Bioresource Technology 175 (2015) 517–528

Contents lists available at ScienceDirect

Bioresource Technology

journal homepage: www.elsevier.com/locate/biortech

Technoeconomic analysis of large scale production of pre-emergent *Pseudomonas fluorescens* microbial bioherbicide in Canada

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HIGHLIGHTS

- Commercial production of *Pseudomonas fluorescens* BRG100 bioherbicide was analysed.
- Capital investment scaling and profitability are analysed using SuperPro Designer®.
- Total capital investment for a BRG100 fermentation plant is $17.55 million.
- *NPV* shows that the fermentation plant is profitable over wide operating scale.
- Small plants require need *NPV* breakeven prices but are less capital cost sensitive.

ARTICLE INFO

Article history:
Received 10 August 2014
Received in revised form 24 October 2014
Accepted 27 October 2014
Available online 4 November 2014

Keywords:
Technoeconomic
Bioherbicide bacterial fermentation
Bioprocess design
Capital investment
Net present value

ABSTRACT

The study presents an *ex ante* technoeconomic analysis of commercial production of *Pseudomonas fluorescens* BRG100 bioherbicide in Canada. An engineering economic model is designed in SuperPro Designer® to investigate capital investment scaling and profitability. Total capital investment for a stand-alone BRG100 fermentation plant at baseline capacity (two 33,000 L fermenters; 3602 tonnes annum^{-1}) is $17.55 million. Total annual operating cost is $14.76 million. Raw materials account for 50% of operating cost. The fermentation plant is profitable over wide operating scale, evaluated over a range of BRG100 prices and costs of capital. Smaller plants require higher *NPV* breakeven prices. However, larger plants are more sensitive to changes in the cost of capital. Unit production costs decrease as plant capacity increases, indicating scale economies. A plant operating for less than one year approaches positive *NPV* for periods as low as 2 months. These findings can support bioherbicide R&D investment and commercialization strategies.

1. Introduction

Over the past two decades, there have been significant efforts aimed at the development and commercialization of microbial bioherbicides (bacteria, fungi, and virus) to control both pre- and post-emergent grass and broad-leaf weeds (Bailey, 2010; Bailey and Falk, 2011; Bailey et al., 2010; Ash, 2010; Charudattan and Dinoor, 2000; Hynes and Boyetchko, 2006; Glare et al., 2012). These endeavours have been driven by growing concerns over environmental and health impacts of chemical herbicides (Glare et al., 2012), and a search for viable alternatives for controlling economically important weeds that have developed resistance to chemical herbicides (Beckie et al., 1999, 2013; Heap, 2014). There has also been a slowdown in the discovery of new chemical leads since 2005, with increasing difficulty in converting a new lead into a new product launch from at least 140,000 chemicals that must be screened to find one new, commercially acceptable, synthetic pesticide; this has led to a very drastic decline in new product launches from 2002 to 2010 (Bailey and Falk, 2011; Glare et al., 2012). This slowdown has been aggravated further by the wide and rapid adoption of new traits in primary crops such as corn, cotton, soybean, and canola containing herbicide tolerance and insect resistance genes.

In spite of considerable efforts to commercialize bioherbicides and indeed other biopesticides, the sector is still characterised by small to medium-scale firms, and it continues to play a relatively minor role in crop protection as a percentage of the more than $40 billion world pesticide market. This is notwithstanding positive growth rates reported for the biopesticide sector whose market size was estimated at $1.3 billion in 2011 and projected to increase to $3.2 billion by 2017, representing a compound annual

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http://dx.doi.org/10.1016/j.biortech.2014.10.130
0960-8524/

growth rate of over 15% over that period (Bailey and Mupondwa, 2006; CAB-International, 2010; Glare et al., 2012). Research and development of bioherbicides, including their commercialization, has not advanced as rapidly as that for insect and phytopathogen pests. For instance, *Bacillus thuringiensis* (*Bt*) based active ingredients marketed for control of crop and forestry lepidopteran insect pests account for over 90% of microbial biopesticides (Bailey and Mupondwa, 2006; CAB-International, 2010; Glare et al., 2012). The commercialization of bioherbicides has been constrained by factors including small market size confined to niche applications, uneconomic mass-production, and lack of commercial backers (Bailey and Falk, 2011). For instance, BioMal from the fungus *Colletotrichum gloeosporiodies* f. sp. *malvae* was Canada's first bioherbicide; it was discovered and developed during 10 years of research at Agriculture and Agri-Food Canada (AAFC) in collaboration with commercialization partner Philom Bios (based in Saskatoon) in the mid-1980s to 1990s. However, after a 2-year registration, the company halted the product due to decreased market, unprofitable commercialization cost, and high production cost (Bailey et al., 2010).

In addressing these constraints, Canada has continued concerted research and development (R&D) endeavours to develop and commercialize microbial bioherbicides. Recent public sector R&D by the Science and Technology Branch of AAFC has focused on the discovery and development of active ingredients based on the bacterium *Pseudomonas fluorescens* for use in mainstream crops to control economically important annual grass weeds such as green foxtail and wild oats, two very important weeds in North American agricultural production regions. In particular, BRG100, a strain of the bacterium *P. fluorescens*, has been shown to possess 85–90% efficacy in weed control as a single treatment pre-emergent bioherbicide, by inhibiting weed seed germination and suppressing root growth. This new technology is described by AAFC inventors Boyetchko et al. (2005) in US Patent 6,881,567 issued to AAFC with a corresponding Canadian Patent 2,377,054 issued in 2006. The technology basically provides isolated microbial bacteria from a *P. fluorescens* strain that can be formulated as a granular bioherbicide and applied to soil before, during or after planting to a wide range of economically important weed species including green foxtail (*Setaria viridis* [L.] Beauv.), foxtail barley (*Hordeum jubatum*), crabgrass (*Digitaria sanguinalis*), annual ryegrass (*Lolium rigidum*), barnyard grass (*Echinochloa crusgalli*), yellow foxtail (*Setaria glauca*), Italian rye grass (*Lolium multiflorum*), Goose grass (*Eleusine indica*), and wild oat (*Avena fatua*) (Boyetchko et al., 2005). These weeds, in particular wild oats and green foxtail, are among the most bothersome weeds for farmers producing major cereal crops such as wheat, barley, rye, oat, triticale and other cereal crops, due to full season competition with crops, resulting in significant reduction in crop yield and major economic losses for farmers (Beckie et al., 1999).

In terms of bioprocessing technology, BRG100 is mass produced via submerged liquid fermentation (as opposed to solid state fermentation) (Boyetchko et al., 2005). According to Stowell (1991) and Jackson et al. (1996), submerged liquid fermentation is considered to be the most economical and efficient commercial mass-production method for most microbial biopesticidal agents, as demonstrated by Churchill (1982) and Stowell (1991) for two commercial mycoherbicides, Collego® (now re-registered as Low Down®) and Devine®, which are manufactured in the United States using submerged liquid fermentation. On the other hand, solid substrate fermentation (the growth of microorganisms on a solid matrix with low free water content) is less frequently used due to what is regarded as higher labour costs, technical challenges in preserving sterility, inability to control culture conditions, and problems in retrieving microbial spores from the feedstock (Churchill, 1982). Hence, in terms of commercial application, effective commercialization of biopesticides has been largely influenced by economics of low-cost large-scale fermentation, production, and formulation of highly efficacious and stable microbial populations (Ash, 2010). In terms of formulation, BRG100 is formulated as a Pesta (Boyetchko et al., 2005). The term 'Pesta' refers to a pasta-like granular product made from a cereal grain flour in a process that encapsulates biocontrol agents as described for instance in Connick et al. (1991, 1996). In terms of product development, granular formulation "Pesta" was the first granular inoculum developed to deliver BRG100 as a grass weed bioherbicide, and which has been demonstrated to prolong the shelf-life of a dried encapsulated bioherbicide (Connick et al., 1991, 1996; Daigle et al., 2002). The role of formulation and efficacy has been well articulated (Boyetchko et al., 2002; Boyette et al., 1996; Daigle et al., 2002; Hynes and Boyetchko, 2011).

Although BRG100 has potential for large-scale application in mainstream cropping systems, past challenges associated with the development of bioherbicides point to a shortage of investment models for guiding R&D within the biopesticide innovation chain. There is a dearth of studies in the public domain that have provided a complete technoeconomic evaluation of microbial bioherbicide fermentation technology especially at the crucial pre-commercialization phase, complete with capital investment analysis. A few exceptions include two recent technoeconomic analyses of bacterial biopesticide fermentation for the mass production of *Bt* bioinsecticide (Rowe and Margaritis, 2004; Brar et al., 2007). Rowe and Margaritis (2004) modelled a stand-alone fermentation plant in Ontario for mass production of *Bt* bioinsecticide whose total capital cost was estimated at $18 million and assumed to operate 24 h day^{-1} 330 days annum^{-1} with a production capacity of 3×10^7 billion international units (BIU) annum^{-1} based on low density fed-batch fermentation in a 281,000-L fermenter utilizing 322.6 kW of energy. This is a large capacity production process representing 8–15% of world annual *Bt* production estimated at 13,000 tonnes annum^{-1} (Rowe and Margaritis, 2004). In a related study, Brar et al. (2007) conducted technoeconomic analysis of a similar 3×10^7 BIU annum^{-1} stand-alone fermentation plant in southern Ontario based on earlier analysis by Rowe and Margaritis (2004). Their estimated total capital investment ranged from $18 to $21 million for various process scenarios. In both of these studies, the estimated capital cost was 1.5 times installed equipment cost. By comparison, total capital investment for a monoclonal antibody biopharmaceutical plant with 60,000 L bioreactors is around 12 times the total equipment cost (Flickinger, 2013).

The objective of this study is to conduct a detailed *ex ante* technoeconomic analysis of the manufacturing process for the large-scale production of BRG100. The study provides a range of quantitative metrics for guiding research direction in the early phase of bioherbicide technology development. This includes a projection of costs associated with BRG100 mass production and other scale-up costs to enable future investment decisions, as well as parameters for determining some significant go/no-go decisions within the innovation chain.

2. Methods

2.1. Ex ante analysis and definition of BRG100

Pseudomonas fluorescens BRG100 technology is still under development. Hence, this analysis is conducted as an ex ante study within the context of the innovation value chain model (Kline and Rosenberg, 1986) which simply refers to sequence of phases from discovery, technology scale-up, fermentation and formulation, mass-production, and commercialization. This study focuses