TECHNOLOGICAL, COMMERCIAL, ORGANIZATIONAL, AND SOCIAL UNCERTAINTIES OF A NOVEL PROCESS FOR VANILLIN PRODUCTION FROM LIGNIN

by

Jason Timothy Wong
Bachelor of Science, University of British Columbia, 1992
Doctor of Philosophy, University of Manitoba, 1998

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Name:	**Jason Timothy Wong**
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Supervisory Committee:

____

Dr. Pek-Hooi Soh
Senior Supervisor
Associate Professor, Technology Management & Strategy

____

Dr. Jill Shepherd
Second Reader
Adjunct Professor, Technology and Operations Management & Policy

Date Approved: ____

Abstract

Lignin is a potentially rich source of aromatic compounds. *Rhodococcus jostii* RHA1 Δ*vdh* was bioengineered to accumulate vanillin when grown on lignin. Certain technological, commercial, organizational and social (TCOS) uncertainties will need to be addressed for RHA1 Δ*vdh* to be successfully adopted for commercial applications. Technologically, opportunities exist to utilize lignin for value-added chemicals. Commercially, entering the competitive vanillin market will be difficult. Opportunities exist to develop differentiated products and offer those products in emerging markets. Organizationally, commercialization might be expedited by licensing the technology to existing manufacturers. Socially, an opportunity exists to provide vanillin products from sustainable resources. Secondary stakeholders will need to be identified and engaged. Successfully addressing TCOS uncertainties of vanillin production using the new technology can demonstrate the viability of using lignin as a feedstock, potentially opening the door to using lignin as a source of other value-added chemicals such as resins, adhesives, polymers or biofuels.

Keywords: lignin; vanillin; vanilla; *Rhodococcus jostii* RHA1 Δ*vdh*; TCOS.

Dedication

To my family, whose constant support allows me to achieve more than I ever could alone.

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Glossary

biocatalysis	The use of natural catalysts, especially protein enzymes, to perform chemical transformations. Both isolated enzymes and enzymes still residing within living cells have been employed in biocatalytic processes.
catabolism	Metabolic reactions which break down molecules into smaller units, with the release of energy; "destructive" metabolism.
kraft process	Also known as the sulfate process, a technology for converting wood into wood pulp by separating the lignin and cellulose components of wood.
lignin	A complex heterogeneous organic polymer, comprised largely of aromatic subunits. Lignin comprises 19-33% of the biomass of trees and is also found in the cell walls of other plants. Lignin is removed from wood pulp before the pulp is used for paper making.
lignosulfonates	The sulfonated lignin byproducts from the production of wood pulp via the sulfite pulping process. Lignosulfonates can be used for downstream purposes such as derivation of economically useful chemicals.
liquid chromatography-mass spectrometry	A method in analytical chemistry, commonly used for separation and identification of chemical compounds in a complex mixture. The technique combines the physical separation of compounds by liquid chromatography with mass analysis of those compounds by mass spectrometry.
metabolism	Biochemical reactions occurring within living cells to sustain life.
pH	A chemical measure of the activity of the hydrogen ion in solution. Solutions with a pH less than 7 are said to be acidic, while solutions with a pH greater than 7 are basic or alkaline.
Rhodococcus	A genus of aerobic, Gram-positive bacteria in the order Actinomycetales. *Rhodococcus* species are known for their genetic and metabolic diversity, able to catalyze bioactive steroid production, fossil fuel biodesulfurization, and acrylamide production (McLeod et al., 2006).

R. jostii RHA1	A *Rhodococcus* bacterium, first isolated from soil, which is able to degrade lignin. *R. jostii* RHA1 (RHA1 for short) is able to utilize a range of aromatic compounds, carbohydrates, and other compounds as sources of carbon and energy (McLeod et al., 2006).
R. jostii RHA1 Δ*vdh*	RHA1 Δ*vdh* for short, a mutant form of RHA1 whose *vdh* gene was genetically inactivated by researchers at the University of British Columbia (Eltis, Bugg, Chen, & Sainsbury, 2012). RHA1 Δ*vdh* accumulates vanillin when grown on lignin.
sulfite process	A technology for converting wood into wood pulp by separating the lignin and cellulose components of wood using various sulfite and bisulfite salts.
vdh	Vanillin dehydrogenase, an oxidoreductase enzyme which catalyzes the conversion of vanillin to vanillic acid.

Abbreviations

GDP: gross domestic product

GM: genetically modified

LC-MS: liquid chromatography-mass spectrometry

LCA: life cycle analysis

MES: minimum efficient scale

R&D: research and development

TCOS: technological, commercial, organizational, social

UBC: University of British Columbia

UILO: University-Industry Liaison Office

1. Background and Overview

1.1 TCOS Lab: Project Sponsors

The sponsor of this project is the TCOS Lab at the Beedie School of Business at Simon Fraser University. The principal investigator of the TCOS research group is Dr. Jeremy Hall. According to the project sponsor, innovation (defined here as the successful commercialization of an invention) is by its nature risky, complex, and idiosyncratic (Hall & Vredenburg, 2005; Langford, Hall, Josty, Matos, & Jacobson, 2006; Simon, 1956). Given these inherent challenges of managing innovation, the mandate of the TCOS Lab is to investigate the technological, commercial, organizational, and social (TCOS) uncertainties associated with turning promising technologies into viable innovations.

Currently, the TCOS framework is being applied to a project funded by Genome Canada to harness microbial diversity for the sustainable use of forest biomass resources. This project is performed in collaboration with the laboratory of Dr. Lindsay Eltis in the Department of Microbiology and Immunology at the University of British Columbia. The overall objectives of the collaboration are to advance the understanding of forest soil microbial communities, and to translate that understanding into technologies which are both commercially important and environmentally beneficial. To achieve these overall objectives, the specific aims are to (1) investigate organic matter metabolism in forest soil microbial communities, including the discovery of novel biocatalysts; (2) develop biocatalysts for useful transformations of lignocellulose; and (3) to develop novel products from lignocellulose, in particular from lignin. As part of these objectives and aims, the present report describes the efforts to characterize the TCOS uncertainties of a novel technology for generating a value-added chemical, namely vanillin, using lignin as a starting material. Upon completion of this report, the project sponsor and their collaborators will be able to move forward to address the outstanding relevant TCOS uncertainties associated with the new technology for generating vanillin. In particular, the early information on commercial, organizational and social issues will help the science team led by Dr. Eltis to shape the technology for more effective diffusion of the technology. Furthermore, some of the lessons learned will be applicable to other aspects of the larger Genome Canada funded project. It is hoped that by systematically working through the TCOS uncertainties of the technology for producing vanillin, the utility and feasibility of using lignin as a chemical feedstock can be demonstrated.

1.2 Lignin and Challenges to its Use as a Chemical Feedstock

Lignin is a complex, heterogeneous biopolymer composed largely of hydrophobic and aromatic subunits linked by carbon-carbon and ether bonds (Lebo, Gargulak, & McNally, 2001). Lignin is found in the cells walls of plants and comprises 19-33% of the biomass of trees (Das & Singh, 2004; Lebo et al., 2001). Economically, lignin is viewed as a rich potential source of organic compounds which may find applications as biofuels, chemicals, and lignin-based polymers (Bjørsvik & Liguori, 2002; Mabee & Saddler, 2010; Park, Doherty, & Halley, 2008; Sena-Martins, Almeida-Vara, & Duarte, 2008; A. Singh et al., 2010). The technical challenge of extracting economically useful compounds from lignin is at least twofold: First, the lignin polymer needs to be degraded (depolymerized); second, compounds of interest need to be produced in useful quantities. Biocatalysis, the use of enzymes and/or living cells to transform chemical substrates into desired compounds, has been explored as a means of unlocking the chemical potential of lignin. The use of biocatalysts is a green alternative to current chemical methods of degrading lignin, which typically entail extremes of temperature, pressure, and pH (Sena-Martins et al., 2008). Beyond the technical requirements, the successful commercial adoption of any new technology requires that the various TCOS uncertainties be satisfactorily addressed (Chataway, Tait, & Wield, 2004; Hall & Martin, 2005; Hall & Vredenburg, 2003, 2005; Hall, Matos, & Langford, 2007; Hall, Matos, Silvestre, & Martin, 2011; Stone, 2002).

The most well characterized organisms that are able to degrade lignin are fungi, such as white-rot fungi; however, difficulties of working with fungi on an industrial scale have prompted the search for other organisms which can degrade lignin, including bacteria (Ahmad et al., 2010, 2011; Bugg, Ahmad, Hardiman, & Singh, 2011; Sena-Martins et al., 2008). A number of bacterial species with lignin-digesting abilities have been identified. One such species is *Rhodococcus jostii* RHA1 (Ahmad et al., 2011; McLeod et al., 2006). This catabolically active bacterium which can degrade lignin thus satisfies the first requirement of a technology for extracting useful compounds from lignin. To satisfy the second requirement, that of producing useful quantities of an economically useful compound, scientists at the University of British Columbia have generated a mutant form of RHA1, termed *Rhodococcus jostii* RHA1 Δ*vdh* (RHA1 Δ*vdh* for short). This bacterium is able to accumulate vanillin, a compound with practical applications, when grown on lignin. Thus, this bacterium can potentially satisfy the above two technical criteria of a technology for generating useful compounds from lignin.

Additionally, for this technology to be successfully implemented on a commercial scale, the TCOS uncertainties of the technology must be addressed.

1.3 Objectives and Approach

The overall objective of the present report is to investigate the TCOS uncertainties surrounding the commercialization of RHA1 Δ*vdh* as a technology for producing vanillin from lignin. Early insights on these issues will inform the science team developing RHA1 Δ*vdh* to help them shape the technology for more effective diffusion of the technology. Many of these uncertainties will be applicable to the use of lignin for generating other compounds. Demonstrating the viability of generating vanillin from lignin may open the door to using lignin as a source of other useful compounds.

I shall begin in the next chapter with a discussion of the world vanillin market and current means of vanillin production. Chapter 3 will consider Porter's Five Forces affecting the vanillin industry, which will provide a description of the intensity of competition which a new entrant can expect to face. A large portion of this report will be an examination in Chapter 4 of the TCOS uncertainties surrounding the development of the RHA1 Δ*vdh* technology as a commercial means of vanillin production from lignin. Included in Chapter 4 will be a detailed description of the TCOS framework. Finally, Chapter 5 concludes with a summary of the current issues surrounding RHA1 Δ*vdh*, and identifies areas of study and development which will need to be addressed to further the technology.

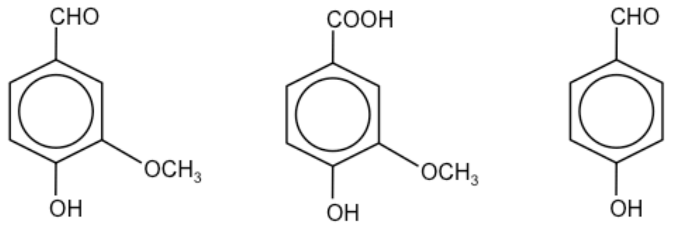
2. Vanillin and the World Vanillin Industry

This chapter will provide a description of vanillin, production methods, and the world vanillin industry. The first section describes vanillin itself and the market for vanillin. The next section will describe natural vanilla, which is highly valued for its richness and complexity of flavour. However, due to highly labour-intensive production and consequent expenses, natural vanilla meets only a fraction of world demand. Consequently, synthetic vanillin from petrochemicals and lignin supplies the bulk of world demand. These two types of vanillin will be described in Sections 2.3 and 2.4.

2.1 Vanillin and the Vanillin Market

Vanillin is the main chemical component of extracts from the dried pods of the vanilla plant, and is one of the most widely used flavouring and aroma agents in the world (Esposito et al., 1997; Walton, Mayer, & Narbad, 2003). Vanillin is the common name for the aromatic compound 3-methoxy-4-hydroxybenzaldehyde (Figure 1) (Esposito et al., 1997). Approximately 60% of industrial vanillin is used in the food industry; 33% as fragrances in perfumes and cosmetics; and 7% in pharmaceuticals (Priefert, Rabenhorst, & Steinbüchel, 2001). In the food industry, vanillin is used as a flavouring agent and is widely found in confectionery, chocolates, baked goods, non-alcoholic and alcoholic beverages, and many other foods. Other applications include use in animal feeds and agrochemicals. Non-food applications of vanillin are found in cosmetics, personal care products, detergents, and perfumery. In the pharmaceutical industry, vanillin is a starting material in the manufacture of a number of drugs. The anti-hypertensive drug Methyldopa is the most common drug derived from vanillin, while other drugs include L-Dopa (a treatment for Parkinson's disease) and the anti-infective agent Trimethoprim (Esposito et al., 1997). Vanillin itself has anti-microbial properties, and is also used as an excipient (inactive component of the drug carrier) in drug formulations. Experimentally, medicinal properties ascribed to vanillin include protection against carcinogens and metastasis of cancer cells; sensitization of cancer cells to a chemotherapy drug; and antioxidant properties (Akagi et al., 1995; Durant & Karran, 2003; Kumar, Priyadarsini, & Sainis, 2004; Lirdprapamongkol et al., 2005).

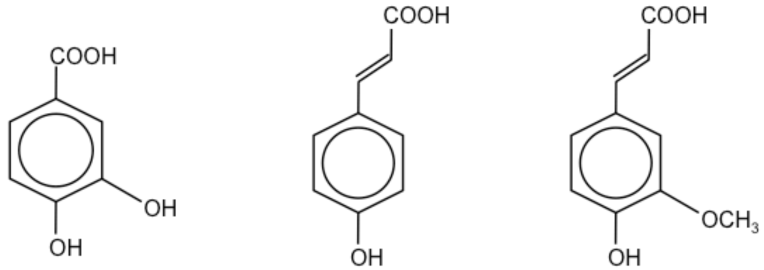
Figure 1. Chemical structures of vanillin and related compounds



Vanillin

Vanillic acid

para-hydroxy benzaldehyde



Protocatechuic acid

para-coumaric acid

Ferulic acid

Three major production methods currently serve the commercial vanillin market: natural vanilla extract from vanilla beans, vanillin produced from chemicals petrochemical sources, and vanillin produced from lignin derived from the wood pulping process (further details below). As of 2011, world production of vanillin was approximately 16,500 tonnes annually (Loe & Høgmoen, 2011). Of this, approximately 15,000 tonnes (91% of the global supply) are from petrochemical-based sources; 1500 tonnes are produced from lignin; and 30 tonnes of natural extract from vanilla beans. In addition, there are 3000 tonnes of ethyl-vanillin produced per year (Loe & Høgmoen, 2011). Prices for vanillin from petrochemicals are $12-15 per kilogram for large orders (greater than 500 kg) or $20-25 per kilogram for small orders (greater than 1 kg) ("Vanillin," n.d.). Lignin-derived vanillin, which is marketed as a premium product, is priced at $100-200 per kilogram (Borges da Silva et al., 2009). Natural vanilla extract can command $1200 to $4000 per kilogram (Walton et al., 2003). Overall, the worldwide vanillin market has been estimated to be worth $400-700 million (Butstraen, 2009; Eltis et al., 2012). Annual growth of vanillin consumption in mature markets in North America and Europe is approximately 2%, while growth in the emerging Chinese market was more than 10% as of 2006 (Fletcher, 2006).

Global vanillin production is concentrated in France, the United States, Norway, Japan and China ("Heavy Tasks in Vanillin Production," 2004). The Solvay Group is the world's largest vanillin producer. In September, 2011, the Solvay Group acquired Rhodia of France, which was the world's largest producer up to that time (Borges da Silva et al., 2009; Unknown, 2011). Rhodia supplied 48-50% of the world's vanillin market (Butstraen, 2009; de Margerie, 2009a). Borregaard of Norway is the world's second largest vanillin producer, and is the only company to produce vanillin from lignin (Borges da Silva et al., 2009). While lignin from the wood pulping process was regarded as a potential renewable source of vanillin, vanillin production from lignin decreased during the 1970s and 1980s for economic and environmental reasons, leaving Borregaard as the sole provider of vanillin from lignin (Hocking, 1997). Borregaard produces vanillin from spruce wood lignin, which has been described as having a “more intense” taste and a “creamier, rounder and more of a vanilla taste” than vanillin from petrochemical sources (Borges da Silva et al., 2009; Halliday, 2008; Loe & Høgmoen, 2011).

2.2 Natural Vanilla

Vanilla is a genus of plants in the orchid family Orchidaceae, comprising approximately 110 known species (Ramachandra Rao & Ravishankar, 2000). Of these, the species of greatest industrial importance is *V. planifolia* (Ramachandra Rao & Ravishankar, 2000). The mature fruits of the vanilla orchid, also known as beans or pods, develop their characteristic flavour properties upon curing. The cured beans are also referred to as vanilla. Cultivating the plants is a labour-intensive process. Due to the closed structure of the flowers, natural pollination is all but impossible; farmers must manually pollinate the flowers using bamboo sticks. Furthermore, the flowers are in bloom for less than one day and must be fertilized during a small window of time to ensure fruit development (Ramachandra Rao & Ravishankar, 2000). Beans mature approximately 10-12 months after fertilization. The harvesting and curing (fermentation) process is also labour-intensive and lengthy. Details of the curing processes can vary among producers, but the major steps common to all the processes are known as scalding/killing, sunning/sweating, drying, and conditioning, and can take up to six months (Dingnum, Kerler, & Verpoorte, 2001; Ramachandra Rao & Ravishankar, 2000). The cured beans contain vanillin at approximately 20 g/kg dry weight. Extraction of the vanilla flavour using ethanol or ethanol/water solutions can take 2-9 days depending on the method employed, followed by aging of the extract for one year. Natural vanilla extract is composed of 98% vanillin (Esposito et al., 1997). Vanilla cultivation requires a warm, moist tropical climate. Industrial production is largely concentrated in Madagascar (36% of the world production of 6680 tonnes in 2010), Indonesia (28% of world production in 2010), and China (20%) ("Countries by commodity," n.d.). Destruction of vanilla crops by tropical storms can have adverse effects on vanilla yields in a given year, leading to sharp price increases ("Vanilla crops hit by cyclone," 2004; "Vanilla thriller," 2002). Due to the labour-intensive process and low yields, naturally grown vanilla does not come close to meeting the global demand for vanilla flavouring. The shortfall in supply is made up by synthetic vanillin produced from petrochemicals and lignin, described in the next two sections.

2.3 Vanillin from Petrochemicals

The major petrochemical feedstock for industrial vanillin production is guaiacol (Esposito et al., 1997; "Heavy Tasks in Vanillin Production," 2004). Production methods starting with guaiacol include the nitrosation process and the glyoxylic acid process (Esposito et al., 1997; "Heavy Tasks in Vanillin Production," 2004) . The nitrosation process is the older of the two processes, and produces considerable pollutants and toxic byproducts, but as of 2004, was the main process employed by the Chinese producers. It has been gradually eliminated in most other countries, with approximately 70% of vanillin in those other countries being produced via the newer glyoxylic acid process ("Heavy Tasks in Vanillin Production," 2004). This process starts with the condensation of guaiacol with glyoxylic acid, followed by an oxidation step and a simultaneous acidification and decarboxylation step to yield vanillin (Figure 2) (Ramachandra Rao & Ravishankar, 2000). This process yields a high quality product with low pollution ("Heavy Tasks in Vanillin Production," 2004). Rhodia/Solvay is the world's largest producer of vanillin using this process.

With the current interest in the sustainability of industries, a relevant social-political concern is the ultimate source of feedstock chemicals, and whether those sources are renewable. The major industrial pathway for the production of guaiacol is shown in Figure 3. The starting materials for preparation of guaiacol are benzene and propylene, both of which are petrochemicals whose industrial source is mainly from petroleum (Folkins, 2003). Thus, while the conversion of guaiacol to vanillin does not produce toxic byproducts, the ultimate source of guaiacol is from petroleum and can be subject to fluctuations in world petroleum prices (Borges da Silva et al., 2009).

Figure 2. Vanillin synthesis via condensation of guaiacol with glyoxylic acid

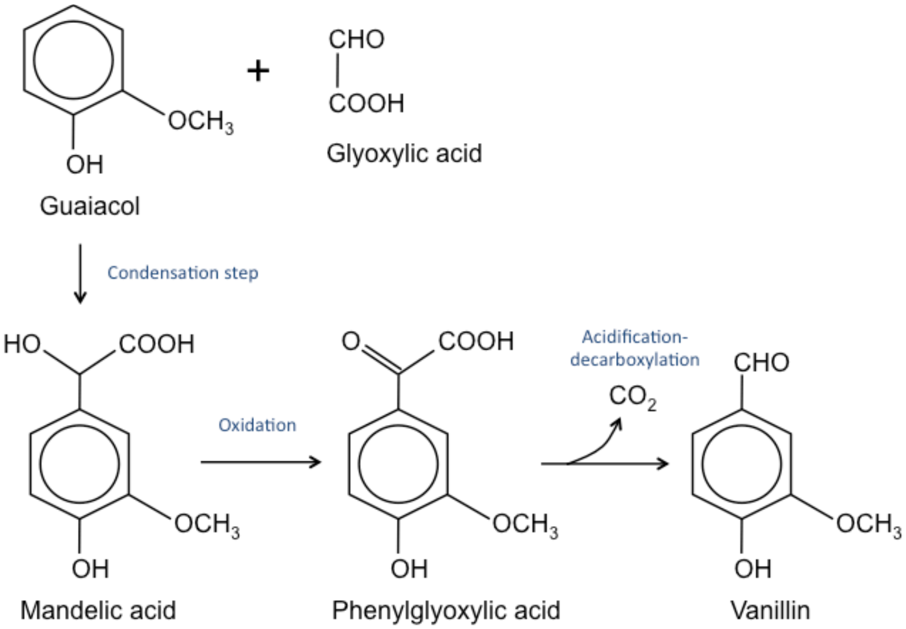
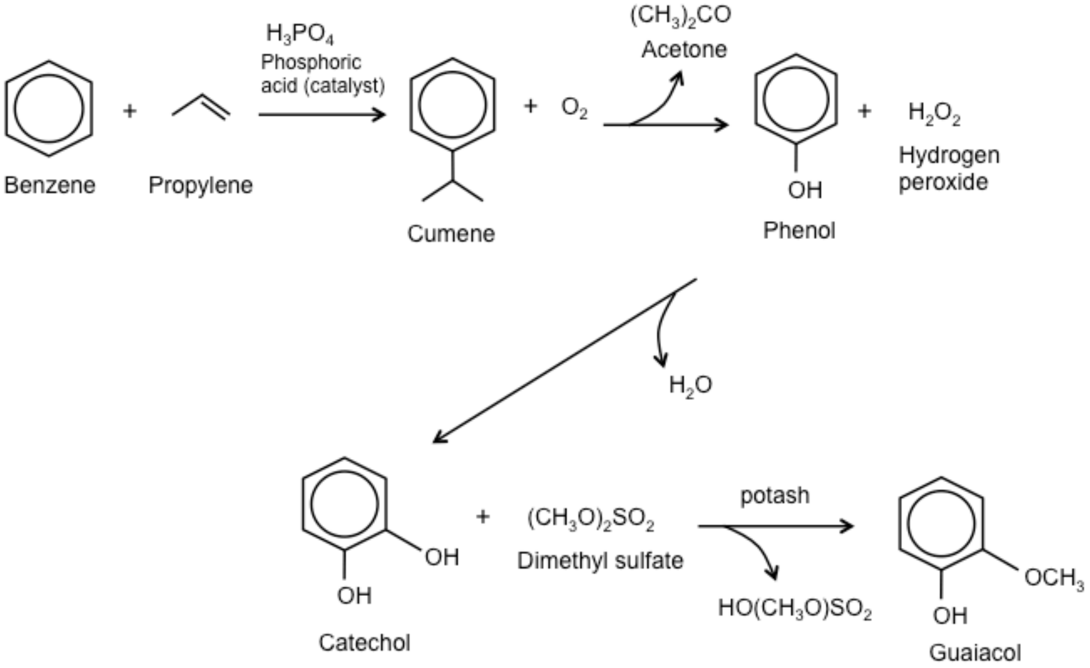


Figure 3. Guaiacol synthesis from aromatic petrochemicals



2.4 Vanillin Produced from Lignin

Lignocellulose, which comprises the wood-like material in plants, is a complex heterogeneous polymer of lignin, cellulose and hemicellulose (Das & Singh, 2004). Lignin comprises 19-33% of the biomass of trees and is also found in the cell walls of other plants (Das & Singh, 2004; Lebo et al., 2001). Lignin is removed from the other wood components to make pulp for paper making. Economically, the lignin component is a potentially rich source of organic aromatic compounds which may find applications as biofuels, chemicals, and lignin-based polymers (Sena-Martins et al., 2008). Vanillin is a higher value chemical which can be derived from lignin. In order for lignin to be utilized as a source of chemicals, it must first be separated from the other components of lignocellulose, typically in high temperature and pressure processes. Two major processes used in the pulp and paper industry to separate lignin from the cellulosic components are the sulfite pulping process and the kraft or sulfate process (Borges da Silva et al., 2009; Pandey & Kim, 2010). Both of these processes involve the solubilization of the lignin component, leaving the cellulose and hemicellulose components as insoluble material, followed by recovery of lignin from the soluble fraction.

Until the 1980s, the source of lignin for industrial vanillin production was the lignosulfonate component of spent sulfite liquors from the sulfite pulping process (Borges da Silva et al., 2009; Hocking, 1997). The lignin from these spent sulfite liquors was converted to vanillin via an alkaline oxidation process. The major products of this reaction are vanillin, vanillic acid, and acetovanillone, along with up to 12 other aromatic compounds (Bjørsvik & Liguori, 2002; Bjørsvik & Minisci, 1999). Vanillin yield is approximately 8% by this process. However, this process was largely abandoned by major producers in North America by the late 1980s over concerns about the toxic pollutants generated by the process (Borges da Silva et al., 2009; Hocking, 1997). This process generated 160 kg of “caustic liquids” for each kilogram of vanillin produced (Hocking, 1997). Today, Borregaard is the only company which produces vanillin from lignin, specifically using lignin derived from Norway spruce trees via the sulfite pulping method (Bjørsvik & Liguori, 2002; Bjørsvik & Minisci, 1999).

The kraft pulping process has largely replaced the sulfite process as the dominant process for paper-grade pulp production, with an estimated 80% or more of pulp currently being produced via the kraft process (Borges da Silva et al., 2009). As of 2005, approximately 65 million tonnes of kraft lignin was produced worldwide (Voitl & Rohr, 2010). Newer processes of alkaline or acidic oxidation of kraft lignin have been proposed, which may yet make kraft lignin a viable industrial source of vanillin (Borges da Silva et al., 2009; Voitl & Rohr, 2010; Žabková, Borges da Silva, & Rodrigues, 2007a). Thus, there may be an opportunity to develop a scalable, economically favourable process for vanillin production from kraft lignin. From a sustainability and environmental point of view, lignin represents a renewable resource with a potentially smaller carbon footprint than petrochemicals (Loe & Høgmoen, 2011). Any process utilizing kraft lignin would also need to be demonstrated to not produce harmful byproducts of the kind which contributed to the phasing out of sulfite-derived lignins for vanillin production in the 1970s and 1980s.

2.5 The Invention: A Novel Bacterial Mutant which Accumulates Vanillin

An alternative to the thermochemical transformation of lignin is to perform biological transformation using microorganisms. The use of cells and/or enzymes to transform organic starting materials to desired chemical products is referred to as biocatalysis. A biocatalytic process using lignin is expected to have environmental and sustainability advantages over using petrochemicals as a starting material. A biocatalytic method using kraft lignin would have to provide economically similar or better yields of vanillin compared with chemical transformations of that type of lignin. The biological degradation of lignin has been relatively well studied in fungi. However, technical difficulties associated with fungal proteins and genetics have prevented their use in industrial scale applications. Thus, more recent work has focused on lignin-metabolizing bacteria (Bugg et al., 2011). Bacteria known to degrade lignin include *Pseudomonas*, *Streptomyces*, *Nocardia*, *Bacillus* and *Rhodococcus* species (Ahmad et al., 2010; Ramachandra, Crawford, & Hertel, 1988; Shimoni, Ravid, & Shoham, 2000; Zimmermann, 1990). Scientists working in the Department of Microbiology and Immunology at the University of British Columbia have developed a mutant strain of a *Rhodococcus* species, termed *R. jostii* RHA1 Δ*vdh* (referred to herein as RHA1 Δ*vdh*), which can degrade kraft lignin and accumulate vanillin. Further technical details about this mutant strain will be described in Chapter 4 describing the TCOS uncertainties of commercializing the invention. The next chapter will examine the structure and competitive dynamics of the vanillin industry by applying a Porter's Five Forces framework.

3. Industry Structure and Competitive Dynamics

If the new RHA1 Δ*vdh* technology is eventually used to produce vanillin product(s), those products can expect to face certain competition in the vanillin industry. It would thus be useful to gain an understanding of the competitiveness of the industry, and whether the industry is an attractive one to enter. This chapter applies Porter's Five Forces to examine the structure of the vanillin industry and its competitive intensity.

3.1 Overview of Porter's Five Forces

Porter's five competitive forces provide a framework for analyzing the competitive intensity of an industry, which in turn influences the overall sustainability of industry profits. A very competitive industry will tend to provide lower economic profits than a less competitive one. Economic profit refers to revenues less the total costs of inputs, where total costs include the opportunity costs of those inputs. The following is a summary of Porter's Five Forces framework (Baye, 2010; Porter, 1998).

<u>Rivalry among existing firms</u>. Rivalry tends to be more intense, and hence the sustainability of profits tend to be lower, in less concentrated industries, *i.e.*, those with more firms and/or smaller firms (Baye, 2010). Rivalry tends to be more intense where there is less differentiation among products, and firms resort to competing more on price. Low consumer switching costs also tend to intensify rivalry among firms. The size and trends of the industry can affect rivalry (Baye, 2010; Porter, 1998). For example, in slowly growing industries, rivalries tend to intensify as firms seeking to expand must do so at the expense of other firms; in other words, the competition to expand is a fight for market share. Low product differentiation tends to increase rivalry among firms.

Threat of entry to the industry. New entrants will tend to increase competition in the industry and reduce the profit margins of existing firms (Porter, 1998). Porter identified at least six sources of barriers to entering an industry (Porter, 1998). The presence of *economies of scale* (*i.e.*, the phenomena of declining unit costs of a product with increasing scale) in an industry compels newcomers to enter at a large scale in order to achieve favourable unit costs. Alternatively, if entrants come in at a smaller scale, they place themselves at a cost disadvantage relative to incumbent firms. *Product differentiation*, which contributes to customer loyalty, presents a barrier to entry by forcing entrants to expend resources and effort to differentiate their product and overcome existing customer loyalties. High c*apital requirements* create a barrier by forcing entrants to invest large financial resources. *Switching costs* present a barrier to entry by requiring customers to incur costs to switch to a new product. New entrants must offer improvements in cost or performance to entice customers to switch. The need to secure *access to distribution channels* can be a barrier to entry, as entrants must convince existing channels to accept their product, for example through price breaks which reduce the new entrants' profits. Finally, *government policy* can pose barriers to entry. For example, licensing requirements can limit entry, as can regulation of such industries as trucking or alcohol retailing.

Bargaining power of input suppliers. Where input suppliers have more power to negotiate favourable terms for their inputs, industry profits tend to be lower (Baye, 2010; Porter, 1998). Supplier power is increased where inputs are differentiated rather than standardized, there is greater relationship-specific investment between the buyer and the seller, there are high switching costs, suppliers need not compete with substitute products, or where input markets are concentrated (*i.e.*, when there are few alternative suppliers and/or large suppliers).

Bargaining power of buyers. Where buyers of products or services have more power to negotiate favourable terms of purchase, industry profits tend to be lower (Baye, 2010; Porter, 1998). Buyer power tends to be higher when buyer concentration is high, *i.e.*, where there are few buyers, little fragmentation among buyers, or high volume buyers. Conversely, if buyer concentration is low (more customers, lower volume customers), then buyer power tends to be low. Buyer power is also lower where there are high switching costs, relationship-specific investments, fewer close substitutes for the product, or when products are well differentiated.

Threat of substitutes. The availability of close substitutes tends to erode industry profitability. The price and value of rival products affect their ability to act as substitutes. The degree to which rival products represent close substitutes can be quantified using elasticity analysis and models of consumer behaviour (Baye, 2010; Porter, 1998). In addition to substitutes, the availability of complements can also affect industry profitability. Good complements can enhance the demand for your product. For example, the profitability of Apple in the mobile devices market via their iPhones and iPads is enhanced by the large number of apps available for the Apple iOS platform. The possible existence of network effects can enhance profitability.

3.2 Analysis of Porter's Five Forces in the Vanillin Industry

3.2.1 Rivalry Among Existing Firms

Industry concentration. The industry concentration is related to the size and number of existing firms. The Concentration Ratio (CR) for an industry is the proportion of market share held by the four largest firms in the industry. An industry in which a large portion of the market held by a small number of firms is said to be concentrated, and rivalry tends to be intense. In the case of vanillin producers, the top two firms alone (Rhodia/Solvay and Borregaard) hold approximately 65% of the world vanillin market (Butstraen, 2009; De Guzman, 2006; de Margerie, 2009b; Loe & Høgmoen, 2011). As such, the vanillin industry is expected to have characteristics of an oligopoly (Baye, 2010). If we specifically consider lignin-derived vanillin to be the segment of the industry which is particularly relevant to the discussion of RHA1 Δ *vdh*, then a single company, Borregaard, is the sole supplier for the world market of that form of vanillin. By definition, Borregaard currently has a monopoly on the market for lignin-derived vanillin.

Market trends. A more slowly growing market tends to increase rivalry, as firms fight for market share. In contrast, rivalry tends to be less intense in growing markets as firms can increase revenue due to expanding market. World-wide, annual growth in demand for vanillin is 3-4 % (De Guzman, 2006). In mature markets in Europe and North America, growth is approximately 2% annually (Fletcher, 2006). In contrast, China is a rapidly growing market with more than 10% annual growth, adding up to 100 million new consumers for vanillin per year (De Guzman, 2006; Fletcher, 2006).

Product differentiation. Low product differentiation tends to increase rivalry. For vanillin derived from guaiacol, there is little product differentiation, as this product is chemically uniform. This product thus has characteristics of a commodity with prices in the range of $15-20 per kilogram. As guaiacol is a petrochemical, prices for vanillin from guaiacol can fluctuate with world oil prices (Halliday, 2008). There is some opportunity for product differentiation associated with vanillin from lignin. Borregaard's lignin-derived vanillin, marketed as "EuroVanillin Supreme", is said to have a "creamier, rounder", more natural taste than guaiacol vanillin (Loe & Høgmoen, 2011). The product is marketed as a premium product for the food industry, with prices up of to $200 per kilogram (Borges da Silva et al., 2009). In addition, Borregaard also offers vanillin blends specifically formulated for use in chocolate, dairy, baked goods, and confections ("Borregaard Ingredients," n.d.; "EuroVanillin," n.d.).

In sum, due to the above factors, the intensity of rivalry in the vanillin industry is expected to be high.

3.2.2 Threats of Entry and Entry Barriers

Patents or trade secrets can restrict entry to an industry as such intellectual property can provide a competitive advantage to firms which possess them. The major current methods for producing vanillin (via condensation of guaiacol with glyoxylic acid or alkaline oxidation of lignin) are well established and are not subject to patent protection. A bacterial fermentation processes using RHA1 *Δ vdh* should be eligible for patent protection and licensing for use as an industrial application. Such an application of the novel process should provide a degree of differentiation and potential competitive advantage, forming a possible barrier to further entry.

Capital requirements and asset specificity. Capital requirements compel would be entrants to make investments in equipment, production facilities, and the like. Specific assets would be difficult or impossible to put to other uses in case of industry exit. Furthermore, incumbent firms which have invested in specialized assets will seek to prevent others from taking their market share. Industrial production of vanillin would require some capital investment in equipment and facilities including fermenters, purification equipment, storage equipment, and plant space. Much of this equipment, such as bacterial fermenters, are not highly specialized and readily available ("Bioreactors / Fermenters," n.d.). Purification equipment is well established in the industry, though some specialized research and development may be required to develop purification methods for a new process of production (Borges da Silva et al., 2009; Zhang, Jiang, Gao, & Li, 2007; Žabková, Borges da Silva, & Rodrigues, 2007a; Žabková, da Silva, & Rodrigues, 2007b).

Minimum efficient scale (MES) is the level of production where unit costs of production are at their minimum. The presence of high MES is a barrier to entry. Calculating MES can be difficult (Fuss & Gupta, 1981). Mathematically, MES is the smallest output where the long run average cost curve is minimized (SFU Business 751, Managerial Economics, Mark A. Moore, instructor). A search of Business Source Complete and Google Scholar did not yield any studies which have been performed regarding MES for vanillin production. The need for capital expenditures (some of which were identified above) would serve to increase MES.

Government policies can be a barrier to entry. Novel food, drug and chemicals are subject to regulatory approval in the appropriate jurisdictions. Health Canada's definition of “novel foods” includes food derived from a process not previously used for food and foods modified by genetic modification; thus, vanillin produced by RHA1 Δ*vdh* fermentation would require approval from Health Canada as being safe for humans and animals. Other jurisdictions such as the United States and Europe have similar requirements. Regulatory requirements will be discussed further in Section 4.5.4 on regulatory requirements for a novel food product.

<u>Product differentiation</u>, in addition to alleviating some rivalry among incumbents, also raises barriers to entry. Differentiation among vanillins was discussed in the previous section.

Due to the combination of the above barriers to entry, the overall threat of entry to the industry is expected to be low.

3.2.3 Bargaining Power of Suppliers

The main inputs to vanillin production are either guaiacol from petrochemical companies or kraft lignin from pulp companies. In terms of product differentiation among suppliers, there is little if any differentiation between guaiacol from different companies. The chemical is a commodity. Thus a large company such as Solvay, which produces approximately 50% of the world’s supply of vanillin from guaiacol, should be able to exercise some power to negotiate the best prices for guaiacol. More differentiation is found between lignin from different suppliers, as lignin is a highly heterogeneous product which can vary depending on the types of trees from which it is derived and the process by which it is produced. There can be differences in lignin depending on the species of the trees and whether the trees are coniferous or deciduous (Hocking, 1997). Such differences are relevant because the final vanillin product can differ depending on the type of lignin that the vanillin was produced from. Thus, the source of the lignin can entail some relationship-specific investments between the seller and buyer. For example, Borregaard produces vanillin from spruce wood lignin; there is thus the possibility that Borregaard can become reliant on the suppliers of spruce wood or spruce wood lignin, thereby giving some power to its suppliers. Countering the bargaining power of suppliers is the fact that Borregaard is a major buyer, being the only company producing vanillin from lignin. Furthermore, Borregaard is a large company that makes varieties of other products from lignin, supplying diverse industry sectors such as agriculture, construction, animal feeds and others ("Borregaard Lignotech Industries," n.d.). Borregaard should thus be able to exercise some buying power for lignin and/or wood.

On the whole, supplier power is expected to be "medium", since bargaining power which the suppliers may be able to exercise is balanced by the large buying power of the major vanillin producers.

3.2.4 Bargaining Power of Buyers

Buyers are typically powerful if they are concentrated, *i.e.* where there are few buyers, each buying a large portion of the industry's output. This is not the case for purchasers of vanillin, where there are a large number buyers across industries such as food, cosmetics and fragrances, personal care goods, agriculture, and pharmaceutical industries. Thus, buyer concentration and buyer power for vanillin is low. As Borregaard is currently the only commercial supplier of lignin-derived vanillin, buyers who are reliant on this product may have little power to negotiate better terms. Similarly, Solvay, as the largest supplier of guaiacol-derived vanillin supplying approximately 50% of the world market, is a powerful supplier of this product. On the whole, buyers are expected to have weak overall power due to their fragmentation, and the considerable bargaining power of the major vanillin producers.

3.2.5 Threat of Substitutes

Economically, two products are substitutes for each other if an increase in the price of one product leads to an increase in the demand of the other product (Baye, 2010). The existence of close substitutes limits the ability of firms to raise the prices of their products. In the vanillin industry, vanillin from lignin and vanillin from guaiacol are likely to be substitutes for each other. Furthermore, as lignin-derived vanillin is currently marketed as a premium product, we might expect demand for this product to decrease during economic recessions as consumers will likely turn away from premium food products. Ethyl-vanillin from petrochemicals, marketed by Borregaard as EuroVanillin Aromatic, is another potential substitute for vanillin. Ethyl-vanillin has approximately 3-4 times the flavour intensity of vanillin ("Heavy Tasks in Vanillin Production," 2004; Hocking, 1997).

Products are complements for each other if an increase in the price of one product leads to a decrease in the demand for the other product. An increase in demand for a product can contribute to increasing the demand of its complements (Baye, 2010). Vanillin enhances chocolate flavour and is frequently used in combination with cocoa in many food products. As cocoa imparts the chocolate flavour to chocolate products, cocoa has been cited as a complement to vanillin ("Aromatic Chemicals & Essential Oils," n.d.;

Paterson, 2010). Cocoa is available in the form of cocoa powder, cocoa butter, or cocoa liquor (“Aromatic Chemicals & Essential Oils,” n.d.). Vanillin is used in a wide range of baked goods, candies and other sweets; as such, sugar and flour are expected to be complements for vanillin.

While not always the case, certain food products which use vanillin as a flavouring agent can also be economic complements to vanillin. Specifically, premium food products such as fine chocolates and premium alcoholic beverages and liqueurs can be complements to lignin-derived vanillin such as Borregaard’s EuroVanillin Supreme. Other complements can be perfumes or personal care products which use vanillin as a fragrance.

Overall, guaiacol-derived vanillin and lignin-derived vanillin can be substitutes for each other. Ethyl-vanillin is a substitute for vanillin in general. The threat of substitutes of vanillin can be considered medium.

3.2.6 Summary of Porter’s Forces for the Vanillin Industry

The players relevant to Porter’s five forces affecting competitiveness in the vanillin industry are summarized in Figure 4. The relative strengths of the forces and the underlying factors contributing to those forces are summarized in Figure 5. Overall, this examination of Porter’s forces indicates that the current market place is a highly competitive one. The market for vanillin is concentrated, with up to 70% of the world market concentrated in the top two producers, Solvay and Borregaard. This concentration is expected to contribute to the intensity of the vanillin industry. Mature markets are growing at approximately 2% annually, while emerging markets in China are experiencing growth in excess of 10%. Product differentiation is low among producers of guaiacol-derived vanillin, but Borregaard offers a range of lignin-derived vanillins targeted to various segments of the food industry. Such differentiation relieves some of the rivalry in the industry.

The need for capital expenditures in facilities and equipment present a barrier to entry to the industry. Government requirements for regulatory approval of a novel process for producing vanillin are a further barrier to entry. If a patent for RHA1 Δ*vdh* fermentation is granted, this would serve as a barrier to further entry to the market.

Petrochemical companies supplying guaiacol, forestry companies supplying wood for pulping, and pulp companies supplying lignin all tend to be large companies, due at least in part to the high capital intensity of those industries. These companies are thus expected to wield considerable supplier power. Countering the supplier power is the fact that the few largest vanillin producers control a large portion of the world market.

The bargaining power of buyers for vanillin is expected to be weak relative to the bargaining power of the major producers, as there are many buyers spread out across diverse industries. Furthermore, Borregaard, currently the only producer of lignin-derived vanillin, is effectively a monopoly supplier of that product. Similarly, Solvay is in an oligopoly-like position, controlling approximately 50% of the market for guaiacol-derived vanillin.

There are few substitutes for vanillin, though vanillin derived from guaiacol and vanillin from lignin are substitutes for each other. Ethyl-vanillin is another substitute. The presence of these substitutes limits the ability of suppliers to raise prices. These substitutes will tend to increase the price elasticity for vanillin, and would curb industry profitability (Baye, 2010). Cocoa, sugar, and flour are economic complements to vanillin. Premium quality foods and beverages can also be complements to lignin-derived vanillin, such as Borregaard's EuroVanillin Supreme.

Overall, the present analysis of Porter's forces for the vanillin industry points to a mature, highly competitive environment. The next chapter will provide a more detailed examination of the TCOS issues specific to the development of the novel RHA1 Δ*vdh* technology for use as a method for producing vanillin from lignin. The analysis identifies the outstanding TCOS uncertainties, and reveals both opportunities and challenges for the new technology.

Figure 4. Players contributing to Porter's Five Forces in the vanillin industry

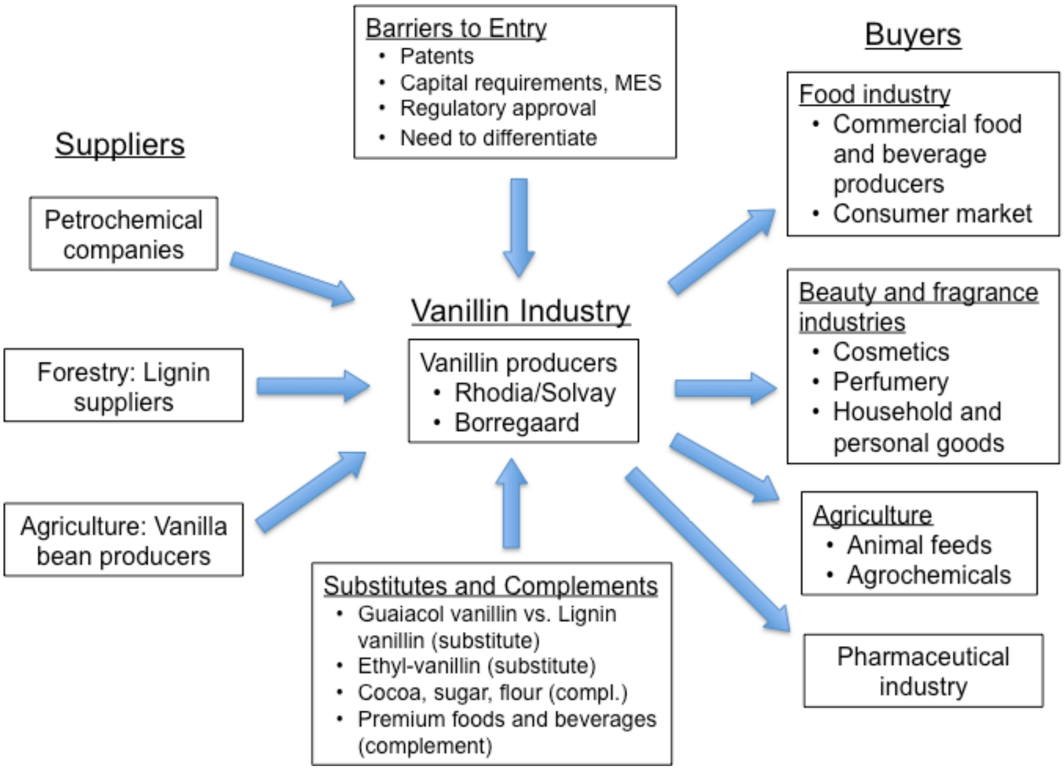
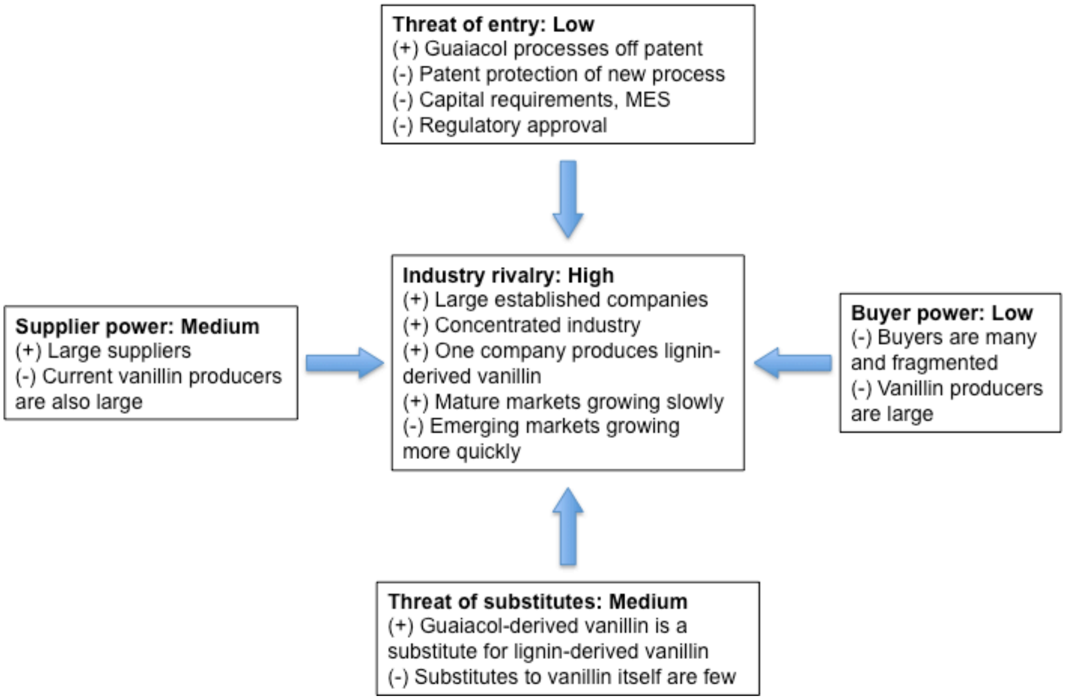


Figure 5. Summary of Porter's Five Forces in the vanillin industry



4. TCOS Analysis

4.1 Overview of TCOS Uncertainties

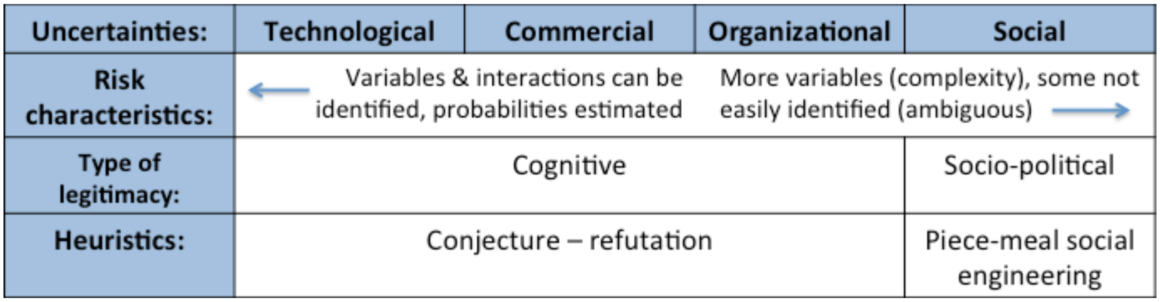
According to Hall and colleagues, an invention can be considered a viable innovation when it has satisfied certain technological, commercial, organizational and social (TCOS) uncertainties (Hall et al., 2011; Hall & Martin, 2005). A framework for understanding and exploring TCOS uncertainties is summarized in Table 1. For technological uncertainty to be overcome, the invention or idea must be shown to be *technologically feasible*. For commercial uncertainty to be overcome, the invention must be able to compete successfully in the market place to become *commercially viable*. Organizational uncertainty concerns whether the invention is consistent with the firm or inventor's "overall strategy and capabilities, complementary assets and its ability to protect intellectual property" (Hall et al., 2011). Social uncertainty refers to the impact of the invention on or from various secondary stakeholders. Primary stakeholders are those that are within the innovation value-added chain and have a direct impact on the firm. Secondary stakeholders are outside of the innovation value-added chain of the firm but can influence or affect, or be influenced or affected by, the firm (Hall & Martin, 2005). The impact of this set of stakeholders must be recognized and accommodated.

Hall and colleagues argue that the technological, commercial, and organizational (TCO) uncertainties are cognitive in nature, where most of the important variables and interactions among them can be identified, and probabilities of outcomes can be estimated (Hall et al., 2011; Hall & Martin, 2005). A "conjecture-refutation" approach, first described by Popper (Popper, 1963), analogous to the testing of scientific hypotheses, can be used to address the TCO uncertainties. The TCO legitimacy of the putative innovation is validated or refuted based on performance superiority criteria, *i.e.*, whether a new technology outperforms an older technology based on technological or commercial criteria (Hall et al., 2011; Hall & Martin, 2005) .

As opposed to the cognitive nature of the TCO uncertainties, the social uncertainties of an invention are considered to be socio-political in nature (Hall et al., 2011; Hall & Martin, 2005). The social uncertainties are more complex and ambiguous, due to the presence of a greater number of key variables, some of which may be difficult or infeasible to identify. The situation is complicated by the presence of secondary stakeholders who may be motivated by different values or objectives compared to the primary stakeholders within the innovation value-added chain (Hall & Martin, 2005). Such complexity has been referred to as stakeholder ambiguity (Hall & Vredenburg, 2005). To address the social uncertainties, Hall and colleagues propose to apply Popper's "piecemeal social engineering" approach (Hall et al., 2011; Hall & Martin, 2005; Popper, 1945). A piecemeal approach addresses secondary stakeholder concerns regarding new inventions on a case by case basis, as distinguished from a centrally imposed "utopian social engineering" policy which Popper saw as being characteristic of communist or fascist governments (Hall & Martin, 2005; Popper, 1945). Hall and colleagues argue that social uncertainties are at least as important as TCO uncertainties when attempting to establishing the legitimacy of a putative innovation (Hall et al., 2011; Hall & Martin, 2005). To alleviate social uncertainties, the side effects of new inventions on, and the impact from, secondary stakeholders need to be recognized and addressed. Hall and colleagues propose further that social considerations can provide "leverage" for furthering new inventions, by lending socio-political legitimacy to help the justify investments to address TCO uncertainties (Hall et al., 2011).

Table 1. TCOS framework for exploring risks and uncertainties of an invention

Adapted from Hall *et al.* (Hall et al., 2011)



Uncertainties:	Technological	Commercial	Organizational	Social
Risk characteristics:	← Variables & interactions can be identified, probabilities estimated		More variables (complexity), some not easily identified (ambiguous) →	
Type of legitimacy:	Cognitive			Socio-political
Heuristics:	Conjecture – refutation			Piece-meal social engineering

4.2 Technological Uncertainties, Opportunities and Challenges

4.2.1 A Lignin-Degrading Bacterium Engineered to Accumulate Vanillin

Rhodococcus is a genus of actinomycetales bacterium found in soil and water which exhibits a wide range of metabolic activities. Due to their broad metabolic capabilities, rhodococci have found a number of industrial applications, including production of bioactive steroids, biodesulfurization of fossil fuels, and production of acrylamide and acrylic acid (A. Banerjee, Sharma, & Banerjee, 2002; McLeod et al., 2006; Van der Geize & Dijkhuizen, 2004). The *Rhodococcus* species *R. jostii* RHA1 (RHA1 for short) has a demonstrated ability to transform lignin, a complex biopolymer, to yield monocyclic aromatic compounds (Ahmad et al., 2010; Bugg et al., 2011; Chen et al., 2011). The complete genome of RHA1 has been sequenced (McLeod et al., 2006). Among the aromatic compounds produced from the breakdown of lignin is vanillin; however, the bacteria would normally further metabolize the vanillin into other downstream metabolites (Figure 6) (Chen et al., 2011). Vanillin dehydrogenase (encoded by the *vdh* gene) catalyzes the oxidation of vanillin to vanillic acid, also known as vanillate. Vanillate O-demethylase, a two-component enzyme encoded by the genes *vanA* and *vanB*, in turn catalyzes the conversion of vanillic acid (Chen et al., 2011). Recently, scientists in the Department of Microbiology and Immunology at the University of British Columbia and the Department of Chemistry at the University of Warwick, have developed mutant strains of RHA1 with defects in lignin metabolic pathways (Eltis et al., 2012). These bacterial mutants were shown to accumulate certain metabolites, some of which may be of practical interest. One such mutant, designated *R. jostii* RHA1 Δ*vdh*, has a deletion of the vanillin dehydrogenase gene. Due to this mutation, RHA1 Δ*vdh* does not oxidize vanillin to vanillic acid, and instead accumulates vanillin when grown on lignin. Kraft lignin and wheat straw lignocellulose have been tested as lignin sources. In one experiment, the bacterium was grown on wheat straw lignocellulose, and the aromatic compounds in the media were analyzed (Figure 7). Major metabolites included vanillin, *para*-hydroxybenzaldehyde, and protocatechuic acid (also known as 3,4-dihydroxybenzoic acid). As summarized in Table 2, vanillin yields of 4.8 to 6.0 % were achieved when this bacterium was grown in solutions of kraft lignin (P. Sainsbury, H.P. Chen, L. Eltis and T. Bugg, personal communication). Such yields are similar to those obtained from alkaline oxidation processes using lignosulfonates from sulfite pulping (Bjørsvik & Liguori, 2002; Bjørsvik & Minisci, 1999). Minor aromatic metabolites from the fermentation included vanillic acid, *para*-coumaric acid, and ferulic acid.

Figure 6. Downstream metabolism of vanillin by *R. jostii* RHA1

From Chen *et al*. (Chen et al., 2011).

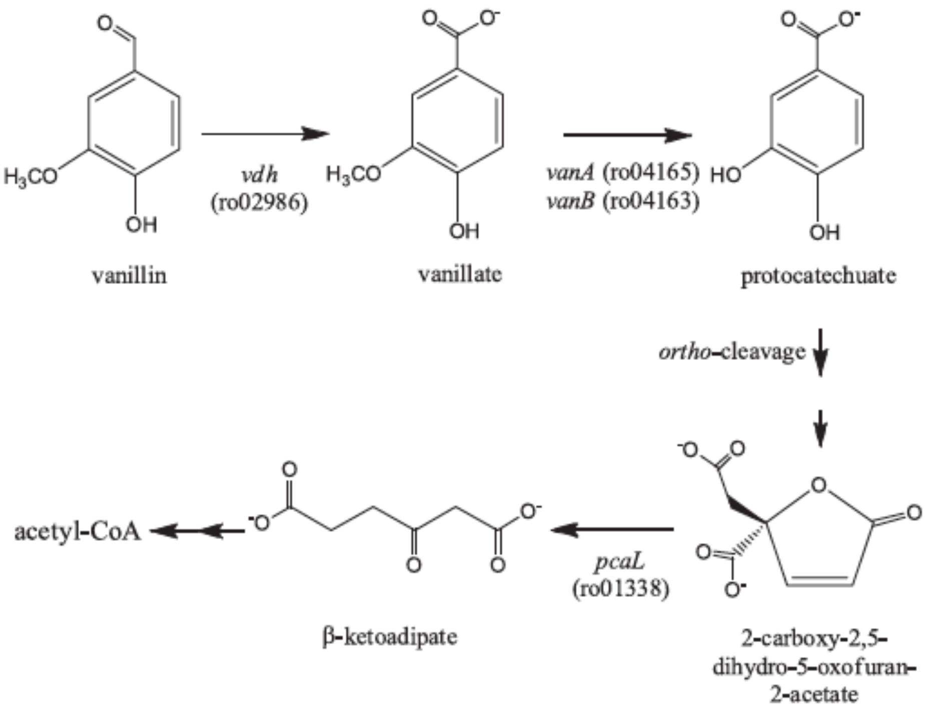
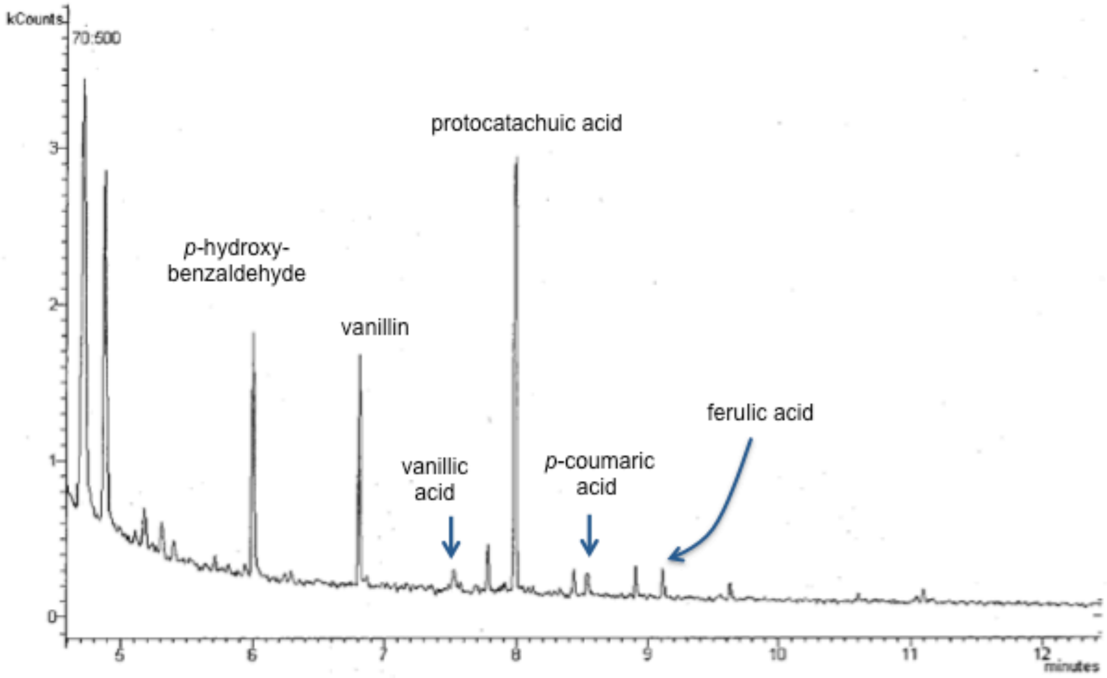


Figure 7. Metabolites from *R. jostii* RHA1 Δ*vdh* grown on wheat straw lignocellulose



R. jostii RHA1 Δ*vdh* was grown on wheat straw lignocellulose, 1 g/L in minimal media at 37 ºC. Results are shown as a total ion chromatogram of a LC-MS analysis. Major peaks at 6.0, 6.8 and 8.0 min correspond to p-hydroxybenzaldehyde, vanillin, and protocatechuic acid, respectively. Smaller peaks correspond to vanillic acid, p-coumaric acid, and ferulic acid. Source: P. Sainsbury, H.P. Chen, L. Eltis, and T. Bugg, personal communication.

Table 2. Experimental yields of vanillin via RHA1 Δ*vdh* fermentation of lignin

Concentration and type of lignin (% w/v)	Volume (L)	Amount of lignin (g)	Glucose (% w/v)	Incubation time (days)	Final vanillin concentration (µg/mL)	Total vanillin generated (mg)	Yield = vanillin (g)/ lignin (g)
0.1% wheat straw lignocellulose	0.1	0.1	0.0	7	28	2.8	2.8 %
2.5% wheat straw lignocellulose	1.0	25	0.05	6	96	96.0	0.38
0.5% kraft lignin	0.1	0.5	0.5	7	30	3.0	0.6
0.05% kraft lignin	1.0	0.5	0.5	6	30	30.0	6.0
0.25% kraft lignin	1.0	2.5	0.0	6	121	121.0	4.8

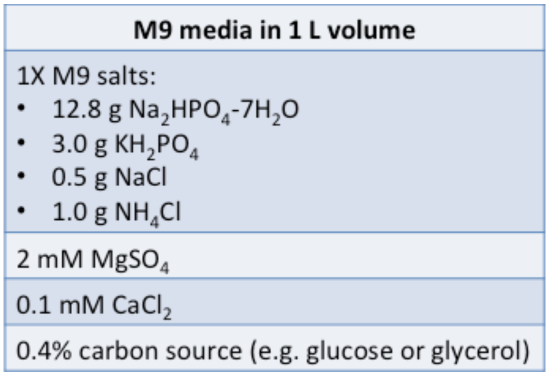
4.2.2 RHA1 Δ*vdh* Compared with Existing Lignin Conversion Technology

Borregaard uses an alkaline oxidation process to convert lignin to vanillin and other chemical products. Vanillin is among so-called “first generation fine chemicals” obtained from lignin, as these are products from the first round of hydrolytic and oxidative de-polymerization of the lignosulfonates from the sulfite pulping process (Bjørsvik & Liguori, 2002; Bjørsvik & Minisci, 1999). Second and third generation fine chemicals were obtained by further transformations of the functional groups or molecular structures of the chemicals. The sulfite pulping process itself entails elevated temperatures and pressures; typical conditions involve digestion for 6-7 hours at 126-129 ºC or 140-145 ºC, in the presence of calcium and sulfite ions (Bjørsvik & Liguori, 2002). Several methods exist for the hydrolysis and oxidation of the resulting lignosulfonates to generate first generation fine chemicals. The method most widely used in industry uses hydrolysis and oxidation under basic (alkaline) conditions, in the presence of sodium hydroxide and a copper(II) catalyst (Bjørsvik & Liguori, 2002). These reactions were carried out at 185-190 ºC, 12 atmospheres pressure, pH approximately 13.5, for 50-60 min (Bjørsvik & Minisci, 1999). The three major reaction products, vanillin, vanillic acid and acetovanillone, were obtained at yields of up to 7.2% under optimal conditions. In addition to the above-mentioned major reaction products, byproducts of the reaction included up to 15 other aromatic compounds. Other byproducts were high molecular weight carboxylic and phenolic compounds, organic acids, and inorganic compounds such as sodium and calcium salts and copper oxides (Bjørsvik & Liguori, 2002).

In contrast to the elevated temperatures and pressures of chemical transformations of lignin, bacterial fermentations typically take place at ambient pressure and ambient to

37 ºC temperatures. The experiments carried out by the UBC scientists and their collaborators were performed at ambient pressure and 30 ºC. Furthermore, potentially harsh chemicals such as sulfites, sodium hydroxide and metal catalysts are not required. Rather, bacterial cultures are grown on bacterial media typically containing sugars, salts, proteins, and amino acids. A recipe for M9 bacterial medium, on which RHA1 Δ*vdh* was grown for the above experiments, is shown in Table 3. Spent media usually does not contain toxic wastes but is sterilized by autoclave prior to disposal. A summary of key technological parameters for the major routes of vanillin production discussed herein is shown in Table 4.

Table 3. Recipe for M9 media for bacterial fermentations



M9 media in 1 L volume
1X M9 salts: • 12.8 g Na_2HPO_4-$7H_2O$ • 3.0 g KH_2PO_4 • 0.5 g NaCl • 1.0 g NH_4Cl
2 mM $MgSO_4$
0.1 mM $CaCl_2$
0.4% carbon source (e.g. glucose or glycerol)

Table 4. Key technological parameters of vanillin production methods

Production method	Source	Other inputs	Temperature (ºC)	Pressure (atm)	Incubation time	Yield of vanillin (% w/w)	Byproducts	References
Guaiacol via glyoxylic acid condensation	Petro-chemicals	Alkaline pH, copper oxide catalyst	80 - 130	Not provided	Not provided	Not provided	Other aromatic and organic compounds	(Buddoo, 2003)
Lignin via alkaline oxidation	Wood pulp lignins	NaOH, copper(II) catalyst	185 – 190	12	60 min	Up to 7.2	Other aromatic and organic compounds; salts, oxides	(Bjørsvik & Liguori, 2002; Bjørsvik & Minisci, 1999)
Lignin via bacterial fermentation	Wood pulp lignins	Bacterial media	30	1	Up to 7 days	Up to 6.0	Other aromatic compounds; spent fermentation media	L. Eltis and T. Bugg, personal communication

4.2.3 Technological Uncertainties and Challenges of RHA1 Δ*vdh*

A key technological uncertainty facing the development of RHA1 Δ*vdh* is whether production can be scaled up from a laboratory scale to an industrial scale. To date, the laboratories of Drs. Eltis and Bugg have yet to perform studies at scales larger than 1 L. By comparison, industrial fermentations can range up to 100,000 L or more ("Bioreactors / Fermenters," n.d.; "Industrial Fermenter," n.d.). The next logical step to industrial production will likely be pilot-scale fermentation studies. A further challenge is that purification methods will also need to be scaled up. To date, identification of metabolites was performed using analytical scale liquid chromatography-mass spectrometry (LC-MS). Industrial production will require large scale purification. Among the methods proposed in the literature are the use of adsorption resins, ion exchange systems, ultrafiltration, membrane-based extraction (Sciubba, Di Gioia, Fava, & Gostoli, 2009; Zhang et al., 2007; Žabková, Borges da Silva, & Rodrigues, 2007a; Žabková, da Silva, & Rodrigues, 2007b).

How large a scale would be needed? Table 5 summarizes some theoretical scales of production. Based on the experiments of Eltis, Bugg, *et al.*, the figures in this table assumes a vanillin yield of 5% (w/w) from kraft lignin, and a 1% (w/v) solution of kraft lignin. Thus, 20 kg of kraft lignin would be needed to produce 1 kg of vanillin; 20 tonnes of lignin to produce 1 tonne of vanillin; or 30,000 tonnes of lignin for 1500 tonnes of vanillin, which would approximately equal the world's annual production of lignin-derived vanillin (Loe & Høgmoen, 2011). 30,000 tonnes of lignin represents approximately 0.05% of the world's kraft lignin production of 65 million tonnes annually (Voitl & Rohr, 2010). Industrial fermenters of 50,000 to 100,000 L in volume are readily available (“Bioreactors / Fermenters,” n.d.; “Industrial Fermenter,” n.d.). Moving forward, the key technical challenges will be to demonstrate the fermentation and purification on these larger scales.

Table 5. Theoretical scales of vanillin production

To produce this weight of vanillin	kraft lignin needed	Total Volume
1 kg	20 kg	2000 L
1 tonne	20 tonnes	2×10^6 L
1500 tonnes	30,000 tonnes	3×10^9 L

4.3 Commercial Uncertainties, Opportunities and Challenges

4.3.1 Commercial Uncertainties of Lignin-Derived Vanillin

The preceding chapter’s examination of Porter’s forces pertaining to the vanillin industry indicated that new entrants can expect to find a highly competitive industry. Commercial uncertainty relates to the question of whether a technology can be commercially viable and compete successfully in a given marketplace (Hall et al., 2011). For the RHA1 Δ*vdh* technology, the commercial uncertainties at this time are whether the technology can yield a commercially competitive vanillin product. Much research and development (R&D) remains to be done to produce a marketable product. Whether the inventor possesses the requisite capabilities and complementary assets to develop a competitive product and bring it to market is an organizational question, and will be discussed in the next section on organizational uncertainties. The following describes the attributes that distinguish various vanillin products. The attributes have been cited as relevant to vanillin products (De Guzman, 2006; Esposito et al., 1997; Halliday, 2008; Loe & Høgmoen, 2011):

- **Flavour profile.** Natural vanilla is prized for its richness and complexity of flavour. While vanillin comprises 98% of natural vanilla extract, more than 200 trace compounds contribute to the distinctive qualities of natural vanilla (Esposito et al., 1997; Paterson, 2010; Sinha, Sharma, & Sharma, 2008). Vanillin products from lignin contain more trace compounds than vanillin from guaiacol, and is thus considered to have a rounder, more natural taste (Halliday, 2008; Loe & Høgmoen, 2011).
- **Fragrance profile.** For some applications, such as in perfumes or other products where vanillin is used as a scenting agent, fragrance attributes may be more important than flavour attributes (Esposito et al., 1997; "Heavy Tasks in Vanillin Production," 2004). Certain trace compounds, such as ethyl-vanillin, can contribute to fragrance properties ("Heavy Tasks in Vanillin Production," 2004). Thus, separate vanillin products might be developed based on fragrance profile.
- **Particle size distribution and solubility of crystals**. The particle size and shape of crystals can affect attributes such as flavour, solubility, and distribution in the solvent (Esposito et al., 1997). Thus, the size distribution of the crystallized product is a consideration when developing the product.
- **Viscosity of solutions**. Compounds such as malto-dextrin can be added to vanillin to improve the viscosity of solutions (De Guzman, 2006).

The above mentioned attributes should be considered when using the new technology to develop vanillin products. The next subsection will consider challenges and opportunities of entering existing markets or creating new ones.

4.3.2 Challenges and Opportunities: Existing Markets versus Blue Oceans

Assuming a product can be developed, a question of commercial strategy that will eventually need to be addressed is whether to enter existing markets or to adopt a “blue ocean” strategy as coined by Kim and Mauborgne, *i.e.*, to forge a new market in as-yet unserved areas (Kim & Mauborgne, 2005). Entering an existing market would entail introducing a new technology to a market already occupied by incumbent technologies, and would face certain entry barriers and entail attempts at taking market share from incumbents. Many of the challenges to entering the existing vanillin industry were identified in the Porter’s Five Forces analysis in Chapter 3. In contrast to entering existing markets, a blue ocean strategy holds the promise of accessing hitherto untapped or under-served markets while avoiding the fray of competing for market share in existing markets. Kim and Mauborgne outlined six “paths” to finding blue ocean markets: (1) look across alternative industries; (2) look across strategic groups within industries; (3) look across the chain of buyers; (4) look across complementary product and service offerings; (5) look across functional or emotional appeal to buyers; and (6) look across time. A full exploration each of these blue ocean paths would form the basis of a separate project, but herein I identify some initial areas where such blue ocean paths might be found.

Industries which currently use vanillin include food, fragrance and beauty industries, agriculture and agrochemicals, and pharmaceutical industries. An analysis of Porter's Five Forces pertaining to the vanillin industry illustrated how competitive the current vanillin market is. To attempt to compete with guaiacol-derived vanillin would be difficult. This is a mature market with a slow growth rate of approximately 2% annually. Guaiacol-derived vanillin has many of the characteristics of a commodity. It sells for \$15-20 per kilogram, shows little product differentiation, and existing producers have well established cost structures with regard to production, marketing, and distribution. It would be difficult if not impossible for vanillin from a novel biotechnology-based source to compete with incumbent firms on the basis of cost and efficiencies of production and distribution. Looking at specific groups within industries, a more attractive option would be to enter as a "premium" product, with a similar concept as Borregaard's EuroVanillin Supreme from spruce tree lignin. At \$200 per kilogram, EuroVanillin Supreme has much higher profit margins than guaiacol vanillin, but sells at a fraction of the price of natural vanilla extract at up to \$4000 per kilogram. The premium market offers an opportunity for further product differentiation, helping to enter under-served market segments. For example, further research and development would be required, but the taste and fragrance characteristics of vanillin from different lignin sources could be explored. In addition to using different types of trees, lignin from other plants could be explored, such as various types of straw, stems, leaves, cereals, or fruits and vegetables which are damaged or otherwise currently deemed unfit for sale (Das & Singh, 2004; Di Gioia et al., 2007). A range of vanillin offerings could be differentiated from the Borregaard product, and could be marketed to makers of premium and/or luxury food, beverages, perfumes, and personal care products.

Looking across buyer chains, most of the discussion thus far has centered on industrial purchasers of vanillin. However, a potential blue ocean buyer group is the retail consumer market. Here, differentiation of the product from guaiacol-derived vanillin would be especially relevant, as the product could be marketed as being closer to natural vanilla extract in taste and aroma. Furthermore, as the source of lignin can yield vanillin with differing taste and aroma characteristics, a range of vanillin products might be offered depending on the source of lignin. Looking across functional or emotional appeal to customers, various taste and aroma properties can be emphasized to appeal to consumers. For example, differentiated lignin-derived vanillins could be marketed as "gourmet" cooking products.

Looking across time, one can anticipate trends in emerging markets. For example, China and India have led the world in GDP growth in recent years, with China's GDP growing by 9.2% from 2010 to 2011, and India's growing by 8.4% in that time (Chandrasekhar, 2012). Both of these countries are experiencing rapid growth in the middle class (Beinhocker, Farrell, & Zainulbhai, 2007; "Tracking the growth of India's middleclass," 2012; "'Rise of middle classes in India, China key to growth in Asia' - Economic Times," 2012). The expanding middle class in these countries could drive increasing demand for premium and luxury goods across industries. Indeed, the markets for luxury goods are growing by more than 20% annually in both China and India ("Boom time for luxury market in China," 2012; "India emerges as fastest growing luxury market in the world," 2009; "Luxury goods market predicted to grow six to seven percent in 2012," 2012). Overall demand for vanillin in China is growing more than 10% annually (De Guzman, 2006). Given the rapid growth of luxury markets in China and India, the opportunity for premium vanillins could be even greater. Thus, a blue ocean strategy would be to market premium lignin-derived vanillin to both industrial buyers and the consumer market in those countries. Industrial buyers might include producers of food and beverages, perfumes, and personal care goods intended for the growing middle class.

4.4 Organizational Uncertainties, Opportunities and Challenges

4.4.1 Organizational Uncertainties of Developing RHA1 Δ*vdh*

Organizational uncertainties relate to how the inventor organizes and manages the requisite resources, which include intellectual and technical capabilities, complementary assets, and protection of intellectual property, to capture rents from an invention (Hall et al., 2011). Teece described a framework to understand how economic profits can be derived from an invention, and whether the innovator or a later entrant profits from the invention (Teece, 1986). We can use Teece's framework to analyze the organizational issues of managing the relevant resources (such as human and financial capital, and complementary assets) to develop the technology and produce the product. If the firm does not vertically integrate such activities, it can contract out for access to external resources. The next subsections apply Teece's framework to the organizational uncertainties of developing the RHA1 Δ*vdh* technology for vanillin production.

4.4.2 Profiting from Technological Innovation: Teece's Framework

Teece's framework consisted of three fundamental building blocks: (1) the appropriability regime, (2) the dominant design paradigm for the industry, and (3) complementary assets needed to bring the invention to market. Teece argued that, to better one's chances of profiting from innovation, the innovating person or firm needs to consider each of these fundamental areas.

The important aspects of the appropriability regime are the effectiveness of legal protection for the invention, and the nature of the technology. Legal instruments include patents, copyrights, and trade secrets. For patent purposes, a distinction is to be made between a *discovery* and an *invention*. A discovery is the uncovering of something which previously existed in nature, such as a previously unknown species of microorganism. An invention is the creation of something which did not previously exist. The patentability of genetically engineered microorganisms was established in the case of Diamond versus Chakrabarty in 1980. In this case, the United States Supreme Court ruled that Chakrabarty's mutant bacterium, which was genetically modified to break down chemical components in crude oil, was a human-made product which did not exist in nature and thus represented a patentable material (O'Connor, 1993). Hence, RHA1 Δ*vdh*, being a novel mutant form of *R. jostii* RHA1, would be eligible for consideration for patent protection. As a first step to applying for a patent, an invention disclosure for RHA1 Δ*vdh* has been filed with the UBC University-Industry Liaison Office (UILO) (Eltis et al., 2012). The nature of the technology refers to whether the technology is a product or a process, and the degree to which knowledge about the technology is tacit or codified. Patent protection is generally stronger for products, but is especially ineffective at protecting innovative processes. A microorganism can be considered a product for patent purposes. However, while not necessarily easy to achieve, a mutant bacterium which accumulates vanillin could conceivably be imitated by knocking out the *vdh* gene in other lignin-digesting bacteria such as *Pseudomonas* or *Bacillus* species (Kasana, Sharma, Sharma, & Sinha, 2007; Shimoni et al., 2000). Codified knowledge is more easily communicated, and is thus more vulnerable to copying by competitors. Tacit knowledge is by definition less explicit and more difficult to codify and communicate. Transferring tacit knowledge often requires demonstration by those who possess the knowledge (Teece, 1986). Knowledge about a microorganism such as RHA1 Δ*vdh* is codifiable and can be used by any personnel trained in microbiology.

Regarding a dominant design paradigm, Teece argued that industries typically undergo *preparadigmatic* and *paradigmatic* stages of development (Teece, 1986). The preparadigmatic phase, typical of the early stages of development of an industry, is characterized by multiple product designs which are subject to modifications and improvements, and manufacturing processes which are similarly subject to adaptation. Firms may compete based on competing designs. Through trial and error in the marketplace, a set of product design features emerge and achieve wide acceptance in a new product market, which is called a dominant design. When this occurs, the industry is said to have entered a paradigmatic phase. Competition shifts away from design toward price and production costs. Economies of scale and learning become much more important. Innovation shifts toward optimizing the design and production processes. The current vanillin production industry has many characteristics of an industry in a paradigmatic phase. The industry is dominated by a small number of large firms using a small number of production methods. As discussed in Chapter 1, the largest producer, Rhodia/Solvay, utilizes the guaiacol-glyoxylic acid production method and accounts for more than 50% of the world vanillin market. Furthermore, vanillin itself appears to have become commoditized, with most sellers offering it at $15-20 per kilogram ("Vanillin," n.d.). The other major producer, Borregaard, uses a similarly well established production method, namely the alkaline oxidation of spruce wood lignin. In contrast to guaiacol vanillin, spruce wood vanillin is somewhat less commoditized; as mentioned, Borregaard's "EuroVanillin" is marketed as a premium product with prices up to $200 per kilogram. Vanillin production using RHA1 Δ*vdh* would be considered a process innovation. However, specific novel vanillin products produced through this process might be considered product innovations.

Teece argued that the successful commercialization of an innovation almost always requires that complementary capabilities or assets be deployed. These complementary assets include marketing and sales, competitive manufacturing, complementary technologies, distribution, and after-sales support (Teece, 1986). Teece made a further distinction between generic and specialized complementary assets. Vanillin production using RHA1 Δ*vdh* would likely utilize relatively generic manufacturing methods, as bacterial fermenters are readily available. Other complementary activities, such as marketing, securing input supply agreements, distribution, and after-sales support will likely not be highly specialized; if such activities are to be performed in-house, the hiring and training of appropriate staff would be carried out.

4.4.3 In-House Development versus Out-Licensing

A question facing the innovator is whether to develop the technology in-house or to out-license the technology. This question can be examined through Teece's framework. In terms of appropriability, patent protection would be needed whether the technology is to be developed in-house or licensed. As the generation of the mutant bacterium was performed in a UBC laboratory, the UBC UILO would assist in the patenting and licensing activities.

At one extreme, full in-house development and commercialization of the novel bacteria-based technology would involve the vertical integration of all of the complementary assets and activities, including the requisite process learning. Incumbents in the industry will already be exploiting economies of scale and learning. Such economies are possible in the paradigmatic phase of an industry. In Teece's words, incumbents exercise an "opportunity to amortize specialized long-lived investments" by making use of reduced uncertainty over product design (Teece, 1986). A new entrant with a view to vertically integrating these activities will need to make new investments in complementary assets such as human resources with the requisite types of expertise (including technical knowledge, marketing, management, etc.), input channels, manufacturing facilities, marketing and sales, and distribution channels.

In contrast to a fully integrated model, licensing the technology to an existing manufacturer would obviate the need to develop the complementary assets *de novo*. Out-licensing a technology is an avenue whereby an innovator can capture some of the rents of an invention by tapping into an incumbent firm's investments in economies of scale and learning. Out-licensing is especially effective in cases where patent protection is strong (“tight appropriability”) and where complementary assets are generic (Teece, 1986). Out-licensing becomes somewhat less effective when more specialized complementary assets are required, because one or both parties must commit capital to investments which would become worthless if the relationship between the inventor (licensor) and the licensee breaks down. However, sufficiently strong patent protection may allow the inventor to integrate the more specialized assets while staying ahead of would-be imitators. In environments of weaker appropriability and an industry in the paradigmatic phase, access to specialized assets become more important. Firms controlling specialized assets are in an advantageous position relative to the inventor. With regard to vanillin production using RHA1 Δ*vdh*, important assets will include production facilities for bacterial fermentation and purification of the products. Bacterial fermenters are not particularly specialized. A purification method to isolate the vanillin produced will be required, though it may be possible to adapt existing methods; further R&D in this area will be needed. It is not clear at this time as to how specialization the purification equipment will be. We might include as complementary assets the human resources required, in the form of trained personnel to run the facilities, managers, and marketing and sales staff. These personnel can be found in the existing food industries and are thus not highly specialized.

In the case of vanillin production, the industry is in a mature paradigmatic phase, and the large incumbent firms control well-established complementary assets, though these assets, in general, are not highly specialized. A key question facing the development of the RHA1 Δ*vdh* technology is the strength of the appropriability regime. How strong can a patent on the technology expected to be? A distinction is to be made between a *process patent* and a *product patent* (Cohen, 2001; Erramouspe, 1995;). A process patent gives the patent holder the right to exclude others from using a particular process of producing a product, unless the other parties reach a license agreement with the patent holder. However, the process patent does not prevent others from using a different process to produce the same product. A product patent gives the holder the right to exclude others from making, using or selling the product without a license. A product patent generally offers broader protection. The process of vanillin production using RHA1 Δ*vdh* should qualify for patent protection as a novel process. Specific novel vanillin products produced from the process may qualify for product patents.

The question as to whether to develop RHA1 Δ*vdh* for commercialization in-house (*i.e.* vertically integrate) or to out-license the technology can be summarized using Teece's decision flow chart for integrating versus contracting out complementary assets (Figure 8) (Teece, 1986):

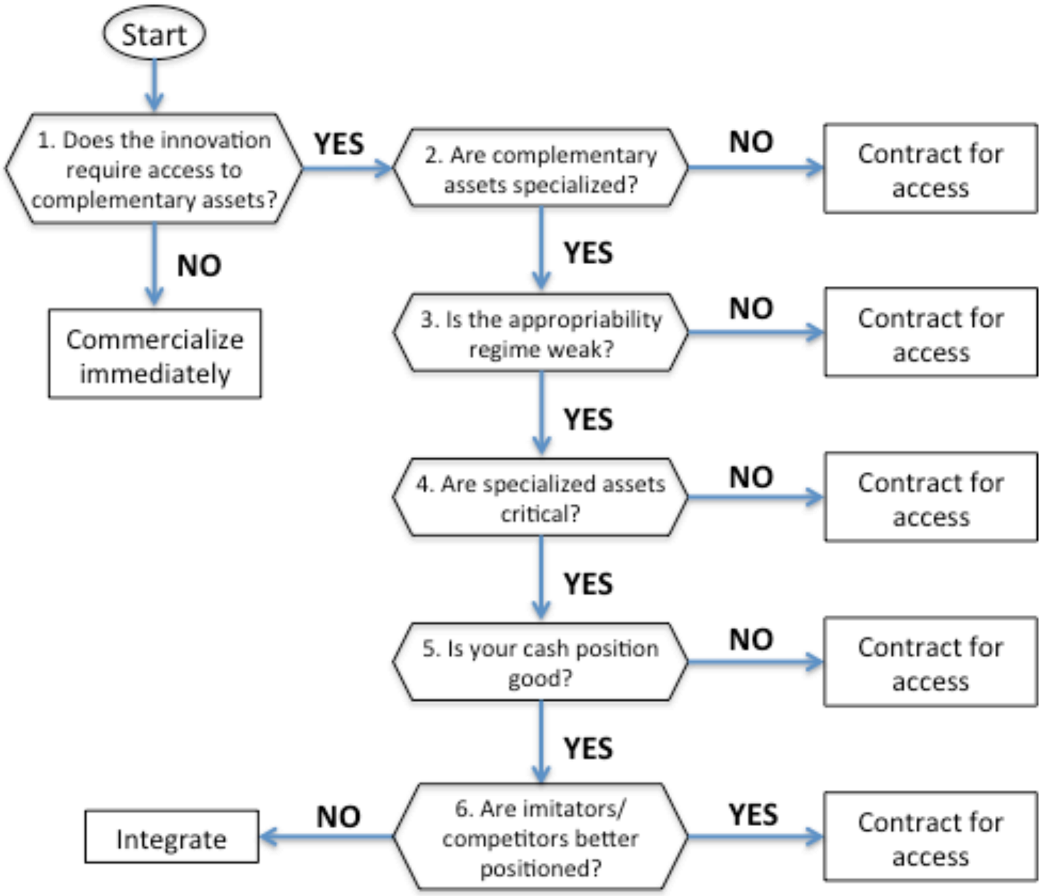
1. Does the innovation require access to complementary assets? Yes.
2. Are the complementary assets specialized? At this time, most of the complementary assets identified are not expected to be highly specialized.
3. Is the appropriability regime weak? A process patent on the use of RHA1 Δ*vdh*, and patents on potential products, should favour an answer of "No" for this question. As mentioned, a vanillin-accumulating bacterium could conceivably be imitated by knocking out the *vdh* gene in another bacterial species. However, generating such a bacterium and developing it for vanillin production is not a trivial undertaking. A patent on RHA1 Δ*vdh* should thus afford the patent holder time to commercialize the invention.

4. Are specialized assets critical? At this time, not many specialized assets have been identified.
5. Is your cash position good? No, there is currently no cash of funding in place to commercialize technology.
6. Are imitators/competitors better positioned? Yes, all of the incumbents in the vanillin industry are well positioned with respect to complementary assets.

In summary, most of the answers to the decision tree point to the out-licensing of the technology.

Figure 8. Teece decision tree for access to complementary assets

Adapted from Teece (Teece, 1986).



4.5 Social Uncertainties, Opportunities and Challenges

4.5.1 Social Uncertainties Surrounding RHA1 Δ*vdh*

Social uncertainties consider the impact of the invention on or from various secondary stakeholders and society at large, and can be at least as important as the opportunities and challenges posed by technological, commercial, and organizational issues (Hall et al., 2011; Hall & Martin, 2005; Hall & Vredenburg, 2005). For example, Monsanto was clearly a leader in developing genetically modified (GM) crops, having addressed the relevant technological, commercial and organizational challenges related to the new technologies. However, the successful commercialization of the novel technologies was severely challenged by social issues in the form of public opposition to GM seeds in the food supply. Monsanto's experience serves as a cautionary tale that firms cannot ignore the social uncertainties surrounding a new technology, even when technological, commercial and organizational issues seem to be satisfactorily addressed. In the next subsection, I shall start by considering some key social opportunities for the RHA1 Δ*vdh* fermentation technology relative to the other technologies.

4.5.2 Social Opportunities of RHA1 Δ*vdh* for Vanillin Production

Many of the social opportunities identified herein, which can act as social levers or justification to further the technology, relate to the potential environmental impact of the new bacterial fermentation technology. An extensive life cycle assessment (LCA) was commissioned by Borregaard to examine the environmental impact of various products produced by the company, including their lignin-derived vanillin (Modahl & Vold, 2011). The types of environmental impact factors which were considered in the LCA included

CO_2 equivalents (a measure of "global warming potential"), energy use, and waste generation, among a number of other categories. An extensive LCA has yet to be performed for the RHA1 Δ*vdh* fermentation technology, but its potential environmental impact can be compared on a qualitative basis to Borregaard's alkaline oxidation technology. The fermentation technology can also be compared qualitatively to the guaiacol-glyoxylic acid condensation technology.

A renewable resource. Vanillin from lignin represents a product from a renewable resource, as opposed to vanillin from petrochemicals. As outlined in Chapter 1, the ultimate source of the guaiacol used in vanillin synthesis is via chemical transformation of benzene, a petroleum product (Folkins, 2003). More trees would not necessarily need to be cut down for vanillin production; currently, the lignin that is used for vanillin production represents less than 0.05% of the world's production of kraft lignin (Voitl & Rohr, 2010). Furthermore, 98-99% of the 65 million tonnes of kraft lignin produced annually is burned for energy at pulp plants or put into waste streams (Lora & Glasser, 2002; Thielemans, Can, Morye, & Wool, 2001). Expanded vanillin production could divert just a small fraction of this lignin.

CO_2 emissions. Borregaard's alkaline oxidation method produced 1090 kg of CO_2 equivalents per tonne of vanillin produced, representing approximately 10 % the CO_2 emission of the guaiacol-glyoxylic acid method (Table 6) (Loe & Høgmoen, 2011; Modahl & Vold, 2011). Of this, approximately 30.8% was due to oil consumption, and 30% was due to production and transport of energy carriers. Vanillin produced via bacterial fermentation is performed at much lower temperature and pressure compared with the alkaline oxidation method. Thus, there is a potential to consume less energy, thereby making the CO_2 emission levels of a fermentation method even lower than Borregaard's method.

Table 6. Sources of CO_2 emissions from vanillin via alkaline oxidation at Borregaard

Source: (Modahl & Vold, 2011).

Source	kg CO_2 equiv. / tonne vanillin produced	% contribution to total
Oil combustion	336	30.8
Production and transport of inputs	300	27.5
Production and transport of energy carriers	282	25.9
Combustion of waste	136	12.5
Other: transport to customer; other internal processes	36	3.3
Totals	1090	100.0

Lower energy consumption. Borregaard consumed a total of 32,200 megajoules (MJ) of energy to produce 1 tonne of vanillin (Table 7). Of this, 36% was from fossil fuels, while the remainder was from renewable sources, nuclear, energy from waste, and other sources. The actual mix used by other production facilities will likely vary with location. As mentioned, a fermentation process is expected to require less energy overall.

Table 7. Sources of energy demand from vanillin via alkaline oxidation at Borregaard

Source: (Modahl & Vold, 2011)

Source	Megajoules of energy / tonne vanillin produced	% contribution to total
Fossil energy	11,585	36.0
Renewable energy	7979	24.8
Nuclear energy	6348	19.7
Waste and other sources	6288	19.5
Totals	32,200	100.0

Pollution and toxic wastes. The alkaline oxidation process used until the early 1990s generated 160 kg of "caustic liquids" per kilogram of vanillin produced (Hocking, 1997). It was concerns over these toxic byproducts that played a large role in the abandonment of the alkaline oxidation process in North America by the 1990s. However, according to Borregaard's LCA report, their toxic waste generation as of 2010 was less than 0.1% of the total waste generated in producing vanillin. The total waste was 1331 kg per tonne of vanillin produced; of this, 98.5% entered the landfill waste stream. A study of the RHA1 Δ*vdh* fermentation process will need to be conducted to determine if it is comparable to or cleaner than Borregaard's method. Nonetheless, a bacterial fermentation is not expected to generate more toxic waste than Borregaard's method, if any, as spent fermentation is typically sterilized (e.g. by autoclave) before entering a regular (non-toxic) waste stream (Fleming & Hunt, 2000).

A higher value product. There is an opportunity to use lignin to produce a higher value product, instead of burning it or putting it into a waste stream. Vanillin from lignin is currently sold at up to $200 per kilogram; other commercial considerations for vanillin from lignin was discussed above. In addition to the revenue generated, the successful development and commercialization of vanillin from lignin could serve as a proof of principle for the use of lignin to generate value-added products. Such products can include resins, carbon fibers, and biofuels such as bio-ethanol. The TCOS considerations for generating these products by bacterial fermentation of lignin are currently being explored by Hall *et al.* at the Beedie School of Business at SFU.

4.5.3 Social Hurdles to a Biotechnology Process for Vanillin Production

The Monsanto case amply illustrated that firms are well advised to consider social hurdles which may be presented by secondary stakeholders. Secondary stakeholders are those outside the value-added chain of the firm but who can nonetheless influence or be influenced by the firm or the adoption of its technologies (Hall & Martin, 2005). The identification and eventual engagement with secondary stakeholders is complicated by the ambiguity surrounding who the stakeholders are and what their potential concerns may be (Hall & Vredenburg, 2005). Furthermore, the concerns of various secondary stakeholders can be conflicting and/or difficult to reconcile (Hall & Martin, 2005).

Potential concerns over using RHA1 Δ*vdh* for producing vanillin could arise from the fact that it is a genetically modified organism. Scientifically, there is not expected to be any health or safety issues arising from the use of RHA1 Δ*vdh* for vanillin production, though this will have to be empirically demonstrated in order to gain regulatory approval (regulatory requirements will be discussed in the next subsection). The first reason there is not expected to be negative health effects is the fact that rather than having foreign genes being introduced into the RHA1 bacterium, a naturally occurring gene has been deleted to allow vanillin to accumulate instead of being further metabolized. This situation is in contrast to, for example, Monsanto's Bt maize and Bt cotton, where genes from the bacterium *Bacillus thuringiensis* have been introduced into plants, which then express foreign insecticidal proteins. Whether real or perceived, the safety and environmental concerns of introduced genes are a subject of often intense public debate (Downing, 2011; Skerritt, 2000; Stone, 2002). The second reason that negative health effects are not expected from RHA1 Δ*vdh* is that the genetically modified organism itself is not meant for consumption; rather, the vanillin produced will be purified and separated from the fermentation media containing the bacteria. Chemically, the vanillin produced will be the same as that from other sources. Third, unlike transgenic crop seeds from Monsanto or other agricultural products, the bacteria will be contained in laboratories or production facilities rather than being planted outdoors where there is a possibility of spread into the larger environment. Appropriate studies will need to be conducted to verify the safety of RHA1 Δ*vdh* as a vanillin producer.

While empirical studies are necessary to show safety, they are not necessarily sufficient on their own to garner socio-political legitimacy and public acceptance for the technology. The public debate on genetically modified foods has amply demonstrated that the scientific data form only a part of the discourse involving scientists, politicians, governments, non-governmental organizations, industry groups, consumer groups, activists, among others (Downing, 2011; Stone, 2002). Public opposition over safety concerns, whether real or perceived, can delay or hinder the introduction of novel food technologies. Thus, while public opposition to vanillin produced from RHA1 Δ*vdh* is not expected, some due diligence in the form of consultation with potential secondary stakeholders is warranted. Who, then are such potential secondary stakeholders? Some of the potential secondary stakeholders described herein were identified by analogy with the debate over the use of genetic engineering and biotechnology in agriculture. Other potential secondary stakeholders were identified as those who may have interests related to forestry.

<u>The genetically modified (GM) foods debate.</u> Among the most vehement opponents to genetic modification of food have been certain environmental groups or green lobby, such as Greenpeace or Friends of the Earth (Stone, 2002). Individual activists include Jeremy Rifkin and Vandana Shiva. The potential impact of such groups should be considered, as these groups have opposed GM foods in all their forms, including those modified to have improved nutritional qualities. An example of a nutritionally enhanced crop that was nonetheless opposed by anti-GM groups is the so-called Golden Rice developed by research groups led by Ingo Potrykus and Peter Beyer, which has genes added to produce beta-carotene (a precursor for vitamin A) (Ye et al., 2000). The original Golden Rice and a subsequent strain with even higher levels of beta-carotene (Paine et al., 2005) were meant to alleviate vitamin A deficiency in areas lacking traditional vitamin A food sources, but has yet to be grown for human consumption, due at least in part to public opposition to GM foods (Moskowitz, 2008). Geographically, public opposition to GM foods has been strongest in Europe, in contrast to the greater degree of acceptance observed in North America (Stone, 2002). As Europe is a large market for

vanillin, especially "premium" vanillins such as the lignin-derived vanillin offered by Borregaard, the interests of anti-GM groups as well as general public acceptance should be considered.

Forestry stakeholders. As noted above, the amount of lignin required to supply the world vanillin market would represent less than one percent of the annual production of kraft lignin. However, in addition to vanillin synthesis, lignin can potentially be used as a feedstock for production of other added value chemicals, such as resins, adhesives, carbon fibers, and biofuels. The combined uses of all of these chemicals represent markets many times larger than the current vanillin market, and if fully realized could utilize a much larger portion of kraft lignin production, which could in turn affect timber use and forestry management. Stakeholder groups which have been identified in discussions of forest use and management issues include forestry companies and industry associations, various levels of government, local communities, environmental and social NGOs, international bodies (such as the Intergovernmental Panel on Climate Change), forestry scientists and researchers, and First Nations (McGurk, John Sinclair, & Diduck, 2006; Parsons & Prest, 2003; S. Sharma & Henriques, 2004). A consideration of the potential interests of all of these and other stakeholders is beyond the scope of the present discussion; however, these are some of the groups whose interests will need to be taken into account if the use of lignin as a chemical feedstock becomes sufficiently widespread so as to affect usage patterns of forest products.

The list of secondary stakeholders identified herein is by no means complete, but illustrates the diversity of secondary stakeholders who may claim a voice in the discussion of the socio-political legitimacy of the RHA1 Δ*vdh*. It may be that we find no meaningful opposition to the new technology, but past experience suggests that a certain level of due diligence with regard to secondary stakeholders is in order.

4.5.4 Regulatory Requirements for a Novel Food Product

In Canada, “novel foods” derived by means of biotechnology must be approved by Health Canada as being safe for humans, animals and the environment (“Food – Biotechnology – Science and Research,” 2008). Health Canada defines novel foods as:

- Foods resulting from a process not previously used for food;
- Products that have never been used as a food; or
- Genetically modified or engineered foods or biotechnology-derived foods.

Vanillin derived from lignin using RHA1 Δ*vdh* would be considered a novel food by the first and third criteria, and would therefore require approval from Health Canada before it can be sold in Canada. The approval process will consider the following when assessing the safety of the novel food (“Food – Biotechnology – Science and Research,” 2008; “Frequently Asked Questions - Biotechnology and Genetically Modified Foods,” 2006):

- How the food was developed, including the molecular biological data which characterizes the genetic change.
- The composition of the novel food compared to non-modified counterpart foods.
- Nutritional information compared to non-modified counterparts.
- The potential for introducing new toxins.
- The potential for causing allergic reactions.
- Microbiological and chemical safety of the food.

According to the Health Canada website, similar approaches are taken in the United States, European Union, Australia, New Zealand, and Japan. We can thus expect that a similar level of safety will need to be established for the sale of vanillin from RHA1 Δ*vdh* in those countries.

Teece argued that the combination of patent protection and regulatory approval works to strengthen the appropriability regime for a new innovation (Teece, 1986). Would-be imitators who try to replicate the technology, for example using a different genetically engineered bacterium, will still need to get regulatory approval in markets where they wish to sell their product. Having a patented and approved product would thus strengthen the case for licensing out the technology to companies which have the necessary complementary assets in place.

5. Summary and Discussion

5.1 Summary of Uncertainties and Issues for RHA1 Δ*vdh*

Lignin, a complex organic polymer, has the potential to become a rich chemical feedstock providing a wide range of industrially important aromatic compounds. The key to unlocking the chemical potential of lignin is the depolymerization of the very stable lignin macromolecule, a task which has been approached both by conventional chemical methods and via biocatalytic means. Chemical methods typically entail the use of chemicals under extremes of pH, temperature, and pressure. Enzymatic or biocatalytic approaches offer the promise of digesting the lignin macromolecule at ambient pressure, slightly elevated temperatures (room temperature to 37 ºC), and neutral or near-neutral pH. In practice, lignin degradation has been well studied in white-rot fungi, but these organisms have proven difficult to use on an industrially meaningful scale. More recently, soil bacteria have been investigated for their lignin-degrading abilities. The advantages of using bacteria are that they are generally amenable to genetic engineering and methods for growing them on an industrial scale are well established. Species of *Rhodococcus* bacteria have been well studied for their lignin degrading properties. Eltis *et al*. have generated a mutant version, designated *R. jostii* RHA1 Δ*vdh*, which accumulates vanillin and other related compounds when grown on lignin from trees or wheat straw. The present exploration of the issues surrounding the RHA1 Δ*vdh* technology started with an examination of Porter's Five Forces related to the vanillin industry, providing a description of the intensity of rivalry in the industry. Given the current market realities, the discussion then focused on the TCOS uncertainties currently surrounding the application of this novel technology to vanillin production on an industrial level. The

TCOS analysis identified outstanding issues facing the new technology as R&D for the technology moves forward.

The analysis of Porter's forces affecting the vanillin industry revealed a highly concentrated market, with two companies controlling almost two thirds of the world vanillin market. Furthermore, a single company (Borregaard) currently produces lignin-based vanillin, giving it an effective monopoly on the product. Rivalry is intensified by the commoditization of guaiacol-derived vanillin, though this is balanced by a degree of product differentiation among lignin-derived vanillins. There is thus the possibility of competing using a further differentiated product, avoiding the prospect of competing solely on a cost basis with a low margin, commoditized product. Barriers to entry include capital expenditures on facilities and equipment and the need for regulatory approval of novel food products. Patent protection of a novel process would be a barrier to further entry to the market. The power of large suppliers, namely the petrochemical companies and forestry product companies, is balanced by the fact that the two main vanillin producers are also large multi-national companies. Vanillin buyers span a multitude of diverse industries, thus greatly diluting buyer power. Few substitutes for vanillin were identified, though vanillin from guaiacol and lignin are substitutes for each other, and ethyl-vanillin is substitute for both types of vanillin. Complements to lignin-derived vanillin are cocoa, flour, and sugar. Luxury foods, beverages, and beauty and fragrance products may also be complements. Overall, rivalry in the vanillin industry appears to be intense. Combined with high entry barriers, it appears to be a difficult industry to enter and compete effectively in. However, an examination of the TCOS issues surrounding the RHA1 Δ*vdh* technology revealed both opportunities and challenges to the commercial implementation of the technology.

The key TCOS opportunities and challenges identified for the various vanillin production methods are summarized in Table 8. Technologically, lignin is a renewable resource, providing a potential opportunity for adoption over the non-renewable resource of guaiacol from petrochemicals. Furthermore, the RHA1 Δ*vdh* technology uses less energy with a potentially smaller carbon footprint than the existing technology of alkaline oxidation of lignin. The technology also represents a novel method of lignin degradation which should be amenable to industrial scale applications. Technological challenges include the fact that the technology is unproven beyond laboratory scales of 1 L batches. Thus, industrial scale pilot studies would need to be conducted. Commercially, an examination of Porter's Five Forces affecting the vanillin industry indicates that the present industry is highly competitive. An alternative to competing directly with current suppliers is to attempt to adopt a "blue ocean" strategy of identifying new and/or under-served markets. Such a strategy presents both opportunities and challenges. For lignin-derived vanillin, there is the opportunity to develop and market a "green" product. There is also an opportunity to offer differentiated vanillin products, including premium-style vanillins for luxury markets. Emerging economies such as China and India offer an opportunity to supply such products to rapidly growing middle classes with developing tastes for luxury goods.

If a new invention is technologically and commercially sound, capturing rents from that invention entails addressing organizational uncertainties. RHA1 Δ*vdh* is an early stage technology, and the inventors can expect to face certain organizational uncertainties surrounding the development and commercialization of the technology for vanillin production. Such uncertainties concern the organization of intellectual and technical capabilities, complementary assets, and intellectual property protection. I applied aspects of Teece's framework to help address the organizational uncertainties of developing the RHA1 Δ*vdh* technology. Teece's framework sought to explain how economic profits can be derived from the economic environment, taking into account the prevailing appropriability regime, an industry's dominant design paradigm, and the necessary complementary assets for commercialization of technology. Teece's decision tree summarizes the decisions facing firms or inventors choosing between vertically integrating assets or contracting out for access to assets. For production of vanillin using RHA1 Δ*vdh*, the most pertinent answers to the decision tree are that assets are not likely to be highly specialized; patent protection should be possible; there is no cash available to purchase assets; and incumbents in the industry are better positioned. Thus, all considerations indicate that licensing the technology is the most likely route for commercialization at this time.

As demonstrated by the ongoing public debate over genetically modified foods, the social legitimacy of a new technology cannot be overlooked if it is to be implemented and ultimately gain public acceptance. I have identified both opportunities and challenges facing the social acceptance of the RHA1 Δ*vdh* technology. Opportunities are that it uses a renewable resource, it will likely use less energy and emit less CO_2 than the alkaline oxidation of lignin, pollution is expected to be low, and that lignin would be used to generate a higher value product rather than being burned at pulp factories. Potential challenges or support may come from secondary stakeholders, which may include environmental groups and stakeholders related to the forestry and pulp industries.

Table 8. Summary of TCOS opportunities and challenges for various vanillin production methods

UNCERTANTIES		**VANILLIN PRODUCTION METHOD**			
		Natural vanilla beans	**Guaiacol-glyoxylic acid condensation**	**Lignin via alkaline oxidation**	**Lignin via RHA1 Δ*vdh* fermentation**
Technological	**Opportunities**	Technologically simple; renewable resource; established methods	Established method; efficient; high volume	Renewable resource; established method; high volume	Renewable resource; lower energy and CO_2; novel lignin digesting technology
	Challenges	Labour and time intensive; very limited capacity; no innovations in technology	Uses non-renewable petrochemicals	Potentially polluting byproducts	Novel technology, requires further development for industrial scale-up
Commercial	**Opportunities**	Few growth opportunities as the market is very mature and small	Low cost production; large established markets	A premium product; potential to continue growing premium market	Potential for a premium, green product; growing markets, e.g. in Asia
	Challenges	World production is at maximum capacity; crops subject to tropical storms	A commodity with low margins; subject to world oil prices	Growing the premium market is also a challenge	R&D to develop new products; entering existing markets or new markets
Organizational	**Opportunities**	Consolidation of smaller plantations	Petrochemicals for vanillin production is a very small part of world petrochemical use	Currently, lignin used for vanillin production is less than 1% of world lignin production	Potential for patent protection; opportunity to out-license the technology
	Challenges	Few challenges as organizational regimes are well established	Few challenges as organizational regimes are well established	Gaining access to specific types of lignin	Gaining access to complementary assets; need to secure patent protection
Social	**Opportunities**	Well established product	Well established product	Lignin is a renewable resource	Renewable resource; lower energy and CO_2; a higher value product from lignin
	Challenges	Expansion of existing crops may come at the expense of food crops	Growing concern about using non-renewable resources	Growing concerns about polluting byproducts	Public acceptance of biotechnology food; regulatory approval

5.2 Discussion: Further Studies and Future Applications

Successful implementation and acceptance of novel technologies require that technological, commercial, organizational and social uncertainties be satisfactorily addressed (Chataway, Tait, & Wield, 2004; Hall et al., 2011; Hall & Martin, 2005; Hall & Vredenburg, 2003; 2005; Hall, Matos, & Langford, 2007; Stone, 2002). The present report reflects the status of the TCOS uncertainties surrounding the RHA1 Δ*vdh* technology. Moving forward, work remains to satisfactorily answer uncertainties in each of the four TCOS areas. Technologically, larger pilot scale studies will be needed. To date, the largest fermentation reactions to have been performed are on 1 L scales; volumes approaching industrial scales will need to be tested. Such scales include testing fermentation batches in the ranges of hundreds, thousands, to tens of thousands of liters in size, to reflect the fact that industrial fermentations are commonly performed in fermenters ranging in sizes of 50,000 to 100,000 L or more. As part of the larger scale testing, purification systems will need to be tested. In terms of product differentiation, much R&D will be required to test vanillin production from lignins from various sources, including different types of trees and other plants including cereal, fruit and vegetable matter which may currently be under-used for value-added applications. Product development in terms of flavour and fragrance profiles will need to be tested if the resulting vanillin products are to be differentiated for a premium market.

Commercially, a challenge is whether to engage existing markets or to forge inroads into emerging economies in Asia and elsewhere. An examination of organizational capabilities using a Teece framework indicates that licensing the technology to existing companies such as Borregaard is likely the most realistic route toward commercialization in both established and emerging markets. Forays into emerging markets such as China and India will entail activities related to business development. Such activities will be many and are likely to include, among others, market research to determine tastes and demand in those markets; engaging distribution channels; and possibly forming partnerships with existing companies in those markets. Included among organizational uncertainties is the need to secure patent protection for the RHA1 Δ*vdh* technology. The UBC UILO will assist with the patent application process.

Social challenges remaining to be addressed include identifying and engaging relevant secondary stakeholders, gaining public acceptance of a biotechnology-derived food product, and gaining regulatory approval in the relevant markets. The social opportunities identified herein can serve as levers to gain socio-political legitimacy for the new technology, and help to justify the investment and effort needed to further the technological, commercial and organizational aspects of developing the technology.

As mentioned, 98-99% of “waste” lignin produced in the pulping process is currently burned for energy at pulp plants. Beyond the current technology for producing vanillin from lignin, successful implementation and commercialization of this technology can serve as a proof of principle for the use of lignin as a viable feedstock for other value-added chemicals. Such chemicals include resins, adhesives, polymers, pharmaceutical chemicals, and biofuels (Bjørsvik & Liguori, 2002; Borges da Silva et al., 2009; Mabee & Saddler, 2010; Park, Doherty, & Halley, 2008; A. Singh et al., 2010). The lessons learned in exploring the TCOS uncertainties surrounding the present technology can be built upon when addressing TCOS issues of using lignin for other applications, thereby opening the door to the expanded use of lignin for producing a wide range of useful chemical products.

6. References

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