	10,000		36.4kg per annum

3.3.Inventory Analysis

Previous LCAs found in the literature were completed using data generated using industry design and analysis software such as BioSolve (Biopharm Services), which is not typically accessible outside of a manufacturing facility or design company. In an effort to aid reproducibility and open research, this LCA was completed from first principles, beginning with a process mass balance to determine volumetric requirements of the process, followed by equipment and facility design, from which the inventory analysis data was produced.

3.3.1. Process Mass Balance

3.3.1.1.Perfusion Cell Culture

The process was assumed to run for 300 days per annum to allow for shutdown periods for maintenance and equipment downtime. Cell culture operations were continuous, with a perfusion period of 60 days assumed, while harvest and purification operated in a batchwise fashion.

The perfusion rate, D, is calculated as the inverse of the maximum residence time, RT_{max}:

$$D = \frac{1}{RT_{max}}$$

The resulting cell-specific perfusion rate, *CSPR*, is given by:

$$CSPR = \frac{D}{X}$$

Where *X* is the average cell density.

The resultant product titre from the cell culture is then calculated by:

$$T_{p,i} = \frac{q_p}{CSPR}$$

Where q_p is the cell specific productivity.

The mass flowrate of product from the cell culture per day is given by:

$$\dot{m}_{p,i} = T_{p,i} DV_{bioreactor}$$

The key manipulated variable was the volume of the production bioreactor, $V_{bioreactor}$, as this directly influenced the production volume. This variable was also used to determine the volumetric requirements of the upstream solution preparation vessels for growth media. Growth media preparation was assumed to take place daily, and provide enough growth media for 2 days bioreactor production. Growth media storage was assumed to be required to support 3 days bioreactor production.

3.3.1.2.Harvest and Purification

The cell culture fluid is harvested continuously, stored and pooled together for clarification and tangential flow filtration. Depth filtration area is given by:

$$A_{df} = \frac{t_d \frac{\dot{V}_{p,i}}{t_{df}}}{P_{df}}$$

Where $V_{p,I}$ is the volumetric flowrate per day from the bioreactor, P_{df} is the depth filtration membrane flux, t_d is the pooling duration for the clarification step and t_{df} is the operating time of the depth filtration step. Harvest storage was required to store enough harvest to support two UFDF1 runs worth of harvest and concentrated harvest each.

Following depth filtration, the clarified cell culture fluid undergoes tangential flow filtration to concentrate the solution and adjust the solutions pH prior to loading on the capture chromatography column. A second tangential flow filtration step is utilised following polishing chromatography to concentrate the drug substance solution to a stable storage value and to exchange purification buffers with formulation buffer to stabilise protein and ensure efficacy and safety for administration.

The membrane area required is given by:

$$A_{UFDF} = \frac{\dot{V}_{UFDF,P}}{P_{UFDF}}$$

Where P_{UFDF} is the UFDF membrane flux, and $V_{UFDF,\,P}$ is the required permeate flow through the membrane, which in turn is given for the first UFDF step by:

$$\dot{V}_{UFDF,P} = \frac{V_{UFDF,i}(1 - \frac{1}{C_F})}{t_{UFDF}}$$

Where C_F is the target concentration factor and t_{UFDF} is the operating time of the UFDF step.

For the first UFDF step, the target concentration factor is an independent variable unrelated to protein concentration. For the second UFDF step, the concentration factor is a dependant variable to the required protein concentration for storage, and is given by:

$$C_F = \frac{c_{UFDF,i}}{c_f}$$

Where c_F is the target concentration and $c_{UFDF,I}$ is the initial concentration of the product solution.

Product loss across the membrane is given by:

$$L_P = 1 - e^{(x_R - 1)(\ln C_F + N_V)}$$

Where x_R is the membrane rejection coefficient and N_V is the number of diavolumes.

Following the first UFDF step, the concentrated, clarified cell culture fluid is stored and pooled onto the capture chromatography column. The number of UFDF batches pooled to load the capture chromatography column is denoted by n_d. The volumetric requirements of the UFDF equipment was determined by the volume of the solution following concentration and by the membrane area.

Three chromatography steps are carried out to remove residual host-cell proteins, bacterial endotoxins, viral inactivation agents and protein aggregates. The chromatography column diameter is given by:

$$D_C = \sqrt{4 \frac{m_{p,i}}{\frac{DBC}{\pi h_b}}}$$

Where $m_{p,I}$ is the mass of product loaded onto the column, *DBC* is the dynamic binding capacity of the resin and h_b is the resin bed height. The chromatography resins volume requirement could then be calculated by:

$$V_{resin} = \frac{\pi {D_c}^2 h_b}{4}$$

For each chromatography step, the volume of buffer solution required was expressed in terms of column volume.

Buffer preparation was assumed to take place daily at intervals necessary to support purification activities. Buffer vessel volume was based on the largest preparation volume, and so was derived from the volume of the chromatography column. Buffer storage was contingent on the buffer preparation size, and was required to store buffer for a full purification run with a 50% safety factor.

Table 7 contains typical values of critical process variables described in previous equations and which formed the basis for the process inventory analysis.

Table 7: Typical values of critical process variables for the perfusion process

Unit Operation	Parameter	Designation	Unit	Range
Bioreactor	Cell-specific productivity	q_p	pg/cell/day	1-100
	Protein Residence Time	RT	Day-1	0.1-1
	Viable Cell Density	X	million cells/mL	5 - 60
	Production Bioreactor Volume	V	L	5-1000
	UFDF1 Run Interval/Pooling Duration	t_d	Days between UFDF1 runs	0.5-8
Depth Filtration UFDF1 UFDF2	Membrane Flux	P	L/min/m^2	1-3
UFDF1	Target Concentration factor	F_C	N/A	10-30
	Rejection Coefficient	α	N/A	0.975-0.999
	Number of Diavolumes	$N_{D,1}$	N/A	1-7
	UFDF1 Runs/Purification batch	n_d	Number of UFDF1 runs per Purification Batch	1-8
Chromatography	Resin Binding Capacity	DBC	g product/L resin	10-100

Unit Operation	Parameter	Designation	Unit	Range
UFDF2	Target Concentration	c_f	mg/mL	10-50
	Rejection Coefficient	α	N/A	0.990-0.999
	Number of Diavolumes	$N_{D,2}$	N/A	10-30

3.3.2. Equipment Sizing

3.3.2.1. Basis for Sizing of Equipment

The basis for sizing the process and utilities equipment was the volume of process and utilities liquids required and then the application of assumptions and rules of thumb to determine the final size requirements.

- Initially, the process mass balance was used to inform the equipment sizing required for the main process vessels (production bioreactor, chromatography columns, etc.)
- Ancillary process equipment was then sized based on the process mass balance variables:
  - For growth media preparation and storage vessels, the size was based on the amount of media required per day, from the production volume and perfusion rate, and assumptions of 3 days of growth media storage and a requirement to produce 1.5 days worth of growth media in the vessel on a daily basis.
  - For buffer preparation and storage vessels, the size was based on the frequency of the purification train and the volume of distinct buffer solutions (load, elution, cleaning) required, with assumptions of 1.5 batches of storage required and capability of producing 1.5 distinct buffers per vessel per day.
- Once all process equipment had been sized, cleaning requirements and flowrates were generated. The cleaning requirements assumed cleaning contact times based on the process solutions in contact with the vessel. Cleaning flowrates were generated based on the diameter of the vessel and achieving fully turbulent falling-film flow on the vessel walls.
- Utilities vessels were sized based on the process equipment requirements, assuming a peak demand where the two largest vessels were cleaned simultaneously, with the

generation based on 20% of this demand and the storage providing a minimum of 30 minutes worth of peak demand.

3.3.2.2.Stainless Steel Process Equipment Sizing and Cleaning Requirements

For all process equipment, it was assumed that the vessels were cylindrical stirred tank vessels equipped with hemispherical heads and with length:diameter ratio in range of 1-3 and a volume safety factor of 20% times the production volume. A uniform stainless-steel thickness of 8mm was selected, due to the vessels being subjected frequently to CIP/SIP. Vessel diameter was determined by:

$$D = \frac{4V}{\left(\pi \frac{L}{D}\right)^{1/3}}$$

The vessel head volume was calculated by:

$$V = \frac{\pi D^3}{24}$$

Vessel weight was then given by:

$$W = (\frac{\pi(D + 2t - D)^2 h}{2} + \frac{\pi(D + 2t - D)^3}{12})\rho_{stainless\ steel}$$

For the growth media, bioreactor, purification intermediate and buffer vessels the above equations were utilised, and the amount of supporting pipework and structural steel were assumed to constitute twice the weight of the vessel alone.

For the UFDF vessels, the total weight of pipework and structural steel were assumed to constitute three times the weight of the vessel alone, due to the complexity of the pipework required and the requirement to support the membranes.

For the chromatography columns and supporting pipework, the vessels were assumed to be cylindrical, with diameter based on the column volume and bed height required. A volume safety factor of 500% was assumed, based on the low volume of the resin.

To determine cleaning requirements, the equation for falling film Reynolds number was utilised:

$$Re_f = \frac{4\Gamma}{\mu}$$

Where Γ is the mass flow rate of cleaning agent per unit vessel circumference and μ is the fluid viscosity.

A falling film Reynolds number of >1500 indicates turbulent flow (Fuchs et al., 2015), which is required to ensure removal of soils from the vessel walls. Therefore, the required Γ value was calculated by rearranging the Re_f equation:

$$\Gamma = \frac{Re_f \mu}{4}$$

The mass flow rate for each vessel was then calculated as:

$$\dot{m}_c = \Gamma L_V$$

Where L_V is the vessel circumference.

A cleaning regime of ambient reduced ion water (RIW) rinse, hot sodium hydroxide wash, hot citric acid wash and hot water for injection (WFI) rinse was utilised for all equipment with the exception of the UFDF skids and chromatography columns, which were cleaned with ambient sodium hydroxide and ambient WFI only, to prevent degradation of the membranes or chromatography resin.

Wash and rinse contact times for cleaning were estimated at 10 minutes for buffer and media preparation equipment, 15 minutes for harvest and downstream equipment and 60 minutes for upstream equipment.

3.3.2.3.Single-Use

The materials of construction for single-use materials were determined based on commercially available equipment. Table 8 gives the range of materials investigated and their typical applications.

Table 8: Summary of single-use materials and their typical applications

Material	Application	Reference
Low-density polyethylene (LDPE)	Storage Bags	Scientific, T. (2020)

Polyethylene terephthalate (PET)	Storage Bags	Scientific, T. (2020)
Thermoplastic elastomer (TPE)	Process tubing	Saint-Gobain (2020)
Polycarbonate (PC)	Process fittings, connections and housings	Merck Millipore (2020)

For the single-use systems, sizing of equipment was determined by the largest commercially available formats. For vessels, a limit of 5000L was applied, based on the largest available single-use bags, for UFDF membranes, a limit of $10m^2$ was applied and for chromatography columns, a diameter of 60cm was applied. Due to the expense associated with UFDF membranes and chromatography columns, they were not treated as truly "single-use". UFDF membranes for the first UFDF step were cleaned post-use and changed annually, while for the second UFDF step they were used once and disposed of. Chromatography columns were reused for multiple purification batches and then disposed. For the intermediate and large scale production scenarios, the number of UFDF1 skids and purification trains was determined by the process intensity, and where the UFDF1 skid was used at intervals of less than 3 days, or purification unit operations were required to run at intervals less than 1 day, additional equipment and facility space was required.

Existing single-use technology vendor data was used to estimate weights of steel and plastic required for process equipment. For the mixing vessels, the weights and dimensions of the ThermoFisher HyPerforma and Impulse vessels were used, with the weight assumed to consist entirely of stainless steel. The bag weights were determined using these dimensions by the formula:

$$W = \left(\frac{\pi(D + 2t - D)^2 h}{2} + \frac{\pi(D + 2t - D)^3}{12}\right)\rho_{plastic}$$

Where *t* was equivalent to the thickness of each plastic layer of the single-use bags. For the stationary storage of growth media, harvest and buffer, the storage vessels were assumed to be cuboidal in shape and to take up 1 square meter floor area for the 1000L and 3000L storage vessels. The weight of these vessels and associated bags was given by:

$$W = ((L + 2t)(B + 2t)(h + 2t) - (LBH))\rho$$

Where *t* was equivalent to the thickness of the stainless steel vessel structure or the thickness of each plastic layer of the single-use bags, and ρ represents the density of steel, for the storage vessels, or the density of plastic, for the storage bags. Table 9 gives calculated values for the weights of bags and vessels of varying size.

Table 9: Values for stationary and mixing bags of various volumes

	Weight			
Bag Size/Type	**LDPE**	**PET**	**TPE**	**Stainless Steel**
1000L Stationary	1.45	0.15	0.14	306
3000L Stationary	3.39	0.35	0.31	708
5000L Stationary	5.04	0.53	0.47	1049
1000L Mixed	1.4	0.15	0.13	516
3000L Mixed	2.91	0.3	0.27	1730
5000L Mixed	4.28	0.45	0.4	3251

Process tubing requirements for each unit operation was based on an average distance of 5 metres between processing equipment, with all tubing assumed to be made from TPE.

For the UFDF and Chromatography skids, the stainless-steel weight was taken from existing vendor data for the Pall Allegro, Mobius FlexReady, Pall Cadence and Millipore Pellicon. Tubing requirements were evaluated assuming a requirement for three times the length and width of the skid.

All single-use plastic equipment was assumed to be gamma irradiated. An irradiation dosage of 50kGy was assumed for all equipment. Using this dosage and the mass of plastic componentry required in the process, the minimum mass of radioactive isotope, Cobalt-60, which would supply this dosage was determined. As no life cycle impact data was available directly for Cobalt-60, data for uranium mining and processing was used in place, as uranium is required to produce Cobalt-60 in a nuclear reactor.

For the irradiation facility, the life cycle impacts associated with the built facility was not considered, as it was assumed to be existing. The facility throughput as a function of the mass

of plastic componentry supplied to the biopharmaceutical facility in question was a key variable, as this determined the available residence time for components, which then affected the mass of radioactive isotope required. The facility was assumed to package plastic components in a Grade C cleanroom, and the tonnes of plastic componentry packaged per square metre of cleanroom was another key variable investigated.

3.3.2.4.Utility Equipment

The utility equipment required for the system included the water system for production of RIW and WFI, a pure steam production for SIP of vessels, cleaning systems to supply cleaning agents to vessels and waste systems to store and treat liquid waste.

The RIW and WFI system were sized based on usage. The RIW system fed the two CIP skids and the WFI system. The WFI system had several sub-loops, supplying hot WFI to the two CIP skids, and supplying ambient WFI to growth medium, buffer, UFDF and purification rooms for process use. WFI was maintained at 70°C while being circulated to self-sanitise and prevent microbial growth, with cooling utility supplied to reduce to ambient temperature as required. The WFI generation system was sized to supply 20% of the peak demand continuously, and the WFI storage vessel was sized for 30 minutes at peak demand. The RIW storage vessel was sized at 40% in excess of the WFI storage vessel.

The pure steam generation system was supplied with WFI and supplied steam for sterilisation of the seed and production bioreactors. The standby steam flowrate required was determined to be 20% of the flowrate required to maintain the production bioreactor at 123°C during SIP while heat is lost to the room by forced convection.

The cleaning system was composed of two CIP skids, one servicing growth medium preparation, cell culture and harvest operations, the other servicing buffer preparation and purification operations. Both skids were equipped with two hold vessels with hemispherical heads, one for RIW and cleaning agent makeup and recirculation, the other as a break vessel for the hot WFI rinse.

3.3.2.5.Water Production and Usage

The primary water usage was WFI for process use in making growth media and buffer solutions and for use in cleaning. WFI was assumed to undergo multiple-effect distillation using plant steam at 8 bar(g). The distillation energy required was taken as 843 kJ/kg WFI. Total WFI usage was determined by the number of cleans of each vessel and the cleaning volumes

required as calculated from the cleaning flowrates and contact times, in addition to sanitisation requirements consisting of flushing of the system daily for 5 minutes at maximum flowrate and smaller parts prior to usage in process or cleaning applications. Cleaning agents sodium hydroxide and citric acid were assumed to be used at a concentration of 1% w/w. Energy for WFI production was assumed to come from a mix of natural gas and electricity to produce the plant steam, which was then used to generate WFI.

3.3.2.6.Facility Sizing

For facility sizing, the facility footprint was based on the manufacturing cleanroom as shown in Figure 9. The facility was assumed to be four stories in height, with the ground floor dedicated to utilities and waste systems, the first floor dedicated to the manufacturing cleanroom, the second floor dedicated to access to the cleanroom and supply of utilities from headers and the third floor to house the air handling units for the HVAC system. The facility footprint was based on vessel dimensions calculated as per Section 3.3.2.1.

The HVAC energy requirements used are detailed in Table 10. Bunnak et al. (2015) used figures ranging from 47-854 kWh/m^2 per annum, while Capparella (2013) gives figures of 257 kWh/m^2 per annum for office buildings and 3,819 kWh/m^2 per annum for the average pharmaceutical plant. To harmonise these values, the value of 3,819 kWh/m^2 per annum was taken to be the upper bound for a Grade B cleanroom, a controlled non-classified (CNC) room was taken to be 257 kWh/m^2 per annum and intermediate values were selected for Grade D (12.5% of Grade B value) and Grade C (25% of Grade B value) cleanrooms.

Table 10: HVAC EUI values, harmonised from those reported by Bunnak et al. (2015) and Capparella (2013)

Area Classification (EU Annex 1)	**Energy Usage Intensity (EUI) kWh/m^2/annum**
CNC	257
D	478
C	955
B	3819

The room classifications were determined by the operations within them. For both scenarios, the seed bioreactor was assumed to be in a Grade B area, and the production bioreactor in a Grade D area. Growth medium preparation, buffer preparation, harvest storage and depth filtration and UFDF operations were assumed also to take place in Grade D conditions. Purification operations up to and including viral filtration took place in a Grade C area, while post-viral filtration operations including bioburden reduction filtration and final filling into storage bags took place in a Grade C area for the single-use scenario and a Grade B area for the stainless-steel scenario, due to the greater containment provided by the single-use scenario. All energy for the HVAC system was assumed to be provided by the electricity grid.

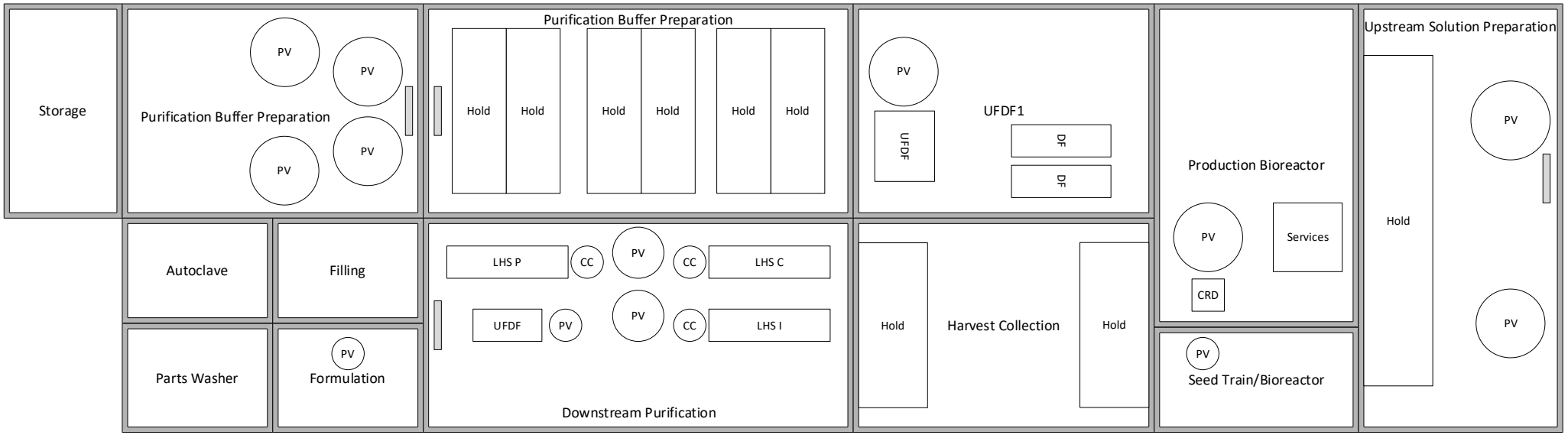


Figure 9: Manufacturing facility layout used as basis of study, showing the individual unit operations in designated suites and various equipment including process vessels (PV), intermediate storage (Hold), chromatography columns (CC) and liquid handling skids (LHS), the cell retention device (CRD) and the depth filters (DF)

3.4.Life Cycle Impact Assessment

The ReCiPe for LCA method (Huijbregts et al., 2017) was used to evaluate the life cycle impacts from materials and energy sources identified in the inventory analysis. The ReCiPe for LCA method uses a number of characterisation factors to relate the material and energy flows to and from the environment into a finite number of environmental impact scores, allowing for direct comparisons of otherwise distinct systems. This method was chosen as:

- It is used across various industrial systems for LCA
- It has been used in biopharmaceuticals previously (Pietrzykowksi et al., 2015)
- It is readily accessible, with characterisation factors available for download in spreadsheet form (ReCiPe, 2020)
- Alternative options such as SimaPro or Gabbi software were not utilised as they are not open-source and as such limit the replicability of the LCA

The ReCiPe for LCA method is comprised of 18 midpoint and 3 endpoint categories. Material and energy flows generated in the inventory analysis were analysed, and those flows which significantly differed between the single-use and stainless-steel scenarios were investigated, to reduce the amount of characterisation data necessary to compare. Material and energy flows with values that differed between scenarios by >10% were investigated. Figure 10 describes how the data generated in the inventory analysis was related to the characterisation data and the midpoint and endpoint categories.

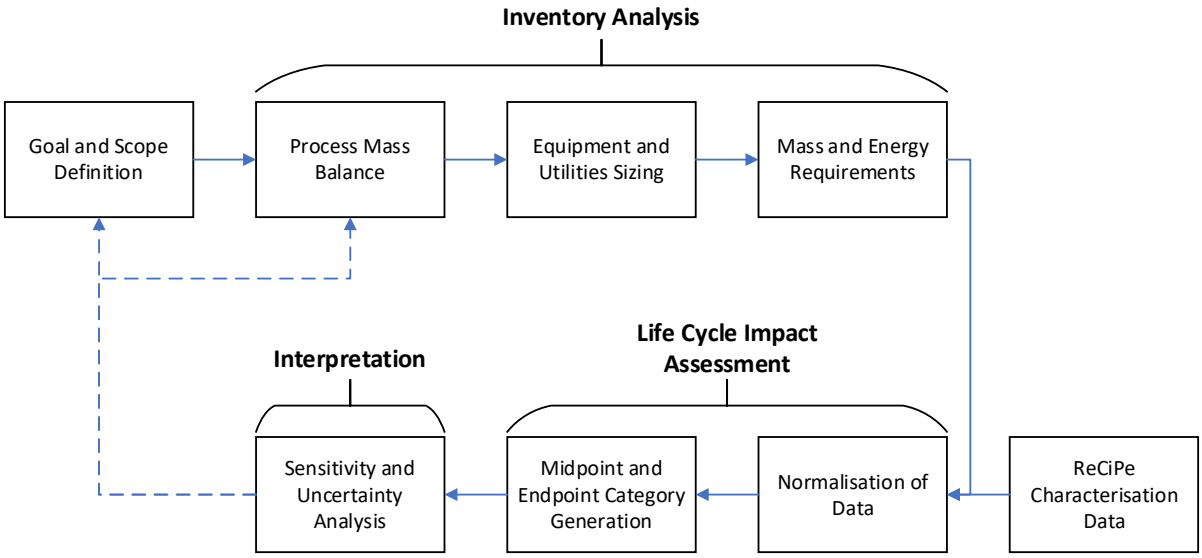


Figure 10: Flowchart for life cycle assessment showing how inventory analysis is related to midpoint and endpoint categories

Midpoint and endpoint categories are described as part of ReCiPe for LCA method (ReCiPe, 2008). Figure 11 demonstrates how the midpoint and endpoint categories are evaluated from the LCA flowchart in Figure 10 and the characterisation data, sourced from literature, displayed in Table 11.

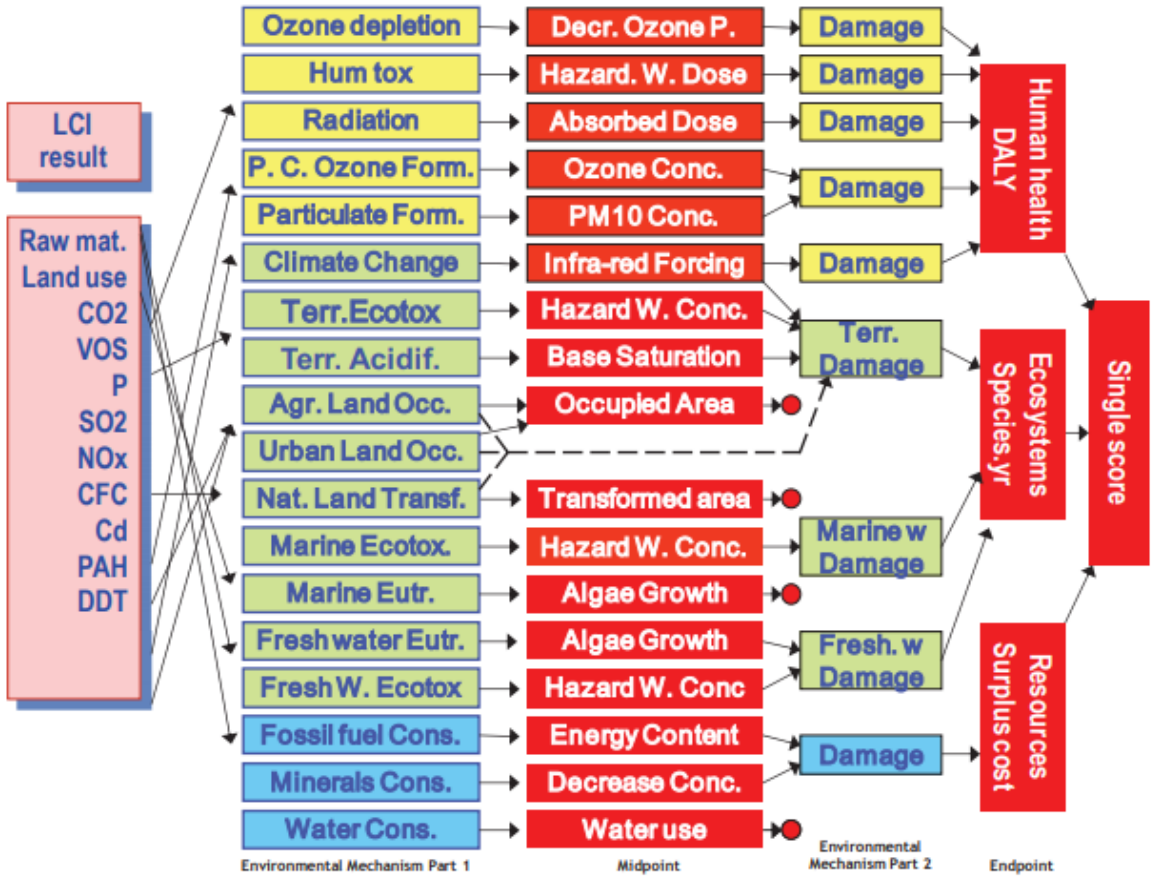


Figure 11: Development of midpoint and endpoint categories from characterisation data (ReCiPe, 2008)

For those categories for which characterisation data was not readily available, no comparison was completed, and concerns with these potential shortcomings were addressed as part of the uncertainty analysis.

3.5.Interpretation

Interpretation of the data was completed for two purposes; identification of critical variables, and analysis of their influence to fully evaluate the impact on the difference between the two scenarios; and to conduct uncertainty analysis and evaluate the potential for error propagation throughout the experimental system. A two-way analysis of variance (ANOVA) experiment was carried out to evaluate the impact of variables from the inventory analysis phase on the

difference in life cycle impacts between the two scenarios, while a Monte Carlo simulation was carried out on the life cycle impact assessment data to determine uncertainty and potential impact on the study outcomes.

Table 11: Characterisation data utilised in the study

Material/Energy Source	Unit	GW	SOD	IR	HDOF	FPMF	EDOF	TA	FE	ME	TE	FEC	MEC	HCT	HNCT	LT	LO	WC	MRS	FRS	Reference
		kg CO2 eq	kg CFC11-eq	kBq Co-60 to air eq	kg NOx-eq	kg PM2.5-eq	kg Nox-eq	kg SO2-eq/kg	kg P-eq. to freshwater/kg	kg N-eq to marine water/kg	1,4-DCB eq. emitted to industrial soil	1,4-DCB eq. emitted to freshwater	1,4-DCB eq. emitted to seawater	1,4-DCB eq. emitted to urban air	1,4-DCB eq. emitted to urban air	m^2 land transformed	m^2 land occupied	m^3 water consumed	kg Cu-eq/kg ore	kg oil-eq/unit of resource	
Stainless Steel	kg	4.28			0.01	0.02	0.01	0.04										81.54	0.1	0.59	ISSF (2010)
Plastics																					
Low density polyethylene (LDPE)	kg	3.59						0.03			0.04	0.21	1610							1.88	Harding et al. (2007) Franklin Associates (2011)
Polyethylene terephthalate (PET)	kg	4.12						0.02			0.01	0.11	1290							1.55	Harding et al. (2007) Franklin Associates (2011)
Thermoplastic Elastomer (TPE)	kg	5.43											1333							2.03	Harding et al. (2007) Franklin Associates (2011)
Polycarbonate (PC)	kg	3.25						0.05			0.04	0.23	1850							1.82	Harding et al. (2007) Franklin Associates (2011)

Material/Energy Source	Unit	GW	SOD	IR	HDOF	FPMF	EDOF	TA	FE	ME	TE	FEC	MEC	HCT	HNCT	LT	LO	WC	MRS	FRS	Reference
		kg CO2 eq	kg CFC11-eq	kBq Co-60 to air eq	kg NOx-eq	kg PM2.5-eq	kg Nox-eq	kg SO2-eq/kg	kg P-eq. to freshwater/kg	kg N-eq to marine water/kg	1,4-DCB eq. emitted to industrial soil	1,4-DCB eq. emitted to freshwater	1,4-DCB eq. emitted to seawater	1,4-DCB eq. emitted to urban air	1,4-DCB eq. emitted to urban air	m^2 land transformed	m^2 land occupied	m^3 water consumed	kg Cu-eq/kg ore	kg oil-eq/unit of resource	
Process/Cleaning Materials																					
Cellulose	kg	1																			Manda et al. (2012)
Sodium Hydroxide	kg	0.63																			Thannimalay. (2013)
Citric Acid	kg	0.41																			Nica & Woinaroschy (2010)
Chromatography resins	kg	20.5																			Kim et al. (2009)
Water	kg																	0.001			N/A
Utilities																					
Natural Gas	kWh	0.20437																		0.0756	SEAI (2020)
Electricity	kWh	0.4091																		0.1512	SEAI (2020)
Cobalt-60 (Co-60)	mg	2.193																			Nian (2015)

Chapter 4: Life Cycle Assessment Results and Discussion

4.1.Inventory Analysis

The inventory analysis was completed for a base case using values described in Table 12. In addition to process variables previously described, additional variables which were assessed as relevant to the study outcomes are included. Results for the intermediate functional unit, 18.2kg product/annum production, will be described in full as a sample.

Table 12: Critical variable values for the base case.

Parameter	Unit	Base Case
Cell-specific productivity	pg/cell/day	30
Protein Residence Time	Day^{-1}	0.4
Viable Cell Density	million cells/mL	35
UFDF1 Run Interval/Pooling Duration	Days between UFDF runs	5*
Target Concentration factor	N/A	20
Rejection Coefficient	N/A	0.975
Number of Diavolumes	N/A	5
UFDF1 Runs/DS Lot	Number of UFDF1 runs per DS Lot	4
Resin Binding Capacity	g product/L resin	40
Target Concentration	mg/mL	35
Rejection Coefficient	N/A	0.999
Number of Diavolumes	N/A	20
Durable life of steel	Years	6
Chromatography column lifespan	Cycles	50
Transportation – local	Kilometres	150

Parameter	Unit	Base Case
Transportation – domestic	Kilometres	750
Transportation – international	Kilometres	3000
WFI/Steam Energy Mixture	% natural gas: electricity	80
Irradiation facility throughput	% facility share	10
Plastics packaging facility throughput	m^2 cleanroom /tonne plastic	3
Geography – electricity	Country	US
Steel – recycled	% steel recycled	40
Plastic – recycled	% plastic recycled	50

*applicable to stainless-steel scenario only, for single-use scenario, value is a function of maximum membrane area commercially available, $10m^2$.

Initially, a process mass balance was developed to provide volumetric requirements for both scenarios, the results of which are detailed in Figures 12, 13 and 14. Following this, utilities requirements and volumetric flowrates for cleaning fluids were estimated. These volumetric requirements were used to determine room areas for the different classifications, along with the overall facility area. A summary of the facility utilities and area requirements are shown in Table 13.

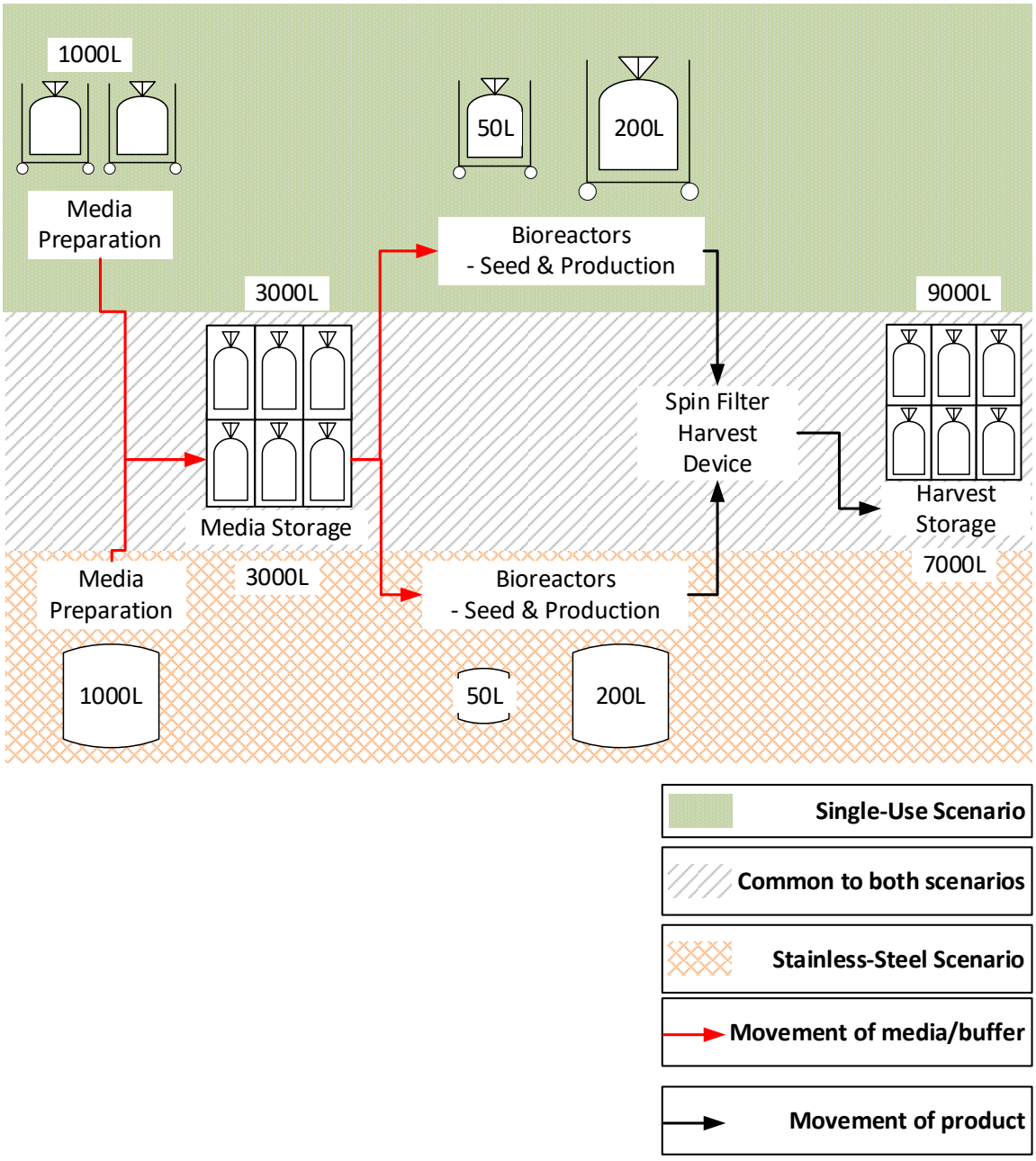


Figure 12: Cell culture fermentation volumetric requirements for single-use and stainless-steel scenarios for the intermediate functional unit, 18.2kg product/annum

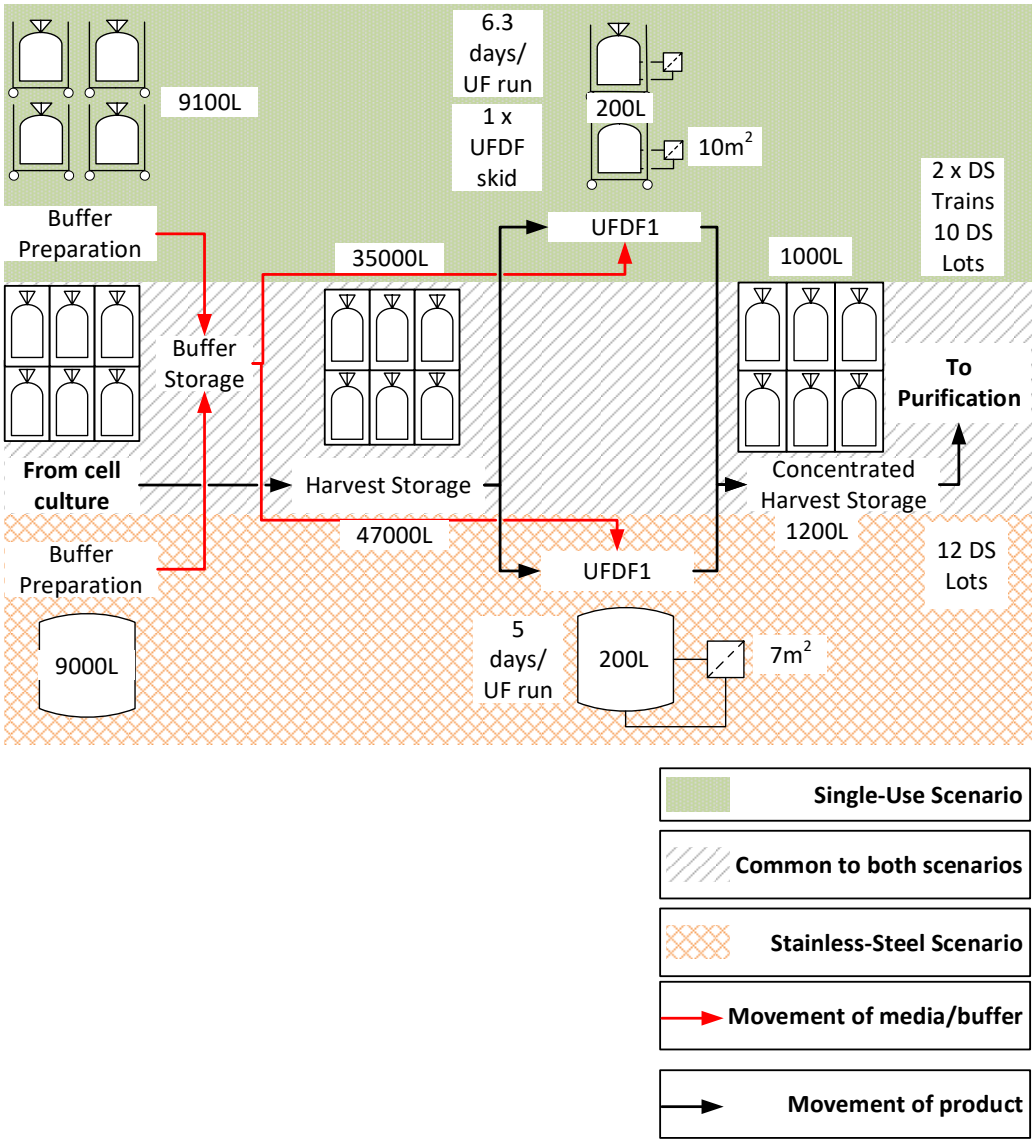


Figure 13: Harvest volumetric requirements for single-use and stainless-steel scenarios for the intermediate functional unit, 18.2kg product/annum

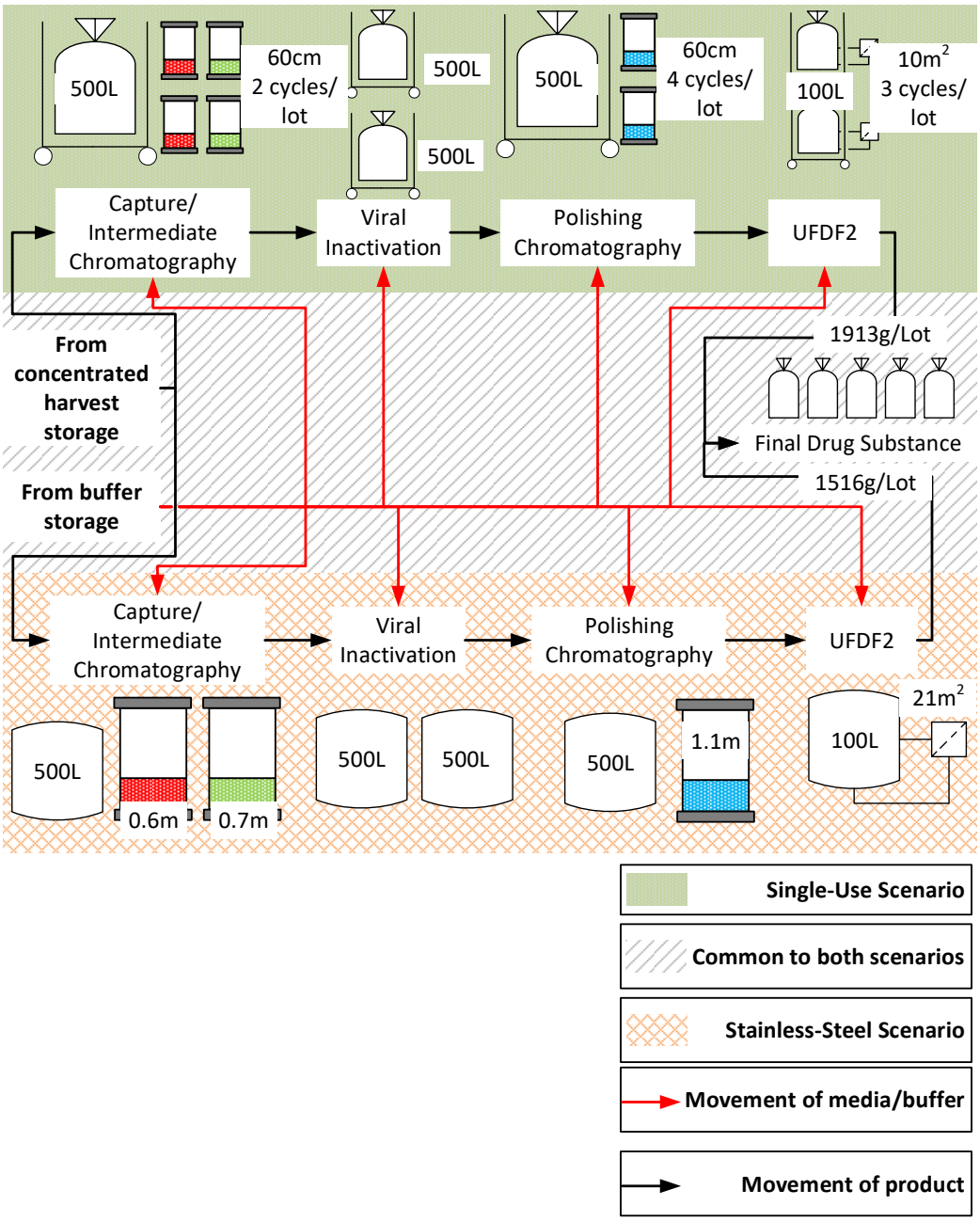


Figure 14: Purification volumetric requirements for single-use and stainless-steel scenarios for the intermediate functional unit, 18.2kg product/annum

Table 13: Comparison table (stainless-steel (SS) vs single-use (SU)) of vessel dimensions, cleaning flowrates, utilities requirements and facility floor areas required for the intermediate functional unit, 18.2kg product/annum

Quantity	SS	SU
Vessel Volumes (L)		
Media	1000	1000
Bioreactor	200	200
Buffer	9000	9100
UFDF1	200	200
DS Hold Vessels	500	500
UFDF2	100	100
Cleaning Flowrates (LPM)		
Media	163	N/A
Bioreactor	24	
Buffer	196	
UFDF1	32	
DS Hold Vessels	49	
UFDF2	26	
Utilities Requirements		
RIW		
Generation (LPM)	97	22.5
Storage (L)	20000	4050
WFI		
Generation (LPM)	97	22.5
Storage (L)	15000	1350
Pure Steam		
Generation (kg/hr at 2.2barg)	5.8	N/A
Facility Floor Areas (m^2)		
Grade D	194.4	132.2
Grade C	260.1	203.3
Grade B	12.4	3.4

Following the determination of all facility volumetric requirements, material and energy flows were obtained from each quantity, as described in section 3.3. These material and energy flows are expressed in Table 14 in terms of the functional unit, standardised to the production of a gram of product, to allow for direct comparison across all combinations of scenarios and functional units.

Table 14: Inventory analysis results for the base case

Functional Unit	Scenario	Stainless Steel	LDPE	PET	TPE	PC	Cellulose	Sodium Hydroxide	Citric Acid	Chromatography Resins	Water	Natural Gas	Electricity	Cobalt-60 (Co-60)
kg product/ annum		kg material/g product										kWh/g product		mg/g product
3.64	SU	11.95	2.37	0.247	4.79	3.68	1.98	0.26	0	0.11	733.82	179.7	1533.86	2.7139
	SS	21.21	1.16	0.121	0.29	2.29	2.37	1.29	1.35	0.05	3070.13	754.93	2018.67	1.0901
18.2	SU	2.4	0.86	0.09	0.35	2.63	1.93	0.26	0	0.11	345.63	84.64	316.09	1.6407
	SS	5.25	0.42	0.044	0.02	1.48	1.9	0.74	0.8	0.03	1115.68	274.99	588.33	0.7071
36.4	SU	1.76	0.63	0.066	0.28	1.22	1.9	0.26	0	0.11	292.84	71.71	282.28	1.1633
	SS	3.16	0.32	0.033	0.02	0.75	1.66	0.54	0.46	0.04	718.95	177.47	366.84	0.6019

From Table 14, it can be seen that there are significant differences between material and energy flows for the two scenarios. As expected, the stainless-steel scenario requires more stainless-steel, sodium hydroxide and citric acid, due to the vessel materials of construction and cleaning requirements. This also explains the larger water and natural gas requirements to support the generation of RIW and WFI. The single-use scenario uses more plastic componentry, most notably TPE which is used in place of pipework for transfer of process fluids. The single-use scenario also utilises more chromatography resins, as they are used more per batch than the larger scale variety in the stainless-steel scenario. More Co-60 is also required by the single-use scenario for irradiation of the plastic components. The stainless-steel scenario utilises more electricity, due to the increased footprint of the manufacturing facility necessary from the

stainless-steel equipment, and the decreased containment contributing to increased HVAC requirements.

4.2.Life Cycle Impact Assessment

4.2.1. Midpoint Impact Categories Comparison

Following the generation of inventory analysis data, the characterisation data detailed in Table 11 was used to evaluate the impact of each functional unit by impact category for impact categories for which data was available. Data was standardised to a value in the range of 0-10. Table 15 shows the data for all life cycle impact categories.

Table 15: Midpoint impact categories by functional unit displayed by standardised values, with table indicating standardisation values.

Impact per gram product	GWP tonnes CO2 eq	HDOF kg Nox eq	FPMF kg PM2.5 eq	EDOF kg Nox eq	TA kg SO2 eq	TE kg 1,4-DCB eq to industrial soil	FE kg 1,4-DCB eq to freshwater	ME 10,000kg 1,4-DCB eq to seawater	WC 1000m3 water	MRS kg Cu eq	FRS 100kg oil eq
3.64 SU	0.78	0.12	0.24	0.12	0.74	0.24	1.37	1.73	0.98	1.2	2.77
3.64 SS	1.09	0.21	0.42	0.21	1	0.14	0.78	0.66	1.73	2.12	3.83
18.2 SU	0.18	0.02	0.05	0.02	0.26	0.14	0.8	0.68	0.2	0.24	0.64
18.2 SS	0.33	0.05	0.11	0.05	0.3	0.08	0.43	0.35	0.43	0.53	1.17
36.4 SU	0.15	0.02	0.04	0.02	0.15	0.07	0.42	0.37	0.14	0.18	0.54
36.4 SS	0.21	0.03	0.06	0.03	0.17	0.04	0.24	0.2	0.26	0.32	0.73

At midpoint level, the impact of the functional unit is notable as economies of scale are achieved, with reductions in overall impacts per category as the functional unit increases. The single-use scenario has reduced impacts in all categories at all functional units with the exception of terrestrial, freshwater and marine ecotoxicity, with the marine ecotoxicity impact the most notable.

4.2.2. Endpoint Impact Category Comparison

The three endpoint categories assessed as part of the ReCiPe for LCA methodology were impact to human health, measured in disability-adjusted life years (DALYs), ecosystem damage, measured in species loss per year (species.yr) and resource scarcity, measured in increased cost to produce resources ($). Midpoint values from Table 11 were used to calculate the impacts in the three endpoint categories.

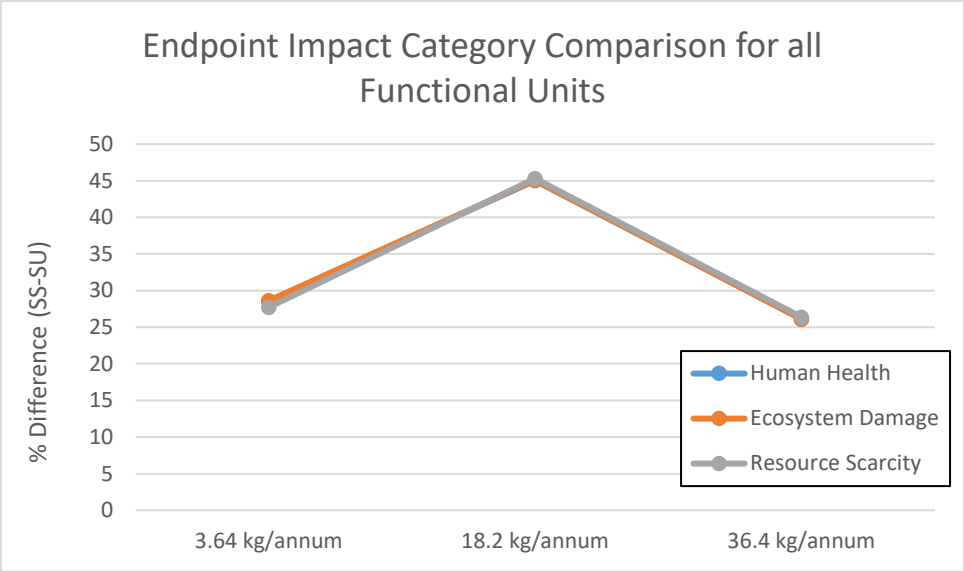


Figure 15: Results comparing the difference in environmental impact of the scenarios across all functional units and impact categories

Life cycle impacts from the full process train indicate the single-use scenario yields lower environmental impacts compared to the stainless-steel scenario across all functional units as detailed in Figure 13. The difference is seen to increase as the functional unit increases from the 3.64kg/annum to 18.2kg/annum, due to the additional CIP/SIP requirements from the stainless-steel scenario outweighing the additional componentry required in the single-use scenario. The difference then decreases from the 18.2kg/annum to 36.4kg/annum functional units, as the additional purification trains and scale required for the single-use scenarios exceeds the additional CIP/SIP requirements at the larger scale.

4.2.2.1.Endpoint Impact Category Contribution

The endpoint impact categories for the stainless-steel and single-use scenarios were investigated at the 18.2kg/annum functional unit to determine the primary contributions from the midpoint categories from Section 3.2.1. Figure 16 shows the composition of the endpoint impact categories.

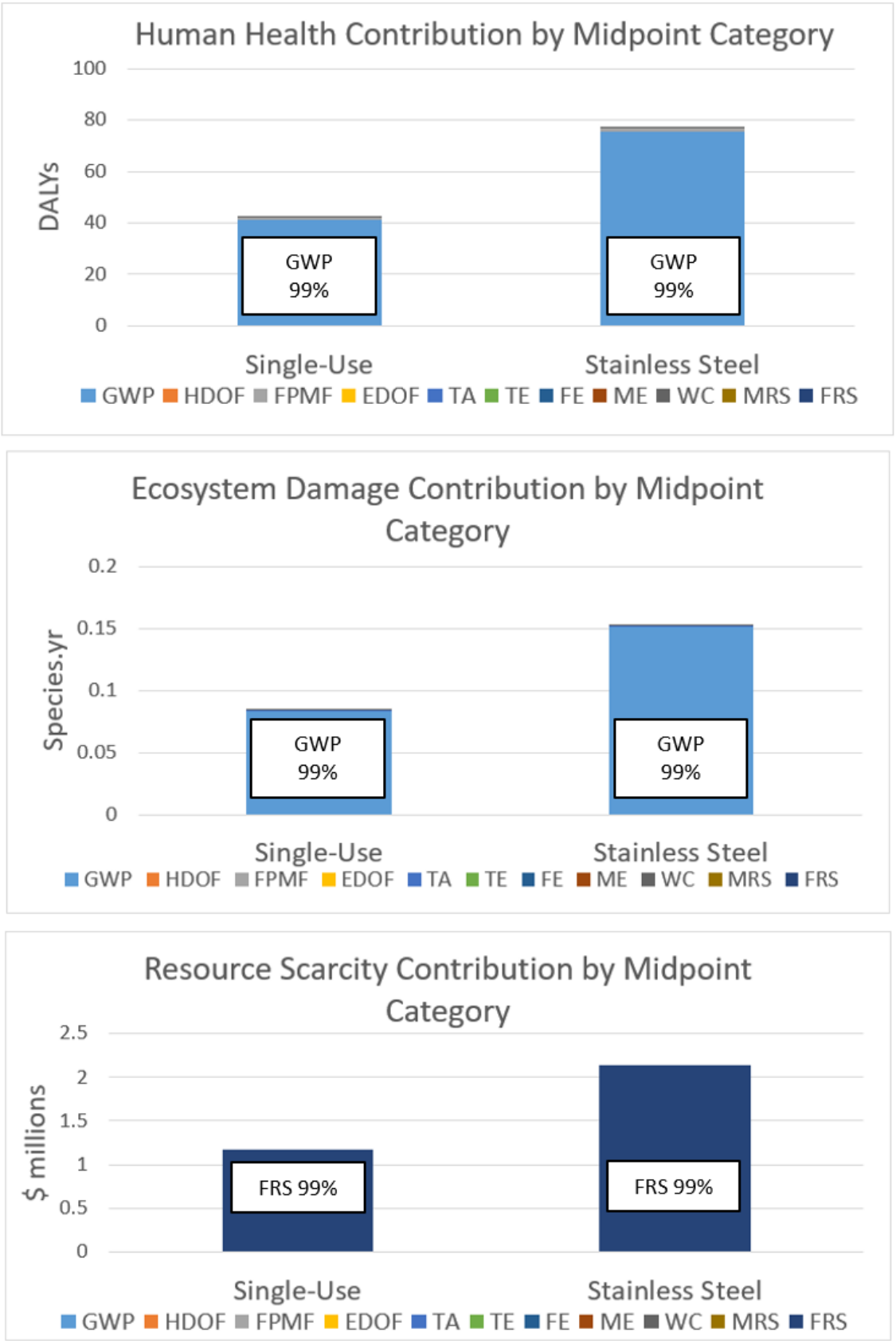
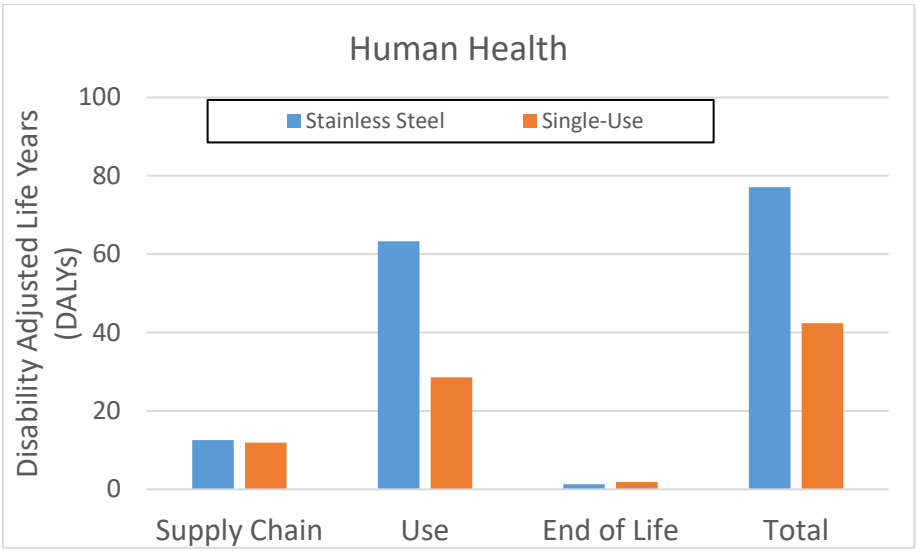


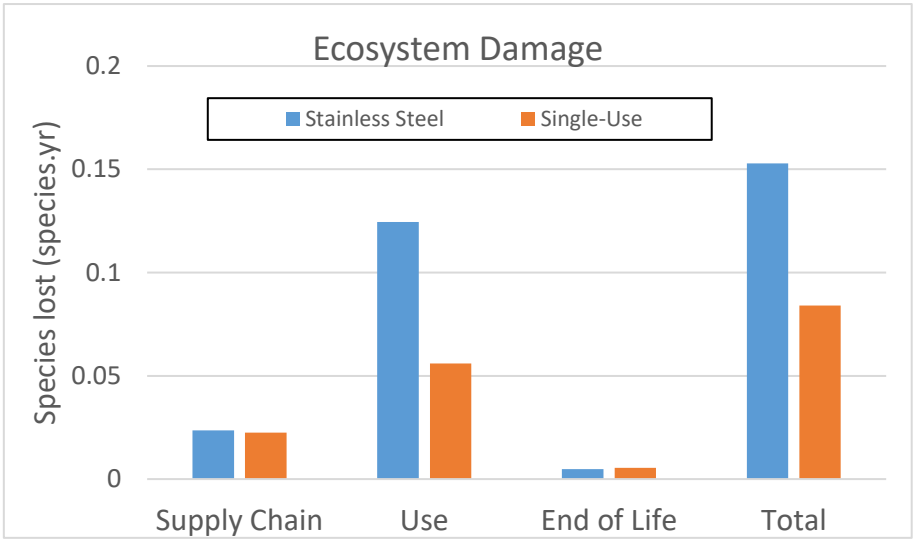
Figure 16: Primary contributions to endpoint impact categories from midpoint impact categories showing Global Warming Potential (GWP) and Fossil Resource Scarcity (FRS) as the primary midpoint categories contributing to each endpoint category

The primary contributions to endpoint impact categories from midpoint impact categories came from the global warming potential (GWP), fine particulate matter production (FPMF) and water consumption (WC) categories for the impact to human health and ecosystem damage categories, and from the fossil resource scarcity (FRS) category for the resource scarcity category. Each of these impacts is principally derived from the mining and burning of fossil fuels for material and energy production. This is important to note from an amelioration perspective, as reducing environmental impacts is therefore contingent on the supply of alternative energy and materials sources.

4.2.2.2.Endpoint Impact Category Comparison for Stainless-Steel and Single-Use

To further evaluate the difference in the endpoint impact categories between the stainless-steel and single-use scenarios, both categories were investigated at the 18.2kg/annum functional unit to determine at which phase of the lifecycle most impacts occurred. The results of this analysis are presented in Figure 17.





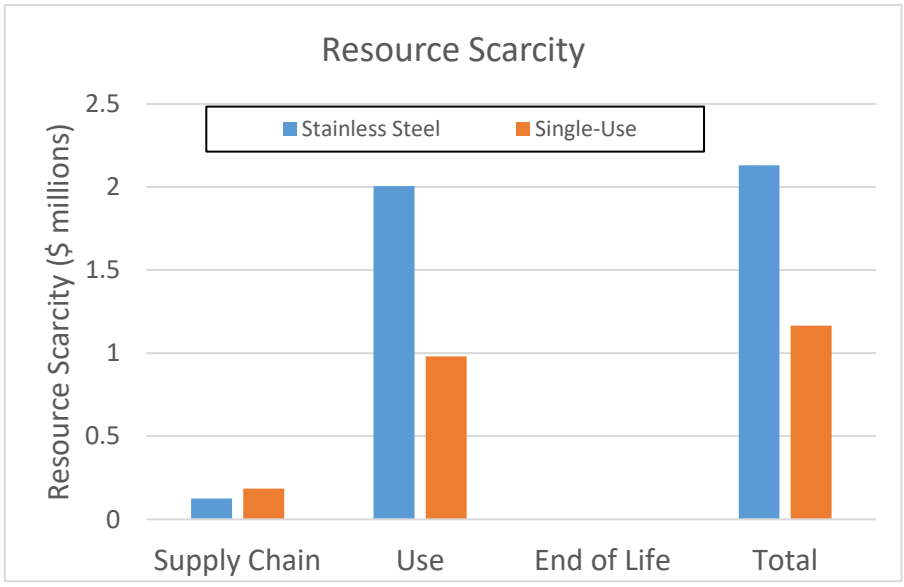


Figure 17: Comparison of endpoint impact categories between the stainless steel and single-use scenarios

It can be seen that the primary difference between the scenarios is the impact in the Use phase. The Use phase consists of the energy and water requirements to supply utilities for CIP/SIP of vessels, process fluids and the HVAC requirements to maintain the classified areas. The impacts at the Supply Chain and End-of-Life phases are comparable, indicating no significant difference between the procurement, transportation and disposal of stainless steel equipment compared to single-use equivalents.

4.3.Interpretation

4.3.1. Interpretation of the base case

The identified material and energy flows of interest were primarily related to equipment materials of construction and cleaning and sterilisation materials for both scenarios. As expected, the material and energy usage per gram of product reduced with increasing overall production mass as economies of scale were achieved. There were no process reagents with significant disparities between scenarios, which was to be expected as these are influenced by the production mass as opposed to equipment volumes. The vast majority of impacts were as a result of fossil fuel use for material manufacture and transport and energy and water production and usage. The principal difference between the single-use and stainless steel scenarios was the elimination of the majority of CIP/SIP requirements in the single-use scenario, which contributed to smaller utility equipment requirements and a lower water and energy demand.

Further interpretation of results was completed to establish which unit operations had the largest contribution to environmental impacts, and discern any differences between scenarios. An analysis was conducted at the 18.2kg/annum functional unit for each scenario at the endpoint impact categories, depicted in Figure 18.

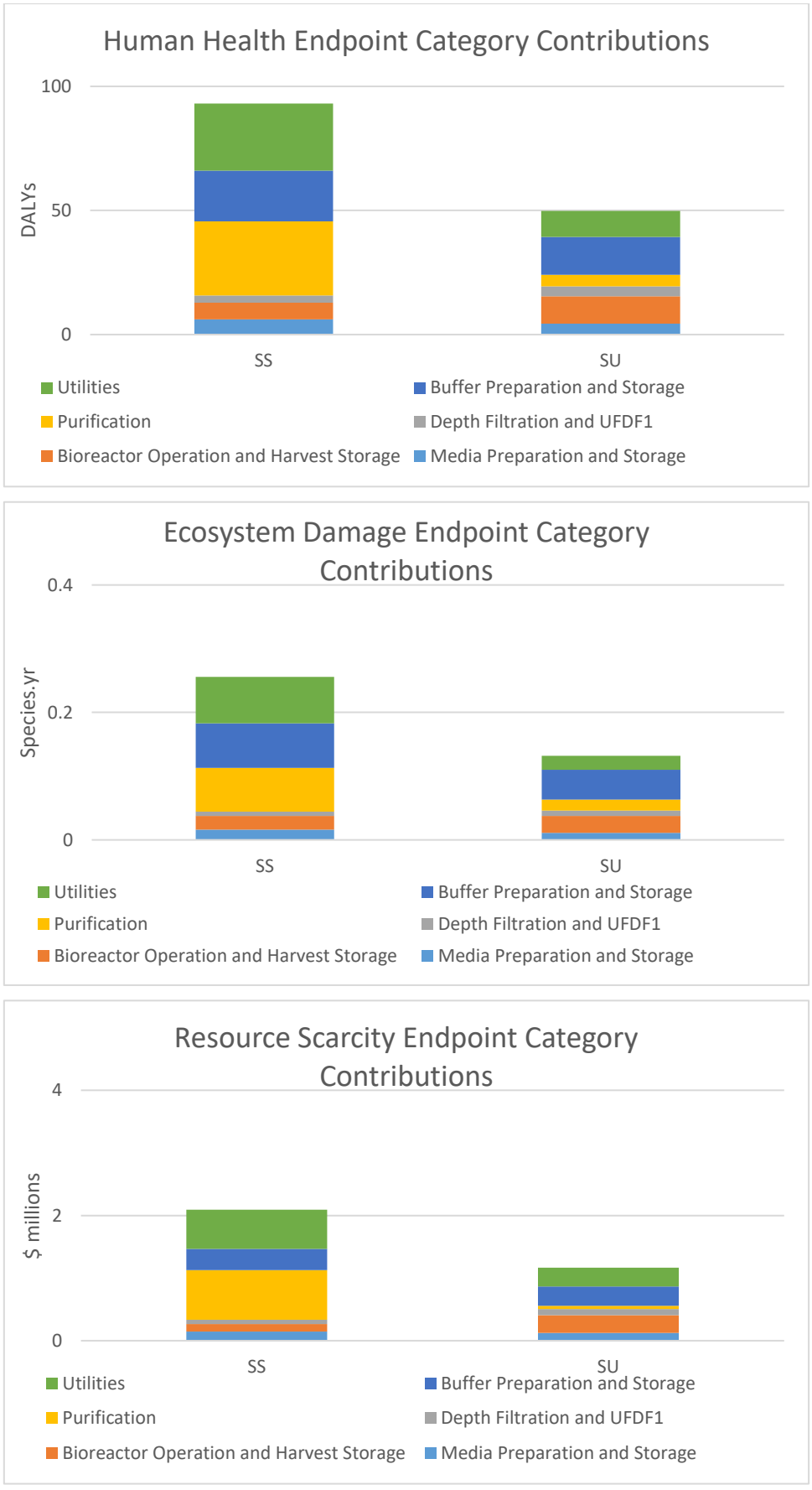


Figure 18: Endpoint impact category contributions by unit operation category

Across each endpoint impact category for the 18.2kg/annum functional unit at the base case, the utilities category, comprising the water storage and generation equipment and maintenance and the ancillary plant areas such as storage, and the purification category, comprising the chromatography, viral inactivation, UFDF2 and hold vessels equipment and cleaning, showed the largest variation between scenarios. The difference in the utilities category can be explained by the larger scale WFI generation necessary to support the CIP/SIP system throughout the facility, contributing to increased water and energy consumption. This also explains the difference in the purification category, due to the CIP requirements for the stainless steel equipment. In all other categories, there is no significant difference between scenarios.

The base case yields interesting results. The primary difference between the stainless-steel and single-use scenarios is the increased water and energy usage of the stainless-steel category from the generation of WFI for CIP/SIP. This corresponds with existing research for fed-batch biopharmaceutical production, showing that for common cell culture modalities for biopharmaceuticals, it is more environmentally benign to utilise single-use technology than traditional stainless-steel.

While single-use technology is proven less environmentally impacting than stainless-steel, there are still significant impacts to be seen across all endpoint categories. It is clear that further technological development is required to achieve lower and perhaps zero impacts from biopharmaceutical manufacturing. These impacts would achieve the largest gains if they were to revolutionise WFI generation, currently almost exclusively by multi-effect distillation, and the use of non-fossil fuel derived plastics. Other amelioration efforts, such as the use of renewable energy sources for the HVAC systems, and the use of reduced-impact stainless steel, require development not only in the biopharmaceutical industry, but across modern society.

4.3.2. Sources of Impacts throughout the Life-Cycle

It can be seen that the primary impacts observed in both scenarios is as a result of Global Warming Potential (GWP) and Water Consumption (WC) for the Human Health and Ecosystem Damage impact categories. For purposes of comparison, it is of interest to compare the sources of these impacts throughout the life-cycle, which is completed in Table 16 and 17.

Table 16: Comparison of sources of global warming potential (GWP) for SS and SU along the life cycle for 18.2kg/annum scenario

Major sources of GWP along life cycle	SS		SU	
	tonnes of CO_{2_eq}	% of total	tonnes of CO_{2_eq}	% of total
Supply Chain				
Stainless Steel	198.2	3.3	75.3	2.3
LDPE	24	0.4	36	1.1
PET	3.3	0.1	5	0.1
TPE	6	0.1	39.3	1.2
PC	12	0.2	36	1.1
Cellulose	30	0.5	26.2	0.8
Chromatography Resins	12	0.2	29.5	0.9
Cobalt-60	24	0.4	32.8	1
Other raw materials	852.9	14.2	599.5	16.4
Transport	180.2	3	114.7	3.5
Use	0		0	
Natural Gas	702.7	11.7	190	5.8
Electricity	3885.9	64.7	2014.7	61.5
End of Life	0		0	
Plastic Disposal	72.1	1.2	140.3	4.3
Total	6006	100	3276	100

Table 17: Comparison of sources of water consumption (WC) for SS and SU along the life cycle for the 18.2kg/annum scenario

Major sources of WC along life cycle	SS		SU	
	tonnes of water	% of total	tonnes of water	% of total
Supply Chain				
All sources	1235.6	6.1	2490.9	39.6
Use				
Process Water	19069.8	93.9	3799.1	60.4
Total	20305.4	100	6290	100

From Table 16 and 17, it can be seen that there is variability in the impacts throughout the life-cycle between scenarios. For the GWP impact category, the impacts are primarily in the use phase due to the large electricity and natural gas requirements for WFI generation and HVAC maintenance. There are larger impacts on a percentage basis from the end-of-life phase for the single-use scenario, while there is some variability in the supply-chain phase, due to the differences between scenarios in plastic and stainless-steel requirements. For the WC impact

category, it can be seen that there is dramatically lower water requirements for the single-use scenario, with a significant shift from the use phase to the supply-chain phase compared to the stainless-steel scenario. This is as a result of the increased requirements for water for cleaning and steaming for the stainless-steel scenario, coupled with the increased supply-chain impacts of the single-use scenario.

4.3.3. Analysis of Variance and Uncertainty Analysis

4.3.3.1.Analysis of Variance

A two-way analysis of variance (ANOVA) was carried out to investigate the impact of selected process variables on the difference in impact observed. Table 18 details the variables investigated and their low and high coded values.

Table 18: Variables investigated by two-way ANOVA at high and low levels.

Variable	Coding	High	Middle	Low	Unit
Protein residence time	RT_MAX	0.6	0.4	0.2	days
Durable life of steel	LIFE_SS	10	6	2	years
Chrome column lifespan	LIFE_CC	70	50	30	cycles
Transportation – Local	T_LOC	250	150	50	km
UFDF1 Batch Interval	UFDF_INT	9	5	1	Days between UFDF1 batches
WFI/steam energy mixture	E_MIX	0.95	0.8	0.65	% natural gas/electricity
Transportation – domestic	T_DOM	1000	750	500	km
Irradiation facility throughput	IRR_P	15	10	5	% facility share
UFDF1 batches per purification batch	PUR_INT	6	4	2	UFDF1 batches per purification batch
Plastics packaging facility throughput	FAC_P	5	3	1	m^2 cleanroom/tonne material
% steel recycled	REC_SS	0.8	0.4	0	%
% plastic recycled	REC_P	0.9	0.5	0.1	%
Geography - electricity	G_ELEC	Australia	US	EU	country
Transportation - international	T_INT	5000	3000	1000	km
Average resin binding capacity	RBC	50	40	30	g product/L resin

These variables were investigated using an L-16 orthogonal matrix at all three functional units. Figure 19 details the results of the experiment.

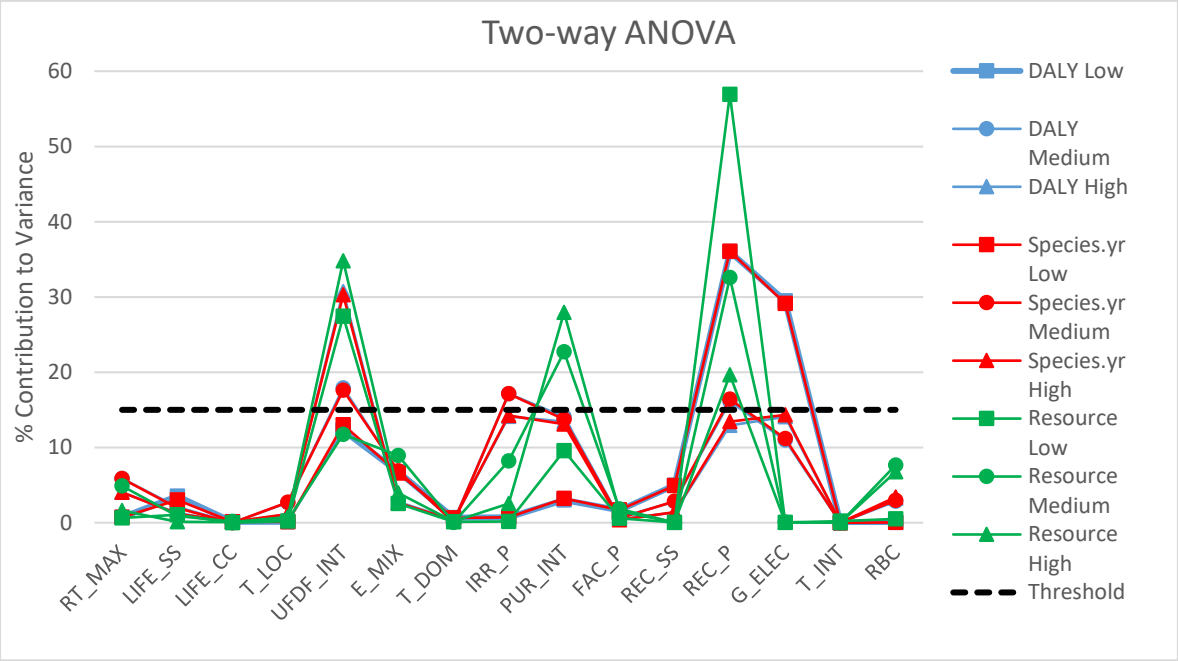


Figure 19: Results of the two-way ANOVA indicating the variables which contributed significantly to the variance in difference between the scenarios

The analysis of variance yielded five significant variables which contributed to >15% of the observed variance in the sample data as shown in Figure 10. Of these, two were classed as operational variables, while the remaining three were classed as infrastructural variables. This classification was made to distinguish the variables which can be influenced at the organisational level by key decision-makers, the organisational variables, from variables requiring cooperation from multiple stakeholders at societal and governmental levels, the infrastructural variables.

The significant operational variables were the UFDF1 Batch Interval, the contribution to variance of which decreased as the functional unit increased and the number of UFDF1 batches per purification batch, which had increasing contribution to variance with increasing functional unit. These variables are selected at the concept and design phase of the process and facility design, and are influenced primarily by the capital costs associated with equipment. Increasing the UFDF1 batch interval decreases the number of UFDF1 batches required, which results in larger equipment but reduced cleaning requirements, and was of reducing influence as the functional unit increased. The number of UFDF1 batches per purification batch influences the size of the purification process train, as if there are more UFDF1 batches per purification run,

it results in larger equipment and reduced cleaning. The contribution to variance increased as the functional unit increased. It can be concluded that as the functional unit increases, the process intensity at the UFDF1 stage is of interest due to its influence on the purification process train equipment size and cleaning requ

The infrastructural variables of significance were the geographical electricity mixture and the % plastics recycled. Both of these are reliant on the available services from private and government agencies and the infrastructure available. Where there is an abundance of electricity available from renewable and/or carbon-neutral sources, the environmental impacts of electricity usage are reduced, while if electricity is produced from primarily fossil fuel sources, the environmental impacts are increased. Similarly for plastics recycling, the location and logistics of disposal of single-use materials impacts the potential for recycling of plastics and reduction of impacts from incineration. Additionally, the amount of plastic which can be recycled may be limited by regulations on disposal of materials in contact with genetically-modified organisms (GMO), removing potential of recycling plastic and resulting in incineration being the only available disposal method.

4.3.3.2.Uncertainty Analysis

To overcome uncertainties introduced in the selection of LCIA data as detailed in Section 3.4, an uncertainty analysis was performed to investigate the propagation of errors in the dataset which could impact the result of the LCA. Based on the data presented in Section 3.4, and the nature of the material and energy flows identified for investigation, the primary impacts associated with the process under both scenarios came from the burning of fossil fuels, with the exception of Cobalt-60, which had an additional potential concern from ionizing radiation. Values for those data which were missing were estimated, as presented in Table 19. This estimation was based on interpolation of existing data assuming impacts were entirely from fossil fuel impact and applying them to missing data points to provide an estimate. For example, data was available for all impact categories for stainless steel, of which the source of impacts was primarily fossil fuel emissions. Therefore, it was assumed that the ratio of impacts was directly correlated to the global warming potential (GWP) emissions:

$$Impact\ category = f(GWP)$$

Therefore, for other materials/energy sources which did not have complete data, an interpolation was completed by leveraging the GWP data, which was available for most items.

$$Impact\ category = \frac{GWP_{material/energy\ source}}{GWP_{stainless-steel}} Impact\ category_{stainless-steel}$$

A Monte Carlo simulation of 3000 runs was then carried out, with variability introduced to the data using a random number generator following a normal distribution over a range of 0-2 times the data in Table 19. Given the variability introduced in the data followed a normal distribution, the null hypothesis for the Monte Carlo simulation was that the output data, the difference between scenarios, would be normally distributed with a mean of zero, i.e. it was equally probable that either scenario exhibited lower impacts. Figure 20 displays the Monte Carlo simulation results.

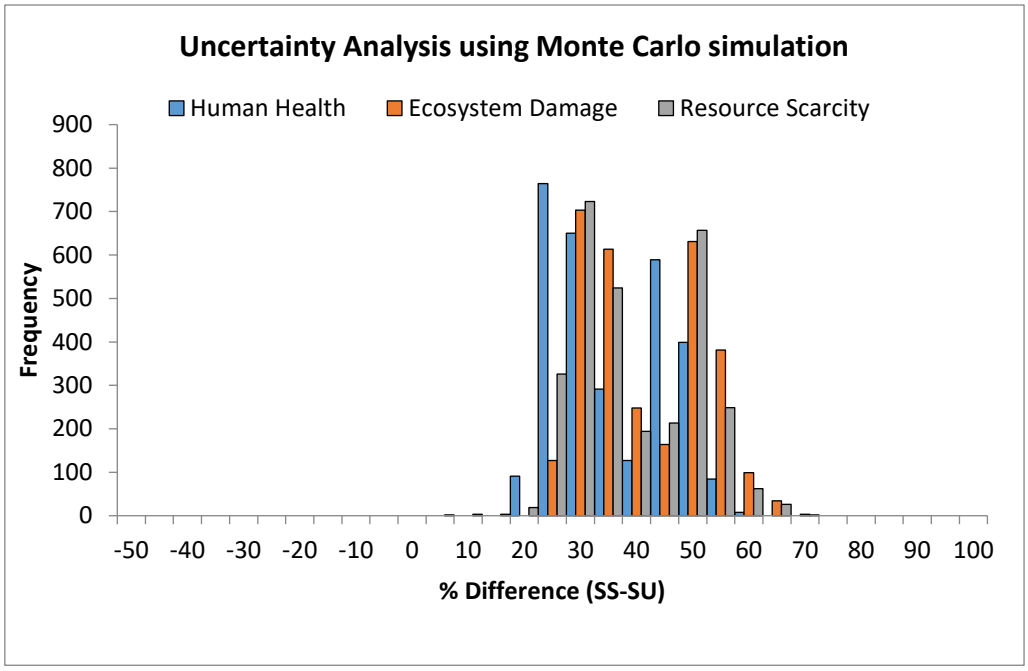


Figure 20: Monte Carlo simulation at 3000 runs showing >99% probability of reduced environmental burden for single-use scenario in comparison with stainless-steel

Table 19: Data utilised for uncertainty analysis, with estimated data displayed in bold text

Material/Energy Source	Unit	Global Warming	Stratospheric Ozone	Ionizing Radiation	Human Damage Ozone Formation	Fine Particulate Matter Formation	Ecosystem damage ozone formation	Terrestrial Acidification	Freshwater Eutrophication	Marine Eutrophication	Terrestrial Ecotoxicity	Freshwater Ecotoxicity	Marine Ecotoxicity	Human carcinogenic toxicity	Human noncarcinogenic	Land transformation	Land occupation	Water consumption	Mineral resource scarcity	Fossil resource scarcity
Stainless Steel	Kg	4.28			0.01	0.02	0.01	0.04			0	0	**1500**					81.54	0.1	0.59
Low density polyethylene (LDPE)	Kg	4.37			**0.02**	**0.02**	**0.02**	0.03			0.04	0.21	1610							2.17
Polyethylene terephthalate (PET)	Kg	4.91			**0.02**	**0.02**	**0.02**	0.02			0.01	0.11	1290							1.84
Thermoplastic Elastomer (TPE)	Kg	6.21			**0.02**	**0.02**	**0.02**	0.01			0	0	1333							2.32
Polycarbonate (PC)	Kg	4.03			**0.02**	**0.02**	**0.02**	0.05			0.04	0.23	1850							2.11
Cellulose	Kg	1			**0.005**	**0.005**	**0.005**	**0.011**			**0.009**	**0.053**	**423**							**0.483**
Sodium Hydroxide	Kg	0.63			**0.003**	**0.003**	**0.003**	**0.006**			**0.005**	**0.03**	**237**							**0.271**
Citric Acid	Kg	0.41			**0.001**	**0.001**	**0.001**	**0.003**			**0.003**	**0.015**	**122**							**0.139**
Chromatography resins	Kg	20.5			**0.102**	**0.102**	**0.102**	**0.254**			**0.203**	**1.17**	**9411**							**10.733**
Water	Kg																	0.001		
Natural Gas	kWh	0.20437			**0.001**	**0.001**	**0.001**	**0.002**			**0.002**	**0.012**	**90**					**8**		0.0756
Electricity	kWh	0.4091			**0.002**	**0.002**	**0.002**	**0.004**			**0.004**	**0.023**	**185**					**16**		0.1512
Cobalt-60	kg	2192750		**23165860**	**10880**	**10880**	**10880**	**27205**			**21765**	**125145**	**1006597395**					**85758985**	**0**	**1148065**

The uncertainty analysis was used to evaluate the propagation of errors throughout the experiment due to variability in data quality or due to a lack of data. Estimated data values identified are based on impacts being from fossil fuel usage, as there are no other perceived environmental impacts from the material and energy flows investigated with the exception of Cobalt-60. For this, the potential radioactive waste was determined by the amount of fission products from production, and the estimated value was for 1% of this waste escaping to air.

Several categories were not included in the uncertainty analysis, as no accurate data could be estimated for them, and it was determined that there would be no significant difference between scenarios based on this lack of data.

Data output from Monte Carlo simulation in Figure 18 displays a bimodal distribution, with a major peak in the 20-40% range and minor peak in the 40-60% range. A significance test, the Student *t*-test was carried out to determine the significance of the results. The significance test was carried out with the generated distributions in Figure X and a sample normal distribution with a mean of 0 and standard deviation equivalent to each distributions. A threshold of $p<0.05$ was set, which indicated that if the significance test returned a value above 0.05, then there was insufficient evidence to reject the null hypothesis, and a value below 0.05 indicated there was sufficient evidence to reject the null hypothesis. Table 20 shows the results of the significance tests.

Table 20: Results of significance test for Monte Carlo simulation

Endpoint Category	Standard Deviation	Results of *t*-test
Human Health	9.9%	0.0079
Ecosystem Damage	10.3%	0.0062
Resource Scarcity	10.6%	0.0056

The results of the significance test indicate that there is sufficient evidence to reject the null hypothesis, allowing a conclusion that the data quality did not significantly impact the results of the life cycle assessment.

4.4.Conclusions

This study has determined that the manufacture of biopharmaceuticals by perfusion cell culture using single-use technology results in reduced environmental burden than by conventional stainless-steel technology. The results of this work corresponds with the previous study by

Pietrzykowski et al. (2015) for fed-batch cell cultures, and shows that single-use technology reduces the overall environmental impacts of biopharmaceutical production regardless of the cell culture production mode utilised.

A number of questions are yet to be answered in the biopharmaceuticals manufacturing space. Focusing solely on environmental impacts, the consequences of cell culture production mode using single-use or stainless-steel technology should be investigated further. While Bunnak et al. (2016) determined that fed-batch production had reduced environmental impacts compared to perfusion production, further study should be conducted to determine the influence of technology selection on this result. In addition, evaluation of the potential for recycling of various materials used in the manufacturing process is required to mitigate end-of-life impacts, development of new technologies for the generation of WFI and possible implementation of raw materials from alternative sources such as biologically-sourced plastics may offer further reductions in environmental burden from the single-use scenario.

Viewing the sustainability of biopharmaceuticals manufacturing holistically, the impact of economic decisions on environmental impacts, and vice-versa, is required. As seen by the ANOVA completed in this study, decisions which are made at an organisational level to ensure economic sustainability have impacts on the environmental burden from the process. In such cases where decisions are made, it may be prudent for organisations to evaluate the economic and environmental impacts in tandem in order to ensure a viable economic model without compromising the environment.

Part III: Transitions to sustainable biopharmaceuticals manufacturing

Chapter 5: Green biopharmaceuticals: towards environmentally sustainable biopharmaceuticals manufacturing

As outlined in Chapter 4, the utilisation of single-use technology over traditional stainless-steel technology yields a reduction in environmental impacts on human health, ecosystem degradation and resource scarcity indices. While this presents an opportunity for reducing unsustainability in biopharmaceuticals manufacturing, it does not take a further step towards creating truly sustainable processes, not simply more efficient processes which continue to damage the ecosystems upon which we depend on to survive. For a rapidly expanding industry such as biopharmaceuticals manufacturing, having seen an explosion in activity since the discovery of recombinant human insulin in the early 1980s, increasing efficiencies is not enough to outpace growth patterns, ultimately leading to increasing overall environmental burden beyond the boundaries our planet can support. As such, the purpose of this chapter is to present the opportunities and challenges of creating environmentally sustainable processes for biopharmaceuticals manufacturing that can allow for near-total reduction in environmental burdens such that future generations can continue to benefit from biopharmaceutical treatments.

From Chapter 4, it can be seen that the primary environmental burdens of biopharmaceuticals manufacturing processes are as a result of the material and energy flows for the manufacturing of equipment, be it stainless-steel or single-use, energy usage for the maintenance of manufacturing cleanrooms, the generation of WFI for use in CIP/SIP as well as for process use such as in growth media and buffer preparation, and the raw materials used in the manufacturing process such as growth media and buffer components. A summary is displayed in Table 21.

Table 21: Summary of environmental burden from 18.2kg/annum scenario investigated in Chapter 4

	Single-Use			**Stainless-steel**		
	DALYs	**Species.yr**	**$ millions**	**DALYs**	**Species.yr**	**$ millions**
Stainless-steel	2.9	0.005	0.027	6.3	0.011	0.059
Polymeric materials	4.3	0.009	0.153	2.3	0.005	0.076
Cleanrooms	23.5	0.047	0.696	43.8	0.088	1.295
WFI	9.8	0.02	0.29	23.8	0.048	0.702
Raw Materials	0.6	0.001	0	0.3	0.001	0
Total	41.1	0.082	1.166	76.5	0.153	2.132

Each of these environmental impacts will be considered in turn to quantify the environmental impact, identify practices and technologies with the potential to ameliorate the environmental impact, and the challenges facing the implementation of these practices and technologies.

5.1.Equipment manufacturing – stainless-steel

5.1.1. Existing methods and requirements

Traditional equipment for biopharmaceuticals manufacturing is required to be designed in such a manner as to reduce the potential for microbial growth which may compromise the safety of the product. As such, a number of key criteria and practices are utilised to prevent microbial growth. For the most part, 316L stainless-steel with a surface finish of <0.2Ra is used for surfaces which are in process contact. Stainless-steel is used as it is resistant to degradation or "rouging" which could lead to oxidation and the leaching of oxides into the process causing potential interference with the product or its safety. A high surface finish is required to prevent microbes from being retained in microscopic cracks or crevices which could lead to contamination. Surfaces which are not in process contact, such as supporting beams or platforms in the cleanroom areas, are generally composed of 304L stainless-steel, to maintain a hygienic environment in the manufacturing area.

5.1.2. Environmental burden

Stainless-steel fabrication is an energy-intensive activity due to the energy necessary to extract, refine and transport raw materials before the steel process proceeds using processes such as electric arc furnace, argon oxygen decarburization and cold and hot rolling to generate bulk stainless-steel as sheets, slabs and rods, among other shapes. This bulk material is then further processed into desired shapes such as rolling into pipework or shaping into vessels and vessel tops, followed by treatment by electropolishing and passivation to generate required surface finishes for hygienic manufacturing. Stainless-steel production in modern processes also utilises predominantly scrap steel, with recycling levels of up to 80% seen in European manufacturing. Overall, stainless-steel fabrication composes a modest portion of the overall impacts, approximately 6-10%, from the biopharmaceuticals manufacturing process, with larger impacts seen when using virgin stainless-steel and less modern processes.

5.1.3. Achieving sustainability – opportunities and challenges

There are limited possibilities to reduce the impacts from stainless-steel fabrication on the environmental burdens of biopharmaceuticals. The elimination of stainless-steel in favour of

single-use technology has shown benefits based on reduction in facility footprint and cleaning/steaming requirements. Reductions in environmental impacts can be seen by utilising recycled stainless-steel in place of virgin material, and in addition, increasing the lifetime of process equipment can contribute to impact reductions. Such extensions in service life can be achieved by proper equipment maintenance by prevention of oxidation or "rouging" through a preventative maintenance program or by reducing contact duration with harsh chemicals including high/low pH and high ionic strength solutions. This may not be feasible, as it is contingent on the process nature and so could prove unviable for many processes.

5.2.Equipment manufacturing – polymeric materials

5.2.1. Existing methods and requirements

A wide range of polymeric materials may be used in the biopharmaceuticals manufacturing process. Common materials of construction for various equipment includes:

- **Bag Films**
  - **Product contact layer:** LDPE, EVA
  - **Gas barrier layer:** EVA, PET
  - **Support layer:** Nylon, LDPE
- **Tubing**
  - **Silicone**
  - **Thermoplastic elastomers:** C-Flex (Saint-Gobain)
- **Filters**
  - **Filter membranes:** PVDF, PES, Cellulose
  - **Filter supports:** Polycarbonate
- **Fittings/Connectors –** AseptiQuik (CPC)
  - **Polycarbonate**
  - **Polypropylene**
  - **Polysulfone**

There are a large amount of items to consider when implementing a polymeric material in the manufacturing process. By their nature, polymeric components are more fragile than their stainless-steel counterparts, and so require supporting equipment such as containers to prevent damage. Compatibilities with conditions such as temperature and pressure are also challenges as there are limitations on what polymeric components can be subjected to without failure.

The most pressing concern with polymeric materials is the propensity for compounds to migrate from the polymeric component into the process stream and ultimately into the drug product. These compounds could then impact the safety or efficacy of the drug product. Extensive qualification may be necessary to verify materials are suitable for use in a particular manufacturing process should risk factors such as extended processing durations, excessive temperatures or extremes of pH be present.

The majority of polymeric materials used in the biopharmaceuticals manufacturing process are subjected to sterilisation prior to use, either by steam sterilisation or, more commonly, by gamma irradiation using a radioactive isotope such as cobalt-60. Validation of this process per standards such as ISO11137 (ISO, 2018) is required to ensure sterilisation is adequately completed, and this process is completed in a dedicated facility, as opposed to in-house as part of the biopharmaceuticals manufacturing process.

5.2.2. Environmental burden

The primary source for the raw materials used in polymeric materials manufacturing is fossil fuels. In addition, the manufacturing process is energy-intensive. Sterilisation by gamma irradiation requires the use of radioactive isotopes which necessitate the mining and refining of uranium followed by the bombardment of cobalt in a nuclear reaction to generate cobalt-60, and as such is highly energy-intensive, although the sterilisation of even large amounts of polymeric material does not require a significant volume of cobalt-60. Holistically, the use of single-use polymeric components accounts for 4-8% of the overall impact of a typical biopharmaceuticals manufacturing process primarily through impacts from global warming potential from the use of fossil fuels.

5.2.3. Achieving sustainability – opportunities and challenges

While fossil fuels are a traditional primary source for the raw materials necessary to produce polymeric materials, there are a host of biologically-sourced polymers being developed globally. For example, biologically-sourced polyethylene may be manufactured using ethylene sourced from bioethanol produced by fermentation of agricultural products or by-products. This presents an opportunity to eliminate the use of fossil fuels in polymer production by using biologically-sourced raw materials in place. Figure 21 shows the life cycle of polyethylene synthesised from fossil fuel and biological sources.

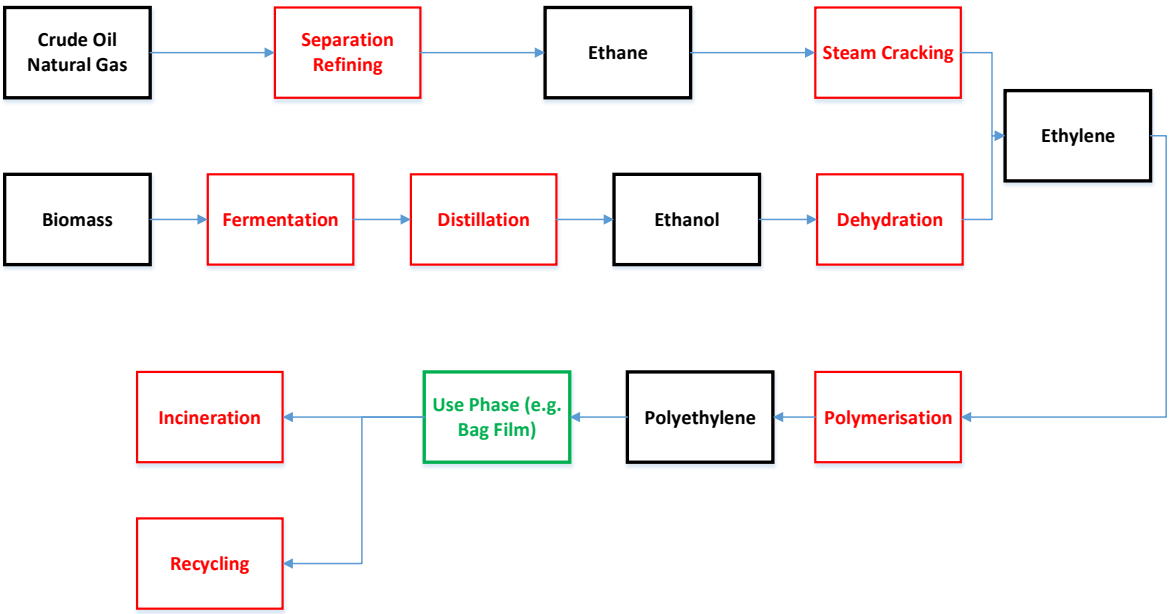


Figure 21: Polyethylene derived from fossil fuel and biological sources

Challenges to using biologically-sourced polymeric materials for biopharmaceuticals manufacturing come from the lack of data on potential for these materials to migrate into the drug product. For market competitiveness, the source of single-use technology manufacturer's raw materials is not immediately apparent, and so it is difficult to determine whether it comes from a conventional source or from biologically-sourced materials. This dearth of data prevents a comprehensive review of any biologically-sourced polymer for key criteria such as in vitro and in vivo toxicity or biocompatibility necessary for use in biopharmaceuticals manufacturing. In addition to this, it is not immediately possible to evaluate whether all required polymeric materials are available from biologically-derived sources. In order to implement such materials, these hurdles must be overcome to be confident of their application.

Should biologically-sourced polymeric materials be realised for all polymeric materials used in the biopharmaceuticals manufacturing process, it would mean an overall reduction in environmental burden from the reduction in reliance on fossil fuels as a source of the necessary raw materials. However, to achieve sustainability, further improvements are necessary in the manufacturing process for these biologically-sourced polymeric materials. Such processes frequently rely on existing agricultural production methods which contributes to eutrophication and acidification from the use of fertilisers, which may also be sourced from fossil fuels. The land area required for cultivation of the source crops may compete with ecosystems and with food crops, resulting in further potential impacts. The downstream purification process may also be energy-intensive, such as in the case of bioethanol production, which requires

distillation. Finally, biologically-sourced polymeric materials are not always readily biodegradable, and so waste management remains a complication, with incineration potentially offering a more attractive route. While there are benefits to storing biologically-sourced polymeric materials from a carbon sequestration perspective, issues with leachates to the environment and other negative impacts of landfill may dictate the approach taken. For biologically-sourced polymeric materials to be truly sustainable, further development is required in these areas.

5.3.Cleanroom energy usage

5.3.1. Existing methods and requirements

In order to maintain hygiene and minimise microbial risk to the biopharmaceuticals process and product quality, the environment in which the process is carried out must be maintained in a defined manner to reduce potential for microbial and particulate contamination. Per EU Annex 1 guidelines, there are defined area classifications which must be monitored and maintained to specific standards of particulate and microbial cleanliness. The area classification required is dependent on the nature and criticality of the process step being executed. For closed processes which are not directly exposed to the area and processes such as indirect component preparation, lower classification may be used. For open processes with direct exposure to the area environment and processes in proximity to the final drug product, higher classifications are required to reduce or eliminate microbial risk. Cleanroom environments are maintained through a combination of technologies such as High Efficiency Particulate Air (HEPA) filtration systems to remove microbes and particulates from the air; monitoring systems such as settle plates to detect airborne microbes or sampling heads measuring particulates such as dust or fibres which may act as a vehicle for microbes or which may contaminate the product; and procedures such as garbing, cleaning regimes and aseptic transfers to prevent contaminants carried by personnel into the cleanroom.

5.3.2. Environmental burden

Maintaining a cleanroom environment leads to significant electricity demands. Electricity is required to maintain the airflow in the cleanroom, which ranges from <20 air changes per hour to >100 air changes per hour depending on the classification. The temperature and humidity of the air is also controlled to prevent moisture from forming in the cleanroom which may facilitate microbial growth, and to maintain a comfortable environment for cleanroom

personnel. Overall, maintenance of cleanrooms contributes as much as 50-60% of the environmental burden for biopharmaceuticals manufacturing.

5.3.3. Achieving sustainability – opportunities and challenges

Reducing the environmental burden from cleanroom maintenance can be achieved in two ways; the utilisation of low-emission forms of electricity, such as those from renewable sources; and the reduction or elimination of the requirement to maintain cleanrooms for manufacturing processes, by reducing or eliminating the risk to the process or product quality from the external environment.

To move towards low-emission forms of electricity, areas in which manufacturing facilities are built must have sufficient infrastructure to provide low-emission electrical power at costs that make it economically competitive to utilise low-emission electrical power. As such, it is independent of the nature of the manufacturing process as to whether a move towards low-emission electrical power is feasible, and is instead contingent on the provision of low-emission sources such as wind, tidal or wave energies at prices sufficient to motivate manufacturing facilities to utilise such services.

De-risking the manufacturing process from a microbial perspective is a challenging prospect. By their nature as biomolecules, biopharmaceuticals are subject to contamination from microbes which can prosper in the conditions under which biopharmaceuticals are manufactured. Microbial contamination can result from open processes, non-aseptic processes and practices, and from inherent components in the manufacturing process such as host-cell viruses present in the cell culture, or from microbial contaminants in raw materials. The threat of microbial contamination to the patient is amplified by the route of administration of most treatments which bypass crucial areas of the body's defences. Impacts of microbial contamination can include infections from microbial contamination and reactions to endotoxins produced by certain bacteria which can cause reaction (endotoxemia) in the body leading to severe injury and death. For these reasons, precautions deemed excessive in some quarters are necessary to protect patient safety from the dangers of microbial contamination.

To eliminate the risks posed by microbial contamination, a variety of approaches may be taken. The simplest precaution is the elimination of open processing. This is achieved through process design to prevent open additions of components such as solids and liquids and the use of sterile connections which maintain the sterile boundary. Open processing is generally necessary now at two points in the process; during the initial seed train, where the cell culture vial is revived

from cryogenic storage and inoculated in a variety of small scale flasks and shakers; and during the final filling stage, where the product is filled into its drug product container under sterile conditions. At all other points in the process, it is possible that the process can be contained from the external environment in such a manner as to prevent microbial ingress. The use of sterile connectors such as the Presto (Pall) or the AseptiQuik (Colder) presents the possibility of making even critical connections towards the latter stages of the process in environments similar to those of an office area, as opposed to the higher levels of classification traditionally utilised.

In addition to the elimination of open processing, the use of single-use technology can prevent microbial ingress to the process stream. Traditionally, most process equipment is cleaned prior to use in order to maintain low levels of bioburden and endotoxin and to ensure clearance of cleaning agents and residual products. For critical operations, steaming may be used to effectively sterilise equipment, eliminating all traces of bioburden from the process contacting surface. While at some points in the process a sterile environment is necessary, such as during the cell culture phase where the presence of bioburden can hinder cell growth and viability and damage the product, and at critical steps in later stages of the process such as during filling, a sterile environment is not always a necessity, as simply cleaning equipment can suffice in eliminating bioburden. This may be difficult at large scale, where equipment may inherently be exposed to greater risks from deadlegs, moisture or other factors enabling microbial contamination. In these cases, higher area classifications may be necessary to reduce risks of microbial growth, in tandem with validated cleaning and steaming cycles. Single-use technology, on the other hand, is commonly sterilised by gamma irradiation, which can sufficiently penetrate all surfaces of the process contacting equipment to eliminate bioburden. In conjunction with closed processing via sterile connections and process design, this can reduce the risk of microbial ingress, leading to a reduction in classification requirements and concomitant reduction in the environmental burden from maintaining cleanrooms for the manufacturing environment.

5.4.WFI generation

5.4.1. Existing methods and requirements

WFI is utilised throughout the manufacturing process as a process fluid and for cleaning and steaming of process equipment. As previously discussed, microbial contamination poses a significant risk to patient safety, and water is a critical medium by which microbes can be

transferred. As such, controlling this water to specific criteria, i.e. by maintaining it as WFI, is necessary to prevent microbial growth. To class a water stream as WFI, the equipment used to generate and convey the water stream should be designed in such a manner as to prevent holdup, stagnation or deadlegs which could cause microbial growth. Monitoring systems should be in place to detect microbes in the process stream, to detect endotoxins produced by water-borne bacteria which may be present in the water stream, and to measure indicators of biological matter content such as total organic carbon (TOC) which can contribute to microbial growth.

The generation of WFI begins with the receipt of municipal water of drinking water quality to the facility. Municipal water may be pre-treated by methods such as deionisation, ultrafiltration, reverse osmosis or UV treatment to reduce microbial, endotoxin and TOC load. Following this, the water stream is subjected to distillation or an equivalent process to remove chemicals and microbes. Following distillation, water stream is maintained and conveyed at temperatures exceeding 65°C and under turbulent flow conditions such that it is self-sanitising, and may be stored under ozone to further prevent microbial ingress. Generally, distillation is the preferred method of producing WFI, and until recently, was the only acceptable method defined in various compendia including the US Pharmacopoeia, European Pharmacopoeia and Japanese Pharmacopoeia (Kojima et al., 2011).

5.4.2. Environmental burden

WFI generation, being generally achieved using distillation, is an energy-intensive process due to the requirements to effectively boil large volumes of water. Energy for this process may be supplied as electricity or, more often, by plant steam produced from a boiler fired by fossil fuels such as natural gas. WFI generation is therefore heavily dependent on fossil fuels, and contributes as much as 30% of the environmental burden of the manufacturing process. In addition, the conveyance of WFI at elevated temperatures shortens the service life of the equipment used to convey it, and so must be replaced at frequent intervals, more frequent depending on the temperature it is conveyed at, leading to further increases in environmental burden.

5.4.3. Achieving sustainability – opportunities and challenges

A straightforward method of reducing the environmental burden from WFI generation is the reduction or elimination of WFI requirements in the manufacturing facility, primarily through the use of single-use technology which does not require cleaning or steaming. For all processes,

WFI is still required as a process fluid in growth medium, buffer and for process uses such as filter flushing and conditioning. For these uses, a change in the orthodox method of WFI generation, distillation, must be implemented.

In order to move away from distillation as a method of WFI generation, significant efforts must be made by a manufacturing facility to demonstrate and validate the water produced meets compendial requirements for microorganism, endotoxin and TOC clearance. The viable alternative to this, reverse osmosis, has been accepted by the US and Japanese Pharmacopoeia for many years, yet has only recently become acceptable to European regulators (Kojima et al., 2011). In many WFI generation processes, municipal water is treated prior to distillation in a manner such that it meets compendial requirements, and so may be demonstrated as acceptable for use in a biopharmaceutical manufacturing process. From an environmental perspective, this is highly favourable as it removes the necessity to send water through an energy-intensive phase change requiring the use of fossil fuels in many cases.

While eliminating distillation is of promise from an economic and environmental viewpoint, the implementation of a viable alternative, reverse osmosis, is not without risks. Of particular concern is the formation of biofilm, a complex matrix of bacteria and their by-products which can form on surfaces and be extremely resistant to removal. Biofilm can form on membranes, pipework and other surfaces and can lead to microbial contamination and elevated endotoxin levels, posing significant threats to the WFI quality. Biofilms may be removed by hot water sanitisation, or the use of cleaning agents such as peracetic acid, however, since reverse osmosis processes are not conducted at elevated temperatures, they may be susceptible to biofilm formation. This may be ameliorated by operating the systems continuously hot, which reduces the environmental benefits that can be realised by the implementation of a reverse osmosis WFI system.

In addition to eliminating the requirement for distillation, the implementation of process analytical technology (PAT) for the on-line detection of microorganisms could eliminate requirements for conveyance of WFI at elevated temperatures and the risks posed by biofilm to reverse osmosis systems. Conventional methods of monitoring WFI systems consist of routine sampling of WFI and incubation of samples to promote microbial growth in the event there are viable organisms present in the sample. The result of this is an extended duration between sampling of the system and detection of the failure, often up to 5 days. As such, extensive qualification is required to verify the system is controlled within compendial criteria.

The use of on-line detection technologies could eliminate this uncertainty by allowing for real time detection of microbial contamination, allowing for sanitisation at pre-defined intervals or once a threshold limit has been reached. Further environmental burdens from the conveyance of WFI at elevated temperatures could therefore be avoided without loss of process robustness against microbial contamination.

5.5.Raw materials

5.5.1. Existing methods and requirements

A broad range of raw materials are required in the biopharmaceuticals manufacturing process. For the cell culture fermentation process, of primary importance is the growth medium used to cultivate the cell culture. Growth medium is composed of a variety of components including carbohydrates such as glucose, amino acids such as glutamine and key factors for cell growth such as various trace metals including zinc and copper. For perfusion processes, growth medium is continuously supplied and harvest removed, whereas in fed-batch cultures a variety of feeding strategies may be utilised with varying growth media being added throughout the cell culture duration. Growth medium is instrumental in controlling critical parameters for the fermentation process, influencing cell growth and viability, generation and accumulation of cellular waste products, nutrient consumption, post-translational modification and glycosylation patterns of the target molecule and the overall titres achieved from a cell culture fermentation. Recent improvements in growth media has driven the achievement of ever-increasing titres and powered the growth in biopharmaceuticals production globally.

In addition to growth medium, raw materials including process gases and buffers are also necessary to maintain an optimal fermentation environment. Oxygen is necessary for cellular aerobic respiration, and so optimal levels of dissolved oxygen in the fermentation supernatant are maintained to maintain a viable cell culture and prevent generation of lactic acid which may be detrimental to the cells and the target biomolecule. Dual-band pH control is common in most cell cultures, utilising carbon dioxide gas and sodium carbonate buffer solution to maintain a suitable pH and prevent cell death and product degradation. Antifoam solutions may also be required to prevent problematic foaming in the cell culture vessel which can lead to potential breaches in the sterile boundary. Harvested supernatant may be treated for pH to prevent further cellular respiration prior to forward processing which may impact the target molecule.

In downstream purification, the process nature impacts the raw material requirements. Typical processes utilise three chromatography steps (capture, intermediate and polishing) which differ in function, and so may require varieties of chromatography resins and buffer components to sufficiently purify the process stream. Chromatography resins are highly specialised, and require production processes similar to those for biopharmaceuticals. The resins themselves consist of a packed bed of small spheres, generally <1mm in diameter, composed of a base material, such as agarose or sepharose, upon which a functional group is bound. This functional group interacts with the process stream in differing modes to isolate and bind components of the process stream to purify it, either by forming a complex with the target molecule, or by removing known impurities. For almost all chromatography steps, buffering components such as sodium acetate sodium phosphate or Tris are utilised to maintain stable pH and enable product separation. Specific chromatography operations utilise a variety of methods of product separation and so require differing buffering components. Common chromatography modes include protein A, which utilises a complex bacterial protein to bind and separate immunoglobulins such as monoclonal antibodies; immobilised metal affinity, which utilises metals such as zinc or nickel to complex with certain proteins to isolate them; ion exchange, which utilises the ionic strength of the target molecule to separate it, utilising salts such as sodium chloride; and hydrophobic interaction, which utilises hydrophobicity of the target molecule to "salt out" with salts such as ammonium sulfate.

For viral inactivation processes, different raw materials may be used depending on the mode of inactivation. For low pH viral inactivation, where the product solution is brought to sufficiently low pH to damage and render inert enveloped viruses, relatively simple buffers such as sodium citrate and sodium carbonate are used to alter the solution's pH. In solvent-detergent viral inactivation, the lipid coat of enveloped viruses is destroyed using a detergent, commonly a surfactant such as Triton X-100, in the presence of a solvent such as TnBP. While low pH viral inactivation is suitable only for products resistant to low pH, solvent-detergent viral inactivation can be used for most proteins, albeit with a requirement to remove the solvent and detergent downstream, which could result in a requirement for further processing steps.

Perhaps the most important raw materials utilised in the process are the final drug product formulation components, which are ultimately those which will enter the body of the patient. Drug product formulation components consist of compounds which provide product stability during storage and bioavailability and efficacy following administration to the patient. Common drug product formulations contain surfactants to prevent agglomeration or

aggregation of proteins; polyethylene glycol (by PEGylation) to reduce immunogenicity; and components such as artificial cerebrospinal fluid to allow for intrathecal administration in cases where it is required.

5.5.2. Environmental burden

The direct environmental burden from raw materials differs depending on the characteristics of the manufacturing process. Similar to other impact areas, the energy-intensive nature of raw materials production, necessitated by strict quality and regulatory requirements, drives impact due to a general societal dependence on fossil fuels. Raw material impacts can be as low as 5%, although several process steps may drive special case impacts. Chromatography by metal ion affinity, ion exchange or hydrophobic interaction modes can contribute to environmental impacts from heavy metals or nitrogenous compounds such as ammonium sulfate respectively. Solvent-detergent viral inactivation utilises surfactants such as Triton X-100, which is a known endocrine disruptor and so can harm aquatic environments in particular, along with TnBP, a suspected carcinogen. In these cases, environmental burdens are increased to the point of concern.

5.5.3. Achieving sustainability – opportunities and challenges

The choice of production mode considerably impacts the environmental burden of the raw materials used in the manufacturing process. For example, current manufacturing practices dictate the selection of predominantly fed-batch cell culture fermentation due to the higher titres observed compared to perfusion cell cultures. However, this drives requirements for larger purification trains, and concomitant larger demands on chromatography resins and buffer components. In contrast, continuous purification processes such as chromatography are predicted to increase resin utilisation, as smaller chromatography columns can be utilised with improved mass transport properties compared to their larger counterparts. Continuous chromatography also reduces sanitisation requirements of the chromatography resins, which can be damaged by the use of cleaning chemicals such as sodium hydroxide. As such, some studies have indicated favourable findings from an economic perspective for a combination of a fed-batch cell culture feeding a continuous purification train, which is likely to translate into reductions in environmental burden also. For many products, the selection of solvent-detergent viral inactivation could prevent yield impacts from product degradation seen in low pH viral inactivation processes, increasing efficiencies with concomitant reduction in environmental

burdens per gram of product, but would lead to additional environmental impacts from the use of harmful compounds.

The implementation of novel technologies, such as the aforementioned continuous chromatography processing, could lead to further reductions in environmental burdens. A disruptive technology is the use of buffer recycling, a processing technique whereby waste buffer is collected and purified by various means such as counter-current chromatography for reuse in the process, resulting in reductions of up to 99% in WFI required for buffer preparation. Whilst this could prove a technical breakthrough significantly reducing the volume of water utilised in the process and the volume of wastewater treatment required post-processing, it is in the early stages of development, with little or no regulatory guidance published to indicate its acceptability. In addition, this type of system may prove mechanically complex to implement, and the benefits realised by reductions in water usage may be counterbalanced by additional impacts from equipment fabrication, facility footprint and operational requirements.

5.6.Feasibility analysis of reducing environmental impacts from biopharmaceuticals manufacturing

By investigating the prospective impact reductions achievable by utilising the previously described technologies and practices, a feasibility analysis will be completed to determine the theoretical reduction in environmental impacts from biopharmaceuticals manufacturing. Based on life-cycle assessment results observed in Chapter 4, this feasibility analysis will focus on predominantly global warming potential emissions, except in special cases where significant impacts in other impact categories are observed. The 18.2kg/annum functional unit will be the basis for the feasibility study. Table 22 details the GWP emissions for the 18.2kg/annum scenario.

Table 22: GWP emissions from the 5 impact areas described in this analysis**.**

*Note: >10 kg raw materials required per g product produced, as raw materials vary in nature and form, and as such will not be quantified.

	Single-use scenario		Stainless-steel scenario	
Material/Energy Source	Amount	GWP Kg CO2 eq.	Amount	GWP Kg CO2 eq.
Stainless Steel	2.4	10.272	5.25	22.47
Polymeric Materials	5.86	18.9025	3.864	10.04004
Cleanrooms	252.872	103.4499	470.664	192.5486
WFI	147.858	43.16036	392.656	104.3369
Raw Materials	>10*	21.8	>10*	22.9

5.6.1. Stainless-steel

Reductions in environmental impacts from stainless-steel production can be achieved by utilising stainless-steel fabrication processes which use modern methods such as electric arc furnace and exclusively recycled scrap steel. Existing stainless-steel processes emit 4.28 kg CO_2 eq. per kg stainless-steel produced. By utilising the best available technology, this can be reduced to 2 kg CO_2 eq. per kg stainless-steel. Further potential reductions by up to 30% are currently in development as part of various initiatives including COURSE 50 (Tonomura et al., 2016), which could result in impacts as low as 1.4 kg CO_2 eq. per kg stainless-steel by 2050.

As a result of this emission reduction, 47% of the global warming potential emissions can be eliminated for stainless-steel, as detailed in Table 23.

Table 23: Stainless-steel environmental impact reductions

	Single-use scenario		Stainless-steel scenario	
Material/Energy Source	**Amount**	**GWP kg CO2 eq.**	**Amount**	**GWP kg CO2 eq.**
Stainless Steel, Current	2.4	10.272	5.25	22.47
Stainless Steel, Reduced		5.44416		11.9091

5.6.2. Polymeric materials

Reduction in emissions from polymeric materials is a complex proposal due to a variety of competing emissions categories. For the purposes of this discussion, polyethylene will be used as an example as both fossil-fuel derived and bio-based polyethylene are commonly available.

Polyethylene is manufactured from ethylene feedstock which undergoes polymerisation in various manufacturing processes to produce the required grade of polyethylene such as low-density (LDPE) or high-density (HDPE) forms. The primary fossil-fuel source of ethylene feedstock is from crude oil processing, while the primary bio-based source is from fermentation of organic material such as sugarcane to bioethanol followed by processing to ethylene. While bio-based sources eliminate the requirement to extract and refine fossil-fuels, requirements for agricultural cultivation of feedstocks, fermentation, which produces carbon dioxide as a by-product, and distillation to produce suitable bioethanol, results in significant global warming potential emissions from the upstream ethylene production process. Downstream processing of ethylene to the polyethylene form of choice is by a variety of processes utilising high temperatures or pressures or various catalysts. These industrial processes rely on predominantly fossil-fuels as energy sources, which contribute to the overall global warming potential emissions.

From existing literature, it is unclear as to whether bio-based polymeric materials are associated with reduced overall environmental emissions than their fossil-fuel derived counterparts. Optimistically, a 58% reduction in global warming potential emissions could be observed using contemporary technologies (Semba et al., 2018). However, increased emissions to land from agricultural activities, such as the use of fertilisers and harvesting crops, would result in increased terrestrial acidification emissions of up to 28 g SO2 eq and eutrophication potential emissions of up to 5.2 g PO4 3- eq per kg polymer used. In addition, the use of bio-based polyethylene still requires an end of life solution by incineration or by landfill. By using biomass as a feedstock to the process, the use of bio-based polymeric materials results in the sequestration of carbon, up to 2.15 kg CO2 per kg material, however, storage of this in conventional landfill may result in ecosystem degradations. Incineration liberates this carbon back to the environment, but eliminates the waste storage conundrum. Recycling of polyethylene is widespread but inefficient, and recycled material is generally not suitable for such widespread use as virgin polyethylene. For the purposes of this study, incineration will be assumed to be the end-of-life pathway, and that all bio-based polymeric materials currently

used in the biopharmaceuticals manufacturing process can achieve the 58% reduction in GWP emissions, but with an increased terrestrial acidification and eutrophication potential load. Results of this are shown in Table 24.

Table 24: Polymeric materials environmental impact reductions

	Single-use scenario				Stainless-steel scenario			
Material/ Energy Source	**Amount**	**GWP kg CO2 eq.**	**TA kg SO2-eq.**	**FE kg P-eq.**	**Amount**	**GWP kg CO2 eq.**	**TA kg SO2-eq.**	**FE kg P-eq.**
Polymeric Materials, Current	5.86	18.9025	0.1591	0.7954	3.864	10.04004	0.08748	0.43344
Polymeric Materials, Reduced		7.93905	0.32318	0.805456		4.216817	0.195672	0.440071

5.6.3. Cleanrooms

The principal source of GWP emissions from cleanrooms is as a result of electricity usage. The study executed and described in Chapter 4 used the EU electricity mix as a basis for carbon impacts, and as part of the sensitivity analysis compared with the US and Australian electricity statistics. To meet target set by the Paris agreement, zero-carbon electricity is necessary in by 2030, with negative-carbon sources required between 2055 and 2080 to avoid catastrophic warming by 2100 (Bataille et al., 2018). In a similar vein as bio-based polymeric materials, low-carbon electricity is a feasible proposition, but perhaps not one which is readily available to support industrial production, biopharmaceuticals manufacturing included. Reviewing electricity data for 2016, the electricity mix in Sweden contributes 13.3 g CO2 eq/kWh, compared to the >300 gCO2 eq/kWh EU average. For the purposes of this analysis, a value of 100g CO2/kWh will be used as a feasible example, given that the proliferation of this form of low-emissions technology may be achieved contemporaneously. The results of this are displayed in Table 25.

Table 25: Cleanrooms environmental impact reductions

	Single-use scenario		Stainless-steel scenario	
Material/Energy Source	**Amount**	**GWP kg CO2 eq.**	**Amount**	**GWP kg CO2 eq.**
Cleanrooms, Current	252.8720372	103.4499	470.6640059	192.5486
Cleanrooms, Reduced		25.2872		47.0664

5.6.4. WFI

Reduction in WFI GWP emissions is possible presently by the use of reverse osmosis in place of distillation. This eliminates 843 kJ per kg WFI energy requirements, which would primarily require a natural gas fired boiler to supply. Electrical energy for transfer of WFI through reverse osmosis membrane equipment and throughout the facility remains, and a daily sanitisation at 70°C is required to reduce potential for microbial loading of the system. The analysis is displayed in Table 26.

Table 26: WFI environmental impact reductions

	Single-use scenario		Stainless-steel scenario	
Material/Energy Source	**Amount**	**GWP kg CO2 eq.**	**Amount**	**GWP kg CO2 eq.**
WFI, Current	147.8579628	43.16036	392.6559941	104.3369
WFI, Reduced	48.20217538	14.07042	132.489207	35.20514

5.7.Overall achievable reduction in environmental impacts

The overall environmental impact reductions achievable in the single-use and stainless-steel scenarios are presented in Table 27.

Table 27: Overall environmental impact reductions

	Single-Use			Stainless-steel		
	DALYs	**Species.yr**	**$ millions**	**DALYs**	**Species.yr**	**$ millions**
Stainless-steel	1.8	0.003	0.015	3.9	0.0065	0.032
Polymeric materials	2.3	0.0045	0.064	1.2	0.0025	0.032
Cleanrooms	5.8	0.0115	0.17	10.7	0.0214	0.317
WFI	3.2	0.0065	0.095	8.1	0.0163	0.237
Raw Materials	0.6	0.0011	0	0.3	0.0006	0
Total	13.6	0.0265	0.344	24.2	0.0473	0.617
% Reduction	66.9	67.7	70.5	68.4	69.1	71.1

Improvements in environmental performance of >66% can be potentially achieved through the implementation of state-of-the-art technologies and practices, primarily through a reduction in reliance on fossil fuels as a source of raw materials for equipment and as a source of energy. An analysis of the importance of this paradigm shift is presented in Chapter 7 in the context of complex flows throughout the societal, economic and environmental spheres.

Chapter 6: Developing an integrated model of sustainability for biopharmaceuticals manufacturing

6.1. Sustainability assessment – tools, opportunities and challenges

In recent years, the increasing awareness of the complexity of interactions at the interfaces of the economy, society and the environment has resulted in extensive discussions on sustainability. The threat of man-made climate change, the destruction of ecosystems globally and the continued human suffering from inequalities informs this discourse and demands transitions towards sustainability. These transitions require the embrace of evaluation tools respecting the complex and chaotic relationships that exist within the biosphere on which all life relies to survive and thrive, and the acceptance of alternative viewpoints to those which have dominated heretofore. Of concern is the development and proliferation of sustainability assessment tools to direct and shape economic, social and environmental policies to advance sustainability initiatives and end activities contributing to unsustainability. When considering sustainability assessment tools, exploration of the values embedded in the tool, the stakeholder viewpoints and involvement along with the selection of metrics representing single- or multiple-paradigms is important.

Sustainability assessment tools are an established concept which reached the mainstream with the publishing of the Brundtland Report "Our Common Future" (WCED, 1987). In the intervening years, many tools have been developed to measure sustainability, often utilising single metrics or composite indices. However, what and how they measure, and for whom, is far from straightforward. Gasparatos (2010) conducted a thorough review of sustainability assessment tools, recording them in terms of the value(s) embedded within them and as reductionist or non-reductionist tool. Following on from de Groot & Steg (2008) and Milfont et al. (2006), Gasparatos (2010) classified the embedded values as egocentric, homocentric (altruistic) or biophysical in nature. Egocentric value orientation is rooted in self-interest and an individual's entitlement to utilise resources to maximise their own gain. In contrast, homocentric or altruistic value orientation considers the maximisation of societal benefits, with concomitant minimisation of negative human impacts. Biophysical value orientation proposes an ecocentric viewpoint rooted in the biosphere and the ecosystems which compose it, allocating an intrinsic value to all living things. These disparate valuation concepts informed the evaluation of existing sustainability concepts, beginning with reductionist tools which utilise a single indicator (e.g. economic cost/benefit), single dimension (economic,

environmental or social), single scale of analysis, single objective and single time horizon (Munda 2006). Examples of reductionist tools include cost-benefit analysis (economic); materials and energy flow analysis and life cycle assessment (environmental); and social life cycle assessment (social). Expanding to include non-reductionist tools provided the example of multiple-criteria analysis, a family of tools intended on minimising impacts across each category without applying weighting or trade-offs of one component in favour of another, as is typically utilised in reductionist methods.

Sala et al. (2015) conducted analysis of established literature in proposing a framework for conducting sustainability assessment. Arising from this, the authors presented a number of sustainability assessment tools in terms of seven criteria, namely:

- Boundary-orientedness – reference to scientific and policy thresholds
- Comprehensiveness – one, two or three pillars of sustainability
- Integratedness – mono-disciplinary up to transdisciplinary
- Stakeholders involvement – from communication to participation
- Scalability – ranging from fixed local scales to multi-temporal and multi-scale
- Strategicness – accounting to change-oriented
- Transparency – closed to open models

Emerging from this exercise were a summary of the challenges facing the development of sustainability assessment tools and the combination or integration of multiple tools for the purpose of providing a multi-pillar assessment. The challenges detailed were:

- Combining different tools/methods while retaining meaning and ensuring robustness
- Utilising diverse tools to assess and measure emergence of complex socio-ecological systems
- Dealing with the propagation of uncertainty inherent in any modelling tool
- Repeatability of assessments in light of the complex nature of the systems under study
- Achieving transparency of assessments

6.2. Objectives

Bearing these criteria and concomitant challenges in mind, the purpose of this chapter is to compose a conceptual model of sustainability for the biopharmaceuticals manufacturing system, similar to the Class 3 model described in Section 2.6. The objectives of this chapter are:

- ❖ To examine existing sustainability assessment tools and their current/possible application to the biopharmaceuticals manufacturing industry
- ❖ To integrate these tools and propose a conceptual model of sustainability for the biopharmaceuticals manufacturing industrial system
- ❖ To identify the datasets and analyses required to transform this conceptual model to a quantitative model embodying the criteria outlined by Sala et al. (2015)

6.3. Assessment Models

6.3.1. Conceptual economic assessment models

When considering economic models in the context of sustainability, it is prudent to divide them into conceptual models, which consider the values applied by stakeholders as a qualitative measure, and quantitative models, which consider the values in monetary terms through rigorous calculation. In this analysis, both macroeconomic models, those which concern large-scale modelling of the economy as a whole, and microeconomic models, which take account of the interaction between individuals and firms at small-scale, will be presented.

6.3.1.1. Conceptual macroeconomic model – the circular flow of income

The prevailing conceptual model of the economy, that which provides a foundation for macroeconomics, is the idea of a circular flow of income. This model presents the economy as a closed system in which money, goods and services are exchanged between economic agents, with income being conserved. The economic agents involved are, variously, households, firms, governments and financial markets. Figure 22 shows the circular flow of income.

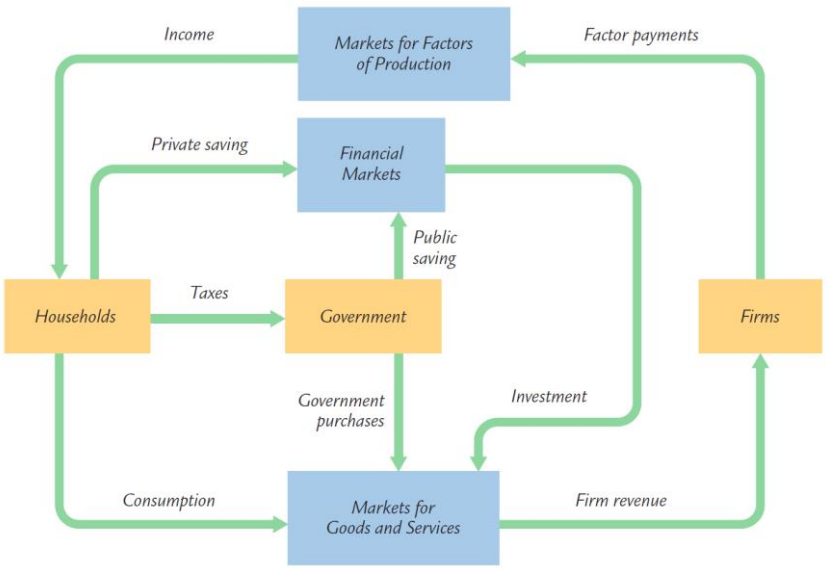


Figure 22: The circular flow of income (Mankiw, 2016)

The circular flow of income conceptual model allows for the interpretation of the economy as an interaction between various actors in a realistic manner. Briefly, the model depicts the functions of producers and consumers in the economy. Households are shown as consumers of goods and services, who derive income from firms' production of goods and services, pay taxes to the government and provide income to financial markets through savings. Firms derive revenue from goods and services and investments from financial markets and governments, with spending required on labour and capital, the factors of production, in order to provide goods and services. The government utilises taxes from households to invest in financial markets and to purchase necessary goods and services from firms.

When applied to the biopharmaceuticals manufacturing industrial system, each economic agent can be substituted for an equivalent. Figure 23 details the application of the circular flow of income model to the biopharmaceuticals manufacturing system.

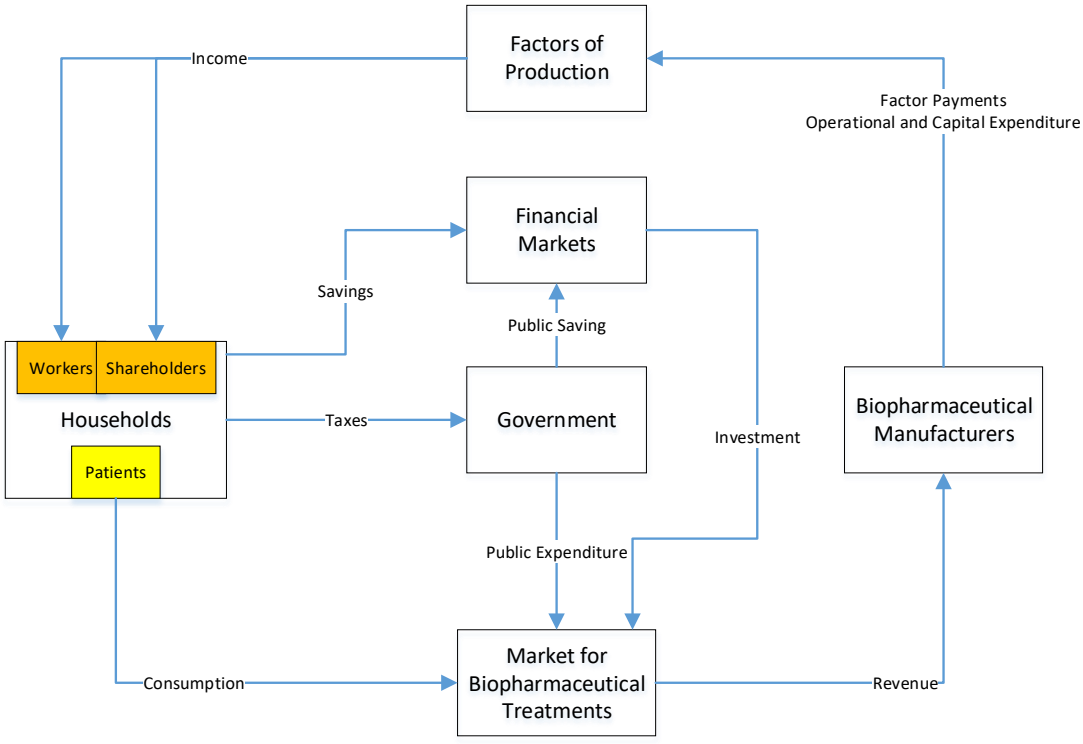


Figure 23: Circular flow of income as applied to the biopharmaceuticals manufacturing system

When considering the application of the circular flow of income applied to the biopharmaceuticals manufacturing system, several components are of critical importance. The factor payments component is comprised of two distinct aspects: the expenditure required to bring a product to market and the expenditure required to manufacture the product. The distinction in this case is due to the nature of biopharmaceuticals manufacturing, which relies

on heavy expenditure on R+D (in excess of $2 billion, as previously discussed) and relatively low expenditure on manufacturing ($260-3000 per gram of active product). Depending on the maturity of the company, all revenue obtained may be subsequently re-invested in development of new products, and the company may rely on continued investment from the financial markets to remain viable.

In addition to the factor payments component, the households' consumption and government expenditure components are important to understand. Biopharmaceuticals by their nature are consumed by individuals to increase life expectancy and quality of life, analogous to the consumption of an item to derive utility from it. The households' expenditure on biopharmaceuticals is subdivided into two potential sources; through households' income from capital or wages, which may be through a healthcare provider or as an out-of-pocket expense; or through government spending on treatments as a public expenditure. Decision-making framework of this component is established through the use of quantitative economic tools such as cost-utility analysis, which is discussed further in section 6.3.2.

For simplification, the circular flow of income will be reduced for the purposes of developing the integrated conceptual model. The simplified model is displayed in Figure 24.

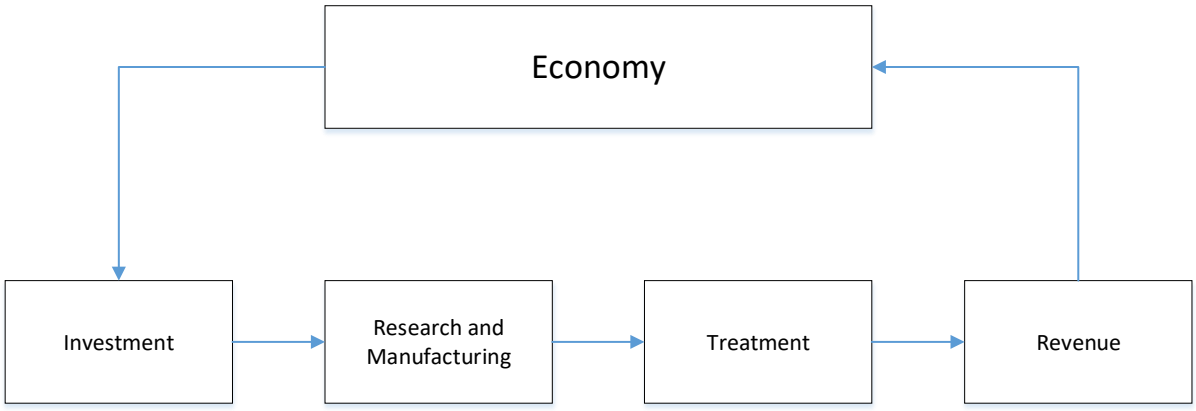


Figure 24: Simplified circular flow of income

When considering this conceptual model, it is apt to frame the revenue in terms of pricing and theories of value. For comparison purposes, two distinct theories of value will be applied: neoclassical subjective theory of value, and neo-Ricardian cost of production theory of value.

6.3.1.2. Neoclassical economic thought – the subjective theory of value and the law of diminishing marginal utility

Neoclassical economics dominates modern economic practice. At its core, neoclassical economics places the consumer, a perfectly rational actor intending to maximise utility based

on the availability of all necessary information. Counter-balancing this are companies which supply products and which aim to maximise profits. The relationship between them can be summarised through use of the theory of marginal utility (Stigler, 1950), that is, the utility gained per unit of consumption decreases with increasing consumption, thus producing the supply and demand curve. A central component of neoclassical thought is the subjective theory of value, that is, the consumer demand for a product fixes the value, as opposed to the resources, whether labour or capital, which was required to produce it.

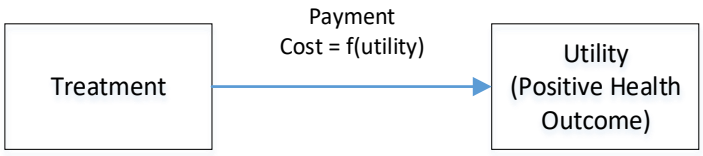


Figure 25: Subjective theory of value applied to a biopharmaceutical treatment

When applied to the biopharmaceuticals manufacturing industrial system, it can be conceived that the consumer is the beneficiary of the treatment, the patient, who intends on maximising their utility while the treatment supplier is the company intending on maximising profits. The scarcity of the treatment is determined by alternative treatments on the market, while demand is determined by patient population. Utility can be measured using life expectancy or quality of life metrics. Through application of the concept of marginal utility and the supply and demand curve, as displayed in Figure 25, it can be inferred that scarce treatments with high patient populations, such as novel treatments like cell therapies for advanced cancers, are assigned the greatest value, while common treatments for low patient populations are assigned the least value. This concept can explain the function of patented and generic treatments, with the exclusivity of supply provided for patented treatments ensuring high demand and associated high value, with the propagation of alternative treatments or generic versions leading to increased supply and the reduction in value. This concept alone does not fully explain the sometimes extravagant prices of treatments, however.

6.3.1.3.Neo-Ricardian economic thought – cost of production theory of value

For further explanation, an alternative theory of value is investigated, namely the neo-Ricardian school's cost-of-production theory. This theory was developed from classical economical thinking of Ricardo as described by Sraffa (1960). In this model, the main factor in price determination is the commodities that were used in the manufacture of the product. These commodities can be classed as capital, the manufacturing facilities, equipment and raw materials required to manufacture the product; and labour, the physical and intellectual labour

required to be completed to research, develop and manufacture the product. The value of the product can be derived by assigning relative values to commodities used in manufacturing, summing these values and applying a profit ratio. By incorporating interest, the value of the product can be determined over the long run by the sum of the input commodities.

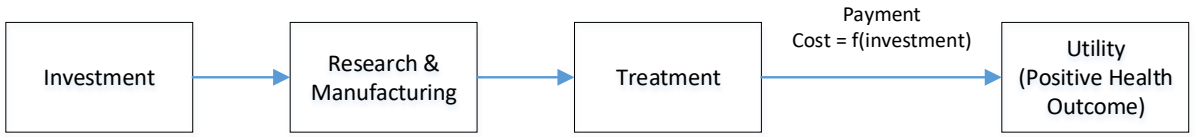


Figure 26: Cost of production theory of value applied to a biopharmaceutical treatment

This conceptual model (shown in Figure 26) can be used in conjunction with the previously described subjective theory of value to further explain the assigned value and pricing of biopharmaceutical treatments. The cost-of-production theory of value can be used to incorporate the value contributions of the factor payments for capital and labour. For the biopharmaceutical industry, the primary costs are associated with the capital and labour required for research and development of new products. These costs may be excessive (greater than $2 billion) and frequently must also account for spend associated with failed products. Of secondary importance are the capital and labour costs associated with manufacturing, which may include land or rent costs, facilities and equipment, raw materials and commodities, and labour costs.

By combining these two theories of value, the influence of utility gained by the consumer and the capital and labour costs may be considered in terms of the circular flow of income. The circular flow of income provides a useful conceptual model for the flow of income throughout the economy, yet it does not account for the fundamental laws of nature which govern the interactions of matter and nature. The extension of economic thinking to address this gives rise to a separate school of economic thought: ecological economics.

6.3.1.4.Ecological economic thought – linear throughput of matter-energy

Ecological economics is a strand of economics which interprets the development of economic theories as a subset of the ecological systems in which they exist and on which they depend to function. A central goal of ecological economics is to reconcile the services provided by these ecological systems with the values and policies of the economic system in order to ensure the flourishing of human society and the biosphere. Central to this is the concept of the linear throughput of matter-energy, as described by Daly (1985). While the economy is expressed in literature as a closed, circular system in which the flow of income is conserved, this idea in fact

renders the economy as a perpetual motion machine, which is in violation of the second law of thermodynamics, which states that the rate of entropy of a system cannot decrease over time. The economic system is predicated on the provision of goods and services, most or all of which require the utilisation of energy and/or matter converted from one form to another. Thus the circular flow of income, while useful for conceptualising the economy as a whole, is an inaccurate representation of the economy which cannot be reconciled with fundamental laws of nature. For this reason, a conceptual model of the economy as a linear system was developed by Daly (1985), and is represented in Figure 27.

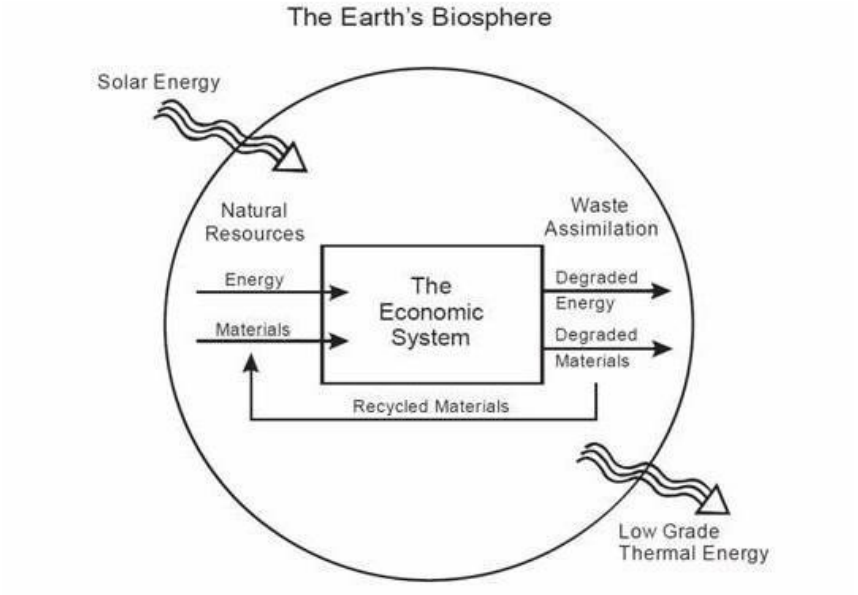


Figure 27: The linear throughput of matter-energy model of the economy

The linear throughput of matter-energy model represents the economy as a system which is continually transforming energy and matter from low- or medium-entropy sources to high-entropy wastes in the process of functioning. Energy is provided to the system as solar energy, is used in irreversible processes and is exhausted as thermal energy. This high entropy dissipative thermal energy is associated with environmental degradation (Wessels, 2006). Matter is transformed into usable forms before being degraded and either discharged as waste or recycled.

Under the dominant economic paradigm, which is predicated on the pursuit of continuous economic growth and avoidance of the dreaded "recession", such as the Great Recession of 2007-8, the linear throughput of matter-energy increases to fuel economic activity and growth, to sustain conventional concepts of prosperity, as measured by metrics such as Gross Domestic

Product (GDP). Fundamental to economic growth is the profits of individual companies as a collective, whereby the quest for profit stimulates investment and payback to the economy, which promotes further investment, and so on and so forth. To achieve profits, companies rely on dual prospects of increasing revenues and decreasing costs of production. The combination of these yields the concept of the "engine of growth" (Jackson, 2009), which promotes ever higher sales (consumption) and ever lower costs of production (efficiency) to enable economic growth and prosperity. This is incompatible with fundamental laws of nature, whereby there is ultimately a finite resource limit which, once reached, cannot simply be exceeded without consequence.

When considering the linear throughput of matter-energy and "engine of growth" concepts for biopharmaceuticals, it can be conceived that energy and materials from the environment, which are finite, are transformed by manufacturing processes into treatments providing a positive health outcome, but with corresponding use of resources and emissions of waste, with this process shown in Figure 28. Through striving for ever more innovations and efficiencies, the relative economic cost of these treatments may reduce, allowing for greater access and therefore more usage, with corresponding increase in materials and energy usage, and concomitant environmental impacts, the so called Jevons' paradox (Polimeni et al., 2006).

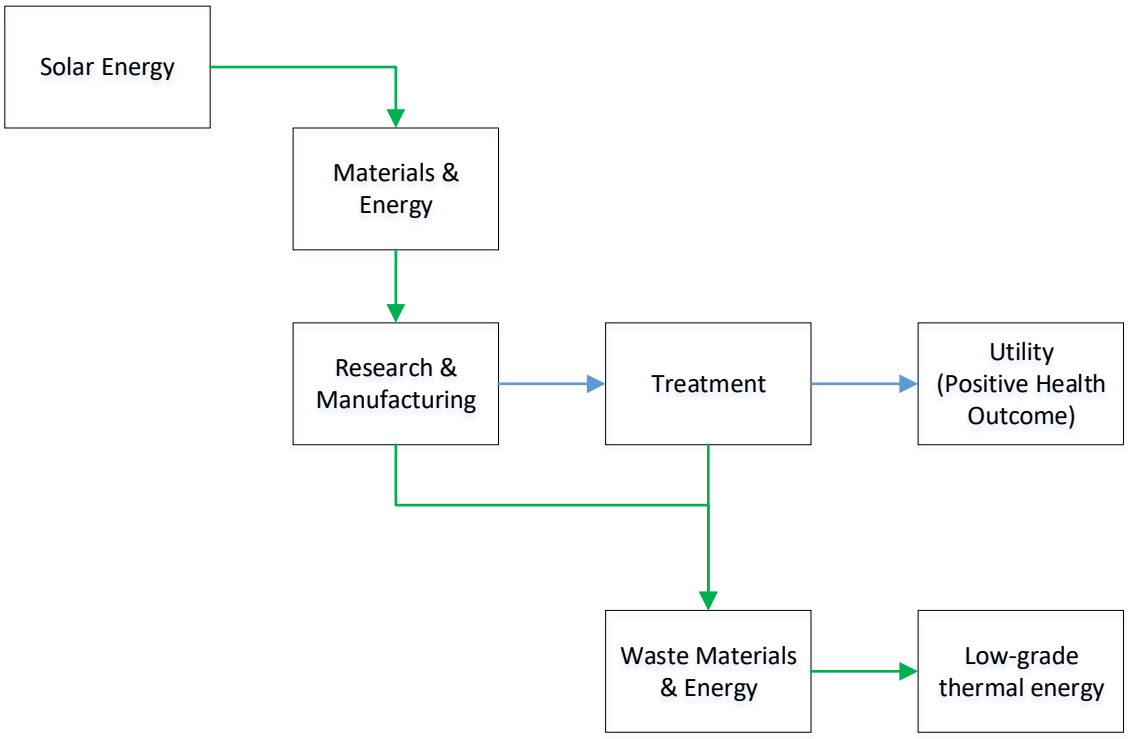


Figure 28: Linear throughput of matter-energy model applied to biopharmaceuticals manufacturing system

6.3.2. Quantitative microeconomic models

6.3.2.1.Health technology assessment (HTA) – cost-utility analysis

Health technology assessments are used to evaluate the economic value of a health intervention and are frequently used by governments as a decision-making tool for reimbursement decisions. HTA works using cost-utility analysis by comparing health states with and without intervention, and determining the economic value associated with the intervention, generally expressed in terms of an incremental cost-effectiveness ratio (ICER) (Patel et al., 2014):

$$ICER = \frac{C1 - C0}{E1 - E0}$$

Where C1, E1 are the cost of intervention and measured utility following intervention and C0, E0 are the cost of intervention and measured utility of the control group. To measure the effectiveness of a given health intervention, utility values must be assigned to a broad range of health states in order to allow for comparison of health interventions. In general, the value assigned to a health state may be expressed in terms of quality-adjusted life years (QALYs), where 1 QALY is a year of life lived in perfect health, while death is assigned a value of 0 QALYs. For values between 0 and 1, a quality-of-life weighting must be evaluated through the use of standardized methods. QALYs measure changes in quality of life in addition to changes in life expectancy associated with a health state or health intervention. Methods for determining quality-of-life weightings include:

- Time trade-off (TTO): a measure of a persons' willingness to forfeit years of life in order to live shorter life-span in perfect health. For example, if a person had the option of continuing to live with a condition for *y* years, or was willing to forfeit *x* years of life to live the remaining (*y*-*x*) years in perfect health, then the condition could be assigned a quality-of-life weighting of (*y*-x)/*y*, thus:

  QALYs = Quality-of-life weighting (y-x)/y * years lived

- Standard gamble: a measure of a persons' willingness to risk adverse events (such as death) from a health intervention in order to return to perfect health. For example, if a person has an option of continuing to live with a condition, or is offered the option of a health intervention which has a probability, *p* of causing a return to full health, and probability (1-*p*) of an adverse reaction, then the health state quality-of-life weighting is equivalent to the probability of returning to full health *p*:

  QALYs = Quality-of-life weighting *p* * years lived

- Use of standardized questionnaires: patients can be provided standardized questionnaires to evaluate disease burden, such as the EQ-5D. The EQ-5D measures health in five categories: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Based on responses, a quality-of-life weighting can be deduced and applied.

In many jurisdictions, the ICER must reach a threshold value to be considered for reimbursement, with typical threshold values ranging from €20,000 - €100,000 per QALY gained (O'Mahony & Coughlan, 2014; Appleby et al., 2007). Variation in this threshold may be explained by the nature of the disorders being evaluated, being higher in the case of rare diseases particularly. Figure 29 gives a simple visual representation of health technology assessment.

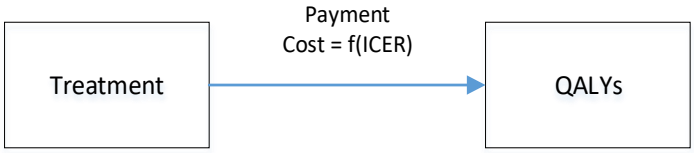


Figure 29: Health technology assessment for biopharmaceutical treatment

Shortfalls of cost-utility analysis include the subjective nature of the evaluation tools, which require input from disease sufferers and may show significant variation, and the difficulties obtaining sufficiently large datasets for interventions treating smaller patient populations due to potential confounding effects.

6.3.2.2.Life cycle costing

Life cycle costing is an economic evaluation tool used in decision-making between options for manufacturing of a given product, taking into account costs from conception through to product disposal. Life-cycle costing can be used to evaluate the cost-effectiveness of engineering projects by discounting their cost over the life-cycle of use, as opposed to evaluating projects based solely on the up-front capital outlay required. Commonly used indices for evaluation include:

- Net present value
- Internal rate of return
- Payback period

Each of these methods can be used as an indicative tool of the potential value an investment will bring offset by factors such as the time value of money due to inflation and costs of capital.

These assessments form an important part of the decision making process for investments for the biopharmaceutical sector, including assessing capital expenditures on research, development and manufacturing facilities, and operational expenditure on production activities. Figure 30 shows life-cycle costing assessment for biopharmaceuticals manufacturing.

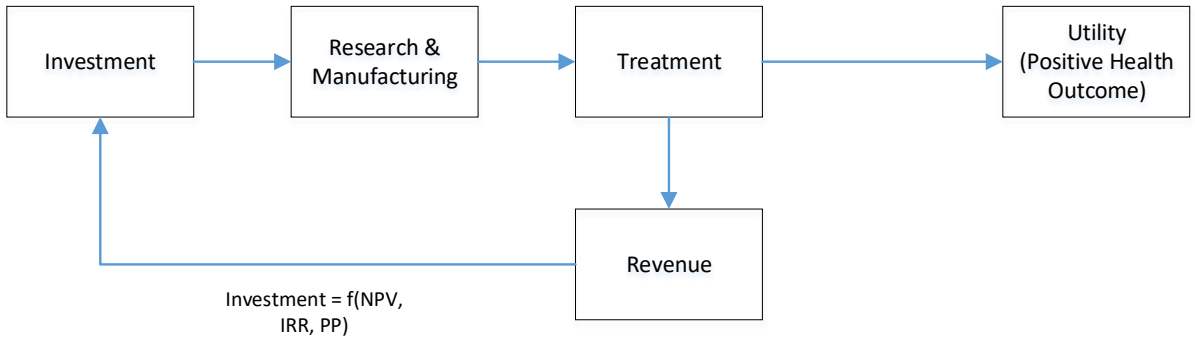


Figure 30: Life cycle costing assessment for biopharmaceuticals manufacturing

6.3.3. Environmental sustainability assessment

6.3.3.1.Environmental impact assessment

An environmental impact assessment is a tool used to evaluate the impact of a specific project or process on the environment in order to determine whether it should proceed or continue, or to identify and implement amelioration efforts to minimise adverse impacts. Environmental impact assessment is intended to be used for environmental management by planning authorities and organisations to prevent developments causing avoidable environmental impacts and their concomitant effects on human and animal life in the immediate area.

Environmental impact assessment involves evaluation of the emissions to land, sea and air as a result of a project or process, and encompasses areas including waste management, access and egress, noise and light pollution, and cultural impacts such as archaeological or architectural impacts. The environmental impact assessment report documents the proposed project from the design phase, detailing the alternatives to a proposed project, an impact assessment of the proposed project, the existing environmental features of the impacted area, and the mitigation and monitoring efforts necessary to maintain a record of the environmental impacts stemming from the project over time. Environmental impact assessment focuses solely on the environmental impacts from an individual project on a specific area, and does not take into account life-cycle impacts. When applied to the biopharmaceutical manufacturing process, environmental impact assessments are typically completed at multiple stages throughout the

product life-cycle, including at the research and development phase, to determine the impact of administration/excretion of the product on the environment, and at the manufacturing phase, to evaluate the impact of the manufacturing facility and activities on the environment.

6.3.3.2.Life cycle assessment

Life cycle assessment is a standardised method for evaluation of the environmental impact of a product throughout the life-cycle of the product i.e. from raw materials, transport, manufacturing, consumption and disposal. ISO14040 governs the requirements and guidelines of life cycle assessment, which is composed of 4 distinct parts: goal and scope definition, inventory analysis, life cycle impact assessment, and interpretation. Life cycle assessment as a whole can be used to evaluate the overall footprint of a product, identify points for improvement in material and energy efficiencies and inform decision-making for manufacturing industries, governments and other key stakeholders.

The output of a life cycle assessment takes the form of measures of environmental performance, an output of the life cycle impact assessment portion of the life cycle assessment, and interpretation of these measures in the context of the involved stakeholders' viewpoints. A common method for completing the life cycle impact assessment is the ReCiPe for LCA (represented in Figure 31). ReCiPe is an aggregation tool, whereby material flows quantified as part of the inventory analysis are transformed into a number of environmental impact categories. In the case of ReCiPe, there are 17 impact categories at the midpoint level, focusing on individual impacts such as climate change and land transformation; and 3 impact categories at the endpoint level, focusing on larger environmental impacts, namely:

- Impact on human health
    - Measured in disability-adjusted life years (DALYs)
    - Defined as a measure of the burden of disease impacting on quality-of-life and life expectancy scores as a result of a product's footprint
- Ecosystem damage
    - Measured in time-integrated species loss per year (species years)
    - Defined as the measure of the loss in biodiversity as a result of a product's footprint
- Resource depletion
    - Measured in surplus cost of retrieving resources ($)
    - Defined as the increased economic costs associated with discovering, mining

and processing natural resources due to increasing scarcity over time

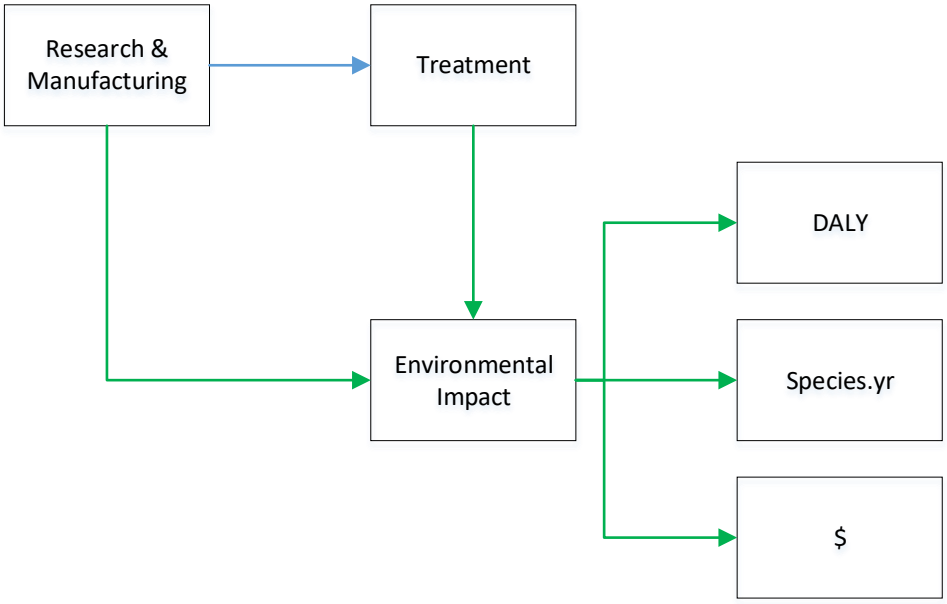


Figure 31: Life cycle assessment of biopharmaceuticals manufacturing

6.3.4. Social models

6.3.4.1.Adverse drug reactions

To guarantee the safety, purity and efficacy of medicines and treatments, health authorities globally subject the discovery, development, testing and manufacturing of substances with potential or demonstrated therapeutic benefits to regulatory oversights, including licensure, inspection and standards of good practice. Of particular concern is the occurrence of adverse events causing patient harm or even death. An adverse drug reaction is defined as a response to a medicinal product which is noxious and unintended (Del Pozzo-Magaña et al., 2015) and can result in mild discomforts such as rashes or nausea, or pose significant harms in the event of anaphylaxis. Long term usage can lead to formations of certain cancers or other chronic diseases. From a societal perspective, the occurrence of adverse drug reactions is detrimental and can substantially harm the sustainability of a treatment in the event of a product recall or withdrawal being deemed necessary by the health authorities. Figure 32 displays the societal impact of adverse drug reactions in the context of the overall biopharmaceutical treatment.

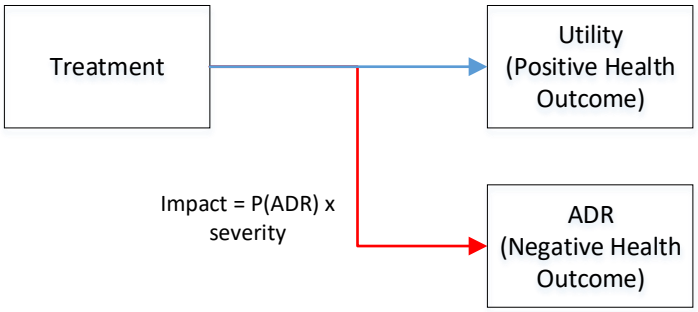


Figure 32: Adverse drug reaction societal impact for biopharmaceutical treatments

6.3.4.2.Social life cycle assessment

Social life cycle assessment is a method of evaluating the impacts of a product over its life cycle on society and socio-economic indicators. These impacts can be qualitative in nature and encompass impact categories such as human rights, labour conditions, instances of corruption and abuses of power and respect of societal heritage. The intent of social life cycle assessment is to determine the extended impacts of a manufacturing process on the fabrics of society in ways which may be excluded from traditional economic or environmental assessment tools. A common framework for social life cycle assessment is the UNEP SETAC Guidelines for Social Life Cycle Assessment of Products (Koellner et al., 2013), which will be used as a basis for social life cycle assessment in Chapter 7. The UNEP SETAC framework evaluates the impacts of a product throughout its life cycle on a variety of stakeholders, including local communities, value chain actors, consumers, workers and society, to ascertain the overall impacts. For each stakeholder, a number of impact categories are identified to qualitatively assess impacts to that stakeholder through a variety of means. When applied to the biopharmaceuticals manufacturing system, there are limited extra requirements compared to a standard industrial system, with similar assessments necessary to evaluate the holistic impacts to society. Further discussions on the application of the UNEP SETAC tool are found in Chapter 7, while a depiction of the societal impacts from biopharmaceuticals manufacturing is seen in Figure 33.

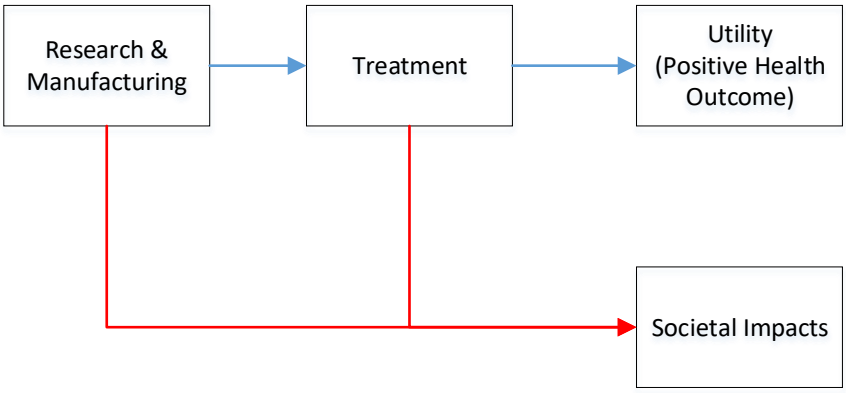


Figure 33: Social life cycle assessment of biopharmaceuticals manufacturing

6.4.Developing the integrated model of sustainability

In order to evaluate the complex web of relationships between the economic, environmental and social indicators of sustainability, an integrated conceptual model was developed to allow for a quantitative study, which is carried out in Chapter 7. The integrated model was developed from the individual models depicted in Section 6.3 and is displayed in Figure 34.

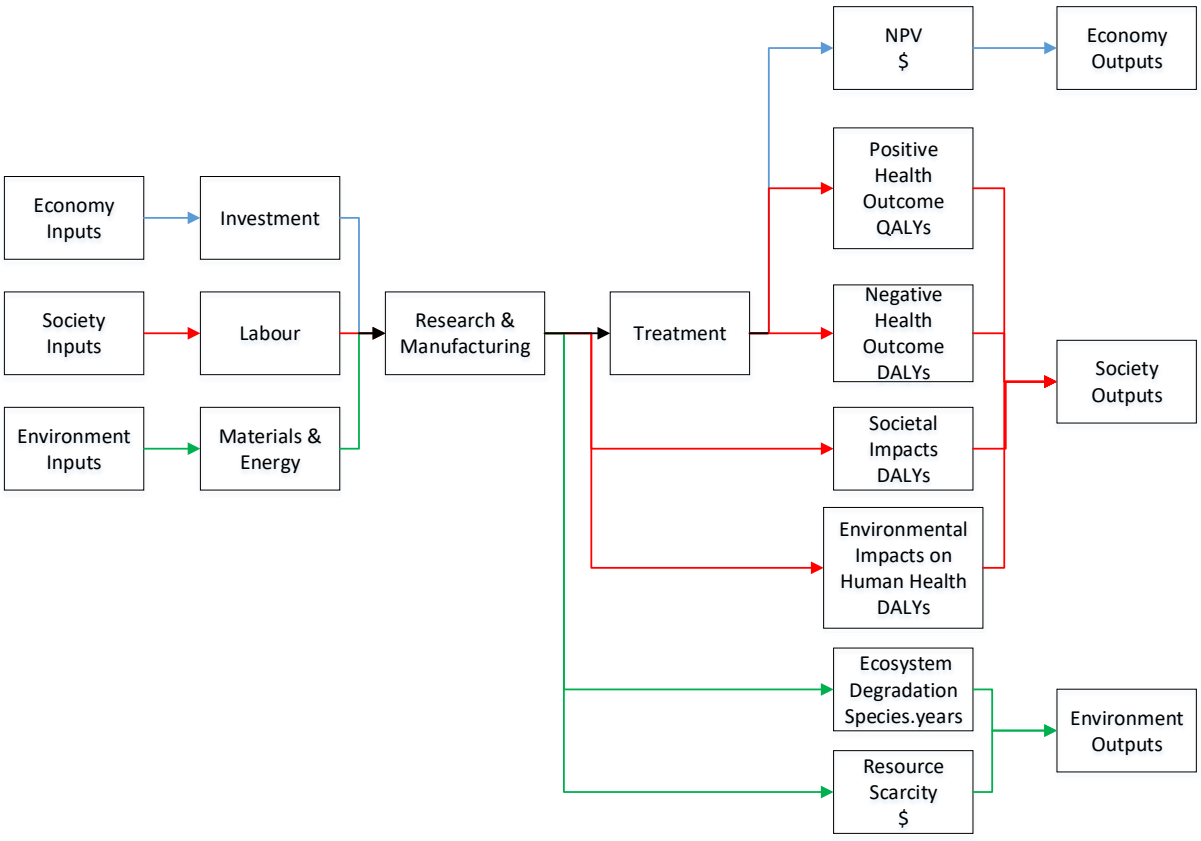


Figure 34: Integrated model of sustainability for biopharmaceuticals manufacturing

The integrated model consists of the key economic, societal and environmental inputs required for biopharmaceuticals manufacturing. For ease of interpretation, it is depicted as a linear system, however it is a circular flow system. From an economic perspective, if the investment required is greater than the revenue generated, it results in a negative economic flow i.e. an economic loss, as the economy must provide inputs in the form of money to maintain supply of the treatment. If the revenue generated is greater than the investment required, the positive flow results in a profit and a flow of money to the economy in the form of stocks or dividends to shareholders, etc. Society, on the other hand, provides an input in the form of labour, the personnel required to discover, develop and manufacture the treatment. Positive societal flows can result from the positive health outcomes associated with the treatment, while negative flows result from adverse drug reactions causing ill-health or death; societal impacts such as discriminatory practices, corruption or other indicators of social malfeasance impacting the flourishing of communities; and the environmental impacts on human health from the manufacturing process. Key inputs from the environment are the raw materials and energy supplied by the natural environment and the ecosystem services within it, while outputs to the environment are the ecosystem degradation resulting from the manufacturing process activities.

The generation of an integrated model of sustainability fulfils the criteria for a Class 3 model described by Allenby and Graedel, and allows for a visualisation of the interrelatedness between the economic, societal and environmental flows and their impacts on humanity and the biosphere in which we exist. The next step is to attempt to quantify the impacts to evaluate the holistic impacts of the industrial system and analyse from the viewpoint of a variety of value orientations, as described in Section 6.1, to determine the potential for trade-offs and to aid in the development of a multiple-criteria decision-making tool for biopharmaceuticals manufacturing systems.

Chapter 7: Flow analysis of biopharmaceuticals manufacturing

The purpose of this chapter is to quantify flows for the integrated biopharmaceuticals manufacturing system under a number of scenarios, to identify under what conditions and assumptions these flows might be negative or positive, the impact these flows can have on creating sustainability or unsustainability, and the impact of stakeholders' value orientations on perceptions of sustainability of the system. The chapter will proceed by outlining key assumptions and variables for each input and output flow, and the underpinning manufacturing scenarios and functional units necessary to allow for a flow analysis. The objectives of this analysis are:

- To quantify flows and investigate variables affecting these flows
- To evaluate resulting flows from various value orientations and consider the potential for trade-offs, if applicable, or the effects of dedicating efforts towards reducing magnitude of negative flows, where trade-offs are unacceptable
- To develop a simple decision-making tool for biopharmaceuticals manufacturing, and the data required for such a tool to provide a realistic assessment of treatment opportunities by all stakeholders and all value orientations

7.1. Quantification of Input and Output Flows

7.1.1. Basis of Analysis

The underpinning scenario for the analysis will be the 18.2kg/annum scenario evaluated as part of the Life Cycle Assessment in Chapters 4 and 5 of this thesis. As such, this involves the supply of an average of 3.64g of active product to an average patient population of 5,000 patients over a period of 10 years.

7.1.2. Treatment Health Outcomes and Cost

Based on a figures provided by Walsh, the average cost of a biopharmaceutical treatment is $45 per day, resulting in an annual cost of $16,425. A review of cost-effectiveness thresholds for Ireland (€45,000 per QALY), the United Kingdom (£40,000 per QALY) and the United States ($50,000 per QALY) provides for the use of a sample cost-effectiveness threshold of $50,000 for the basis of analysis. Assuming the sample treatment meets the limit of this threshold at the average cost provided by Walsh, it can be inferred that the sample treatment provides a positive health outcome of 0.3285 QALYs per patient per annum.

For the purposes of the sample treatment analysis, an adverse drug reaction rate of 10%, with an average severity resulting in 0.1 DALYs per affected patient per annum, based on a review of the literature for global burden of disease from adverse drug reactions (Rolfes et al., 2016; Del Pozzo-Magaña et al., 2014). The impact of non-responders, i.e. patients who are administered with the treatment but for whom there is no positive or negative health outcomes, will not be evaluated. A summary of the treatment health outcomes and cost is presented in Table 28.

Table 28: Treatment health outcomes, costs and overall flows

Administration Volume	Patient Population	Average Cost	Threshold	Health Outcomes	Outcomes per population	Total Flows per annum	Total Flows per 10 year period
3.64g/patient/annum	5,000	$16,425 per annum	$50,000 per QALY	Positive – 0.3285 QALYs	90%	1478.25 QALYs	14782.5 QALYs
				Negative – 0.1 DALYs	10%	50 DALYs	500 DALYs

7.1.3. Net Present Value

Treatment revenues (denoted TREV) are calculated as the product of the average cost of treatment and the patient population, and are displayed in Table 29. This revenue is required to account for:

- The initial investment required for research and development of the product (denoted IRD)
- The cost of goods (denoted as COG), comprising the labour costs and manufacturing facility capital and operations costs over the lifetime of the product
- Cash flow for development of further treatments from the product pipeline (denoted as FRD)
- A return on investment for the original investors (denoted ROI)

For the basis of analysis of a sample treatment, a number of assumptions are made. These assumptions are displayed in Table 29.

Table 29: Cash flow assumptions for the sample treatment

Cash Flow Direction	Variable	Calculation	Cash Flow per annum
Cash Flow In	TREV	5,000 patients per annum $16,425 average cost per patient per annum	$82,125,000
Cash Flow Out	IRD	$2.1 billion (DiMasi et al., 2016)	Sunk cost prior to marketing
	COG	$1,500 per gram (Love et al., 2015) 18,200 grams per annum	$27,300,000
		40% of annual COG for facility construction and qualification - $109.2 million	Sunk cost prior to marketing
	FRD	20% of TREV	$16,425,000

Net present value is calculated using the following formula:

$$Net\ present\ value = \sum_{t=1}^{N} \frac{R_t}{(1+i)^t}$$

Where R_t is the net cash flow, i is the discount rate, which is assumed in this case to be 11%, and t is the time of the cash flow in years. It is assumed that IRD is a sunk cost realised at year 0, prior to the treatment being marketed, and that 40% of COG is sunk also at year 0, to account for the manufacturing facility construction and qualification. The net present value after 10 years is presented in Table 30.

Table 30: NPV calculations for the sample treatment

	Year	0	1	2	3	4	5	6	7	8	9	10
Cash Flow In	IRD	2100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	COG	109.20	27.30	27.30	27.30	27.30	27.30	27.30	27.30	27.30	27.30	27.30
	FRD	0.00	16.43	16.43	16.43	16.43	16.43	16.43	16.43	16.43	16.43	16.43
Cash Flow Out	TREV	0.00	82.13	82.13	82.13	82.13	82.13	82.13	82.13	82.13	82.13	82.13
Net Cash Flow		-2209.20	38.40	38.40	38.40	38.40	38.40	38.40	38.40	38.40	38.40	38.40
NPV		-2209.20	34.59	31.17	28.08	25.30	22.79	20.53	18.50	16.66	15.01	13.52
									NPV ($ millions)			-1,983.05

7.1.4. Environmental Impacts and Outputs

The environmental impacts and outputs used comprise those as direct impacts from the process, as evaluated in Chapter 4. Impacts resulting from activities supporting this process, such as from office maintenance, commuter travel to and from the facility, and other activities, will not be explicitly addressed for the sample treatment. The environmental outputs used will be those evaluated for the stainless-steel scenario from Chapter 4, as displayed in Table 31.

Table 31: Environmental impacts for the sample treatment

Impact Category	Impacts per annum	Impacts per 10 year period
Human Health	7.65 DALYs	76.5 DALYs
Ecosystem Degradation	0.0153 species.years	0.153 species.years
Resource Scarcity	$213,200	$2,132,000

7.1.5. Societal Impacts – Social Life Cycle Assessment

To determine the relevant societal impacts, the UNEP SETAC framework will be utilised to determine the potential impacts to the diverse stakeholders stemming from biopharmaceuticals manufacturing. Initially, this will be completed qualitatively as a risk assessment, identifying risk areas as low, medium or high risk, and providing justification for the risk rating. Following this, areas identified as being high risk will be investigated to produce a quantitative measure of the societal impact in terms of DALYs resulting from these societal impacts. The stakeholders and impact categories are shown in Table 32.

Geographical location is important for SLCA, as in some jurisdictions, community, human and workers' rights form part of the rule of law and is implemented, whereas other jurisdictions lack the ability to enforce these laws. For the purposes of this study, it will be assumed that the manufacturing facility is located in Ireland, as part of the European Union.

Table 32: SLCA Stakeholders and Impact Categories Risk Assessment

Stakeholder	**Impact Categories**	**Risk Rating**	**Justification**
Local Community	Delocalisation and Migration	Low	
	Community Engagement	Low	
	Cultural Heritage	Low	
	Respect of Indigenous Rights	Low	
	Local Employment	Low	
	Access to Immaterial Resources	Low	
	Access to Material Resources	Low	
	Safe and Healthy Living Conditions	Medium	Environmental impacts to human health
	Secure Living Conditions	Low	
Value Chain Actors	Fair Competition	Low	
	Respect of Intellectual Property Rights	Low	
	Supplier Relationships	Low	
	Promoting Social Responsibility	Low	
Consumer	Health and Safety	High	Adverse drug reactions
	Feedback Mechanism	Low	
	Privacy	Low	
	Transparency	High	Price-gouging accusations
	End-of-Life Responsibility	Low	
Worker	Freedom of Association and Collective Bargaining	Low	
	Child Labour	Low	

Stakeholder	Impact Categories	Risk Rating	Justification
	Fair Salary	Medium	
	Hours of Work	Low	
	Forced Labour	Low	
	Equal Opportunities/Discrimination	Low	
	Health and Safety	Low	
	Social Benefit/Social Security	Low	
Society	Public Commitment to Sustainability Issues	Low	
	Prevention and Mitigation of Conflicts	Low	
	Contribution to Economic Development	Medium	Accusations of profiteering
	Corruption	Medium	History of abuse
	Technology Development	Low	

As per Table 32, a number of risk impact categories were identified. Further investigation of these is presented in Table 33, along with an estimation of the societal impact resulting from these impact categories.

Table 33: Estimates of societal impact resulting from impact categories

Impact Category	**Justification**	**Estimated Quantitative Societal Impact**
Safe and Healthy Living Conditions	Environmental impacts from the manufacturing process and associated impacts contribute to degradation of living conditions, as described in Chapter 4	76.5 DALYs
Health and Safety (Consumer)	Adverse drug reactions contribute to negative health outcomes in patient populations	10% of patient population at average severity of 0.1 DALYs (500 DALYs for the sample treatment)
Transparency (Consumer)	Price-gouging efforts by biopharmaceutical manufacturers can result in excessive prices which disqualifies the treatment from reimbursement by governments, leading to societal impacts due to negative health outcomes from no access to the treatment, or economic inequalities leading to reductions in quality of life	For the sample treatment, the uptake rate will be inversely proportional to the price, with 100% uptake at the average price of $16,425 per annum, and 50% uptake at a price 20 times that ($328,500 per annum)
Contribution to Economic Development	Recent conversations around the use of certain jurisdictions as tax-havens has led to suggestions that companies including biopharmaceutical companies utilise areas of lower taxation to increase profits (Warraich and Schulman, 2016)	Impact results from contribution to economic inequality. For the sample treatment, will be assumed that no impact occurs.
Corruption	In the past decade (2010-2020) there have been judgements against pharmaceutical companies on corruption charges for activities including off-label promotion (promoting use of a treatment for which it is not approved by health authorities to treat) and bribery of medical officials (Rodwin, 2013)	Bribery and off-label promotion can result in administration of treatments which may be unsafe or dangerous. For the sample treatment, corruption manifests as an increased adverse drug reaction rate of up to 10% and average severity of up to 0.2 DALYs

7.1.6. Overall Input and Output Flows

The overall input and output flows for the sample treatment system for the basis of analysis are outlined in Figure 35.

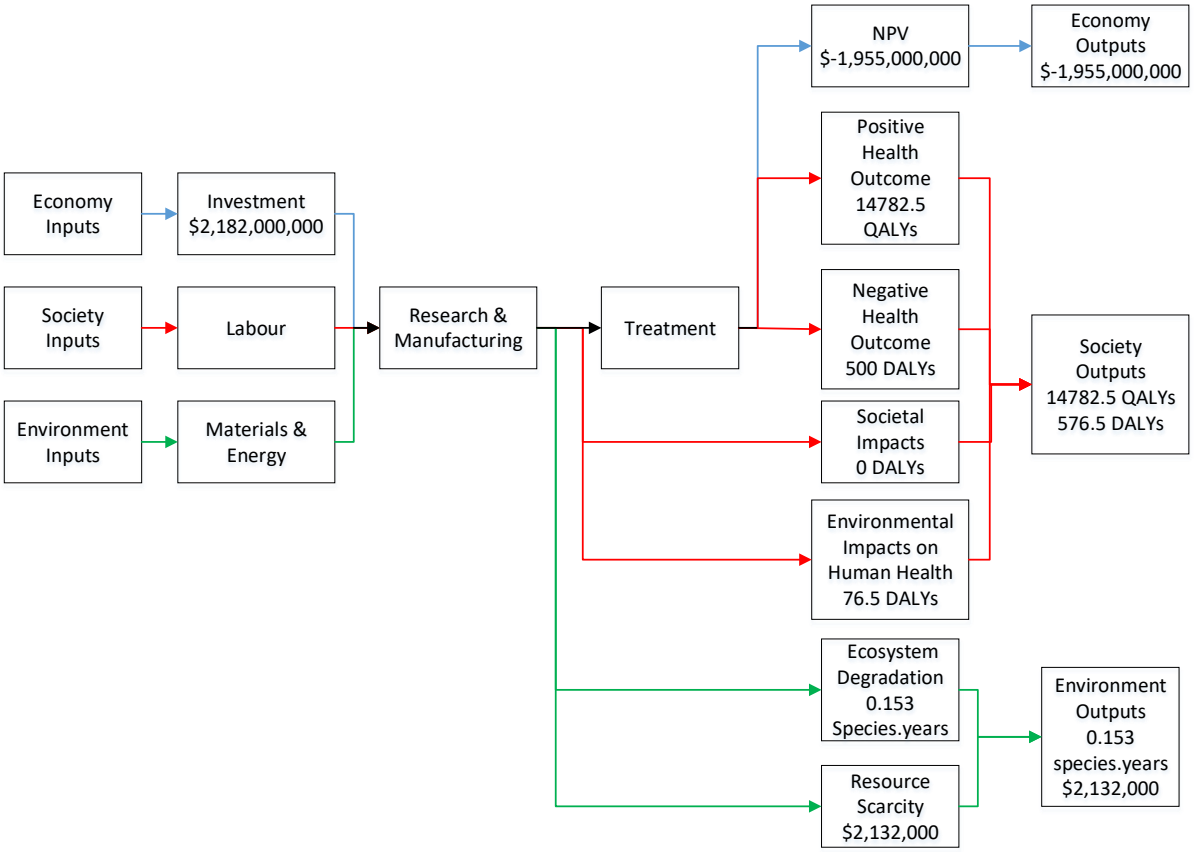


Figure 35: Input and output flows for the sample treatment system

From the analysis of the sample treatment, it can be seen that the economic flow is very large and negative, indicating that significant investment is required from the economy, i.e. investors, to produce the treatment with a significant loss. Contrastingly, the positive outputs to society in terms of QALYs from treatment received outweigh the DALYs from the various sources, with a ratio of 25.6 QALYs:1 DALY observed. From an environmental perspective, an output of 0.153 species.years is observed, indicating damage to ecosystem species over the period of study.

7.2.Value Orientations and Trade-Offs

7.2.1. Stakeholders and Value Orientations

There are a number of stakeholders and value orientations through which the sample treatment system can be evaluated. As described in Chapter 6, there are three distinct value orientations:

egocentric, homocentric (altruistic) or biophysical. The "voice" of each stakeholder with each value orientation is described in Figure 36. The stakeholders in the system are; the patient receiving treatment; economic agents investing in and benefiting from the development and manufacturing of the treatment; and society, impacted by activities to develop, manufacture and marketing of the treatment.

Figure 36: Stakeholders, their value orientations and desires of the sample treatment system

Stakeholder	Value Orientation	Desire
Patient	Egotistic	Maximise utility gained per unit cost
Economic Agents		Maximise return on investment (net present value)
Society		Minimise society-wide negative impacts
Patient	Altruistic	Maximise utility gained per unit cost Minimise society-wide negative impacts Maximise return on investment (net present value)
Economic Agents		
Society		
Patient	Biophysical	Maximise utility gained per unit cost Minimise society-wide negative impacts Maximise return on investment (net present value) Minimise negative impacts on the biosphere
Economic Agents		
Society		

Figures 37 to 39 depict the viewpoints of each stakeholder in each value orientation with respect to the sample treatment system.

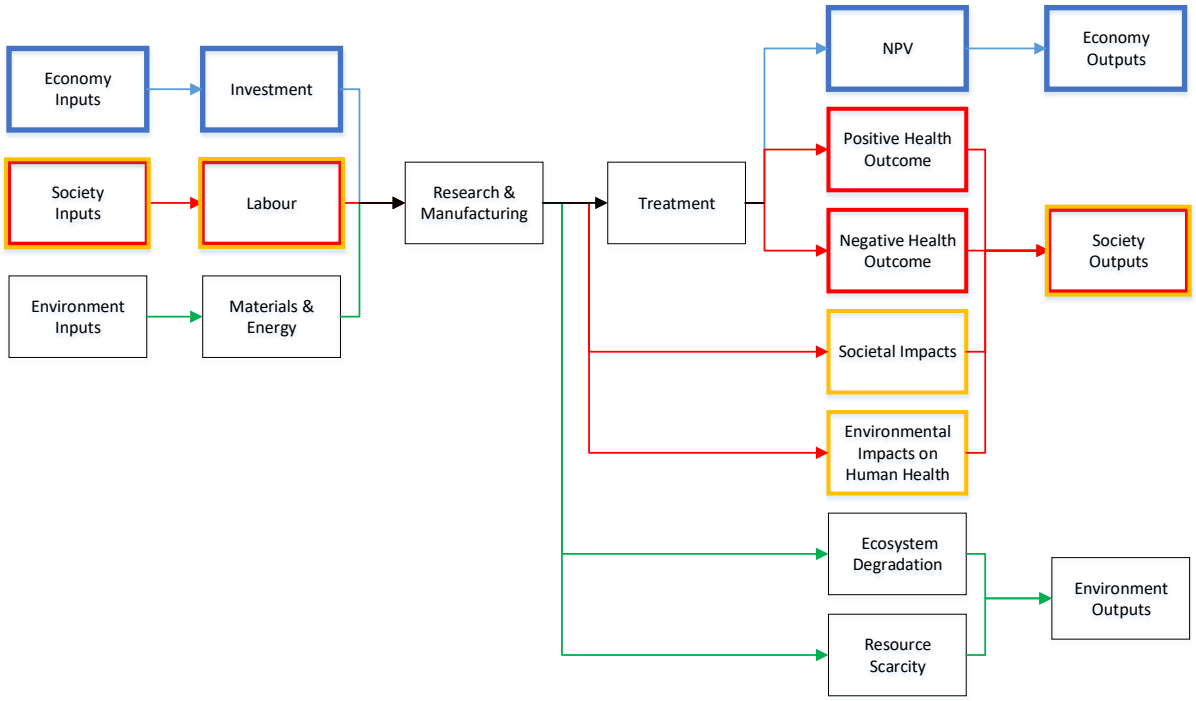


Figure 37: Stakeholders viewpoints under the egotistic value orientation, indicating patient (red border), investors (blue border) and society (yellow border)

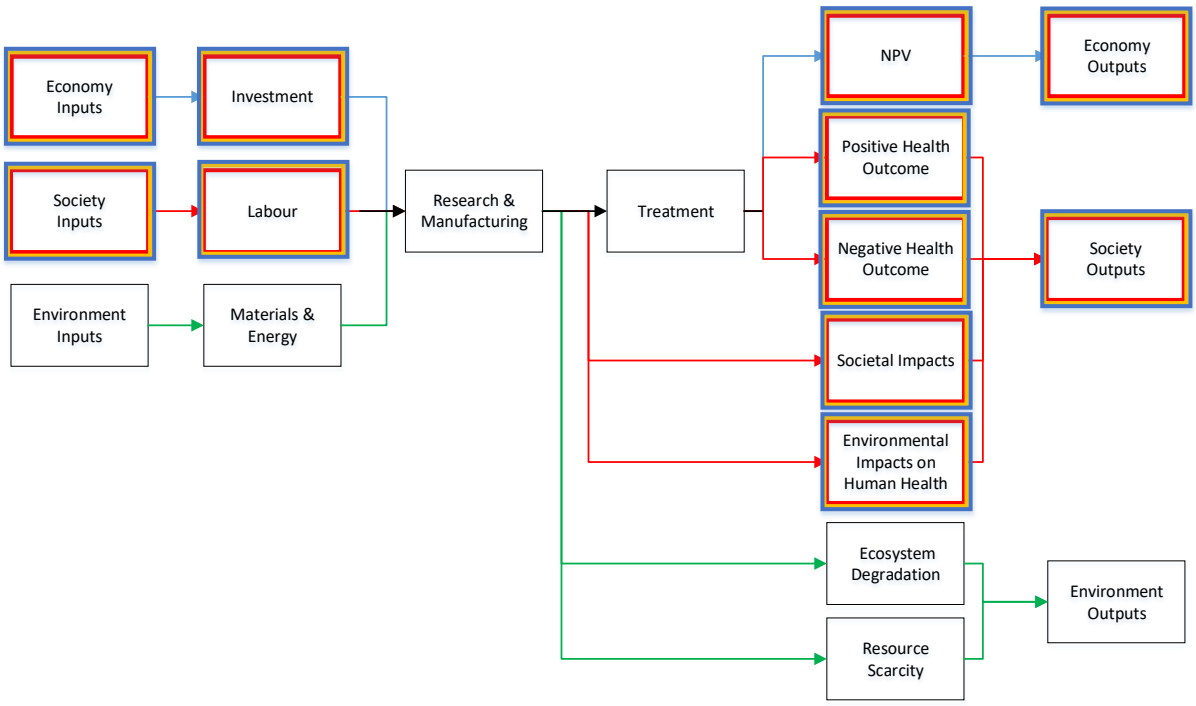


Figure 38: Stakeholders viewpoints under the altruistic value orientation, indicating patient (red border), investors (blue border) and society (yellow border)

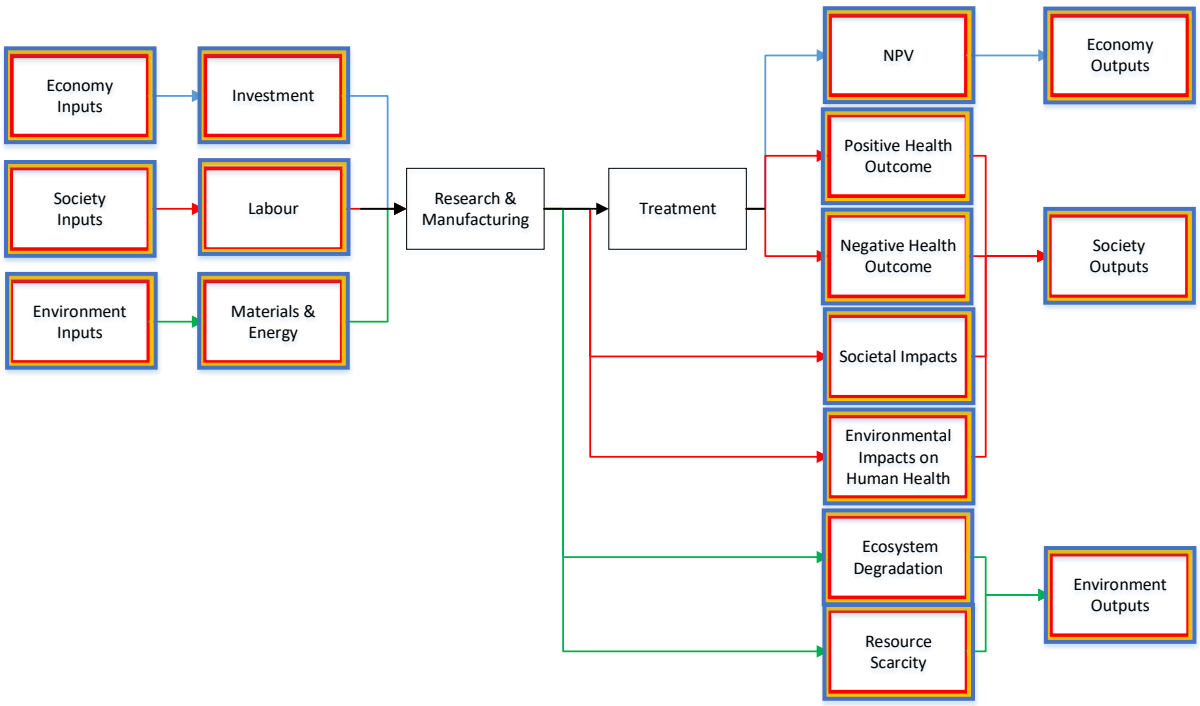


Figure 39: Stakeholders viewpoints under the biophysical value orientation, indicating patient (red border), investors (blue border) and society (yellow border)

Each value orientation will be quantitatively analysed to determine the consequences of the value choices presented to the stakeholders and to determine the impact of trade-offs in the event of assessments utilising a single viewpoint on each stakeholder.

7.2.2. Egotistic Value Orientation – Trade-Offs

The primary remit of the egotistic value orientation is to maximise utility at the expense of other stakeholders and the environment.

7.2.2.1.Investors

As described in Chapter 6, the dominant paradigm of neoclassical economics portrays the individual as a perfectly rational being looking to maximise personal return without consideration of others. From the investors' viewpoint, this indicates a maximisation of profit. The simplest method of accomplishing this goal is to increase the cost of the treatment. Assuming first the same costs to develop and manufacture the treatment, it will be assumed that the treatment is increased in price to $328,500 per annum, with a concomitant reduction in uptake of 50%. It is assumed that despite this reduction in uptake, production rate is constant, and excess material is not administered to any patients. This results in an average revenue of $821,250,000, and a net present value of $2.396 billion, as displayed in Table 34. The resulting

profitability index is 2.098, indicating a discounted 109.8% return on investment over a 10 year period.

Table 34: Net present value for the egotistic investors' scenario

Year	0	1	2	3	4	5	6	7	8	9	10
Cash Flow In ($ millions)	2182.13	43.73	43.73	43.73	43.73	43.73	43.73	43.73	43.73	43.73	43.73
Cash Flow Out ($ millions)	0.00	821.25	821.25	821.25	821.25	821.25	821.25	821.25	821.25	821.25	821.25
NPV ($ millions)	-2182.13	700.47	631.06	568.52	512.18	461.42	415.70	374.50	337.39	303.95	273.83
									NPV ($ millions)		2396.90

Achieving further economic returns without consideration for laws or ethics, which, unfortunately, has a history of occurring in pharmaceutical marketing, can result in further increases in profitability. In this example, corruption through off-label marketing and bribery is assumed to yield a 10% increase in overall uptake by patients who will either non-respond or suffer adverse drug reactions at the same rate as the sample treatment (10%). The results of these activities are displayed in Table 35.

Table 35: Health outcomes from the egotistic investors' viewpoint

Patient Population	Health Outcomes	Outcomes per population	Total Flows per annum	Total Flows per 10 year period
2,500 true patients 250 non-responders	Positive – 0.3285 QALYs	90% of true patients (2,250)	739.125 QALYs	7391.25 QALYs
	Negative – 0.1 DALYs	10% of true patients (250) 10% of non-responders (25)	27.5 DALYs	275 DALYs
	No response – 0 DALYs/ QALYs	90% of non-responders (225)	0 DALYs/ QALYs	0 DALYs/ QALYs

The resulting net present value is $2.881 billion, indicating a profitability index of 2.32. The resulting societal impact is a reduction in QALYs gained and DALYs gained, with expanded

impact to society due to the impact to non-responders. Assuming the environmental flows remain the same, the resulting flows are displayed in Figure 40.

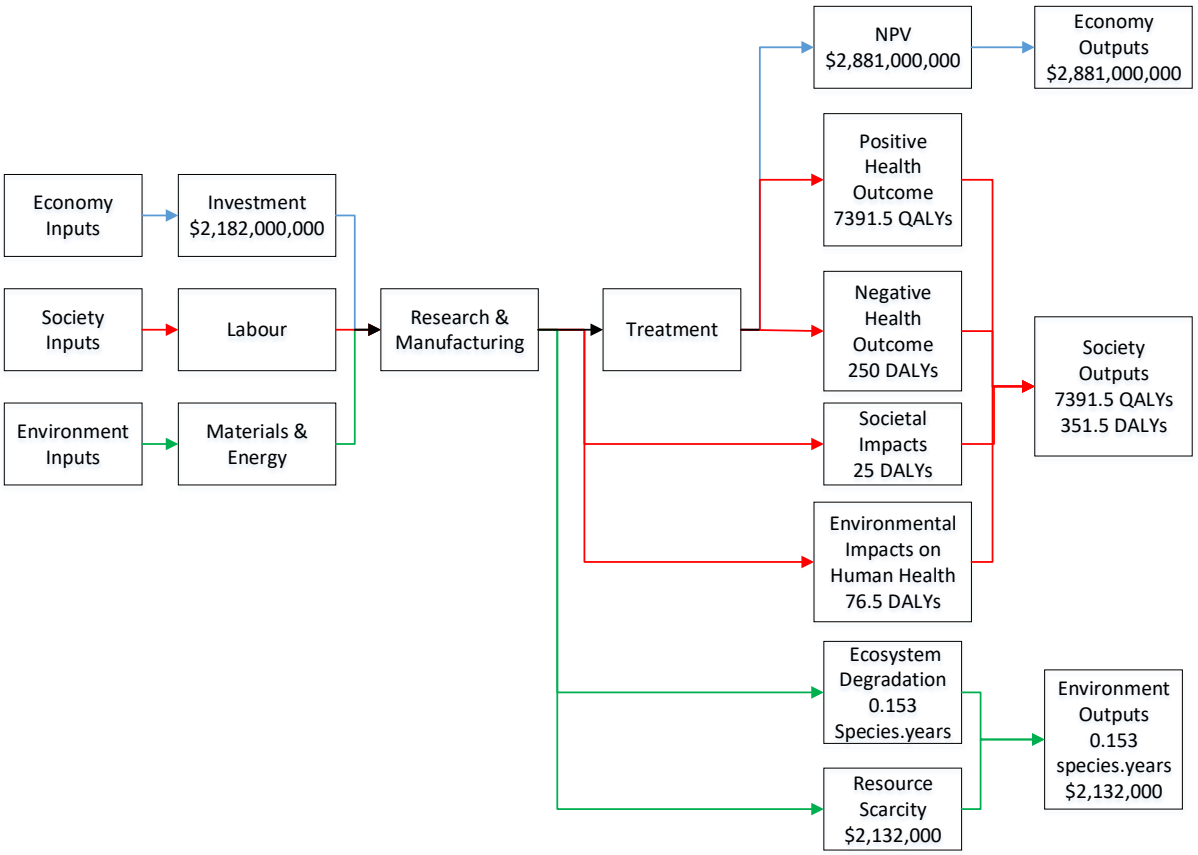


Figure 40: Overall input and output flows from the egotistic investors' scenario

From the analysis of the egotistic investors' scenario, it can be seen that the economic flow is very large and positive, indicating large return on investment for investors. The positive outputs to society in terms of QALYs from treatment received outweigh the DALYs from the various sources, with a ratio of 21 QALYs:1 DALY observed, which is a lower ratio than the sample treatment from Section 7.1. From an environmental perspective, an output of 0.153 species.years is observed, indicating damage to ecosystem species over the period of study. Considering fewer patients are treated, there is an overall increase in the general impact per gram of product across each output flow.

7.2.2.2.Patient

From the sample treatment analysis in Section 7.1, it can be seen that lower treatment costs yield a larger utility gained per unit cost, however, this impacts the return on investment required to develop and manufacture the treatment. From the perspective of the egotistic patient

viewpoint, a cost of zero would theoretically yield infinite utility per unit cost, which is of course impossible. As described in Chapter 6, where a treatment reaches a threshold for government reimbursement, then it is beneficial for the patient as it avoids out-of-pocket costs for treatment or insurance providers. As such, meeting this threshold, or even below it, is desirable to the egotistic patient scenario.

7.2.2.3.Society

From the egotistic society viewpoint, activities from the other stakeholders which impact society as a whole are unacceptable. In this case, the key intention is to maximise the positive health impacts from the treatment while reducing negative impacts from adverse drug reactions, unsavoury business practices and environmental impacts to human health.

Reducing adverse drug reactions can theoretically be accomplished by pursuing stringent clinical testing and requiring large supporting patient datasets prior to granting marketing authorisation. The impact of this is realised in the economic flows, with larger investments required to develop and manufacture product due to increased time costs. For simplicity, this will result in an additional 10% initial investment required, resulting in total initial investment in excess of $2.4 billion, with a concomitant reduction in adverse drug reactions of 5% to a base level of 5%, and reduction in average severity to 0.05 DALYs. Elimination of unsavoury business practices ensures no negative effects to the general population by administration to non-responders, thereby reducing the societal impacts to 0 DALYs. Health outcomes for the egotistic society scenario are shown in Table 36.

Table 36: Health outcomes from the egotistic society scenario

Patient Population	Health Outcomes	Outcomes per population	Total Flows per annum	Total Flows per 10 year period
5,000 true patients	Positive – 0.3285 QALYs	95% of patients (4,750)	1560.375 QALYs	15603.75 QALYs
	Negative – 0.05 DALYs	5% of patients (250)	12.5 DALYs	125 DALYs

For a reduction in environmental impacts to human health, it would be necessary to make investments to utilise technologies outlined in Chapter 5. For the purposes of this example, it

may be necessary to retrofit facilities, and develop these new technologies, resulting in as much as doubling of the initial investment costs for manufacturing from $82.125 million to $164.25 million, resulting in another increase in the initial investment up to $2.482 billion. In addition, utilising these new technologies and the associated risk with novel technologies could result in up to 50% increase in operating expenditures, from $27.3 million to $40.95 million. The resulting social, economic and environmental flows are displayed in Table 37 and 38 with the overall input and output flows shown in Figure 41.

Table 37: Net present value for the egotistic society scenario

Year	0	1	2	3	4	5	6	7	8	9	10
Cash Flow In ($ millions)	2482.00	57.38	57.38	57.38	57.38	57.38	57.38	57.38	57.38	57.38	57.38
Cash Flow Out ($ millions)	0.00	82.13	82.13	82.13	82.13	82.13	82.13	82.13	82.13	82.13	82.13
NPV ($ millions)	-2482.00	22.30	20.09	18.10	16.30	14.69	13.23	11.92	10.74	9.68	8.72
									NPV ($ millions)		-2336.24

Table 38: Environmental impacts for the egotistic society scenario

Impact Category	Impacts per annum	Impacts per 10 year period
Human Health	1.36 DALYs	13.6 DALYs
Ecosystem Degradation	0.00265 species.years	0.0265 species.years
Resource Scarcity	$34,400	$344,000

From Figure 41, it can be seen that the economic flow is once again very large and negative, indicating a large economic loss for investors, exacerbated by the additional costs for development and manufacturing. The result is increased positive societal outputs due to lower adverse drug reaction rate, and decreased negative societal outputs due to reduced severity of the adverse drug reactions coupled with reduced environmental impacts to human health, all of which contributes to a ratio of 124.83 QALYs:1 DALY. Additionally, there is a reduction in environmental impacts to 0.0265 species.years.

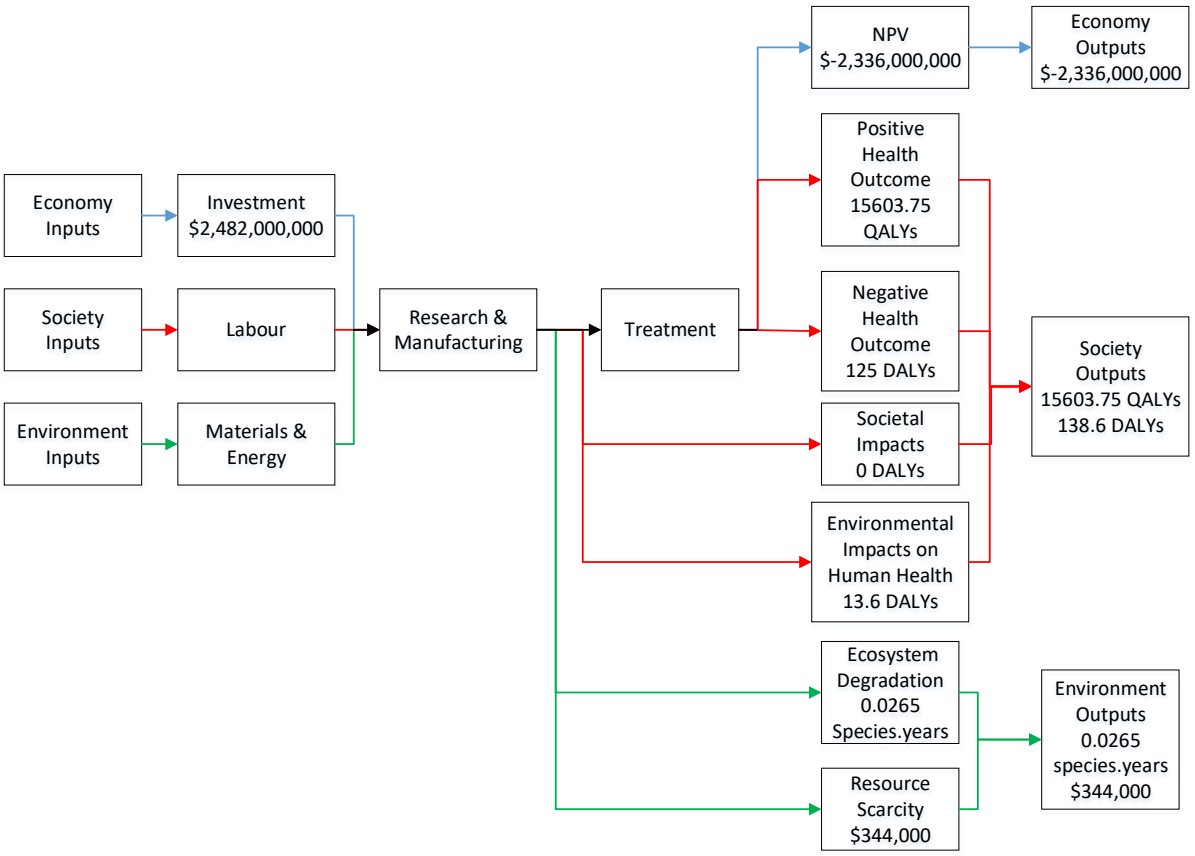


Figure 41: Input and output flows from the egotistic society scenario

7.2.3. Altruistic Value Orientation – Trade-Offs

For the altruistic value orientation, each stakeholder – investors, patient and society – seek to maximise their benefits without compromising each other. As such, it can be analysed as a holistic system as opposed to focusing on individual stakeholder viewpoints. From the investors' perspective, the aim is to achieve profitability without compromising patient health benefits or societal impacts from improper business practices. This level of profitability will be taken to be a discounted return on investment of 8%, to match the average stock market return of the past 30 years or so under the dominant neoclassical economic paradigm. This makes it an attractive investment, ensuring availability of capital to adequately develop and manufacture the treatment while minimising profiteering which may encourage unethical practices. The result of this "responsible" profit expectation is a reduction in patient uptake, as it will necessitate an increase in the unit cost per QALY gained. In addition, while it could be construed that no nefarious business practices could be considered altruistic, this is unrealistic; the standard reached for here is a minimisation of these business practices. As such, an appropriate metric is the maximisation of the QALY:DALY ratio observed. This will then

incorporate the additional DALYs from societal impacts associated with corruption or bribery, and also the balanced efforts expected to maintain attractive profits, while reducing the environmental impacts on human health. The environmental impacts on ecosystem degradation and resource scarcity will be ignored, as they are incorporated only in the biophysical value orientation. In order to achieve the desires of each stakeholder in the altruistic value orientation, a multiple-criteria decision-making analysis is required.

7.2.3.1.Economic Flows

The economic flows of the system consist of the initial investment, operating cash flow and the net present value following a period of 10 years. The initial investment consists of the development costs for the treatment, and the capital costs to build the manufacturing facility. The baseline development cost is taken to be $2.1 billion, with an additional 10% spend resulting in a reduction in adverse drug reaction rate and average severity of drug reaction by 50%. The baseline capital cost is taken as 40% of the overall COG for the treatment ($109.2 million), rising to double that ($218.4 million) in order to reduce the environmental impacts. The overall aim is to achieve a profitability index of 1.08, which is given by:

$$Profitability\ Index = 1 + \frac{NPV}{Initial\ Investment}$$

A discount rate of 11% is assumed for NPV calculation, and it is assumed that development costs for future treatments is fixed at $16.425 million, identical to the original treatment scenario in Section 7.1. Operating costs are assumed as $1500 per gram, a total of $27.3 million per annum, with this rising by 50% to $40.95 million in order to reduce environmental impacts.

7.2.3.2.Health Outcomes and Societal Flows

It is assumed that the treatment results in a positive health benefit of 0.3285 QALYs per annum, with the negative health impacts from adverse drug reactions being contingent on the initial development investment, with a rate of 5-10% and average severity of 0.05-0.1 DALYs per annum. The number of non-responders treated is a result of the level of corrupt business practices employed by the company, which will be presented as a value choice, and results in an increase of up to 10% uptake rate, resulting in some negative health impacts from non-responders suffering adverse drug reactions. The environmental impacts on human health are directly related to the capital and operating expenditures.

7.2.3.3.Altruistic Value Orientation – Results

The results of the altruistic value orientation experiment, whereby the QALY:DALY ratio is maximised while maintaining a profitability index of 1.08, is displayed in Figure 42.

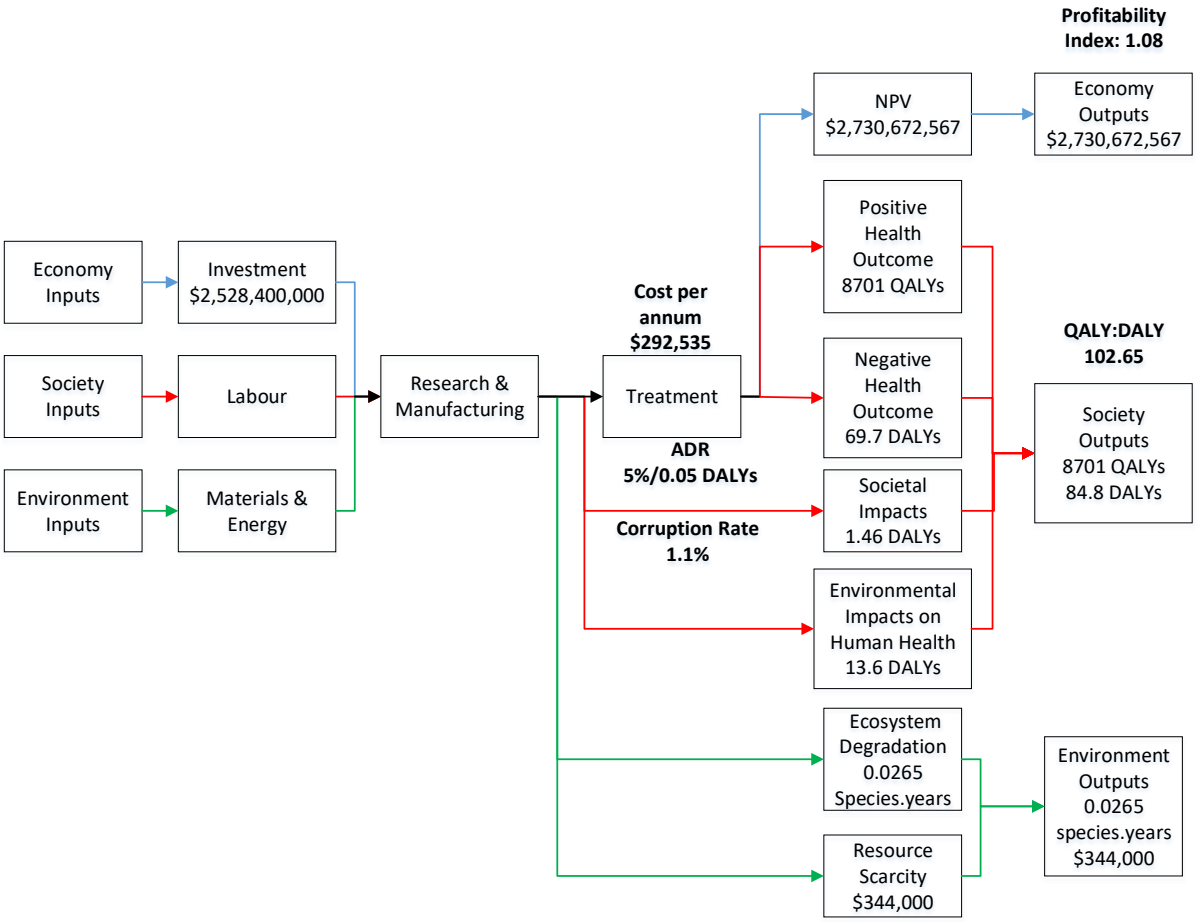


Figure 42: Results for the altruistic value orientation

The results of the altruistic value orientation scenario show a cost of $292,535 per annum to achieve a profitability index of 1.08 while maximising the QALY:DALY ratio at a value of 102.65. It is notable that this is achieved by reducing the environmental impacts on human health, which results in higher expenditures but an increased QALY:DALY ratio. This model is flawed as it does not account for the potential impacts on patients due to the higher cost requirements per annum for the treatment, with a cost per QALY of $890,517, which is 18 times the average threshold for approval.

7.2.4. Biophysical Value Orientation – Trade-Offs

For the biophysical value orientation, it is assumed that all stakeholders work towards the common benefit of all living beings, that is, by achieving the highest possible positive outcomes for society and the environment and corresponding lowest negative outcomes. Each stakeholder seeks to reduce impacts to a minimum, whilst maintaining the purpose of the treatment, the positive health benefits to the patient. From an economic perspective, the principles of ecological economics outlined in Chapter 7 are appropriated simplistically, with the concept of a steady-state economy taken literally. The consequence is an adjustment to investors' attitude from the "maximise return-on-investment" egoist through the "responsible return-on-investment" altruist towards the "only return-on-investment" viewpoint of the biophysical value orientation. Based on this interpretation, the overall return-on-investment for the system is taken to be 0%, with the investors' expectation only that the initial investment is fully recouped, subject to the discount rate over the time period of analysis. For the patients, once again it is assumed that their willingness to pay for treatment extends to ensuring a return for the investors', but also to the additional development requirements to minimise adverse drug reaction rate and severity, and to the additional capital costs necessary to reduce environmental impacts. In addition, there is a full rejection of corrupt practices, eliminating the societal impact but impacting on the patient ability to pay and uptake.

7.2.4.1.Economic Flows

The economic flows of the system consist of the initial investment, operating cash flow and the net present value following a period of 10 years. The initial investment consists of the development costs for the treatment, and the capital costs to build the manufacturing facility. The baseline development cost is taken to be $2.1 billion, with an additional 10% spend resulting in a reduction in adverse drug reaction rate and average severity of drug reaction by 50%. The baseline capital cost is taken as 40% of the overall COG for the treatment ($109.2 million), rising to double that ($218.4 million) in order to reduce the environmental impacts. The overall aim is to achieve a net present value equivalent to the initial investment following the 10 year period. A discount rate of 11% is assumed for NPV calculation, and it is assumed that development costs for future treatments is fixed at $16.425 million, identical to the original treatment scenario in Section 7.1. Operating costs are assumed as $1500 per gram, a total of $27.3 million per annum, with this rising by 50% to $40.95 million in order to reduce environmental impacts.

7.2.4.2.Health Outcomes and Societal Flows

It is assumed that the treatment results in a positive health benefit of 0.3285 QALYs per annum, with the negative health impacts from adverse drug reactions reduced to the minimum rate of 5% and average severity of 0.05 DALYs per annum. The number of non-responders treated is zero, due to the rejection of corrupt business practices. The environmental impacts on human health are directly related to the capital and operating expenditures.

7.2.4.3.Environmental Flows

Environmental impacts from ecosystem degradation and resource scarcity are minimised based on increased initial capital costs.

7.2.4.4.Biophysical Value Orientation – Results

The results for the biophysical value orientation experiment, whereby positive outcomes are maximised for all stakeholders at the cost of a break-even return-on-investment, are displayed in Figure 43.

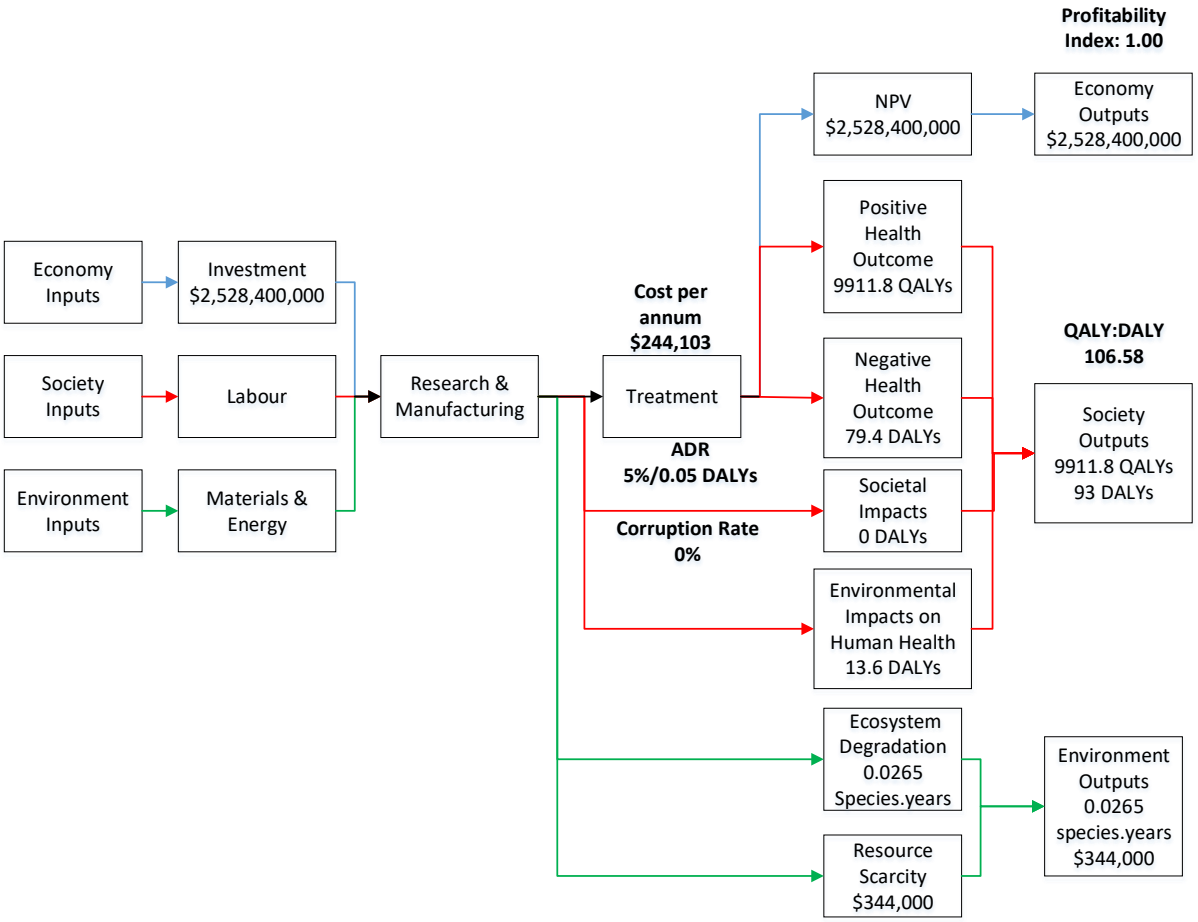


Figure 43: The results of the biophysical value orientation

From Figure 43, it can be seen that the QALY: DALY ratio for the biophysical value orientation is the highest achieved for any of the value orientations and stakeholders. This is a result of the elimination in societal impacts from corruption, the reduction in adverse drug reactions to a minimum, the additional expenditure to minimise environmental impacts, and the increased uptake of the treatment due to cost caused by the break-even profit margins. Whilst ultimately a simplistic and flawed model, it gives us food for thought as to what could be achievable if preoccupation with the economic sphere of influence was disregarded in favour for increases in societal and environmental benefit.

7.3.A multiple-criteria decision-making tool for biopharmaceutical treatments

Based on the scenarios presented previously, the framework identified in this chapter enables the analysis of all investments through the eyes of various stakeholders and value orientations. While some numbers were assumed for the purposes of this analysis, much of the required data is available for specific scenarios and treatments, with examples of sources displayed in Table 39.

Table 39: Examples of sources for economic, environmental and social data for multiple-criteria decision-making for biopharmaceutical treatments

Variable	Description	Source of Data
Development costs	Costs of research and development for the treatment	Industry benchmarks Treatment-specific values
Capital costs	Costs for construction, qualification and approval of the manufacturing facility	Industry benchmarks Engineering indices
Operating costs	Costs for manufacturing of the treatment	Industry benchmarks Engineering indices Established analyses (Love et al., 2013; Farid, 2007)
Cost per annum Cost per QALY	Cost of the treatment both as a sale price and the analysed cost-benefit gained from treatment	Pharmacoeconomics data
Patient uptake rate	Uptake rate of the treatment as a function of the sales price	Epidemiological studies Industry benchmarks
Corruption rate	Estimates of the off-label and kickback rates for the treatment	Manufacturer reputation, history and legal actions
Adverse drug reaction rate and average severity	Estimates based on route of administration and existing clinical data	Clinical data Epidemiological studies (e.g. for intravenous ADRs)

Variable	Description	Source of Data
Environmental Impacts	Life-cycle assessment for manufacturing process and process scale	Industry benchmarks Established analyses

While this multiple-criteria decision-making model is intended to provide a platform for sustainable assessment of a biopharmaceutical treatment incorporating economic, social and environmental facets, it is ultimately a reductionist model, reducing the evaluation to several diverse criteria in place of the typical sole criteria, economic return on investment. Further work is required to develop an evaluative model with greater appreciation and accounting of the complex interactions present in the biopharmaceuticals manufacturing and treatment system. For example, the ratio of personal and government expenditure on biopharmaceutical treatments and the corresponding contributions towards economic inequalities are unexplored in the described model. These contributions could be described as a complex feedback loop between the economic investor receiving the return on investment, the patient receiving the treatment and potentially suffering an out-of-pocket expense or reduced economic incomes due to impairment or debilitation, and the government, which may reimburse patients for the treatment (once it meets the threshold), support those patients which are impaired, and receive varying levels of taxation from the sale of treatments. The pursuit of a model enabling such an analysis is beyond the scope of the work presented in this research thesis, but is a promising proposition.

Part IV: Discussion and Conclusions

Chapter 8: General Conclusions and Future Work

Biopharmaceutical treatments continue to form an integral component of the modern healthcare system, with impacts on the lives of patient populations globally. Concerns exist around the economic sustainability of the industry in its current guise, as it exhibits boom-to-bust behaviour with knock-on effects on treatment pricing and availability, leading to potential reduced uptake among sufferers and concomitant social impacts. Hitherto environmental sustainability has existed on the periphery of decision-making processes, with selection of manufacturing processes governed by economic and technological concerns only. The motivation for this research thesis was centred on evaluation of the biopharmaceutical industry through a sustainability lens, encompassing quantitative and qualitative analysis of the environmental, economic and social sustainability of the industry, along with the variety of influencing factors present in the manufacturing system.

The influence of emerging single-use technologies on the environmental performance of perfusion cell culture manufacturing processes was investigated through the use of the life cycle assessment framework by comparing this technology with traditional stainless-steel technology. In Chapter 3, a life cycle assessment was constructed for a variety of production scenarios to simulate a wide range of treatments including those in the orphan space and those with larger patient populations. The results of this life cycle assessment were presented in Chapter 4, with strong evidence supporting a reduction in environmental impacts from single-use technologies. While this coincided with other established research in the area for fed-batch cell culture processes, it seems to run counter to the popular notion that single-use plastics are at the core of environmental devastation. Changes to cleaning and steaming demands and cleanroom requirements lay at the core of the reduction in environmental impacts, with the impacts moving from the use phase to the supply chain phase. Further investigation was conducted through sensitivity and uncertainty analysis to identify influential variables and address potential data concerns. A number of variables were found to contribute to the variance in the data, some of which are linked to organisational decisions made during facility concept, design and construction, while others are influenced only at a governmental and infrastructural policy level, and as such are likely a function of the location of the facility in which the treatment is produced. Selection of process paradigm and facility design must therefore account for these variables to ensure an appropriate decision is made with respect to environmental sustainability and impacts. Data uncertainty was simulated by the Monte Carlo method, and

demonstrated a low probability that source data impacted the results and conclusions of the life cycle assessment.

In Chapter 5, a vision of environmentally sustainable biopharmaceuticals was presented, indicating the roadmap towards reduced impact treatments to enable future generations to continue to enjoy the benefits of these treatments for many years to come. Using the major impacts identified from the life cycle assessment, the opportunities and challenges for each of the material and energy flows were described in the context of regulatory expectations, technological developments and manufacturing practicalities. From the analysis, a 60% or greater reduction in environmental impacts could be expected from both stainless-steel and single-use scenarios by fully leveraging new technologies without compromising patient safety. As with the life cycle assessment, there is variation in the phase of impact reduction between scenarios, with single-use reductions coming from changes in supply chain material sources, while stainless-steel reductions came predominantly by utilising alternative WFI production technologies. Both scenarios benefited from reduction in emissions associated with energy usage by adoption of renewable energy sources at a regional, national and international level. Theoretically, both scenarios stand to achieve positive environmental gains by employing best available technologies, however, concerns exist as to the pathway towards realising these technologies. In the case of single-use technologies, much of the environmental gains are as a result of the utilisation of biologically-sourced polymeric materials, which have not been realised at scale to date. It may transpire that such polymeric materials are unavailable due to biopharmaceuticals relatively low volumetric requirements in comparison to sectors such as food and beverage production, or that the grade of polymeric materials produced from biological sources is unsuitable for biopharmaceutical manufacturing use due to concerns around patient safety from extractables or leachables to the drug product. For stainless-steel, the use of reverse osmosis in place of conventional multiple-effect distillation is documented in compendia globally, these systems may pose higher risks from microbial contamination and bacterial endotoxin that limits their use for fear of compromising the safety of the drug product. In both scenarios, the reduction in cleanroom impacts are the result of regional to international transfer away from fossil fuel energy production towards carbon-neutral sources in line with the Paris agreement. Were this agreement not adhered to, or were biopharmaceuticals production to migrate towards countries which have not ratified the agreement, then emissions reductions may not be realised.

While environmental sustainability is critical to the flourishing of humanity and the organisms with which we share the biosphere over the coming generations, economic and social sustainability are also important concerns to maintain a fair and equitable society with access to safe and efficacious treatments for those who require them. Discussions on the holistic approach to decision-making and evaluation in the biopharmaceuticals manufacturing industrial system take place in Chapters 6 and 7, with a view towards development of a framework for multiple-criteria decision-making comprising the three pillars of sustainability and the value orientations of the various stakeholders of the industrial system.

In Chapter 6, the theoretical background of the decision-making framework is outlined, with qualitative and quantitative economic, environmental and societal tools discussed to determine the relationship between these tools, the decision-making process and the value orientations of the various stakeholders. Important comparisons are made between such concepts as the neoclassical economic model of the law of marginal utility, where the cost of treatment is represented as a function of the positive health outcome received, and the neo-Ricardian cost of production model, where the cost of treatment is contingent on the capital and labour used to produce it. Similar evaluations of quantitative models such as the life cycle assessment for environmental sustainability and the health technology assessment for economic evaluation are presented alongside qualitative evaluations such as the social life cycle assessment. Finally, a theoretical model is postulated, whereby the economic, social and environmental inputs and outputs are represented by single indices to allow for comparisons of scenarios through the eyes of the process stakeholders under varying value orientations.

The theoretical model for multiple-criteria decision-making is tested quantitatively in Chapter 7, by utilising the 18.2 kg/annum production scenario developed in Chapter 3. A number of simulations are tested by investigating each of three critical stakeholders, the investors, the patient and society as a whole, under each of the three value orientations, egoistic, altruistic and biophysical. The result is five simulations, with significant variability observed between simulations. It can be concluded that the value orientations demonstrated and held by the various stakeholders are of utmost importance in the decision-making process, some of which run counter to societal preconceptions. In this time of polarised political thought, the egoistic value orientation scenarios demonstrate the difficulties of each side thinking solely about themselves, resulting either in excessive financial gain for the investors, damaging uptake and reducing social benefits, or excessive financial loss for the investors, resulting in damage to supply and the innovation required to discover and develop treatments for hitherto untreatable

disorders. The remaining scenarios demonstrate the benefits of compromise, as options for maximising societal benefit while maintaining economic sustainability (under the dominant economic paradigm) and minimising environmental impact by adopting new measures such as ecological economic thought are detailed. While flaws exist in these models, with various assumptions being made and a tendency towards reductionist evaluation, albeit with more than a single metric being evaluated, the models themselves demonstrate an alternative to be further built on by other authors.

Viewed holistically, biopharmaceuticals manufacturing contributes vitally to modern society as a whole. Without it, various chronic and debilitating diseases would be untreatable, many of them caused by simple genetic malfunction, as opposed to being acquired illnesses. As with most industries, the manufacture of biopharmaceutical treatments causes negative environmental impacts, though the utilisation of best available technologies may contribute to a reduction in these impacts. Future societal trends such as the banning of single-use plastics, which is proposed in coming years and decades in many countries, may impinge on the availability of raw materials for use in biopharmaceuticals manufacturing, counter-intuitively harming efforts for reducing impacts. Similarly, the pursuit of environmental sustainability cannot be to the detriment of societal benefits of these treatments. When compared to other industries using single-use plastics, such as food and beverage, the societal benefits for biopharmaceuticals manufacturing are far more realisable, and should not be compromised by oncoming regulations. In such cases, it may be prudent for governments and regulatory bodies globally to assess the potential impact of such bans, and make provisions in economic terms to enable a continuation of single-use plastic adoption by biopharmaceuticals manufacturing whilst avoiding increasing issues such as economic inequalities.

A variety of opportunities are presented for investigation from this work. Further evaluation of the economic, environmental and product quality impacts of the selection of fed-batch or perfusion cell-culture may indicate “sweet spots” where a compromise of maximum yield and economic benefit can be reached while minimising impacts to environment. This could frame the regulatory discussion on the implementation of continuous manufacturing in a widespread fashion, allowing regulators to proactively promote the best available technologies from an environmental, economic and social perspective. This could additionally add impetus to innovative practices in academia and industry to further develop technologies, and provide a general strengthening of sustainability.

With the advent of the COVID-19 pandemic, the use of multiple-criteria decision-making tools could become important as the race for a suitable vaccine takes place. While assessment of these vaccines, which are likely to be unparalleled in speed of development, will rightly be focused on therapeutic efficacy and patient safety, a prime opportunity is presented to evaluate these world-changing treatments through a sustainability lens. Assessments of production methods, technologies utilised, and even distribution and storage impacts will likely show contrasting impacts to the environment, while cost, access and availability are likely to be central to discussion and debate as countries embark on vaccination programs of the scale not seen since the mid-20th century rollout of the first vaccines for polio. A holistic evaluation of these critical treatments could yield dividends for generations to come, and signify a positive step towards more sustainable practices in biopharmaceuticals manufacturing and society as a whole.

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