ANNOTATED BIBLIOGRAPHY OF SINGLE-USE SUSTAINABILITY ARTICLES

CITATIONS

(Sinclair, Leveen et al. 2008; Wells, Boehm et al. 2008; Leveen 2009; Mauter 2009; Pora and Rawlings 2009; Rawlings and Pora 2009; Rawlings and Pora 2009; Ho, McLaughlin et al. 2010; Junker 2010; Junker 2010; Baier 2011; Jiménez-González, Poechlauer et al. 2011; Jimenez-Gonzalez, Ponder et al. 2011; Pietrzykowski, Flanagan et al. 2011; Pollock and Farid 2011; Scott 2011; Mata, Martins et al. 2012; Flanagan 2013; Idris, Othman et al. 2013; Mahajan, Werber et al. 2013; Pietrzykowski, Flanagan et al. 2013; Ramasamy, Titchener-Hooker et al. 2013; Ramasamya, Titchener-Hookera et al. 2013; Flanagan, Pietrzykowski et al. 2014; Jiménez-González and Overcash 2014; Whitford and Scott 2014; Budzinski 2015; Budzinski, Ho et al. 2015; Flanagan 2015; Ramasamy, Titchener-Hooker et al. 2015; Bunnak, Allmendinger et al. 2016; Flanagan 2016; Idris, Chua et al. 2016; Hearn 2017)

BIBLIOGRAPHY (ANNOTATED)

Baier, U. (2011). "Waste Treatment Options, and the Environmental Impact of Single-Use Systems." Single-Use Technology in Biopharmaceutical Manufacture: 173-182.

> Synopsis: Overview of waste management in single-use. Includes the following sections: Introduction; Waste Generation through the Use of Disposables (solid, liquid, off-gas); Reduction and Prevention of Solid Wastes; Recycle -- Energy Recovery from SUS Waste (in-house incineration, combined municipal solid waste incineration, industrial incineration, plastic-derived fuel production, landfill, further options); Reuse -- Material Recycling from SUS Waste; Liquid Waste Treatment; Off-Gas Treatment; Environmental Impact; Summary

Budzinski, K. L. (2015). "Applying Green Chemistry Principles in Biologics Drug Development." Green Chemistry Strategies for Drug Discovery(46): 151.

> Synopsis: Introduction and overview of green chemistry principles applied to biologics drug development. "The growth of the biologics market provides the biopharmaceutical industry the opportunity to invest in innovative processes and facilities to improve their environmental footprint and gain a competitive advantage." Describes eight principles for green biologics: (1) Develop and monitor key parameters to nsure continuous process improvements to achieve the desired product quality attributes; (2) practice process intensification to achieve improvements in operational and process efficiency; (3) design processes and operations to maximize reuse and recycle of resources such as water, raw materials, and consumables; (4) minimize overall waste generation; (5) design processes to use and generate less hazardous substances; (6) use raw materials that are reusable or renewable and recyclable rather than depleting; (7) design

processes to minimize risk of accidents, exposures, or environmental releases; (8) processes and systems should be designed and operated for oeverall energy efficiency.

Budzinski, K. L., S. V. Ho, et al. (2015). "Toward sustainable engineering practices in biologics manufacturing." BioProcess Int **13**(11i): 1-9.

As pharmaceutical companies have incorporated more biologics into their pipeline, the ACS Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) recognized that opportunity to expand its reach. So in 2012, a biopharmaceutical focus group was formed within the roundtable, with the goal of expanding the principles of green chemistry into biologics development and manufacture. To that end, the focus group solicited from member companies suggestions for green engineering practices within process development, cleaning science, and facilities operations. The intent was to highlight innovations within the industry that could improve its environmental footprint without compromising yield or adversely affecting costs.

Bunnak, P., R. Allmendinger, et al. (2016). "Life-cycle and cost of goods assessment of fed-batch and perfusion-based manufacturing processes for mAbs." Biotechnology progress **32**(5): 1324-1335.

Life-cycle assessment (LCA) is an environmental assessment tool that quantifies the environmental impact associated with a product or a process (e.g., water consumption, energy requirements, and solid waste generation). While LCA is a standard approach in many commercial industries, its application has not been exploited widely in the bioprocessing sector. To contribute toward the design of more cost-efficient, robust and environmentally-friendly manufacturing process for monoclonal antibodies (mAbs), a framework consisting of an LCA and economic analysis combined with a sensitivity analysis of manufacturing process parameters and a production scale-up study is presented. The efficiency of the framework is demonstrated using a comparative study of the two most commonly used upstream configurations for mAb manufacture, namely fed-batch (FB) and perfusion-based processes. Results obtained by the framework are presented using a range of visualization tools, and indicate that a standard perfusion process (with a pooling duration of 4 days) has similar cost of goods than a FB process but a larger environmental footprint because it consumed 35% more water, demanded 17% more energy, and emitted 17% more CO2 than the FB process. Water consumption was the most important impact category, especially when scaling-up the processes, as energy was required to produce process water and water-for-injection, while CO2 was emitted from energy generation. The sensitivity analysis revealed that the perfusion process can be made more environmentally-friendly than the FB process if the pooling duration is extended to 8 days.

Flanagan, W. (2013). An environmental life cycle assessment comparison of single-use and conventional bioprocessing technology: A white paper, GE Healthcare Life Sciences.

Overview of GE Healthcare's first LCA study comparing single-use and traditional process technology for mAbs: A life cycle assessment was performed to compare the environmental impacts of producing monoclonal antibodies using either single use or traditional process technology. The study was performed using life cycle assessment methodology in which environmental impacts across the entire life cycle of each process component, from materials extraction and refining through component manufacturing, packaging, distribution, use, and

disposal at end-of-life are all considered. The assessment looked at the production of monoclonal antibodies (mAb) over a 10-batch campaign at three production scales chosen to reflect the clinical phase, scale-up phase, and production phase. The entire process trains were modeled including upstream and downstream processes from N-2 seed fermentation through product purification. Inventory data were derived mainly from Biopharm Services Ltd, developer of BioSolve™, an industry standard bioprocess model that includes standard benchmark operations and costs that can be used to build any process including those for manufacture of mAbs, vaccines and bacterial based products. The results of this study indicate that the single-use process train exhibited lower environmental impacts compared to the traditional fixed-in-place process train in each of 18 environmental impact categories studied. This is primarily due to a reduced need for the energy-intensive water-for-injection, process water and clean steam that are required to perform cleaning and sterilization between batches for traditional fixed-in-place equipment.

Flanagan, W. (2015). "An environmental life-cycle assessment: Comparing single-use and traditional process technologies for Mab production. ." BioProcess Int **13**(11i): 10-26.

An overview article summarizing the results of GE Healthcare's first LCA study on traditional vs. single-use process technology for mAb: A life cycle assessment was performed to compare the environmental impacts of producing monoclonal antibodies using either single use or traditional process technology. The study was performed using life cycle assessment methodology in which environmental impacts across the entire life cycle of each process component, from materials extraction and refining through component manufacturing, packaging, distribution, use, and disposal at end-of-life are all considered. The assessment looked at the production of monoclonal antibodies (mAb) over a 10-batch campaign at three production scales chosen to reflect the clinical phase, scale-up phase, and production phase. The entire process trains were modeled including upstream and downstream processes from N-2 seed fermentation through product purification. Inventory data were derived mainly from Biopharm Services Ltd, developer of BioSolve™, an industry standard bioprocess model that includes standard benchmark operations and costs that can be used to build any process including those for manufacture of mAbs, vaccines and bacterial based products. The results of this study indicate that the single-use process train exhibited lower environmental impacts compared to the traditional fixed-in-place process train in each of 18 environmental impact categories studied. This is primarily due to a reduced need for the energy-intensive water-for-injection, process water and clean steam that are required to perform cleaning and sterilization between batches for traditional fixed-in-place equipment.

Flanagan, W. (2016). "Single-use and sustainability: quantifying the environmental impact." BioProcess Online.

This online article summarizes preliminary findings from GE Healthcare's 2016-2017 updated LCA study comparing single-use, traditional, and hybrid (62% single-use) process technology for biomanufacturing of mAbs. This study differs from the initial LCA study in that it includes a more comprehensive array of contemporary single-use bioprocessing equipment (e.g., Xcellerex(TM) bioreactors and mixers, WAVE bioreactor, HyClone(TM) portfolio, AKTA(TM) ready system, ReadyToProcess portfolio), seven different geographies (Boston; California; Sao Paulo, Brazil; Istanbul, Turkey; Shanghai, China; Dortmund, Germany; and Dublin/Cork, Ireland). The study also

looks at a wider range of end-of-life treatments including autoclave-landfill, shred-autoclave-landfill, incineration, incineration with energy recovery, and recycling.

Flanagan, W., M. Pietrzykowski, et al. (2014). "An Environmental Lifecycle Assessment of Single-Use and Conventional Process Technology: Comprehensive Environmental Impacts." BioPharm International **27**(3).

Many biopharmaceutical companies have replaced or are planning to replace traditional multi-use facilities (fixed-in-place stainless-steel fermenters, tanks, downstream equipment, and associated piping) with single-use systems to improve flexibility and cost. A life cycle assessment was performed to compare the environmental impacts of producing monoclonal antibodies using either single use or traditional process technology. The study was performed using life cycle assessment methodology in which environmental impacts across the entire life cycle of each process component, from materials extraction and refining through component manufacturing, packaging, distribution, use, and disposal at end-of-life are all considered. The assessment looked at the production of monoclonal antibodies (mAb) over a 10-batch campaign at three production scales chosen to reflect the clinical phase, scale-up phase, and production phase. The entire process trains were modeled including upstream and downstream processes from N-2 seed fermentation through product purification. Inventory data were derived mainly from Biopharm Services Ltd, developer of BioSolve™, an industry standard bioprocess model that includes standard benchmark operations and costs that can be used to build any process including those for manufacture of mAbs, vaccines and bacterial based products. The results of this study indicate that the single-use process train exhibited lower environmental impacts compared to the traditional fixed-in-place process train in each of 18 environmental impact categories studied. This is primarily due to a reduced need for the energy-intensive water-for-injection, process water and clean steam that are required to perform cleaning and sterilization between batches for traditional fixed-in-place equipment. Note that this article is a follow-up companion article to the following publication the focused on carbon, energy, and water footprint for the same LCA study: Pietrzykowski, M., W. Flanagan, et al. (2011). "An environmental life cycle assessment comparing single-use and conventional process technology." BioPharm Int 24(S11): 30-38.

Hearn, M. T. (2017). "Recent Progress Toward More Sustainable Biomanufacturing." Preparative Chromatography for Separation of Proteins: 537-582.

Significant progress has been made in recent years to achieve more sustainable biomanufacturing, including areas associated with the downstream processing of protein products. A set of 12 principles relevant to sustainable manufacturing has been collectively proposed as a means to capture many of these issues, as they apply to all essential stages of downstream processing of bioproducts. This chapter examines recent progress toward the incorporation of these concepts into approaches that are increasingly being employed for the more sustainable manufacturing of protein-based products, with emphasis of the downstream aspects of the recovery and purification of value-added protein products derived from biotechnological procedures. Lessons gained from the use of similar approaches developed within the chemical, chemical pharmaceutical, and food ingredient industries are examined in terms of their applicability to the downstream processing of protein products derived from genetic engineering, cell culture, and associated biotechnology strategies.

Ho, S. V., J. M. McLaughlin, et al. (2010). "Environmental considerations in biologics manufacturing." Green Chemistry **12**(5): 755-766.

This perspective originated from our initial environmental assessment of biologics manufacturing as an extension of earlier work on small-molecule pharmaceutics spearheaded by the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR). Systematic analysis was focused on therapeutic proteins due to their current predominance in biotherapeutics. The E factor for process water was found to represent an important environmental index primarily because aqueous solutions are used in practically every processing step, and significant process improvements typically result in sizable reduction in the usage of water and associated chemicals. Compared to small-molecule drugs, manufacture of therapeutic proteins by fermentation requires approximately 10 to 100 times more water per kg of product, but very small amounts of solvent, especially hazardous ones. The amounts of solid waste generated from consumables are comparable between the two groups. A great deal of water is also consumed for non-process operations at bioprocessing plants, which necessitates an E factor for non-process water to help monitor this part of plant operation. Useful environmental indices for biologics manufacturing should also include energy consumption, reportedly dominated by facility operations, especially for cleanroom or controlled space because of the required HVAC (Heating, Ventilation, and Air Conditioning) for its operation. Notable emerging developments for therapeutic protein production include biogenerics, novel bioprocessing technologies, process analytical technology (PAT), single-use (disposable) manufacturing, and alternative production platforms such as cell-free synthesis and transgenic plants or animals. The potential impact of these technologies from an environmental standpoint is discussed.

Idris, A., G. Chua, et al. (2016). "Incorporating potential environmental impact from water for injection in environmental assessment of monoclonal antibody production." Chemical Engineering Research and Design **109**: 430-442.

Biopharmaceutical industries consistently demand water for injection (WFI) in their production. WFI production requires large amount of energy that may leave environmental footprint. However, its potential environmental impact (PEI) is typically not included in environmental assessment. This paper aims to present how WFI generation would contribute to environmental pollution. It was assumed that WFI was generated in multiple effect distillation (MED), where utility steam is used as heating media. Utility steam is generated in a steam boiler, where several gas pollutants are produced as by-product. The PEI of these pollutants was estimated based on a modified waste reduction (WAR) algorithm. For data generation, MED was simulated in SuperPro Designer®. To demonstrate the way to include WFI into an environmental assessment, a hypothetical monoclonal antibody process was used as a case-study. From the case-study, it can be seen that WFI generation contributed the most to energy consumption and to the total PEI value. Therefore, it is important to include PEI from WFI in the environmental assessment for more accurate results, particularly when comparing several process designs as the results may influence decision-making.

Idris, A., M. Othman, et al. (2013). "Systematic methodology for evaluating environmental impact of a biopharmaceutical production: A mAbs case study."

[DOES NOT INCLUDE SINGLE-USE] Evaluating environmental impact of a process by applying systematic methodology is a crucial step to determine its environmental footprint. In this paper, Waste Reduction (WAR) algorithm is applied to evaluate the potential environmental impact (PEI) of a monoclonal antibodies (mAbs) process. From the results it can be concluded that the upstream section (inoculum preparation and cell culture) has higher potential environmental impact than the downstream processing (recovery, purification, viral inactivation etc.). The results of this assessment can be used to assist decision making in process design comparison where lower environmental impact is preferred.

Jiménez-González, C. and M. R. Overcash (2014). "The evolution of life cycle assessment in pharmaceutical and chemical applications–a perspective." Green Chemistry **16**(7): 3392-3400.

This paper provides a broad strokes perspective on the evolution for the application of Life Cycle Assessment (LCA) within the pharmaceutical and chemical industries. This focus is mainly on the challenges faced to produce the needed inventory data and using the resulting LCA output in decision making, which are the backbone of any LCA estimation and practical application in industry. It also provides some of the insights the authors have derived over the last two decades of work in this area, and proposes a series of development needs within life cycle assessment as it becomes more integrated into decision-making in industry.

Jiménez-González, C., P. Poechlauer, et al. (2011). "Key green engineering research areas for sustainable manufacturing: a perspective from pharmaceutical and fine chemicals manufacturers." Organic Process Research & Development **15**(4): 900-911.

In 2005, the American Chemical Society (ACS) Green Chemistry Institute (GCI) and global pharmaceutical companies established the ACS GCI Pharmaceutical Roundtable to encourage the integration of green chemistry and engineering into the pharmaceutical industry. The Roundtable developed a list of key research areas in green chemistry in 2007, which has served as a guide for focusing green chemistry research. Following that publication, the Roundtable companies have identified a list of the key green engineering research areas that is intended to be the required companion of the first list. This publication summarizes the process used to identify and agree on the top key green engineering research areas and describes these areas, highlighting their research challenges and opportunities for improvements from the perspective of the pharmaceutical industry.

Jimenez-Gonzalez, C., C. S. Ponder, et al. (2011). "Using the right green yardstick: why process mass intensity is used in the pharmaceutical industry to drive more sustainable processes." Organic Process Research & Development **15**(4): 912-917.

There have been a many publications and much discussion about green metrics. While many have been proposed, The American Chemical Society Green Chemistry Institute's Pharmaceutical Roundtable has chosen process mass intensity (PMI) as the key, high-level metric for evaluating and benchmarking progress towards more sustainable manufacturing. This paper provides the philosophical and technical arguments on why PMI was chosen above other related metrics such as E factor or atom economy.

Junker, B. (2010). "Minimizing the Environmental Footprint of Bioprocesses, Part 1: Introduction and Evaluation of Solid-Waste Disposal." BioProcess Int **8**(8).

Part 1 of this two-part article introduces the need to reduce the environmental footprint of bioprocesses and evaluated the impact of solid-waste disposal. Part 2 continues by describing the effects of the remaining elements of the bioprocess footprint: wastewater, electricity, and air emissions.

Junker, B. (2010). "Minimizing the environmental footprint of bioprocesses, Part 2: Evaluation of wastewater, electricity and air emissions." BioProcess Int **8**(9).

Part 1 of this two-part article introduced the need to reduce the environmental footprint of bioprocesses and evaluated the impact of solid-waste disposal. Part 2 continues by describing the effects of the remaining elements of the bioprocess footprint: wastewater, electricity, and air emissions.

Leveen, L. (2009). "Single-Use Technology and the Carbon and Water Footprints of Biopharm Manufacturing." American Pharmaceutical Review **12**(6): 72.

Citation found but paper and abstract not in hand

Mahajan, E., J. Werber, et al. (2013). One Resin, Multiple Products: A Green Approach to Purification. Developments in Biotechnology and Bioprocessing, ACS Publications**:** 87-111.

Protein A affinity chromatography is a key purification step used during the purification of recombinant monoclonal antibodies (mAbs) harvested from cell culture fluid (HCCF). During this purification process typically a single Protein A resin is dedicated to purify a specific mAb of interest. For clinical manufacturing and pilot plant runs this can result in significant resin underuse, such that the Protein A resin is only used 10% of its potential lifetime. Herein we demonstrate that significant cost savings can be achieved (annually) if the Protein A resin is reused for multiple products. In this study, a cleaning procedure called the MabSelect SuRe™ Campaign Changeover Procedure (MSSCCP) was developed on lab-scale to reduce protein carryover during the reuse of the Protein A resin for purification of multiple products. Use of the MSSCCP cleaning procedure results in less than 1 ppm carryover of intact IgG into subsequent purification samples. This low protein carryover is 103 fold less protein carryover than that set in safety margins, and demonstrates that the same Protein A resins can be used to purify multiple products. The reuse procedure was successfully implemented on lab scale, and on pilot plant scale for the production of mAb drug substances.

Mata, T. M., A. A. Martins, et al. (2012). "Lca tool for sustainability evaluations in the pharmaceutical industry." Chem. Eng. Trans. **26**.

This article describes an Excel based tool specifically designed to perform the life cycle assessment (LCA) and the sustainability evaluation of pharmaceutical products and /or processes. In the current state of development the tool deals with the case study of the production of a lyophilized product for intravenous injection, with an active pharmaceutical ingredient (API) produced by

fermentation using genetically modified organisms. A gate-to-gate (GTG) analysis is done, considering the API production, the final product formulation, its storage and distribution, and the auxiliary operations involved. These steps are included in the aforementioned tool, and a set of sustainability indicators is proposed to make a quantitative sustainability assessment of this pharmaceutical product and process, based on the relevant impacts identified on its life cycle. Despite the limitations, the LCA and the sustainability assessment tool presented here can be easily modified to other types of pharmaceutical processes, given that good descriptions of them are available.

Mauter, M. (2009). "Environmental life-cycle assessment of disposable bioreactors." BioProcess Int **8**(4): 18-28.

Synopsis: LCA study performed by Yale student with GE guidance and review; just the Wave System 1000 bioreactor, not full process train. Main conclusion: "When evaluating the environmental impact of transitioning from conventional to disposable bioreactors, industrial users focus a disproportionate amount of their attention on waste-stream generation. Water and caustic waste from conventional bioreactors is replaced by plastic waste from disposable bags. Although this trade-off is one component of the environmental impact equation, LCA data reveal a more complex series of trade-offs that are not captured by waste stream analysis alone. In particular, this study has demonstrated that upstream manufacturing processes and operational inputs have a far greater effect on cumulative environmental impact than the process waste stream."

Pietrzykowski, M., W. Flanagan, et al. (2011). "An environmental life cycle assessment comparing single-use and conventional process technology." BioPharm Int **24**(S11): 30-38.

Summarizes first GE Healthcare LCA of monoclonal antibody production by traditional vs. single-use systems (WAVE Bioreactor and ReadyToProcess portfolio). The study includes the full process train at three scales: 100L, 500L, 2000L. The results reported in this article focus on carbon, energy, and water footprint. Additional results (comprehensive environmental impacts) were reported in this subsequent article: Flanagan, W., M. Pietrzykowski, et al. (2014). "An Environmental Lifecycle Assessment of Single-Use and Conventional Process Technology: Comprehensive Environmental Impacts." BioPharm International 27(3).

Pietrzykowski, M., W. Flanagan, et al. (2013). "An environmental life cycle assessment comparison of single-use and conventional process technology for the production of monoclonal antibodies." Journal of cleaner production **41**: 150-162.

Many biopharmaceutical companies have replaced or are planning to replace traditional multi-use facilities (fixed-in-place stainless-steel fermenters, tanks, downstream equipment, and associated piping) with single-use systems to improve flexibility and cost. This article will describe a recentlycompleted comparative study of the environmental impacts of producing monoclonal antibodies using either single use or traditional process technology. The study was performed using Life cycle assessment methodology in which environmental impacts across the entire life cycle of each process component, from materials extraction and refining through component manufacturing, packaging, distribution, use, and disposal at end-of life are all considered. The

assessment looked at the production of monoclonal antibodies (MAb) over a 10-batch campaign at three production scales chosen to reflect the clinical phase, scale-up phase, and production phase. The entire process trains were modeled including upstream and downstream processes from N-2 seed fermentation through product purification. Inventory data were derived mainly from Biopharm Services Ltd., developer of BioSolve, an industry standard bioprocess model that includes standard benchmark operations and costs that can be used to build any process including those for manufacture of mAbs, vaccines and bacterial based products. The results of this study indicate that the single-use process train exhibited lower environmental impacts compared to the traditional fixed-in-place process train in each environmental impact category studied. This is primarily due to a reduced need for the energy intensive water-for-injection, process water and clean steam that are required to perform cleaning and sterilization between batches for traditional fixed-in-place equipment.

Pollock, J. and S. S. Farid (2011). Toward Greener therapeutic proteins. Biocatalysis for Green Chemistry and Chemical Process Development**:** 197.

With the advent of molecular biology and supported by innovative development in large-scale bioprocessing technology, biotherapeutics—biological compounds used for treating diseases—have emerged in the last two decades as an important class of drugs and are now an integral part of product portfolios in most, if not all, major pharmaceutical firms. Biotherapeutics complement small-molecule drugs by expanding accessible targets and, for many indications, provide uniquely effective therapies. However, they span a very broad range of compounds, including peptides, proteins, fusion proteins, antibodies and their fragments, nucleotides, and many forms of vaccines.

Pora, H. and B. Rawlings (2009). "Managing solid waste from single-use systems in biopharmaceutical manufacturing." BioProcess Int **7**(1): 18-25.

Here we summarize the methods available for management of solid waste and provide working examples of disposal options for many single-use components. By offering such information, suppliers of components and systems can help users manage waste from disposable systems and also help them establish a responsible approach in their own environmental management programs. We strongly encourage readers to contact wastemanagement specialists within their own companies to develop their understanding of how plastic waste from other sources (e.g., packaging and labware) is currently handled at their facilities.

Ramasamy, S., N. Titchener-Hooker, et al. (2013). Challenges of developing decision-support LCA tools in the biopharmaceutical industry, CISA Publisher.

The biopharmaceutical industry has been slow in carrying out LCA analyses. However, as the industry matures, the level of scrutiny placed on this industry by international governments will increase and hence, there is an urgent need for the industry to implement decision-support tools for the decision-making processes. Decision-support tools based on life cycle assessment (LCA) can be potentially used for application in the biopharmaceutical industry as an aid to decision making. This paper sets out the challenges associated with developing such decision-support LCA tools. This paper highlights that in order for the industry to overcome these challenges and

successfully develop decision-support LCA tools, they require a broader understanding of the biopharmaceutical manufacturing processes and LCA methodology.

Ramasamy, S. V., N. J. Titchener-Hooker, et al. (2015). "Life cycle assessment as a tool to support decision making in the biopharmaceutical industry: considerations and challenges." Food and Bioproducts Processing **94**: 297-305.

The past decade has seen an increasing focus on the issues surrounding climate change and this has triggered international governments to develop environmental legislation and policies for the energy-intensive industries (EIIs) that can help reduce their anthropogenic greenhouse gases (GHG) emissions. The biopharmaceutical industry is a relatively new EII. The industry is important for global health as it is a main provider of affordable new therapies, achieved through the genetic manipulation of living organisms. Historically, attractive financial returns have encouraged the biopharmaceutical industry to focus on employing decision-support tools to estimate the process economics of manufacture. However, as the industry matures, the level of environmental scrutiny is increasing. Therefore, there is a need for the development of environmental tools specific to this industry to help guide the selection of environmentally favourable manufacturing operations. Life cycle assessment (LCA) is a commonly used environmental tool. We study the potential for application in the biopharmaceutical industry as an aid to decision making. Such tools assess the environmental impacts of a product or process over the entire life cycle. This paper reviews the use of LCA in the context of decision-making when applied to evaluate the environmental impact of the biopharmaceutical industry's manufacturing processes.

Ramasamya, S., N. Titchener-Hookera, et al. (2013). "Challenges of life cycle assessment (LCA) in the biopharmaceutical industry." Life Cycle Assessment: 1103-1110.

The biopharmaceutical industry employs biological processes to create therapeutic drugs through the genetic manipulation of living organisms. Traditional manufacturing processes with equipment largely constructed of stainless steel dominate. However, to improve process flexibility and economics, and to reduce the environmental impact of processes, manufacturing alternatives are now being considered including routes in which equipment is disposed of after a single use. Environmental studies are necessary if the industry is to understand better the environmental contributions of each alternative. LCA provides a methodological framework for the environmental impact evaluation of process and product over the entire life cycle. This paper sets out the challenges associated with such LCA when applied to biopharmaceutical manufacturing processes. The challenges include; i) selecting the LCA system boundary for the manufacturing processes (cradle-to-grave, cradle-to-gate, gate-to-gate), ii) selecting the appropriate type of LCA approach to be applied to the biopharmaceutical sector (attributional LCA, consequential LCA and attributional LCA with system expansion), iii) obtaining the LCI inventory data (obtaining the LCI data for biopharmaceutical processes can be a challenge as LCA is relatively new in the biopharmaceutical industry), and iv) verifying the LCI inventory data. In the study, the process to manufacture monoclonal antibodies was used as the basis to the LCA analysis. The analysis highlights that responding to these challenges effectively requires a broader understanding of the biopharmaceutical processes and LCA methodology. Specific recommendations are provided as to how to address effectively these challenges.

Rawlings, B. and H. Pora (2009). "Environmental impact of single-use and reusable bioprocess systems." BioProcess Int **7**(2): 18-26.

Environmental impact can be assessed in a number of ways: e.g., disposal methods for liquid and solid waste, carbon footprint of an overall process, and a full life-cycle analysis for materials and components. In later publications, we will present other aspects of environmental impact such as waste disposal methods, waste management guidelines for specific components, and cost analyses. Energy consumption was the measure of environmental impact for this study, which forms a part of a course in environmental natural sciences at the Swiss Federal Institute of Technology in Zürich, Switzerland. We had two objectives: (1) To calculate the energy consumption for individual components in a model multistage bioprocessing system; and (2) To compare the total energy consumption of the same process using a traditional stainless steel system and a disposable system. The model systems studied in the paper are based on unit operations typically found in monoclonal antibody (or other recombinant protein) production processes at the 1,000-L scale.

Rawlings, B. and H. Pora (2009). "A Prescriptive Approach to Management of Solid Waste from Single-Use Systems." BioProcess Int **7**(4): S40-S47.

Article is primarily a literature summary. In biopharmaceutical manufacturing, the disposal of solid waste from single-use systems is becoming an increasingly important issue. The new focus is driven by several major factors including a broadening range of disposable technologies enabling, in some cases, the installation of completely disposable multistage systems; improved scalability of singleuse components offering production capacities to thousands of liters; and the environmental impact of waste disposal. The latter concern includes not only regulatory and cost constraints, but also the need for users to implement a responsible approach for environmental sustainability. All those factors must be balanced against the potential benefits of single-use systems over those of traditional stainless steel processes. For example, disposables generate more solid waste but consume much lower quantities of water, chemicals, and energy to use.

Scott, C. (2011). "Sustainability in bioprocessing: not just an afterthought." BioProcess International **9**(10): 25-36.

This special report considers how the bioprocessing industry is beginning to incorporate related ideas into its processes and facilities. What degree of sustainability is realistic to strive for? What hidden costs of not modernizing do companies tend to miss in their evaluations, and what are the real economic advantages of going green? How are companies comparing “apples to oranges” costs of, for example, water for injection (WFI) production and clean/ steam-in-place operations with those incurred in securing an uninterrupted source of disposable materials? Where are the tradeoffs specific to various methods of disposal, and how are they to be evaluated? And what lessons can the US biotech industry learn from attention paid to this topic by many European companies and regulatory agencies?

Sinclair, A., L. Leveen, et al. (2008). "The Environmental Impact of Disposable Technologies: Can disposables reduce your facility's environmental footprint?" BioPharm International: 4-15.

We have compared the environmental footprint of a traditional biopharmaceutical manufacturing facility using fixed-in-place stainless-steel equipment, and a facility implementing disposable technologies for cell culture, solution mixing and hold, product hold, and liquid transfer. We accounted for facility size, water consumption, energy use, and carbon emissions from all steps, including even steel manufacture, transporting plastics to and from the facility, plastic incineration, and employees driving to work.

Wells, B., J. Boehm, et al. (2008). "Guide to disposal of single-use bioprocess systems." BioProcess International **6**: 24-27.

One of BPSA's core activities is to educate users and develop guides on issues pertaining to single-use systems. The organization's disposals subcommittee was chartered to establish a guide to address the issue of disposing of single-use bioprocess components and systems. The purpose of this introductory guide is to address the following questions: (1) What are the options for disposal of a single-use bioprocess component or system? (2) What are the advantages and disadvantages of each option? (3) Where can users get more information? This guide provides information to help concerned professionals and companies better understand the issue of single-use bioprocess component and system disposal.

Whitford, W. G. and C. Scott (2014). "Single-Use and Sustainability." BioProcess Int **12**(4S): 12-17.

Excellent introduction to the concepts of sustainability. How do single-use bioprocessing systems currently measure up? We now know quite a bit about the environmental stress caused by single-use (SU) technologies compared with conventional stainless steel equipment. Most advanced studies have concluded that for most installations, disposables reduced the environmental footprint (ecological stress) and impact of a biomanufacturing facility. Very rigorous comparative analyses indicate that single-use bioprocess technologies exhibit lower environmental impact than reusable bioprocessing technologies in all impact categories examined. From terrestrial ecotoxicity to marine eutrophication to ozone depletion — in the long run, SU-based manufacturing has been determined to be more environmentally friendly.