INDUSTRIAL BIOTECHNOLOGY

Manufacturing opportunities & business challenges for biofuels and biochemicals

The '2014 BIO World Congress on Industrial Biotechnology', organised in Philadelphia (USA) from May 12-15, 2014, presented an unique opportunity to hear from the most sought-after thought leaders on cutting-edge developments in manufacturing, agricultural processing, biofuels and chemicals processing. The business of industrial biotechnology is at a critical moment in its development. Several projects and technologies for producing a host of chemicals and biofuels are now moving out of laboratories and pilot/ demonstration plants and facing several risks in their commercialisation progress: technological, commercial, policy and sustainability. The presentations at the Congress, delivered over three days and across eight tracks, drew attention to common and unique international policy issues, and provided a forum for discussion of new opportunities for business development and company partnerships.

The following sections highlight some of the key thoughts that emerged from the presentations.

VALUE-ADDED PRODUCTS

Attention shifts to speciality chemicals, pharma intermediates & food ingredients

With the business of biofuels still dependent critically on regulatory support, attention of a number of companies have shifted to technology development and commercialisation efforts for biochemicals, bioplastics and other high value products serving the needs of the pharmaceutical and food industries, to cite just two examples.

Corbion – building on a heritage in lactic acid

Corbion, a Dutch multinational with 2013 sales of €744-mn and a joint venture between Purac and Caravan Ingredients, is building on its heritage in lactic acid. The company is focussed on food ingredients and biochemicals based on renewable raw materials. Since 2010, Corbion has developed a process for succinic acid in a joint venture with BASF; acquired Bird, a company with technology for furan dicarboxylic acid (FDCA); and developed fermentation process for making propionates, a class of chemicals used, amongst other applications, as a preservative for food like bread.

By varying the ratio of the D-/L- lactides in the manufacturing process for polylactic acid (PLA), Corbion has been able to expand the temperature range at which the polymer can be used from 70°C to 200°C, making the polymer suitable for many more applications. Corbion is presently operating a 75-ktpa plant for lactide monomers in Thailand since 2011.

Improved process

The company has also significantly improved the earlier generation lactic acid production processes, which suffered from the drawback of using large amount of gypsum to neutralise the acid used. The acid-free process has been tested in a 10-ktpa demonstration plant set up in July, 2013, and according to

Dr. Hans van der Pol, the technology looks promising.

Succinic acid – a platform chemical

Corbion's joint venture with BASF – Succinity – draws on the complimentary skills of the two partners, says Dr. van der Pol, and aims to develop succinic acid as a platform chemical. Bio-based succinic acid is a versatile building block with a significant market potential in the chemical intermediates market. It can be used in a variety of potential applications, such as bio-polymers (e.g. Polybutylene succinate, PBS), polyurethanes, coatings and life science products.

According to Mr. Philipp Walter, Succinity, the existing market for succinic acid – valued at about €200-mn – represents less than 1% of the potential market valued at more than €7.5-bn, with the main contributions coming from adipic acid (35%), butanediol (45%), and plasticisers (20%). But he hastens to add, "economy of scale is needed to realise its full potential."

In March 2014, the joint venture announced the successful start-up of its first commercial production facility. The plant, located at the Corbion Purac site in Montmeló, Spain, has a capacity of 10,000-tpa and is producing commercial quantities of bio-based succinic acid for the global market. Succinity is also planning on a second large-scale facility, and a final investment decision for this facility will be made shortly.

FDCA – key to bio-based polyester

FDCA is being touted as a large-scale opportunity due its use for the preparation of the polyester, polyethylene furanoate (PEF), which can be used in existing infrastructure for processing polyethylene terephthalate (PET) for making fully bio-based bottles with enhanced gas barrier properties. But the range of applications of PEF goes beyond just bottles to include speciality coatings, amongst other applications.

Evolva Biotech – utilising the bio-energy of baker's yeast

Evolva Biotech is focussed on the bio-based production of high value ingredients with relatively low production volumes. The company is aiming to bring four new products to the market in the next three years: vanillin, resveratrol, stevia glucosides and saffron – all produced by the utilising the bio-energy of baker's yeast.

According to Mr. Esben Halkjer Hansen, vanillin currently represents a 16,500-tonne market opportunity, valued at US$650-mn, nearly 98% of which is currently served by the synthetic variety and just 1% produced from natural vanilla beans (a small fraction is currently produced by other fermentative processes). Evolva's technology essentially involves exploiting a three-step biosynthetic pathway in baker's yeast, and the key challenge is to overcome the natural inhibition of yeast growth by the vanillin produced. In the proprietary Evolva process this is achieved by glycosylation of the vanillin – a step that also improves solubility. "The pathway has been optimised to prevent the formation of isovanillin production," notes Mr. Esben.

Evolva is targeting commercial launch of the product in the second half of 2014. In February 2013, Evolva and International Flavors & Fragrances Inc. (IFF), a leading global creator of flavours & fragrances, entered into pre-production phase agreement to develop and scale-up, via a third party, natural vanillin production through the natural and sustainable route.

Value-added monosaccharides from zuChem

zuChem (Chicago, USA) is focussed on the development of proprietary technologies for the manufacture of glycochemicals and carbohydrates for use in the food, specialty and fine chemical markets. Over half the world's drug leads, including more than 78% of all anti-microbials and many anti-cancer drugs are derived from natural products, and a large number of these are glycosylated. Sugars are also involved in tissue targeting, i.e. the delivery of molecules to different parts of body and cell, and also involved in metabolic control. According to Dr. David Demirjian, CEO, these rare sugars are the building blocks for many drugs, but their high cost and poor availability has hindered use. For example, R-Ribose is an extremely expensive sugar to use – not surprising considering the conventional process for making it from glucose has a yield of just 1.35%.

"It is now possible to produce sugars such as L-Ribose, L-Glactose, L-Gulose etc. in kilogram scale using our proprietary technology," Dr. Demirjian notes. In September 2013, zuChem entered into a partnership with Mumbai-based Godavari Biorefineries Ltd. to apply zuChem's proprietary bioprocess technology to produce a bio-sourced xylitol – a naturally occurring sweetener, contributing about 30% fewer calories than sucrose – for use as a food ingredient.

Table 1
Compounded Annual Growth Rate (CARG) for bio-based chemicals

Specialty area	CARG projection	Source
BioPolymers	14.3%	Research and Markets, 2013
Synthetic Lubricants	2.48%	Transparency Research, 2013
BioPlastics	24.3%	Research and Markets, 2013
BioSurfactants	3.5%	Transparency Research, 2013

Product samples from this partnership are expected this year, with commercial supplies expected by 2015.

Speciality carbohydrates from Inbiose

Inbiose, a spin-off from the Ghent University (Belgium), is developing a versatile generic production platform for the manufacturing and supply of specialty carbohydrates – high added value rare and complex carbohydrates that are difficult or impossible to produce with conventional technologies (extraction from nature, chemical and enzymatic synthesis). Prices for these speciality products range from €10 to €1000 per kg, compared to about €0.5 per kg for ordinary sugar.

According to Dr. Wim Sotaert, many applications – in the pharmaceuticals, cosmetics, animal health and nutraceuticals industries, for instance – were hampered until today by the high production cost and very limited availability of these carbohydrates. While extractive processes require natural sources, chemical synthesis approaches are complex, costly and give poor yields, while enzymatic conversions are limited to simple one-step conversions. In contrast, the microbial process developed by Inbiose utilizes cheap substrates to produce complex carbohydrates such as human milk oligosaccharides (HMOs) including fucosyl lactoses, sialyl lactoses etc. The process essentially involves engaging the biosynthetic pathway of the microbe to produce the desired speciality saccharide from the activated carbohydrate. "This is basically a one-step process, which is scalable, but needs diverse technologies including synthetic biology," says Dr. Sotaert.

Inbiose is targeting a production facility to produce 1,000-tpa of speciality carbohydrates, and is seeking partners interested in new targets and licensing the technology for scale-up. "Some of the targets will go up to 10-ktpa scale. There are more than 200 HMOs in mother's milk, although about 12 are predominant. Approval for making and marketing these will come, one at a time," he says.

Enzymatic conversion of EPA and DHA enriched ethyl esters to triglycerides

Commercially available Omega-3 concentrates (containing alpha linolenic acid, ALA, Eicosapentaenoic acid, EPA and Docosahexaenoic acid, DHA) are available in two forms: ethyl ester concentrates (EE) and triglyceride concentrates (TG), but it is the TG form that is preferred due to better bioavailability.

Praj Matrix, the research & development arm of Praj Ltd., has developed a process to convert 50% EPA and DHA containing EE concentrates to their 98% TG form, using an enzymatic process. According to Dr. Mangesh Kulkarni, the process has been optimized to give a conversion of 96%, using a proprietary ratio of glycerol to ester, and vacuum conditions. "The ratio of EPA and DHA can also be adjusted according to the needs of the client," he adds. The technology has relevance in the Indian context as the country produces about 30-kt of sardine fish oil annually, which typically contains 9-14% of EPA and 7-11% of DHA. "Most of this is currently being exported with little enrichment," he says. The global size of the omega-3 oils market, according to him is about 115-kt, with 97% of the demand being met from marine sources and the balance 3% from algal oils. Applications include as dietary supplement and for pet nutrition.

Table 2

Selected players operating/building commercial scale bio-based chemical plants, their primary target molecules, feedstocks & capacities

Bio-based chemical	Company	Feedstock	Capacity (Tonnes)
Lactic acid, derivatives & PLA	B&G, Galactic, NatureWorks, Purac, Synbra	Corn, sugar, molasses	570,000
Ethylene / polyethylene	Braskem, Dow & Mitsui	Sugarcane ethanol	550,000
Epichlorohydrin	Wilmar-Yihai Kerry Group, Jiangsu, Yangnong, Solvay, Vinythai	Glycerine	390,000
Methanol	BioMCN	Glycerine	200,000
Propylene glycol	Oleon/BASF, ADM	Glycerine, sorbitol	120,000
1,3-Propanediol	DuPont Tate & Lyle, Metabolic Explorer, Zhangjianang Glory Biomaterial	Corn glucose, glycerine	92,400
Succinic acid	BioAmber, Myriant, Reverdia, Succinity	Carbohydrate	68,360
Isobutanol	Gevo	Corn	55,000
Farnesene	Amyris	Sugarcane	40,000
Fatty acids, fatty alcohols, FAME & chemicals	REG Life Sciences (LS9)	Corn, sugarcane, glycerine	34,000
Butanol	Butamax Advanced Biofuels	Corn, sugarcane	30,000

Source: LMC International

BRIDGING THE GAP

Challenges in scale-up of biotech processes to commercial size

Successful scale-up of biotechnological processes depends on getting many things right. It implies that the technology performs at least as well in the plant as in the laboratory. It means building with quality, on budget, on time and with maintenance that anticipates faults before they occur. Success in scale-up lies in the details.

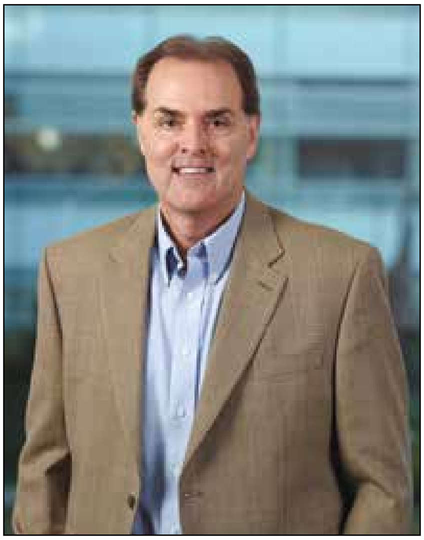
As an example of the long journey from a technology to a commercial reality, Mr. Jeff Lievense, Genomatica, points to the commercialization of a process for making 1,4-butanediol that went to production of 5-mn lbs in five weeks. The process, licensed by BASF to Novamont, involved a five-year effort from concept to commissioning.

Partnerships seem to be key to successful commercialization efforts, given the complexities and risks. For its butadiene bio-process that was proven in the laboratory in 2011, Genomatica is partnering with Versalis and Braskem – two of the world's leading producers of petro-based butadiene. Versalis, which is the second largest producer of butadiene in Europe, is to build the first commercial plants based on the bio-based technology in Europe, while Braskem, which has a sizeable presence in bio-based polyethylene and is the third largest butadiene producer in the world, is to build pilot and demonstration plants and retain certain rights for a commercial plants in the Americas.

Quality of substrate

According to Mr. Chuck Kraft, Amyris (Emeryville, USA), variability in quality of substrate used for bio-based processes, and its impacts on the process, cannot be under-estimated. "Not all sugarcane is the same," he says.

Amyris claims to have a disruptive platform that can produce chemicals, drugs and fuels by utilizing yeast to make terpenes. The company produces farnesene *(Biofene)* at its plant in Brotas (Brazil) located in the middle of sugarcane fields. The plant began operating in December 2012, and achieved steady-state farnesene production in its six 200,000-litre fermenters in July 2013.



Mr. Chuck Kraft

Just as important, he feels, is the need to localize the strain before implementation at commercial scale. "The best way to do this is by building a pilot plant at the place where the commercial plant will be built."

Layout of the plant should also include flexibility, as downstream processing may change with time. "Early on, market demand may go up or down. Plants will accordingly have to go through several shutdowns and start-ups," he warns.

Concurrent technical and commercial scale-up

According to Mr. Marcel Lubben, Reverdia, technical and commercial scale-up need to go hand-in-hand. "It is never too early to start discussions with potential customers. The potential in the marketplace needs to be developed," he says.

He also stresses the choice of right technology – one with low costs, consistent quality and sound economics. "Some

Mr. Marcel Lubben

companies have been forced to change horses mid-stream." Getting quality right and consistent, according to him, has to be the first priority, followed by cost and productivity improvements. "Don't try and solve everything all at once."

According to Mr. Mike Hess, Novozymes, the path to commercialization involves several aspects and systems for defining goals and handover are critical for success. "Make your failures in the small scale to ensure success in the large scale," he advises.

CHALLENGES FOR BIOFUELS

Uncertain blending mandate pose challenges to upcoming cellulosic ethanol plants

The business of biofuels is facing several challenges – commercial, technical and regulatory – especially in North America, the world's largest market. The uncertain policy environment, in particular, could not have come at a worse time for the industry, with several second generation cellulosic ethanol plants expected to come on stream this year and the next.

According to Mr. Jim Greenwood, President & CEO, Biotechnology Industry Organisation (BIO), an industry lobby group, the industry needs to overcome significant challenges. "Fuels America – a new lobby group – has been created to fend off efforts to derail critically needed biofuels," he says.

Weakening political support

Cellulosic ethanol requires a subsidy to compete against gasoline. Hence, its future is insecure as political support weakens in the US & EU.

In the US, the Renewable Fuel Standard (RFS), which has driven the business of first-generation ethanol and set the stage for second-generation fuels, is now being deliberated upon by the Administration, and the form in which new guidelines will emerge will have significant impact on the business of biofuels.

The delay in commissioning of some of the projects for producing cellulosic ethanol has resulted in cuts to their mandate. "Once mandates are cut, a political question is created over their re-introduction," notes Dr. Sarah Hickingbottom, LMC International. Furthermore, stagnating gasoline consumption in the US has created a ceiling for E10 blending volumes – compounded by the failure of E-15.

In the EU, the proposed cap on food-based biofuels is expected to provide a boost to second-generation biofuels. However, this cap has not been made official and the proposal has no specific cellulosic requirement.

'Ensure regulatory stability'

In a keynote speech delivered after receiving the '2014 George Washington Carver Award', which honours an individual for leadership in using industrial biotechnology innovation, DuPont Chair & CEO, Ms. Ellen Kullman called on the US Congress and the administration to ensure regulatory stability for the renewable fuel industry by preserving the RFS. "Legislative and regulatory uncertainty has a direct impact on the growth of this industry," Ms. Kullman said. "If the EPA issues an RFS rule with increasing biofuels volumes, supporting a stable regulatory environment, our industry can thrive."

Several projects nearing completion

A clear mandate will be vital to the success of several projects that are nearing startup – in the US and Brazil.

DuPont, for example, is aiming to commission a 30-mgpy (million gallons per year) cellulosic ethanol facility in Nevada (Iowa, USA) in late 2014. The plant will use 375,000 dry tonnes of stover per year sourced from more than 500 local farmers in a 30-mile supply radius.

Likewise, Abengoa Bioenergy Biomass of Kansas, a wholly-owned subsidiary of Abengoa Bioenergia (Spain), is starting up a 25-mgpy biomass to ethanol plant in July 2014, also based on corn stover. When operational, the plant will require up to 320,000-tonnes of dry biomass annually, which is to be sourced from a 50-mile radius.

Abengoa is also enabling first generation ethanol facilities in Brazil to process bagasse and offers a complete package of process technology, cellulosic enzymes and yeast solutions. Mr. Pablo Gutierrez, Abengoa, also sees huge opportunities for conversion of municipal sewage waste to ethanol.

First generation (exists)	Second generation (in deployment)	Third generation (5-20 years)
• Sugar and starch to ethanol • Oil-seeds into biodiesel	• Cellulosics into ethanol	• Advanced biofuels (e.g., drop-in hydrocarbons, butanol) • Sugar & starch into advanced biofuels • Cellulosics into advanced biofuels • Algal oils into biodiesel or jet fuel

Fig. 1: Terminology in bioenergy deployment

Source: Oakridge National Laboratories

Also in the US, POET-DSM Advanced Biofuels, LLC, a 50/50 joint venture between Royal DSM and POET, is in the final stages of commissioning the world's first commercial cellulosic ethanol plant using crop residue – corn cobs, leaves, husk and some stalk. The facility, in Emmetsburg, Iowa, will initially produce 20-mgpy of ethanol, ramping up to 25-mgpy. Commissioning has begun and the plant is scheduled to open in the second quarter of this year.

In 2014, Brazil's GranBio will open the first cellulosic ethanol plant in the Southern Hemisphere, in São Miguel dos Campos (Brazil). With an investment of R$350-mn, the company's inaugural unit will have a nominal production capacity of about 22-mgpy of ethanol, but the ambitious goal is to eventually raise output to 1 billion liters of ethanol per year by 2020.

Energy crops

According to Mr. Vonnie Estes, GranBio, cultivation of energy crops may be one approach to assuage future concerns with availability of biomass for these massive plants. As compared to sugar cane, energy cane has half the sugar and twice the fibre. Since it is twice as productive, energy cane generates four times as much bagasse, the first-line fuel for manufacturing second-generation ethanol and biochemicals. In Brazil, for instance, efforts are ongoing to grow energy cane having higher biomass content of about 60-tonnes/ha (dry weight basis), compared to 25-tonnes/ha for conventional cane. "This can even go up to 100-tonnes/ha and can be planted on distressed areas of Brazil – an area of about 32-mn ha," he says.

In 2013, GranBio and Rhodia, part of the Solvay group, signed an agreement to create a partnership to produce n-butanol – a chemical used for making acrylates and methacrylates, and in the paints and solvents industry – for the first time using biomass in Brazil. The unit is slated to become operational in 2015.

PROGRESSING TOWARDS COMMERCIAL SUCCESS

Marine microalgae as a source of biofuels & bio-products

Marine microalgae – the most productive plants on earth – have vast potential as a sustainable and scalable source of biofuels and bio-products. They have inherent advantages such as higher solar energy efficiencies, large lipid fractions, utilization of waste carbon dioxide, and cultivation on poor quality land.

If implemented sustainably into the global energy and food portfolio, microalgal products can reduce greenhouse gas emissions, while simultaneously displacing a substantial percentage of our declining fossil fuel resources. Algae could also hold the key to a new wave of sustainable fertilizers that increase plant yields while giving nutrients and structure back to the soil for future harvests.

Biodiversity of microalgae also makes these microorganisms good candidates to produce high added value molecules. To be successful a rich strain bank and a good identification of candidates is necessary, but not enough. Production process and technologies used on each step from breeding to final extraction of the desired molecules need extensive research and fine-tuning.

Focus on fuels ….

In the US, the Department of Energy (US-DOE) is supporting four algae-based projects, with one of the aims being an improvement in the harvest yield to about 2,500-gallons per acre by 2018.

According to Dr. Valerie Reed, US-DOE, the Algae Program is implementing a structured ten-year strategy to investigate opportunities to accelerate algal biofuel commercial readiness through an integrated science-based approach. The programme's goals and milestone targets are aggressive, involving work at multiple scales and time horizons to address broad challenges and make a significant impact in the bio-economy of the future.

Alegenol, based in Fort Myers (Florida, USA) is using blue-green algae to directly produce ethanol and is also working on hydrothermal liquefaction of algae to produce hydrocarbon fuels. Cultivation is done in vertical photobioreactors and success has been achieved in generating an average of 6,000-gallons per acre per year of ethanol.

Solazyme is using heterotrophic algae to produce renewable jet fuel and diesel. It is working with Chevron, UOP Honeywell, and other industry refining partners to produce the fuels for ships, and military & commercial application testing. Performance tests utilizing cellulosic-derived sugars were completed in January 2014.

Bio-Process Algae (Omaha, Nevada, USA) produces kilogram quantities of heterotrophic lipids using a mixo-trophic algal system for refining into on-spec military fuels. The carbon dioxide required comes from a co-located ethanol plant.

Sapphire Energy (Columbus, Ohio, USA) is using open raceway pond cultivation to produce green 'crude' that is subsequently upgraded to jet fuels and diesel. The project has seen continuous operation over 22-acres for more than 15 months.

… and on higher value chemicals

Cellana LLC (San Diego, California, USA) is focused on using marine microalgae to produce nutritional oils, foods, aquaculture & other animal feeds, renewable chemicals and biofuels. The company presently operates a 2.5-acre demonstration facility in Kona (Hawaii, USA) and has produced 13-tonnes of biomass since 2010. The company claims a large private culture collection of non-GMO varieties and the current focus is on strains high in omega-3 oils.

According to Ms. Valerie Harman, Senior Director, R&D, the production platform is a combination of photobioreactors (to generate the inoculum) and open raceway ponds (for subsequent cultivation over three to seven days, depending on the strain). "Combo systems permit low cost, contaminant-free algae production," she says.

The company operates on a bio-refinery model for extensive valorization of the biomass generated: while the algal oils are processed for recovery of high value omega-3 oils, the balance is used for biodiesel production and the residual biomass is used for animal feed applications.

Cellana has a commercial offtake agreement with Neste for the algal oil produced and is currently experimenting with using flue gases from diesel engines as a source of carbon dioxide. "We do not see any significant difference between nitrogen consumption or algal growth rates, nor in the composition of the biomass produced and the lipid profile, when using pure carbon dioxide or flue gases," Ms. Harman adds.

Several challenges ahead

According to Ms. Alice Chen, Keller & Heckmann LLP, several challenges will need to be overcome for algae-based biofuels to have an impact. One of them is the availability of large quantities of fresh water – even for marine systems – to make up for evaporative losses. Some algal strains also produce nitrous oxide, a greenhouse gas, and pose heavy demands on nutrients, in particular nitrogen and phosphorous. "Phosphorus is a finite resource and ways to recycle it and make more efficient use of it are needed," she adds.

BIOMASS CHOICES

Camelina & oil palm seen as viable options for Canada and Malaysia

Camelina, a drought-tolerant, low input and non-food crop, can be a good raw material for high value products. It costs 30% less to grow than the more widely grown canola, and importantly, is resistant to several diseases that affect canola. Camelina can also be planted in the summer fallow, where the land is typically left unused to accumulate moisture for the next season. While conventional camelina has ~60% of polyunsaturated fatty acids, novel lines have been developed that contain 80% oleic acid. "Other lines containing high monounsaturated fatty acids and hydroxyl fatty acids are also being developed in partnership with DuPont," says Mr. Jack Grushcow, Linnaeus Plant Sciences Inc., a Canadian company.

Linnaeus is targeting the plant to provide raw materials to produce lube oil base stocks, polyols for coatings & foams, and for purified fatty acids.

Oil palm in Malaysia

Malaysia has a lot of biomass from palm & rubber plantations and from forest residues. In 2011, the country launched the biomass strategy that identified a potential opportunity to mobilise 30% of oil palm biomass to create an additional $10-bn income for the economy as a whole, aside of the significant job creation potential. The plan is to go beyond the current restricted value-addition of the biomass to fertilizer and steam production.

Mr. Bas Melssen

According to Mr. Bas Melssen, Executive Vice-President, Strategic Impact, Malaysian Innovation Agency, pelletisation of palm biomass for energy production is already happening and is an excellent way of testing the infrastructure before plunging into the production of higher value derivatives like fuels and chemicals. About a dozen companies are already involved in this business and serve both the domestic and the export markets. In his view, biomass-made sugars are likely to become commercial in Malaysia in the next three to five years.