Industrial Biotechnology Process Plant Study

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Disclaimer

NNFCC

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Executive summary

Key findings

- Major investment opportunities to build UK excellence and leadership in C1 gas fermentation and high value products from microalgae
- Requirement and opportunities in sector consolidation and growth for fermentation from cellulosic feedstocks and high value extractives
- Recommendations for co-ordinating actions to promote industry interactions in the areas of biologics, anaerobic digestion and biocatalysis but no additional scale-up facilities anticipated in the next 10 years.
- Staff competence and expertise in supporting process scale-up needs to be developed and retained alongside investment in facilities

Background

Since the publication of the Government initiated Innovation and Growth Team report on Industrial Biotechnology (IB), UK stakeholders have been working to realise the commercial benefits of IB, building on the acknowledged strength of the UK research base.

As access to pilot-scale equipment is commonly cited as a barrier to development of IB processes, NNFCC and Inspire Biotech were commissioned by BBSRC, EPSRC, Innovate UK, and IBLF to identify whether there is a specific need for investment in pilot scale equipment in the UK and to develop the outline case for any investment.

Methodology

A phased approach was taken to

- Identify the existing UK IB equipment asset landscape (pre-processing, processing, refining and extraction) the location, scale, typical use and means of access.
- Identify stakeholder views on equipment needs to address any identified gaps in provision
- Develop outline cases for investment in UK scale-up equipment by presenting the rationale for such targeted investment, taking account of existing UK and other accessible scale-up facilities.

In the asset landscaping exercise information was gathered on 340 relevant individual pilot-scale assets. This included 69 assets involved in biomass pre-processing, 105 assets involved in processing (e.g. fermentation) 42 assets involved in algal cultivation and 124 assets involved in product separation. Data on the availability of different scales of equipment are presented for each relevant IB sector.

To build the case for prioritised public investment in specific IB sectors, information was drawn from the asset register, interviews with key asset 'owners' the stakeholder workshop and from follow-up discussions with key stakeholders.

Cases for Investment

The study described in this report found that overall the UK is currently well served with respect to accessible pilot equipment and competence and is competitive with other European member states. However, a number of emerging technologies were identified as areas worthy of investment and that further more limited investment, focused on specific established sectors, would strengthen UK capability.

Taking account of existing UK capabilities, the developed investment cases look to add to national capability or to expand or consolidate it where it already exists. The cases fall into three broad categories;

A) where there is a need for significant investment to effectively build new capabilities;

B) where there is a need for more limited investment to address gaps in capability in established areas, and

C) other areas where there is little or no need for investment in equipment beyond that provided by existing funding mechanisms.

A) Investment in major UK opportunities to build excellence and leadership

There are two strategic areas, C1 gas fermentation and high value products from microalgae, where investment could have a major impact at a national and international level and where early public support could deliver potentially large benefits to the knowledge base and to the UK bioeconomy. Both of these areas share a number of broad characteristics:

- they are relatively new areas in the IB sector where technology breakthroughs could deliver significant academic and commercial opportunities.
- commercial activity primarily represents early stage companies looking to commercialise technology
- there has been little or no significant investment on a national scale to date.
- there is significant world class expertise in the UK
- commercial investment would currently be seen as a risky proposition.

In these cases, developing significant UK leadership and focused national competence would provide coordination and leadership for academia, institutions and industry nationally and internationally, and ensure there is UK critical mass of equipment, knowledge and people required to deliver credible commercial outcomes.

C1 gas fermentation

C1 gas fermentation offers a significant commercial opportunity in the production of bulk and intermediate chemicals. The size of the business opportunity is substantial and many companies can be expected to enter this growing sector. The biofuels and commodity chemicals are large ($ trillion) global markets and a successful commercial outcome in any of these either as a producer, technology developer or through IP licensing would yield significant economic benefits for the UK bioeconomy.

The C1 gas fermentation and process development capability in the UK is extremely limited and currently only exists at small laboratory-scale, which limits the ability to transition knowledge to larger scale. The UK has world-leading expertise and existing interactions with leading industry interests.

Investment in open-access, flexible, modular capabilities is proposed, in appropriately supported environments. Essential to this will be the development of an environment that supports business engagement and the development of early stage companies. As a guide, were the approach to be an integrated National Centre for C1 gas fermentation this might be expected to cost up to £60m if it is to include a fully integrated pre-commercial demonstration unit. If the operational scale was limited to large pilot scale (circa 500L) then the costs may be reduced significantly (circa. £20m).

Microalgae for high value products

The commercial large-scale culture of phototrophic microalgae has been established and markets for high value products have been developed. However, the development of more effective algal synthetic and systems biology tools, metabolic engineering and chassis improvement methodologies has increased interest in the role of microalgae as a platform for the production of a range of valuable molecules for use in high-value applications such as cosmetics and nutrition. The market for microalgal products is currently estimated at >$5 billion pa[1] including $2.5 billion from the health food sector and $1.5 billion from the production of the omega-3 fatty acid docosahexaenioc acid (DHA).

The UK has a number of world leading academic research groups working on microalgae and innovative UK SMEs. However, the algal research community remains fragmented. There have been several calls to invest in facilities to help co-ordinate activities and provide a 'one stop shop' for process development and technology transfer to the commercial sector.

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[1] Pulz and Gross (2004) Valuable Products from Biotechnology of Microalgae, Appl. Microbiol. Biotech., 65., 635-48.

Investment in open-access, flexible, modular capability is proposed, in appropriately supported environments to support a range of facilities for growth and harvesting of microalgae at laboratory (10L) to pre-pilot (100,000L) scale. This would provide support for activities across the microalgae value chain, e.g. strain manipulation and development, growth and harvesting of biomass and product extraction.

An initial investment estimated at £10M would be required to support the provision of a fully equipped national competence, with an estimated build cost of £30M to construct premises designed to accommodate the specialised facilities for growth of microalgae.

B) Investment in sector consolidation and growth

Fermentation from cellulosic feedstocks and high value extractives were identified as two areas where UK capability at the academic and institutional level should be improved and/or where the narrow focus of assets and capability are limiting the commercial applicability

Fermentation from cellulosic feedstocks

The potential commercial opportunities in this sector are significant, but there remain significant challenges to commercialisation.

A range of facilities already exist around the UK but more limited investment is required in specific bespoke pieces of equipment or associated facilities to increase the flexibility of existing facilities and thereby increase capability.

High value extractives

This is an area at a relatively early stage of development, with a limited number of facilities providing capability for dealing with small-scale pre-pilot processing. A range of processes are required at matched scales across the processing chain.

A suggested possible model would be a facility equipped with core facilities, working with clients to acquire specialist or bespoke equipment for specific projects, possibly supported by a matched funding mechanism.

C) Other strategic areas of investment

These are represented by the IB areas; biologics, anaerobic digestion and biocatalysis. In these cases availability of, and gaining access to pilot-scale equipment was not seen as a barrier to development. Further development of process efficiency could be catered for by existing R&D funding mechanisms. However, there may be a need for co-ordinating actions to promote industry interactions which existing initiatives such as the BBSRC NIBB's would be best placed to assess and co-ordinate.

Other Key Findings

During the process of engagement with stakeholders, it quickly became clear that there are a number of additional issues that need to be taken into account when considering capital investment programmes. These broader considerations included:

Supporting and retaining expertise and competence: staff competence and expertise in supporting process scale-up takes significant time to build – generally through 'learning by doing'. During the study it became evident that there are concerns about wider skills retention and development in IB scale up, that are seen to be as important to sector development as investment in equipment. This knowledge is at risk of loss or dilution where staff retention can be dependent on securing individual contracts or start-up funding and organisations need to develop approaches to address this challenge. This could undermine any investment in new scale-up equipment without ongoing support to retain the staff competence and capability to use it effectively. While this was not a focus for this study, it is highlighted as an issue that requires as much attention as investment in equipment and warrants further examination of how skills retention in the IB scale-up sector could be assisted.

Integrated capabilities: this is the favoured model, where complementary assets (or complete process chains) could be deployed or integrated in a co-ordinated fashion. This extends from the desire to integrate technology to include integration of disciplines and capabilities (e.g. biology, chemistry, engineering, modelling, analytical, etc.).

Process and economic modelling: there is a need to access flexible process and economic models to characterise and optimise early stage processes to deliver a robust set of economics to assess the business case for commercial development at the earliest possible development phase.

Analytical capabilities: access to good analysis skills, services and equipment to monitor and process efficiency.

Constraints imposed by some funding mechanisms: whilst regional or other funding mechanisms have been helpful in establishing pilot facilities, in certain cases it can also become a barrier preventing fully open access e.g. by restricting use to, or prioritising use by companies in the funding region.

While addressing the above issues in detail is beyond the remit of this study, account is taken of these issues where appropriate.

Access to Facilities

Internal project work can restrict access to equipment held at universities and research institutes, but typically the larger the equipment the lower the level of utilisation per annum. Specific vulnerabilities included large-scale steam explosion equipment (for biomass pre-processing) and a number of co-located large scale fermenters (6000 litres and above) based at one commercial company, the loss of which could degrade UK capabilities significantly.

Access to European Facilities

A review of open access European pilot facilities demonstrated the range of pilot-scale equipment that is available and could be accessed at the European level. These form an additional resource base available to UK researchers and industry and should be considered when evaluating future investment decisions.

Contents

1 Background

As access to pilot-scale equipment is commonly cited as a barrier to development of industrial biotechnology (IB) processes, NNFCC and Inspire Biotech were commissioned by The Biotechnology and Biological Sciences Research Council (BBSRC), the Engineering and Physical Sciences Research Council (EPSRC), Innovate UK, and The Industrial Biotechnology Leadership Forum (IBLF) to identify whether there is a specific need for investment in pilot scale equipment in the UK and to develop the outline case for any investment.

A phased approach was taken to

- agree the sectors of interest and the relevant scales of equipment
- identify and catalogue existing open access pilot scale equipment in the UK
- identify the status and use of such equipment in identified key facilities and any associated risk of asset loss
- work with stakeholders representing IB facilities to identify the critical equipment needs affecting achievement of their future aspirations in their respective fields
- identify where any identified needs could be met by accessing equipment outside the UK (to ensure appropriate targeting of funds)
- develop outline investment cases for UK scale-up equipment by presenting the rationale for targeted investment, drawing on the earlier findings.

1.1 Industrial biotechnology areas considered

To provide consistency with the key IB technology areas identified by the 13 Networks in Industrial Biotechnology and Bioenergy, IB technologies were clustered into five categories for the purposes of this study, namely:

- Anaerobic digestion
- Biocatalysis
- Industrial fermentation
- Pharmaceutical fermentation
- Algal cultivation

Anaerobic digestion refers to the production of biogas (a gaseous mixture of predominantly biomethane and CO_2) through microbial degradation of organic substrates under anaerobic conditions.

Biocatalysis refers to the chemical conversion of organic compounds using either purified enzymes or whole cell catalysis.

Industrial fermentation refers to the production of simple organic products (such as ethanol, butanol and lactic acid) using microorganisms cultivated under fermentative conditions.

Pharmaceutical fermentation refers to the production of organic products for the primary interest of the pharmaceutical industry. Products can range from simple organic molecules to complex macromolecules such as proteins.

Algal cultivation refers to the growth of microalgae (photo- or autotophically) for the purpose of extracting intracellular and/or extracellular metabolites. Macro algae (seaweeds) are produced in open sea cultivation facilities and in the context of this study are considered as feedstocks for industrial fermentation or high value chemical extraction.

2 UK industrial biotechnology asset register

2.1 Methodology

To gain an understanding of the existing accessible UK asset base supporting scale-up activities in the target IB sectors, an e-mail survey was undertaken of relevant equipment at academic, research and technology organisations (RTO's) and commercial companies. The scope and scale of equipment defined as within-scope was determined as outlined below.

2.1.1 Asset register scope

IB processes require both upstream and downstream equipment to prepare feedstocks and extract and refine products. Four phases in the product development process were defined as within-scope;

- Pre-processing
- Cultivation
- Processing
- Separation

Pre-processing involves equipment used for the physical refinement of raw materials into suitable substrates e.g. shredding and milling equipment, biomass pre-treatment and fractionation technologies, blending apparatus. This category also includes gasification and pyrolysis units where used to produce fermentation feedstock e.g. synthesis gas.

Cultivation involves equipment used in the growth of microorganisms where the output is microbial cells, rather than a secreted product (fermentation product). In general, this is largely restricted to equipment used for cultivation of algae. However, there may also be instances where bacterial and fungal cultivation equipment is also relevant.

Processing involves equipment used in the biological or chemical conversion of a substrate into products. Examples include fermenters, anaerobic digestion units, and glass reactor suites.

Separation involves equipment used for product recovery and purification following processing. However, equipment required for subsequent product derivatisation is considered out of scope. Examples include evaporators, chromatography units, filtration systems and centrifuges.

2.1.2 Equipment scale

It was problematic to define the exact scales of equipment considered in-scope. The amount of a given product that is required for production to be considered "industrially relevant" is entirely dependent upon the identity of the product. For instance, far smaller amounts of pharmaceutical compounds are required than would be the case for ethanol.

Establishing minimum threshold scales for each piece of equipment was considered too time-consuming and of limited benefit to the success of the project. The defining criteria for equipment captured in the register was *equipment that is of a large enough scale such that it is not routinely found in UK laboratories*. While this definition is largely subjective, laboratory and equipment managers were judged to be best-placed to evaluate whether the scale of their equipment is of industrial relevance or not.

To provide an element of guidance, a capacity of 30 litres was advised as being the minimum threshold for standard fermenters and anaerobic digestion units. Reporting of all relevant upstream and downstream processing equipment was expected to be consistent with reported processing capacity. For non-standard fermenters, such as solid-state fermenters, a minimum threshold of 10 litres was advised. A minimum threshold capacity of 100 litres and above was advised for Microalgae cultivation equipment.

2.1.3 Further asset categorisation

After review, responses were further disaggregated using the following categorisations:

- **Refining/milling**: upstream (or downstream) equipment used in the physical processing of biomass into smaller particles/homogenous mixture. This includes: shredders; chippers; milling equipment; homogenising equipment etc.
- **Pre-treatment/fractionation**: any upstream equipment used for the physical or chemical processing of biomass into separate components. This includes: steam explosion equipment; fibre expansion vessels; sonic processing cells.
- **Hydrolysis**: any upstream equipment used in the production of sugars from the hydrolysis of biomass.
- **Pasteurisation**: equipment specifically for pasteurisation
- **Incubation**: equipment used for microbial cultivation prior to cultivation, including: incubation shakers and seed tanks.
- **Chemical reactor vessels**: any processing vessel used for undertaking chemical (rather than biological) reactions. This includes: glass reactor suites; jacketed tanks/vessels.
- **Fermentation**: any processing vessel used for fermentation.
- **Anaerobic digestion**: any processing vessel used for anaerobic digestion.
- **Algal cultivation**: any processing vessel used for cultivating algae. This includes: photobioreactors and raceway ponds.
- **Control system**: any systems used for controlling processing operations.

- **Centrifugation**: This includes: continuous flow centrifuges; batch centrifuges; disc stack centrifuges.
- **Evaporation**: equipment used for evaporating solvents from a product stream, including rotary evaporators.
- **Filtration**: downstream equipment used for filtration of a product stream.
- **Drying**: equipment used for drying of a product stream. This includes: freeze dryers, spray dryers; filter dryers.
- **Chromatography**: any chromatography equipment used for separation of product streams.
- **Extraction**: any downstream equipment used in product extraction/separation. This includes: distillation units; supercritical CO_2 units; cell lysis equipment.
- **Storage**: any equipment used for storing feedstock or products.

2.1.4 Identified key facilities

Key institutes and companies with relevant equipment assets were identified, drawing on the knowledge of the project team and from interactions with 8 of the collaborative Networks in Industrial Biotechnology and Bioenergy (NIBBs)[2]. A list of relevant institutes (Table 1) and companies (Table 2) was compiled.

The lists are not exhaustive and it is recognised that there are additional companies offering contract manufacturing services (particularly in the pharmaceutical and healthcare sector) and similar facilities that could be used to help scale-up. However, the identified facilities and companies were thought to represent the most prominent and widely recognised open access facilities.

[2] FoodWasteNet; Plants to Products; LBNet; C1NET; AD Network; BioProNET; PHYCONET; Network in Biocatalyst Discovery, Development and Scale-Up

Table 1. List of institutes contacted

Institute	University/ Parent Company
Advanced Biomanufacturing Centre Manager	University of Sheffield
Advanced Centre for Biochemical Engineering	University College London
Anaerobic Digestion Development Centre	Centre for Processing & Innovation
Astbury Centre for Structural Molecular Biology	Leeds University
Bath Plant Lab	University of Bath
BEACON Biorefining Facility	Aberystwyth University
BioComposites Centre	Bangor University
Biorenewable Development Centre	University of York
Centre for Industrial Biotechnology and Biorefining	University of Warwick
Centre for Sustainable Aquatic Research	Swansea University
Cockle Park Farm	University of Newcastle
Cranfield University	Cranfield University
Department of Engineering and Physical Sciences/IBioIC	Heriot-Watt University
Durham Energy Institute	Durham University
Harper Adams	Harper Adams
Hartree Centre	Science & Technology Facilities Council
IBERS	Aberystwyth University
IFR Biorefinery Centre	Institute of Food Research
Imperial Bioreactor Suite	Imperial College London
International Centre for Brewing and Distilling/IBioIC	Heriot-Watt University
London Bioscience Innovation Centre	Royal Veterinary College
National Biologics Manufacturing Centre	Centre for Processing & Innovation
National Industrial Biotechnology Centre	Centre for Processing & Innovation
Plymouth Marine Laboratory	Algal Biotechnology and Innovation Centre
Sustainable Environment Research Centre	University of South Wales
University of Birmingham School of Engineering	Birmingham University
University of Cambridge Department of Plant Sciences	University of Cambridge
University of Manchester School of Chemical Engineering and Analytical Science	University of Manchester
University of Nottingham Industrial Biotechnology Group	University of Nottingham
University of Southampton Bioenergy and Organic Resources Research Group	University of Southampton
University of Swansea School of Engineering	Swansea University
University of Westminster Applied Biotechnology Research Group	University of Westminster
Wales Centre of Excellence for Anaerobic Digestion	University of South Wales
Wolfson Fermentation and Bioenergy Laboratory	University of East Anglia

Table 2. List of companies contacted

Company
AlgaeCytes
Algenuity
Biocatalysts Ltd
Biosyntha
Cobra Biologics
Croda
E3 biotechnology
Fujifilm Diosynth
Green biologics
GSK
Ingenza
Invista
Lonza
New Horizons Global
ReBio Technologies
Synthace

2.1.5 Asset register content

Bespoke asset registers for each facility were produced in MS Excel, initially drawing on existing knowledge in the public domain. Each recipient facility was requested to confirm the content and add information on any additional or associated relevant equipment and identify mechanisms to access the equipment.

The range of information captured included the following:

Asset category type	• fermenter, anaerobic digester, centrifuge etc.
Processing stage	• pre-processing; • processing; • cultivation; • separation
Technology application area	• anaerobic digestion; • algal cultivation; • industrial fermentation; • biocatalysis; • pharmaceutical fermentation
Detailed asset data	• manufacturer • model • size & throughput identifier
Accessibility	• contract research • collaborative research & development • fee for use • negotiable • availability of technical staff support

2.2 Results

Table 3. Overview of facility responses

	Contacted	Response provided	Facilities with relevant assets
Institutes	34	31	26
Companies	16	12	7

Of the 50 facilities contacted, 43 provided a response with 33 possessing relevant assets (Table 3). From these 33, 27 facilities have processing (fermentation/biocatalysis/anaerobic digestion) equipment, 10 facilities have cultivation (non-fermentative) equipment, 15 facilities have upstream "pre-processing" capability and 21 facilities have downstream product separation/extraction capability.

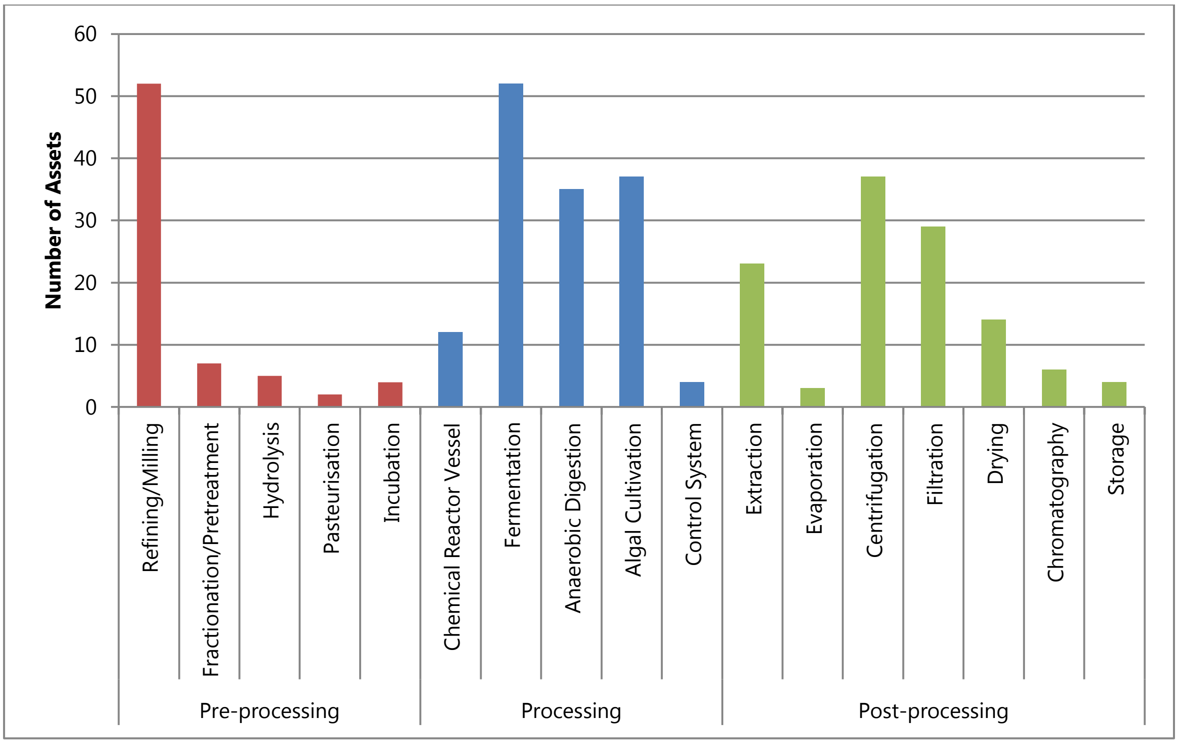
The majority of responses were from academic facilities or Research and Technology Organisations (RTOs)[3]. In many cases assets in private ownership complement those held by the academic sector and RTO's, but reference is made to instances where private facilities offer unique capabilities in type or scale.

[3] RTOs in the context of this study represent a range of companies including university spin-outs to facilities providing scale-up facilities that are supported by research funding from both public and commercial sources, and in some cases by direct public support, where the main activity is provision of technology and process development services.

In total, information on 340 relevant individual assets was captured. This includes 69 assets involved in pre-processing, 105 assets involved in processing, 42 assets involved in algal cultivation and 124 assets involved in product separation.

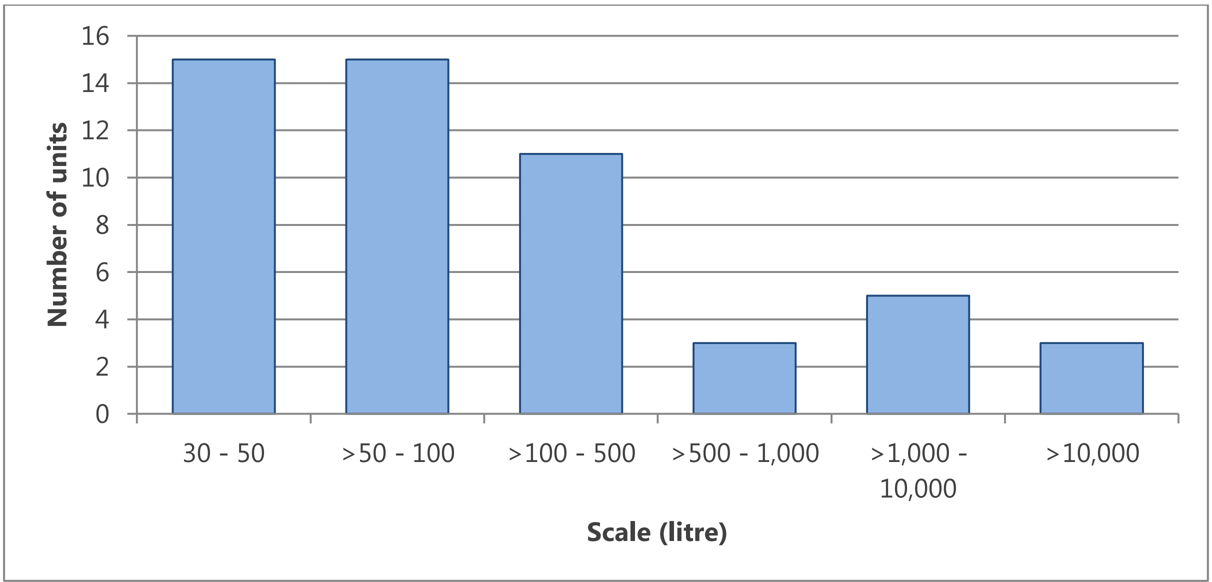
The majority of up-stream equipment registered on the database relates to mechanical processing of biomass, with 52 assets involved in refining and milling (Figure 1). Relatively few assets were recorded as specific to the extraction of sugars from biomass (e.g. fractionation, pre-treatment and hydrolysis). The majority of assets related to processing were categorised as reactors involved in fermentation, anaerobic digestion and algal cultivation. Only 12 assets were registered as chemical reactor vessels (e.g. glass reactor suites; continuous flow reactors). The majority of assets related to processing were categorised as extraction systems (e.g. supercritical CO_2; cell disruption and lysis technologies; distillation units; solid/liquid separation), centrifuges, and filtration units.

Figure 1. Distribution of registered assets



2.3 Fermentation assets

Figure 2. Scale distribution of fermenters registered

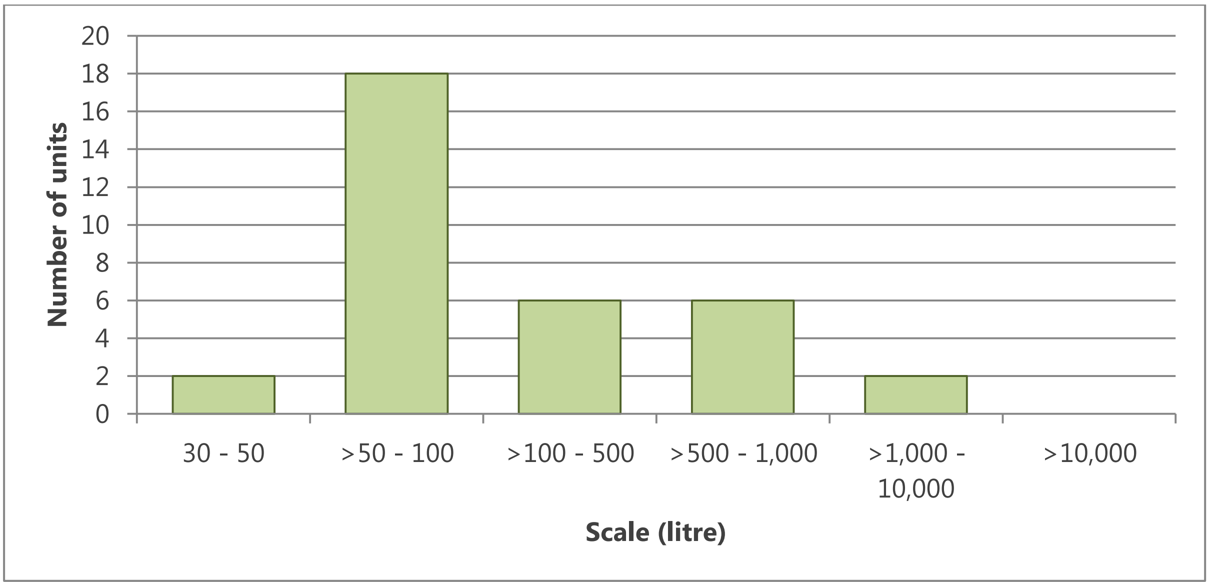


A total of 52 fermenters (of 30 litres and above) are captured on the asset register. The majority of these are standard fermenters with a capacity below 500 litres (Figure 2). There are eight fermenters registered with a capacity above 1,000 litres, the majority of these larger fermenters are owned by private companies. Croda registered two glass-lined 30,000 litre fermenters that are particularly suited to cultivation of marine microorganisms. ReBio Technologies registered a 2,000 litre and two 6,000 litre standard fermenters. Additionally, New Horizons Global has a total of 850,000 litre of algal fermentation pilot plant capacity, consisting of a range of 80,000 litre and 160,000 litre fermenters. However, disaggregated information was not supplied in this case.

With regards to assets in the academic and RTO sectors, only IFR and CPI's National Industrial Biotechnology Centre (NIBC) possess fermenters with a capacity greater than 1,000 litres; IFR has a single 2,000 litre fermenter while the NIBC has a single 10,000 litre fermenter.

2.4 Algal cultivation assets

Figure 3. Scale distribution of algal cultivation assets registered

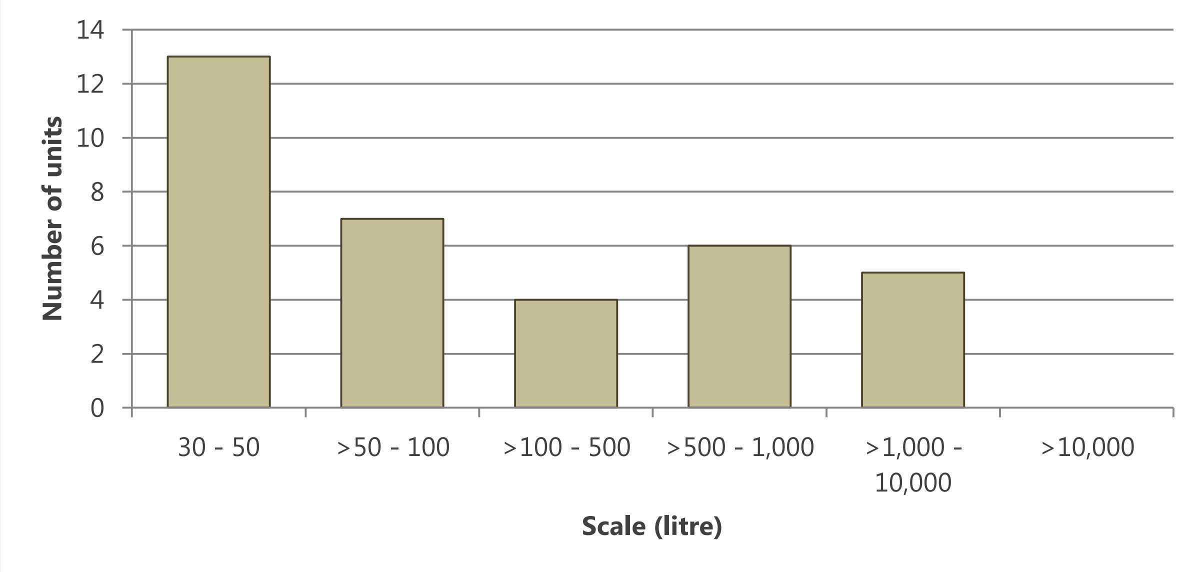


A total of 34 algal cultivation assets have been registered, the majority of which are photobioreactors with a capacity of between 100 and 500 litres. Only Swansea University and Plymouth Marine Laboratory (PML) have facilities capable of cultivating volumes of greater than 1,000 litres. Swansea University has a 2,000 litre vertical tubular bioreactor, along with a variety of other smaller scale bioreactors. Meanwhile, PML has a newly-developed facility which includes a 600 litre tubular photobioreactor, a 1,000 litre vortex bioreactor and a 1,250 litre open raceway pond. The vast majority of photobioreactor assets related to algal cultivation are in the academic or RTO sector, with Algaecytes the only private company reporting such assets.

2.5 Anaerobic digestion assets

A total of 35 anaerobic digester units have been registered, with most assets between 30 and 50 litres in scale (Figure 4). However, assets above 50 litres are broadly distributed between scales of 50 and 10,000 litres. All of these facilities are within the academic or RTO domain.

Figure 4. Scale distribution of anaerobic digester units registered



A small number of facilities offer large scale capabilities. Harper Adams has a 1,000 litre Micro-AD plant, although the institute's large scale anaerobic digestion plant is currently out of action. Both Cranfield and Cockle Park have large scale demonstration AD facilities with Cranfield possessing two 300 litre digesters, two 600 litre digesters and a 1,500 litre digester and Cockle Park possessing two 665 litre digesters. CPI has a dedicated anaerobic digestion centre with numerous vertical digesters ranging between 60 and 1,500 litres in scale in addition to a 4,000 litre horizontal digester (small commercial scale would start around 5000 litres). All the anaerobic digestion facilities registered belong to academic institutions or RTOs rather than private companies.

2.6 Supporting equipment

A wide range and variety of equipment was reported as supporting the above facilities. Feedstock refining equipment ranged from simple mills, chipping and mixing equipment, to presses and pressurised refiners. Steam treatment/hydrolysis facilities were relatively scarce. This is an important issue, since such processes underlie the breakdown of recalcitrant biomass into its constituent sugar polymers and lignin, which is a prerequisite for use of lignocellulosic biomass[4] as a feedstock in biological processes. Steam hydrolysis units can be found at the IFR Biorefinery Centre, Norwich (30 litre), Beacon Biorefining facility (30 litre) and steam fibre expansion facilities at the Biorenewables Development Centre, York (100 litre) while the commercial company Rebio Technologies have 60 litre and 1000 litre steam hydrolysis facilities which are clearly the largest of such facilities in the UK. The Biocomposites Centre at Bangor University also has a novel 37 litre ultrasonic processing pre-treatment cell.

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[4] This represents non-food plant biomass resources that offer the potential to provide lower costs sources of sugar than traditional food sources, using resources that are less likely to compete with land for food production.

In terms of separation equipment, beyond the long list of centrifuges, filters and chromatography units, Supercritical CO_2 units were reported at the Biorenewables Development Centre, the Wales Centre of Excellence for Anaerobic Digestion and The Biocomposites Centre at Bangor University.

3 Typical asset utilisation

3.1 Approach

To gain a better understanding of how key assets identified in the asset scoping exercise were used, telephone interviews were held with asset managers/owners to gain an understanding of

- typical use and typical users,
- funding mechanisms to support the asset
- plans for upgrade or expansion

The objective was to gain an understanding of the pressures/demand on current assets.

Based on the data gathered in compiling the IB Asset Database, eleven key centres were identified. These were selected on the basis that they represent facilities with suites of pilot-scale equipment and/or novel equipment facilities and to ensure that the whole range of technologies of interest were covered (algal, AD and Industrial Biotechnology). Consideration was also made to ensure a representative range of academic, RTO and commercial interests were included where relevant. The facilities contacted are shown in Table 4.

Summaries of interview responses for each facility contacted are available in Annex 1. Table 5 provides a generic overview of how equipment in academic, research institutes and commercial facilities is currently utilised and the issues associated with accessing assets.

3.2 Key findings

Summarising the key findings

- Usage rates for small–scale pilot equipment tends to be very high at academic facilities and research institutes due to pressure from internal projects, which could affect access at certain times.

- As there are relatively few AD facilities and because process runs typically last for a number of days, this can potentially limit the number of contracts that could be serviced.

- Academic, research institutes and RTO's in many cases have a significant associated support capability function, provided by complimentary skill sets in aligned technology areas.

- Equipment at the largest scales in both academic and commercial facilities tends to be less commonly utilised. In some cases this poses a risk that facilities may be lost (ReBio).

Table 4. Centres contacted as case studies for interview

Facility	Sector of interest		Specific Assets	Typical spheres of use
Beacon Biorefining Facility, IBERS	IB	Research Institute	Suite of fermenters 30-70 litre and associated pre-processing steam explosion rig	Biomass refining
CPI – NIBC	IB	RTO	Fermenters from 2,000 to 10,000 litre	High value chemicals from biomass
CPI - ADDC	AD	RTO	AD stirred tanks from 60 to 1,500 litre	AD feedstock and process evaluation
Centre for Sustainable Aquatic Research (CSAR)	Algae	Academic	Suites of photobioreactors and scales from 100 to 2,000 litres	Algal production of high value materials, waste water treatment
Cranfield University	AD	Academic	AD stirred tanks from 650 to 1,500 litres	AD feedstock/ process tests
Croda	IB	Commercial	Fermentation tanks from 2,000 to 30,000 litres (glass lined for marine applications)	High value materials from biomass sources
IFR Biorefinery Centre, Norwich	IB	Research Institute	Unique 2000 litre high torque solid state fermentation facility and small scale steam explosion equipment	Biomass degradation for ethanol and high value chemicals
Plymouth Marine Laboratory	Algae	Academic	Novel algal scale up facilities up to 1000 litres and 1,200 litre raceway. Novel Vortex bioreactor	Algal production of high value materials, waste water treatment
ReBio	IB	Commercial	New IB company with 60-6000 litre fermentation capability and steam explosion facility up to 1000 litre	Cellulosic bioethanol, but looking for other high-value applications
University College London	Biologics	Academic	Small scale assets up to 7.5 litre and investment in 150 litre fermenter	Vaccine and biopharmaceutical production
Warwick University Centre for Industrial Biotechnology and Biorefining	IB	Academic	270 litre fermenter for liquid and solid state applications	Production of novel enzymes from biomass residues

- Specific equipment at risk includes large scale steam explosion kit for biomass processing, and large scale fermentation capacity (6000 litres and above).
- The largest scales of equipment offer the best opportunity to examine continuous processing and processes integration in some cases via scaled 'plug and play' facilities, which enables more effective evaluation of process economics.
- Some public investment mechanisms may restrict wider access to equipment for extended periods.

3.2.1 Security of facilities

Interviews confirmed that most of the identified equipment is secure in the short to medium term, but exceptions include that held by the commercial company ReBio. There is also uncertainty regarding the future security of equipment supported by the BEACON project in Wales after project funding ends (though funding is being sought to extend the project).

In both cases these facilities represent pilot scale plants for the exploitation of biomass for fuels and high value materials, and both contain equipment for biomass processing and refining that is relatively scarce in the UK. In the case of ReBio it hosts the largest scales of pilot-scale biomass processing capability in the UK, and associated scaled equipment for onward fermentation.

ReBio was formed in 2014 and took on facilities formally developed by TMO Renewables for cellulosic ethanol production released as part of the formal administration process. ReBio is looking for opportunities to support the use of the acquired equipment, including opportunities for joint ventures and for contract manufacture that could lead to the plant being no longer capable of offering open access capabilities (see Annex 1). The sale of equipment is also a possibility if uses are not found in the UK, which may mean such equipment moves offshore.

Table 5. Selection of highlights from case study interviews

	Academic Facilities	Research Institutes/RTO's	Commercial facilities
Typical set-up	Equipment is typically shared between departments and research groups to build capacity and competence. Typically batch processing	Greater levels of integration of equipment and capability observed and some unique assets.	Typified by large scale facilities not found in academia or research institutes. Facilities for continuous or semi-continuous processing and associated scaled equipment for downstream processing. Typically represents in-house demonstration facility for commercial product development where spare capacity offers opportunities for use by others. Alternatively represents re-purposing of equipment that has become surplus to need.
Typical period of use	Algal photobioreactors at a range of scales are typically used year-round. Algal vortex bioreactors are used infrequently at PML, but these have a high throughput facility when in use (10-15min/sample). Large 600 litre photobioreactor at PML tied-up typically for 2-3 months at a time with projects. However, has seen little use in last 6 months, following previous heavy use. Algal bubble reactors (120 litres) have 30-	Cellulosic pre-processing equipment is used seasonally reflecting harvest periods for biomass. Secondary processing/fermentation equipment at 30-70 litre scale is in relatively constant use (70%+) at Beacon, with typical project runs of 2 weeks at smaller scales. CPI has a wide range of large scale equipment to support scale-up from TRL 3-4 upwards. Assets tend to be in year-round use.	Utilisation varies significantly but typically 20% occupancy rate for large scale asset (e.g. 30,000 litre fermenter at Croda). Smaller scale facilities (2000 litre) have greater occupancy rates, including smaller 60 litre capacities (ReBio).

	40% utilisation rate. Algal raceway pond used for 10-20% of year Industrial fermenters at UCL (150 litres) used once a fortnight while small scale (7.5 litre) used weekly. Warwick fermenter (270 litre) typically has a 30% occupancy rate AD facilities have typical retention periods of 20-25 days with multiple runs required to validate results. This limits access at Warwick where equipment is limited.	Cellulosic steam explosion equipment is uncommon in the UK. The Beacon facility typically processes 10-15 batches of 50-75Kg of material per day Individual AD studies at CPI can run from 6 weeks to 6 months, limiting access. IB studies, depending on the complexity run from a week to typically 2-6 weeks. IFR's 2000 litre SSF is only used occasionally (once per quarter) after initial high levels of use. Small-scale steam explosion rig (1kg) runs around 5000 times/year. Larger scale projects can occupy assets for extended periods of time as configurations and processes are optimised etc. (CPI).	
Typical users	Mainly academics at the host organisation, but also academic collaborations and use by SME's and companies through either joint project funding or commercial funding arrangements.	Host staff working on internal research projects (primary use in institutes) and with companies working on joint projects with the host (typically supported by research funding) or on development projects (commercially funded access). Interests include academics, RTO's, SME's and large companies across a wide range of application areas.	In house development teams have primary access, with open access offered for spare processing capacity. Typically this is through joint funded projects with commercial partners and academic partners, or commercial subcontracting arrangements with JV partnerships or other commercial interests. Access typically gained through joint

		In Europe innovation voucher schemes have been trialled (BiobaseNWE) to encourage industry to use pilot scale facilities	funding or pure commercial arrangements
Funding mechanisms	Larger centres established by grant funding. European Regional Development Funds used by others as part of the funding mix, including direct capital investment by institutes themselves. CSAR funding is estimated to split 80:20 between academic and commercial project income. Greater emphasis on public and public/private grants than full commercial projects	Research Institutes are primarily grant supported (Central and Local Government, European Structural Funds, Research Councils UK (or similar)) CPI working towards a split of one third public investment, research grant (public/private) and commercial investment. Around 40% of income is currently secured as competitive project grants.	Direct investment by Croda to develop their facilities. ReBio equipment salvaged from TMO administrators. JV operations, partnerships with other commercial interests and projects with academics BDC working with innovation vouchers using public/private funding to support investment in equipment for specific projects.
Issues limiting Access	Due to high level of demand for some facilities e.g. photobioreactors, lead time to access equipment may be up to a month. Delays in accessing AD scale-up equipment expected to be significant as likely to be dedicated to research projects for up to 6 months at a time (especially at Warwick with limited facilities)	Where regional funding mechanisms are involved, this can limit access by companies outside the funding authorities region and also for a period beyond the life of the project (up to 5 years for ERDF funded facilities). No specific problems anticipated in accessing equipment, especially with larger and specialist equipment which tends to have low utilisation rates.	No specific limitations, delays due to use likely to be limited.

Development plans	CSAR commissioning a new 1000 litre LED photobioreactor to add to facilities. CSAR is also looking to develop a national £multi-million algal capability Development plans for some facilities involve developing capability to deal with class 2 and 3 (HSE notifiable) GM materials, requiring specific containment measures, to take advantage of the rapid development and technical promise offered by synthetic biology. New investments given life expectancy of 10+ years (e.g. Warwick AD facility) No facility was seen to be at specific risk, even where equipment was lightly used.	Beacon's equipment is likely to be secured up to 2020, but longer-term security will depend on securing follow-on projects and financial support. CPI asset base expected to be operational for at least 10+ years. CPI has ambitious plans for continued expansion and development with supporting capabilities which if successful should secure the equipment on site. CPI also develops spin-out companies which could help to support asset use.	Some retro-fitting and investment planned to ensure facilities meets the requirements for dealing with GM organisms (Croda) where not already present. Expected financial write down of ca. 15 years. ReBio plant looking for options to support its long-term future, which could entail conversion to commercial production, removing access to facilities. Sell-off of some capability including steam explosion equipment is also a possible 'worst-case scenario'.

4 Pilot plant facilities outside the UK

4.1 Approach

Europe has been investing in similar open-access facilities to those identified in the UK, both through funding directed at universities and specialist research institutes, though to investment in specific pilot plant facilities.

To ensure that any UK investment in equipment is focussed on the most appropriate areas of need, a short review of facilities providing scale-up equipment in Europe was undertaken, with additional information collated for the US where relevant. This exercise was undertaken to identify where any alternative equipment could be available to address equipment deficiencies or access problems encountered in the UK.

A non-exhaustive list of pilot plant focusing on areas of interest to Industrial Biotechnology processes is shown in Table 6. More detail of each of these is provided in Annex 2.

4.2 Likely call on assets outside the UK

The range of examples identified mirrors that in the UK, with for example some facilities (typified by university departments) possessing a limited number of fermenters ranging from a few tens to a few hundred litres of fermentation capacity, with a few specialist units or institutes with fermentation capacities of up to a few thousand litres, and a few exceptional cases of facilities with capacities of up to 15,000-30,000 litres, representing very specialist facilities or contract manufacturing organisations (e.g. Biosentrum).

With the exception of facilities designed for algal production, the range of applications and capabilities varies considerably between different facilities.

4.2.1 Algal pilot plant facilities

There is a great deal of commonality in pilot-scale photobioreactor equipment for algal production in facilities within and outside the UK, but greater investment has been made in open tanks and raceway assets in Europe, particularly in Southern Europe. This is understandable given the climatic requirements to optimise open-air production.

The UK has a number of phototrophic algal production systems sited in University or University-linked departments. As discussed in the previous section, associated project work can limit accessibility to equipment at times, particularly as there are only 2 photobioreactors in the UK with capacities of 1000 litres and above, and only a few further examples in Europe.

Europe has developed open pond or raceway cultivation systems which exceed the capabilities available in the UK currently. However, outside of this, Europe offers additional capacity rather than any unique assets.

Table 6. Open access pilot plant facilities outside the UK and their areas of IB specialism and support

	Chemicals	Energy/ Biofuel	Pharma	Biobased materials	Food/Feed	Algae
VTT, Finland	●		●	●	●	
CVG, France	●				●	
BioBase Europe Pilot Plant, Belgium	●	●			●	
Bioprocess Pilot Facility, Holland	●	●	●		●	
ARD, France	●			●	●	
Biosentrum, Norway	●			●		
Biopolis, Spain	●	●	●	●	●	
Universitat Autònoma de Barcelona, Spain	●		●			
Leibniz Institute, Germany	●			●	●	
INETI, Portugal	●	●	●			
NREL Bioprocessing Pilot Plant, USA	●	●				
Fraunhofer Center for Chemical Biotechnological Processes, Germany	●					●
SINTEF, Pilot Plant for Bioprocesses, Norway			●			
IBET, Portugal			●		●	
EMPA, Switzerland				●		
CEVA, France						●
HTw. Germany						●
Lelystad Open Pond Pilot, Holland						●
Instituto Technologico de Canarias, Spain						●

4.2.2 AD pilot plant facilities

As there is little in the way of engineering innovation in AD systems currently, it is not anticipated that there are any specific equipment demands that could not be supplied by existing UK AD pilot scale facilities. However, as for algal facilities, gaining access to pilot facilities can be difficult at times due to the limited number of UK assets (only 10 AD tanks in the UK at 500 litre or greater), long retention times of process runs, and in some cases academic projects tying up equipment for long periods.

4.2.3 Development of lignocellulosic focused pilot plants

The growing interest in development of biobased fuels, chemicals and materials has led to the development of pilot plant facilities offering suites of equipment to deal with biomass from initial processing through to refinement of end products. These have developed in the UK though facilities such as the IFR Biorefinery, Beacon, ReBio and CPI. Similar developments in Europe include: Bio Base Europe Pilot Plant (Ghent), Bioprocess Pilot Facility (Delft) and developments at the VTT Technical Research Centre (Finland). These typically provide integrated facilities and capabilities to provide flexible capacity to support biotechnology development in the chemicals, fuels, pharmaceutical and food/feed sectors.

Specialist biomass processing facilities include

- steam explosion (VTT and Bioprocess Pilot Facility)
- organosolve treatment processes (VTT, Bio Base Europe)
- acid to alkaline biomass pre-treatment (Bio base Europe, Bioprocess Pilot Facility)
- enzymic hydrolysis (Bio Base Europe, Bioprocess Pilot Facility)

In many cases these mirror facilities and equipment available in the UK, in particularly that held by ReBio, IFR and to some extent Beacon. However, facilities at Bio Base Europe and Bioprocess Pilot Facility are of a particularly large scale in some cases e.g. enzymic hydrolysis capability from 500 up to 50,000 litres. With the exception of steam explosion, requiring bespoke equipment, the above biomass pre-processing operations represent relatively common chemical treatment reactions and so can be addressed relatively rapidly should the need arise, particularly through use of glass-lined reactor vessels.

In some cases European facilities (Bio Base Europe, Bio Process Facility) come with ATEX ratings to support safe working with flammable solvents and gasses, a factor which has attracted some UK biotechnology companies (e.g. Celtic Renewables) struggling to find similar facilities in the UK.

In terms of scale comparisons for fermentation equipment, there are only three fermenters in the UK with capacities above 10,000 litres (at ReBio and Croda) and again access can be limited at certain times where in-house commercial work (Croda) takes priority. Access to such large-scale capacity is also limited in Europe. Bio Base Europe provides fermentation capacities of up to 15,000 litres and Biosentrum up to 30,000 litres as a contract manufacturing facility.

4.2.4 Other pilot plant facilities

Fermenters serving the biocatalysis and pharmaceutical and cosmetics sectors typically range from a few hundred to a few thousand litres and again similar facilities exist both within and outside the UK to serve developments in these sectors. There are also commercial interests available to supply contracted production and development support.

5 Stakeholder workshop

5.1 Approach

Following the 'landscape analysis' of UK scale-up equipment, a stakeholder workshop was organised to facilitate the identification of a) critical assets and b) new asset requirements to support the development of UK competence in relevant IB technologies

Experts representing the various IB sectors of interest were invited to a one-day workshop held in York on the 17th November 2014. A total of 17 invited delegates, representing Universities (5), Research Institutes (8) and Industry (4), were joined by 4 members of the project team and an observer from BBSRC.

Initially, delegates were asked to identify

- Target areas of high level competence in IB identified as objectives for future strategic development by their respective organisations
- Any additional future areas of UK IB competence that delegates individually thought needed supporting by development at a national level to address gaps and potential weaknesses in provision

In this respect, competence refers to relevant equipment, facilities, skills and knowledge provision to support the move from basic research to commercial development

The wide-ranging areas of competency identified as being required to support IB development in the UK were then grouped by the project team into high level strategic areas to facilitate more detailed discussion by groups of delegates with the aim of identifying and developing evidence to support capital equipment investment cases with significant potential to deliver growth in the UK bioeconomy.

The identified broad strategic areas where development of competence was required included:

- Algal culture and processing
- Biocatalysis
- C1 gas fermentation
- Fermentation from cellulosic feedstocks
- High value extractives

Delegates were asked to consider the current national status of scale-up facilities in each of their strategic areas in terms of capacity and current demand on facilities by industry. In addition, they were asked to describe "*What A Good One Looked Like*" (WAGOLL), i.e. to characterise the ideal national situation taking account of assets, expertise and anticipated future requirements. The groups were asked to compare WAGOLL with their assessment of the current situation and through this identify specific gaps in their strategic areas. Each group was then asked to outline their gap analysis and present a justification for future investment to address these gaps based on need and potential return.

Two further strategic areas identified by the project team, Anaerobic Digestion and Biologics, were not well represented amongst the delegates and were therefore not discussed at the workshop. These two sectors were evaluated separately through calls/emails with facilities with relevant scale-up equipment to establish their more detailed needs.

5.2 Cross-sector supporting competency requirements

The key focus of the project was to identify priorities for capital investment in scale-up equipment in a range of IB sectors. However, delegates also identified a number of important considerations that could apply across all areas that should be considered alongside any proposals for capital investment. These considerations were seen to be enabling or supporting capabilities in the IB area as investment in capital assets alone was seen as being potentially counter-productive.

These broader considerations included:

Supporting and retaining expertise and competence: *A major recurring point of discussion was the importance of the skills and know-how of the staff operating the facilities and equipment, and the efficient assessment and project management of IB programs through a staged process of development towards commercialisation. It was recognised that such competence took significant time to build – generally through 'learning by doing' – particularly during scale-up. This knowledge could be lost or diluted as contracts ended or start-up funding ceased. A strong conclusion from discussions on this subject was that deployment of new capital equipment would have limited impact without ongoing support to retain the staff competence and capability to use it effectively.*

Integrated capabilities*: the favoured model with many of the delegates was some form of centre-based arrangement where complementary assets (or complete process chains) could be deployed or integrated in a co-ordinated fashion. A number of different methods of deployment were discussed including 'hub and spoke' for linking clusters of technology/capabilities, and 'all under one roof' arrangements. The importance of 'integration' at various points was stressed, i.e. integration of technology as well as disciplines and capabilities (e.g. biology, chemistry, engineering, modelling, analytical, etc.), and integration with the needs of the commercial end-users.*

Process and economic modelling: *Another supporting and underpinning capability highlighted was access to flexible process and economic models to ensure that early stage processes could be properly characterised and understood. This capability would also deliver* *a robust set of economics that would underpin (or otherwise) any business case for commercial development.*

Analytical capabilities: *Access to good analysis was highlighted by a number of delegates. The type of analysis varied depending upon type of technology and stage of development. For some, analytical facilities should be sited within an integrated centre setting – for others access through a co-ordinated hub and spoke model was sufficient.*

Regional funding issues: *A number of delegates highlighted that, whilst regional or other funding mechanisms had been helpful in establishing pilot facilities, in certain cases it had also become a barrier preventing fully open access. One example was the BEACON biorefinery facility (Aberystwyth University) where the assets could only be used for the purposes of the designated project until 2020. In another case, restrictions were perceived as less critical to access, for example new facilities to be installed at University College London (UCL) at the end of 2014 where the requirement of the RCUK grant was that it be used for Synthetic Biology Applications. This was seen as little or no barrier to access for the majority of IB processes.*

While recognising that the above issues are extremely important when considering any investment being made to deliver strategic and long-term impacts, the key aim in commissioning this work, and the underpinning actions undertaken, was to specifically identify priority areas for capital equipment investment and outline the supporting cases. This does not extend to evaluation of the specific skill, knowledge and other capability needs required to deliver the desired outcomes, nor does it seek to identify in detail how equipment provision and distribution might be best realised to deliver the greatest impact. This project is therefore somewhat limited in its scope and focus. However, taking account of the above issues, reference to the need for co-ordination and to utilise existing centres with supporting capabilities is made where relevant to help support the investment cases.

5.3 Capability requirements in identified key areas

5.3.1 Algal culture and processing

The current global market for products from microalgae is valued at >$1 billion pa (2012), mainly covering applications in the high-value pharma and nutraceuticals sectors. Future moves towards algal biorefineries, incorporating large scale culture and processing, will enable access to large scale markets in the food, animal feed and bioenergy sectors. However, at this stage there are major challenges in both the design of large-scale culture systems and in biomass harvesting where scale-up and demonstration is required.

In further discussion, the group focussing on algal biotechnology identified the potential opportunities for algal culture systems as: carbon capture, production of high value chemicals and waste water treatment. Exploitation in this area required access to large-scale algal collections including marine microalgae, integration of culture systems with downstream product extraction, access to pre-pilot, pilot and demonstration scale facilities.

It was noted that integrated R&D centres already exist, some with 'all in one' facilities (e.g. CalCAB, San Diego, USA and AlgaePARC, Wageningen, Netherlands) and others as specific integrating projects (e.g. EnAlgae and PUFAChain, Europe). Although some UK groups participate in international networks, access to an integrated national facility was considered to be essential if the UK were to avoid falling behind. A proposal for an open access integrated Research Centre (CAPRI, Swansea) was presented and discussed. In this example it would act as a platform for research and development and industrial collaboration, providing pathways to commercialisation of algal culture systems for bioproducts ranging from high value chemicals (e.g. omega-3-polyunsaturated fatty acids) to biofuels. The Centre would use a Fraunhofer funding model (some underpinning 'core' State funding with the bulk provided via public or commercial contracts) and would house facilities from pre-pilot through to demonstration scale. A particular requirement for investment in pilot (1,000L) and demonstration (>10,000L) facilities was identified, with an estimated cost of approximately £7M.

The relevance of developing such facilities in the UK was questioned, given that many of the down-stream commercial applications of phototrophic systems would be outside the UK in areas with higher incident light radiation levels. While this was acknowledged, there were seen to be opportunities for the UK to capitalise on the innovation aspects and income derived from royalty and IP revenues, as well as opportunities for UK exploitation of low volume, high value markets through autotrophic production systems. In addition, there were seen to be key opportunities in the power sector looking to sequester carbon using surplus power to drive energy-efficient LED algal systems and in waste-water treatment applications.

Interim findings from workshop and discussions

- The UK has significant research, and emerging commercial activity in the area but this is distributed across a number of groups in different locations. Targeted investment could provide the required focus for R&D and commercialisation of algal technology and products.
- There is a lack of large-scale scale-up and harvesting capability in the UK which if co-located or coordinated with existing smaller scale facilities and algal expertise could provide the focus referred to above
- Given the relatively low levels of incident radiation in the UK, the best prospects for UK exploitation are in serving high value product markets (though phototrophic or autotrophic routes) utilising UK expertise in strain development and metabolic manipulation to deliver tailored algal chassis developments
- Capital investment in equipment to support wastewater treatment and carbon sequestration applications could provide additional opportunities for UK development and exploitation, but these are currently less well defined.

5.3.2 Biocatalysis

Biocatalysis is a well-established part of the synthetic organic chemistry toolkit, although currently its use is somewhat restricted since many enzymes exhibit narrow substrate specificity or limited stability. Commercial applications have been developed, particularly in fine chemical synthesis with examples at scales >1,000 tonnes p.a., usually as a single biocatalytic step within a multi-step process. The value of the global speciality enzyme market is forecast to grow to $4.7 billion by 2018, driven by therapeutic applications and advancements in enzyme engineering. It therefore represents an area of significant commercial growth potential.

The biocatalysis focus group highlighted that the key need was to integrate existing capabilities within academic groups, where much of the required early-stage scale-up equipment already resides. The group proposed that this could be best achieved through a coordinating Centre based on a 'hub and spoke' model. A centralised facility focussing on process integration of biocatalysis, continuous processing and solvent handling, supported by high-end analytical facilities, would provide an interface between end-users (primarily commercial) and existing centres of expertise (academic), with the ultimate aim of returning advanced manufacturing in the chemical sector to the UK. Emerging technologies such as continuous flow biocatalysis and development of integrated 'one pot' processes combining chemical and biocatalytic reactions were highlighted as examples of focal points.

There was some articulation of a requirement for capital investment in some limited facilities at the larger pre-pilot (c. 50 L) and demonstration (c. 1,000L costing ca. £10m) scales, with particular focus on biocatalysis in non-aqueous systems. However, it was thought that this requirement was currently being met adequately through the existing commercial framework of large and small contract manufacturing organisations.

Interim findings from workshop and discussions

- There appears to be adequate provision of capital equipment at pilot scale with larger scale needs addressed by the private sector.
- Access to larger pilot-scale equipment could be delivered with a distributed 'hub and spoke' model providing access to a consortium of UK partners.
- This sector provides an opportunity to return high value manufacturing to the UK, particularly in the area of fine chemicals and intermediates for pharmaceuticals and agrochemicals.

5.3.3 C1 gas fermentation

C1 gas fermentation is a nascent but growing technology area that involves the bioconversion of C1 gases into higher value products using a variety of engineered microorganisms. The economics of these routes will ultimately determine their commercial success, and, as production costs are largely dominated by input feedstock costs, the use of low cost C1 gases such as syngas (CO, CO_2 and H_2), methane, and industrial flue gases, is expected to deliver overall economic competitiveness and drive market share. The preliminary commercial focus for technology developers in this area has been conversion into biofuels such as ethanol (e.g. Ineos Bio, Lanzatech, and Coskata), but increasingly interest has shifted to important bulk and intermediate chemicals such as butanediol, butadiene, tetrahydrofurans and many others. The global bulk and intermediate chemical market is worth >$1 trillion per annum and these chemical building blocks are incorporated into a vast array of consumer products including rubber tyres, polymers, paints and coatings, textiles, solvents and a variety of household items. As an example, the current market projections for 1,4-butanediol and for butadiene are estimated to be worth $6bn and $28bn respectively by 2018 and the downstream markets for their derivatives are worth many $100 billion.

The delegates highlighted that this area represented a great opportunity for the UK and that significant partnerships already existed with some of the leading global technology developers in this area (e.g. CPI with INVISTA, Lanzatech and Nottingham University). The UK also has one of the world's most highly regarded academic groups in this area led by Professor Nigel Minton at the University of Nottingham. The delegates recognised that there was an unparalleled opportunity for the UK to build on its current position and establish world-leading expertise in both the development of C1 gas fermentation technologies and provide leadership in the key area of microbial chassis development, synthetic biology tools, scale-up and technology integration to deliver market ready solutions. When asked to quantify the UK/Overseas companies likely to need access to scale-up facilities in the next few years, the numbers were low (n=5) reflecting the early stage of the technology.

The delegates outlined how C1 gases could be obtained from a wide variety of UK fossil and renewable sources such as steel waste flue gases (e.g. TATA Steel), reformed natural/shale gas, coal (e.g. Drax), gasification of agricultural residues and municipal waste (e.g. Solena Fuels). The availability and flexibility of feedstocks to feed C1 gas fermentation processes was recognised as a significant advantage versus other approaches to bulk and intermediate chemicals particularly in a UK setting.

The delegates cautioned that whilst we currently have a foothold in this emerging area, our development capability beyond lab scale is extremely limited with no open-access gas fermentation systems above 10L, and very few at 1L scale. If the UK is to expand its know-how and capability, then an expansion of lab, pilot and demonstration facilities will need to be deployed and appropriately supported. Given that this is an emerging technology with high risks to any commercial investment the delegates pointed to the need for an effective risk mitigation strategy during the research and development phases.

Interim findings from workshop and discussions

- This is a nascent sector that could be a rewarding but currently represents a risky area for commercial investment.

- Commercial opportunity could be large - driven by lower costs of production.
- Limited number of lab scale facilities in the UK and no facilities above 10L.
- Working with CO and H_2 is hazardous due to explosion risk – bespoke lab/facility design required.
- Key working relationships with commercial global leaders already established.
- World leading academic group in Nottingham University.

5.3.4 Fermentation from cellulosic biomass

Globally, cellulosic biomass is potentially one of the most plentiful sources of renewable feedstock for conversion into energy, fuels and chemicals. But commercial exploitation is at an early phase. Cellulosic biomass can be processed in a number of ways to deliver a sugar stream that can be fermented to valuable products using a wide assortment of engineered or improved microorganisms. Over the last decade, considerable effort and investment has been dedicated to developing a variety of novel conversion technologies to produce fuels such as bioethanol and biobutanol, and recently to more value-added products such as bulk and intermediate chemicals, drop-in aviation fuels, cosmetics and fragrances. To date, the commercial deployment of such technologies has been slow due to a number of factors including supply chain logistics, a range of techno-economic factors including the difficulty and expense of converting biomass into fermentable sugars, and access to capital to fund new plants.

When asked to identify needs at an institutional and national level, there were a number of clear themes outlined:

At the institutional level, where initial funding for facilities had been through grants, there were concerns about the future once the period of grant support had expired. In particular, the retention of operational staff and associated know-how was highlighted as an issue. There was also consensus that, after some years of operational experience, a broadening of capability was essential. For example, through adding upstream or downstream processing units or supporting capabilities such as specific analytical functions and provision for process and economic modelling. This would enable a better sense of the overall economics and commercial potential of a new technology.

At the national level, the group felt that a national centre acting in collaboration with other smaller facilities was essential. This would facilitate building and retention of core capabilities and help to support groups operating on the academia/industry boundary with limited ability to scale-up beyond bench or pilot scale.

The delegates commented that sources of cellulosic biomass could be quite diverse. In the UK, promising sources of biomass included wheat straw, forest harvest residues, green waste and MSW. Macroalgae (seaweeds) could also become an important feedstock resource.

Delegates highlighted that different feedstocks often needed a different, tailored approach to pre-processing. An integrated bespoke approach that takes account of the supply chain, conversion technologies, product separation and waste handling is essential to assess the overall economics, and commercial viability. This supports the need for flexibility in equipment provision and plant operation to ensure optimum utilisation of facilities focussing on scale-up for potentially bulk markets.

The delegates discussed how significant know-how and resources were required to assemble the necessary infrastructure and the critical mass of capability to be able to develop and validate these bespoke processes in order to demonstrate the robust performance and economics that facilitate commercial deployment.

The delegates outlined the major steps in cellulosic biorefining, including feedstock handling, pre-treatment, enzyme hydrolysis, fermentation and downstream processing and pointed out that there are technical issues associated with each particularly when working at scale. The asset register indicates that whilst there is a reasonable level of fermentation and downstream processing capacity at larger scale, there is a much smaller level of upstream processing capability such as biomass handling, pre-treatment and enzyme hydrolysis (or similar) at large pilot or demonstration scale. This would present a significant barrier to commercialising processes in this sector.

As examples, Croda and ReBio possess large scale fermentation assets, and in the case of ReBio cellulosic biomass processing facilities that are unmatched in the UK and that could currently be accessed by those looking to exploit cellulosic feedstocks, although these are at the larger ‘pre-commercial’ end of scale-up facilities.

The delegates noted that there was a rapidly developing UK R&D base in this sector covering all elements of biomass processing and conversion, but without continuing support for, and expansion of, existing process development and scale-up capability this value would soon be lost outside the UK. Whilst it was difficult to accurately quantify the future needs, the delegates indicated that most of the processing capacity that had been established in the UK at CPI, BEACON, IFR and others was in use for the majority of time.

Interim findings from workshop and discussions

- There appears to be adequate provision at the smallest pilot scale for fermentation and modular downstream processing units. Some additional broadening of capability at the pilot scale would facilitate improved assessment of overall economics and commercial potential. However, there was no strong quantitative evidence to support the level of investment required
- There is potential to access spare capacity at large scale (≥10,000L fermentation) at two companies, Croda and ReBio.
- A clear gap in provision of pre-treatment and enzyme hydrolysis at pilot and higher scales was identified.

- The need for a dedicated, co-ordinating facility was supported by workshop delegates to act as an enabling hub in collaboration with smaller institutional facilities and industry.

5.3.5 Biologics

Whilst the definition of biologics can be quite broad, for the purposes of this report it is used to mean the research, development and commercial production of high value biopharmaceuticals, i.e. drug products that are not chemically derived. These biologics are most frequently bioactive proteins or peptides and the sector is broadly recognised as a significant growth area for the UK.

The workshop had few representatives from the biologics sector and therefore this section outlines the main points from a number of calls/discussions with key opinion leaders (KOLs) from this sector.

All of the KOLs pointed out that this is not the first time in recent years that the biologics sector had been through the investment cycle and evaluated for bottlenecks relating to lack of scale-up equipment and facilities. The National Biomanufacturing Centre (NBC) was established following a report in 1999 highlighting the lack of small-scale production facilities for biopharmaceutical companies in the UK. The centre was completed in 2005 using a mixture of funding (e.g. DTI and regional development funds) and Eden Biodesign was awarded the contract to operate the facility based in Speke near Liverpool. The project also had a £2.7m access fund to allow regional and UK SME's to purchase services from the centre. In 2010, Eden Biodesign was bought by Watson Pharmaceuticals (rebranded in 2013 as Actavis Inc.) and now offers entirely commercial services. At the time, the provision of the NBC was controversial, regarded as public subsidisation and anti-competitive by existing commercial contract manufacturing organisations (CMOs).

More recently, the National Biologics Manufacturing Centre has been established as part of the UK government's High Value Manufacturing Catapult and is due to open in spring 2015. The centre based in Darlington, cost £38m and has a remit to support the growth of the biologic's industry in the UK. Some KOL's felt there was still some debate about the specific role of the NBMC.

Given the support over recent years, some KOLs were unsure whether biologics needed to be included in this study as it had 'all been done before'. All KOLs agreed that more steel in the ground (i.e. fixed vessels) was not needed, even in the absence of detail on what the NBMC will deliver.

It was recognised that the early steps for biotech companies requiring small-scale production of biologic drugs for animal or early human trials was still expensive. Some form of subsidisation to access existing Contact Manufacturing Organisations would be helpful, although this route had been examined previously.

Some KOLs felt that the new opportunities for the UK lay with novel manufacturing capabilities, formulation technology, analytical technologies, training and skills, etc. Others felt that more effort should be placed upon bringing academia and innovative industry players together at earlier stages – this would benefit both sides and also ensure that academia was working on tomorrow's problems not today's.

The recently established BioProNET-Network in Bioprocessing (a BBSRC NIBB) facilitates a network in the field of bioprocessing and biologics that brings together academics, industrialists and other special interest groups with the aim of accelerating innovation, ensuring research is industrially relevant and providing a focus for collaborations. This should address some of the issues raised around encouraging and facilitating collaborations and provide strategic leadership.

The production model for biologics has shifted over the last decade towards small-scale single use bag-systems that are easier and cheaper to operate within a regulated (cGMP) environment required by the pharmaceutical sector.

Interim findings from workshop and discussions

- The development of small-scale manufacturing facilities for biologics has been trialed before and resulted in commercial exploitation of this opportunity.
- Further support for UK biologics sector will be established through the new NBMC at CPI.
- The production model for biologics is shifting towards single use systems and continuous processing – there is no clear need for further investment in scale-up equipment.
- Networking actions should be facilitated through the activities of BioProNET

5.3.6 High value extractives

Extraction of high value chemicals involves processing a wide range of feedstocks, including agricultural crops and waste materials, and requires access to an equally wide range of processing and extraction technologies. Integration of these technologies with feedstock pre-treatment is essential, ideally in a facility with 'plug and play' capability and space for commercial development. Many of the required facilities are available at pilot scale at the BEACON biorefinery (Aberystwyth University), together with equipment for pre-processing of wet biomass.

The Biorenewables Development Centre at the University of York focuses on the extraction of high value products from plants and has a wide range of scale-up and demonstration equipment. Development of a manufacturing process involves selection of preferred equipment for a cost effective manufacturing process, identification of scale-up parameters and an understanding of critical operating parameters for full scale operation. Initial pilot rig work at 10-100L scale is most appropriate for initial evaluation, and access to at-line or on-line process analytical technologies is critical. Further investment in equipment for both biomass extraction and downstream processing is necessary to develop a wider range of capabilities in these areas. Also, it was suggested that development of processes for extraction of specific products need to be accompanied by development of plants as synthetic factories through application of plant breeding and synthetic biology approaches.

Interim findings from workshop and discussions

- Key need for upstream processing facilities and access to analytical monitoring to support development
- No clear case for further investment in scale-up equipment was made, but there was a demonstrated need for a coordinating focus on development of pilot scale plug and play systems to provide versatility to deal with range of feedstocks and deliver early indications of commercial viability. Such coordinating actions would fall into the remit of the High Value Chemicals from Plants NIBB led by the University of York and the John Innes Centre

5.3.7 Anaerobic digestion

Anaerobic digestion (AD) is well established in the commercial sector in the water industry and for treatment of agricultural and food wastes, with many facilities operating at large scale, processing >10,000 dry tonnes of material per year.

AD research facilities at pilot scale are already available within a number of organisations. For example, Cranfield University has recently installed an open access 'plug and play' facility at 1,000 L scale, funded by ERDF principally to support SMEs in the East of England region. Also, the Biorenewables Development Centre (BDC) at the University of York has an integrated facility for small-scale (30L) trials, with comprehensive analytical support available. Through access to EDRF funding the BDC provides support principally to SMEs from the Yorkshire and Humberside region. The CPI also hosts the Anaerobic Digestion Development Centre, designed to support tailored AD process development, through provision of flexible equipment configurations. From discussions it appears that such equipment is well used and the long retention times means that gaining rapid access can be difficult, particularly where research facilities are running internal projects.

Key interests suggest that further investment will be required to develop 'next generation' facilities and processes, initially at pre-pilot scale (<100L) to allow cost-effective process and feedstock development before moving to larger pilot scale facilities. Also, facilities that allow greater levels of upstream characterisation of feedstocks and downstream analysis of AD products would identify possibilities for pre-AD extraction of higher-value products and recovery of volatiles (e.g. fatty acids), resulting in added value from the AD process.

Interim findings from workshop and discussions

- AD is well-established in the commercial sector and there is substantial investment in and benefit from this technology in the UK.
- Any investment should be directed at small scale (<100L) systems which would provide for cost-effective evaluation of next generation processes before moving to pilot and large scale demonstration facilities.
- Pre-pilot is an appropriate stage and scale for initial work on feedstock pre-processing and its development.
- Improvements in the efficiency of AD processes will also potentially require understanding and optimisation of microbial systems. This in turn requires analytical support and capability in DNA/RNA sequencing and 'omics'.

5.4 Conclusions from the workshop

The aim of the workshop was to identify priorities and needs to encourage scale-up in the IB sector to provide a focus for development of more considered cases for targeting capital equipment investment.

The workshop exercise demonstrated broadly that where technologies and processes were established, the key investment requirement was for actions to

a) provide relatively small investments to increase or expand the scope and flexibility of existing capabilities, and

b) support actions to encourage retention of key skills in vulnerable areas

In the latter case, existing support for co-ordinating actions (e.g. BBSRC NIBBs) to encourage greater networking and interaction with industry could help increase project revenues and utilisation of facilities which could help support staff retention.

In situations where the business opportunity was clear and there was deemed to be significant ongoing development to support revenues, the commercial sector has stepped-in to provide large-scale pilot and pre-commercial facilities (as seen in the biologics and biocatalysis sectors). This leaves technologies at the earliest development and pre-commercial stage, representing high-risk investments, as the ones that need specific help in supporting scale-up actions..

The strongest cases made in the workshop for investment in equipment were for the following areas:

C1 fermentation

- Offers a significant market opportunity for the UK but currently regarded as commercially risky.
- Current development capability beyond lab scale is extremely limited.

- Bespoke laboratory design is required along with skilled staff, even at relatively small scale (not easy to retrofit).
- Key priorities were identified as small-scale 'proof of concept' facilities given the associated health and safety issues of working with potentially explosive gasses.

High-value chemicals from micro algae

- Opportunities for the UK in the sector.
- Needs investment in large-scale production and harvesting systems.
- Need to provide a focus to facilitate the integration of dispersed resources between existing centres and to link with supporting specialisms to add to competence.

Areas where there were weaker arguments for significant capital investment, but a role for smaller investments to expand and maintain capability included:

Fermentation from cellulosic biomass

- Investment to enhance and expand upstream and downstream processing and analytical facilities.
- Need to provide mechanisms to retain staff competence – potentially through networking and co-ordinating actions.

High value extractives

- A need for investment in bespoke pieces of equipment to support sector development and increase the versatility of existing centres.

Areas where there were weaker arguments for significant capital investment, but a role for co-ordination actions included;

Biocatalysis

- No clear case for public investment and support for scale-up made as the business opportunity is clearly recognised and currently being exploited by commercial companies. Issues affecting the development of other IB processes that biocatalysis supports are more likely to hamper development.
- May be a need for investment in novel production processes. However, this is more likely to be addressed as research at relevant research scales.

Biologics

- No clear need for investment in scale-up equipment identified.
- Development moving towards small scale, single use facilities to meet high quality requirements of end markets (pharmaceutical).

- Support for co-ordination actions articulated, but existing initiatives should address this need.

Anaerobic Digestion

- No clear case for significant investment in scale-up facilities.
- Need for research at relatively small pilot scale to examine how efficiency of processes might be improved through manipulation or enhancements etc., but much of this will be could be supported through existing research funding mechanisms.
- There is a need to coordinate to develop competency and skills to support existing scale-up facilities. Again existing mechanisms such as the BBSRC-supported Anaerobic Digestion Network (ADNet) should support such actions.

6 Cases for investment in IB scale-up facilities

6.1 Introduction

During the process of engagement with stakeholders, it quickly became clear that investment in equipment without investment in the people and the know-how to run it effectively, i.e. the capability, would be counter-productive to the overall goal of the project – to enable transition of IB processes to the market. Further, there were important strategic areas where scale-up equipment existed and know-how had been established but, risks that this know-how could be eroded and/or the capability lost for example where projects come to an end and funding ceases.

In preparing the investment cases information was drawn from the asset register, interviews with key asset 'owners' the stakeholder workshop and from follow-up discussions with key stakeholders. The cases also draw on the project team and stakeholder sector knowledge of the scales of the opportunities available, technology readiness and knowledge of current business activity in the sector. The cases reflect the strong message from stakeholders in the sector that it is capability rather than large-scale equipment that is key and so the investment cases look to add to existing capability or to expand and/or consolidate it where it already exists. Where possible estimates of the likely scale of investment required to establish and support proposed facilities are provided.

The conclusions fall into three major categories:

A recommendation to invest in pilot facilities in key areas that will support the development of new, or provide significant enhancement to currently constrained UK competence.

This relates two emerging areas in IB.

- C1 gas fermentation
- High value products from microalgae

A recommendation to invest at a more modest level in equipment to maintain or expand specific areas that will retain, complement and/or build upon existing competence.

This relates to:

- Fermentation from cellulosic feedstocks
- High value extractives

And finally;

Other strategic areas where major intervention could not be justified under the remit of this study and/or where sector development needs could be met by funding under existing research and development mechanisms.

This relates to:

- Biologics
- Anaerobic digestion
- Biocatalysis

The rationale for these propositions are outlined in this section.

6.2 Investment to develop new capabilities

There are two strategic areas, C1 gas fermentation and high value products from microalgae, where investment could have a major impact at a national and international level and where early public support could deliver potentially large benefits to the knowledge base and to the UK bioeconomy. Both of these areas share a number of broad characteristics:

They are relatively new areas in the IB sector where technology breakthroughs could deliver significant academic and commercial opportunities.

Both strategic areas have early stage companies looking to commercialise technology but to date there has been no extensive commercial roll-out. Neither area has seen significant investment on a national scale in the UK. Both areas have world-leading academic expertise in the UK. Finally, both represent risky investments and therefore justify support at the national level as funding from other mechanisms might be difficult to secure.

In both of these IB areas, there is a need to

- Provide access to scale-up equipment at relevant pre-commercial scales of operation.
- Provide a focus for research and development activities (to encourage academic involvement, inform research direction and promote collaboration).
- Provide a focus for industry both nationally and internationally to encourage engagement and development.

- Bring together complementary supporting disciplines, (e.g. systems biology; synthetic biology; chemical and process engineering; and process and economic modelling) in a fully integrated fashion to work on the specific problems affecting each sector.
- Provide a focus for sector training and skills development.
- Build staff capability and retain this capability and know-how to deliver the important relationships required to stimulate industrial development.

Delivering such a diverse range of needs could be done through measures to encourage the establishment of centres of competence. These could build on core investments in relevant scale-up equipment to provide the focus for other developments and interventions. This focus would provide the leadership and clarity of vision to deliver strategies for growth in their respective sectors together with the supporting cutting-edge physical assets for technology development. Development of the associated staff knowledge and expertise and interaction with industry would ensure there was an understanding of both current and future industrial challenges to ensure appropriate evolution and development to meet the sector needs.

6.2.1 Investment case 1: C1 gas fermentation

The strategic case

C1 gas fermentation is a new and growing area of renewable technology that uses a range of improved or specifically engineered microorganisms to convert low cost waste gases such as methane, syngas, carbon monoxide and CO_2 into higher value products. Potential sources of C1 gases are extensive and include waste gases from industrial processes e.g. steel mills, oil refineries, and natural gas extraction. Methane can also be obtained in large quantities from landfill sites and anaerobic digestion. In addition, most cellulosic waste, including the organic fraction of municipal solid waste (MSW) can be converted into syngas using existing gasification technology. It is this feedstock flexibility and availability together with the potential for delivering low cost products that makes this technology attractive - particularly in the UK setting.

The microbes used in these fermentations have been difficult to culture and genetically engineer, but with modern synthetic biology approaches these microbes have become more tractable and can be genetically and metabolically engineered relatively quickly to produce an increasingly wide range of valuable products. The UK has one of the world leading academic groups in this field - Professor Nigel Minton at the University of Nottingham. Recently, the BBSRC established a Network in Industrial Biotechnology and Bioenergy (C1NET NIBB) under the leadership of Professor Minton and Professor Fell (Oxford Brookes) to catalyse the engagement of academic, institutional and industrial stakeholders and stimulate further understanding and collaborative research in this area. The BBSRC NIBB is active and currently has almost 200 members with more than 40 from industry.

We have world leading expertise in the UK and significant R&D collaborations with major industrial partners such as the collaboration between CPI, Invista, Nottingham University and Lanzatech for the production of renewably sourced chemical intermediates for nylon manufacture. The UK is actively engaged in the initial growth and exemplification of this new discipline and, with support, could develop and maintain global leadership in the technology development and process integration within this sector. Commercial and pre-commercial plants are currently being constructed and the market uptake of fuels and chemicals produced by this route will be driven strongly by the favourable economics.

The utilization of waste gases by fermentation is very much in line with EU and UK policy on a number of levels including advanced technology development[5] utilising key technologies such as synthetic biology[6]. The potential to improve the environmental performance across a range of industries is significant including those traditional industries using coal or gas. It also addresses efficient resource management and waste reduction[7] for example by diverting waste from landfill and using it instead for the production of useful chemicals and creating a strong exemplar of the circular economy in the UK. In addition, it does not impact food supply or require large land use changes and the logistics are more straightforward than many other approaches to renewable fuels and chemicals.

The UK's chemical sector has an annual turnover of £60 billion and is the largest manufacturing contributor to the national balance of payments[8]. Development of UK competence in gas fermentation could help catalyse the next wave of inward investment in this sector and stimulate the innovation that will ensure global competitiveness for the UK's chemical industry.

Currently there are only a small number of companies operating in this IB sector and they are at various stages in the development and commercialisation cycle (Table 7). This is a reflection of both the relative newness of the sector and also of the many technical and economic barriers that still need to be resolved for these technologies to be commercially successful. These barriers however also provide significant opportunities for the UK research base and for the development of significant commercially focussed collaborative R&D projects.

Initial commercial efforts in C1 gas fermentation have been directed towards the production of biofuels such as bioethanol and more recently towards the production of bulk and intermediate chemicals such as butanediol (BDO), 1,3-butadiene and a range of C2 to C6 commodity chemicals. The economics of these routes will ultimately determine their commercial success and, as production costs are largely dominated by feedstock costs, the

[5] Policy Exchange (2013). Eight Great Technologies
[6] Research Councils UK (2011). A Synthetic Biology Roadmap for the UK.
[7] EU Waste Framework Directive and the various devolved policies in the UK
[8] Chemistry Growth Strategy Group (2013). Strategy for Delivering Chemistry-Fuelled Growth of the UK Economy

use of ultra-low cost C1 gases is expected to deliver overall economic competitiveness and drive market share.

Table 7. Example companies commercialising fermentation processes for C1 gases

Company	Processes/Products	Status
Ineos Bio	Gasification of cellulosic waste to produce syngas, then fermentation to bioethanol	8 MGPY bioethanol plant in Florida, USA
Lanzatech	Steel mill flue gases (carbon monoxide) or other C1 gases to bioethanol and a variety of C2 to C5 intermediate chemicals	Pre-commercial (100k GPY) plants in China. US commercial plants (up to 30MGPY) planned for 2015. Many commercial partners including Virgin Atlantic (for aviation fuels).
Coskata	Gasified biomass, natural gas or steel mill flue gases to bioethanol and chemical intermediates up to C6	Pilot facility and a demo scale plant in the US
Calysta	Methane to plastics and protein	Commercialised for animal feed (bioprotein) in Norway. Research phase for lactic acid in the US
BioSyntha	C1 gases to bulk and intermediate chemicals such as BDO to renewable rubber	Research phase UK SME, lab scale
Genomatica	CO and methanol to various products	Agreement with Waste Management to develop chemicals from syngas derived from MSW
Evonik	Specialty chemicals from syngas	Large German specialty chemicals company. Syngas program in research phase

The biofuels and commodity chemicals are large ($ trillion) global markets and a successful commercial outcome in any of these either as a producer, technology developer or through IP licensing would yield significant economic benefits for the UK bioeconomy. As examples, butanediol and butadiene, two important chemical building blocks, have markets estimated to be worth $6 billion and $32 billion respectively by 2018. The market for their downstream products such as polyester, rubber tyres, textiles, paints and coatings, cosmetics, and solvents is worth many $100 billions[9].

Lanzatech have evaluated the opportunity to utilise the flue gases from UK steel mills and coke processing plants for conversion to biofuel and concluded that more than 1.9 million tonnes (650 million gallons) of bioethanol could be produced[10]. Lanzatech and Virgin Atlantic have estimated that their technology can take the waste gases from up to 65% of the world's steel mills and convert that into up to 19% of the world's jet fuel[11].

Calysta are currently commercialising gas fermentation from methane to produce plastics, bio protein and a range of valuable chemicals. Defra reported (2011) that nearly 300 million tonnes of methane were produced each year from the UK's industrial facilities including landfill and the energy sector[12].

The size of the business opportunity is substantial and many more companies can be expected to enter this growing sector. There is growing interest & market pull from chemical companies to adopt renewable technologies[13] and there is also active interest from companies who produce waste gas from their industrial processes and wish to divert this to more economically and environmentally attractive alternatives (so-called 'feedstock push').

Investment case

C1 gas fermentation is rightly regarded as one of the hottest areas in the IB sector with the capability to access some of the largest global markets for fuels and chemicals. The UK has some of the best academics and is also engaged with some of the most advanced industrial players. The UK is clearly working at the leading edge but despite this unique opportunity the fermentation and process development capability is extremely limited and currently only exists at small (lab) scale. The largest open access reactor is 10L and most of the gas fermentation capability operates at 1L or less. Therefore we do not currently have the assets to transition our know-how to pilot and demonstration scale. This will mean that, as the technology develops and multiple processes and products head towards market, we will not be able to play our part and build upon our current advantages. This opportunity will inevitably go overseas.

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[9] Transparency Market Research, "Butanediol (1,4-BDO), 1,3-butadiene and MEK Market: Applications (THF, PU, PBT, SBR, ABS, NBR, etc.), Bio-based Alternatives, Downstream Potential Market Size and Forecast 2010-2018".
[10] House of Lords Science and Technology Select Committee. Waste or Resource? Stimulating a bioeconomy (2014)
[11] House of Lords Science and Technology Select Committee. Waste or Resource? Stimulating a bioeconomy (2014)
[12] House of Lords Science and Technology Select Committee. Waste or Resource? Stimulating a bioeconomy (2014)
[13] ICIS Special Report: Sustainability Survey, Sept 2014.

Any facility offering competence in C1 gases would need to be open-access, agile, flexible and modular. It will need multi-feedstock capabilities and the ability to model and test various sources of C1 gases right through the process to products. It will need gasification and syngas clean-up systems as these upstream elements are known to strongly impact the fermentation and downstream process. It should be able to demonstrate the end-to-end process clearly and to collect and analyse the data to produce robust datasets suitable for underpinning industry investment decisions.

Staff resources will be required in addition to supporting the provision of equipment, to provide supporting capabilities such as online and offline analysis and chemical and bioprocess engineering. Expertise in operation of process and economic modelling is also required to understand the commercial viability of process concepts at the earliest possible stages of development and to provide tools to better direct research efforts.

Support should also be provided for associated business engagement activities, supporting early stage companies with guidance and incubator space where appropriate and providing a managed framework for assessing and steering projects through the technology readiness levels and accelerating the path to market.

An important point to note is that C1 gas fermentation technology is unlike typical microbial fermentation processes in that it requires specialist facilities and equipment. The fermenters may need bespoke designs to improve gas transfer especially as the scale increases. The fermentation processes are generally run strictly anaerobically and the nature of the gases used (e.g. carbon monoxide and hydrogen) present a significant explosion risk especially at scale. This may also be the case for some of the products (e.g. 1,3-butadiene). This is not therefore a technology that can simply be plugged in and switched on in the same way as typical microbial fermentations. Small-scale facilities cannot easily be distributed across the country. As this is a new technology and an area of significant interest, there will clearly be academic groups and SME's interested to test their strains and novel process concepts at early levels of development and will need access at the small lab scale (i.e. 1L to 10L).

For these reasons development of new competence could happen in a number of ways as the scale of operation is currently so small. The new competence could be developed as part of, or as an extension to, an existing national centre (e.g. NIBF at CPI) situated close to feedstock and/or product end users, or as an expansion of an institute or academic Centre of Excellence. The former would be more appropriate to develop capacity up to pre-commercial scale whereas the latter might be suited for a higher throughput facility operating at lab and small pilot scale (<100L).

An integrated centre of competence for C1 gas fermentation might be expected to cost up to £60m if it is to include a fully integrated pre-commercial demonstration unit. If the operational scale was limited to large pilot scale (circa 500L) then the costs may be reduced significantly (circa. £20m). These costs include facilities, capital equipment and running costs for a five-year period[14]. This is necessarily an approximation based on similar centres in the UK – it is provided as a guide primarily to the order of magnitude and is not based upon a detailed cost breakdown. Clearly proposals for such developments would need to present their own figures with suitable justification.

Revenues in later years could also come from IP licensing and royalties, allowing reinvestment to broaden and strengthen capability. A dedicated facility could provide direct highly skilled jobs for circa 50 to 75 staff and might be expected to engage with 25 to 50 academic or industrial collaborators each year.

Given the early technology development stage of this sector, a strong risk management strategy would need to be adopted to properly evaluate new collaborative opportunities and provide a robust framework for technical progression (stage-gating), monitoring and support.

The timeline horizon for industrial partners in this sector is generally short and therefore quick and effective access will be required in order to gain early commercial traction. Understanding these timelines and business drivers will be essential and require an agile and flexible set-up in order to respond effectively.

Investment in scale-up equipment as part of a range of measures to facilitate the development of national competence for C1 Gas Fermentation would be timely and provide significant benefits at a number of levels:

- Maintain a global leadership position in a nascent IB technology area.
- Potential to deliver significant commercial opportunities in partnership with industry in some of the largest global markets (biofuels and chemicals).
- Deliver significant environmental and waste management benefits and align with the UK and EU policy in these areas.
- Significant opportunities for first class science and engineering to work in an integrated and applied fashion to deliver meaningful commercial outcomes.

[14] Direct public funding: £20m to £60m over 5 years (based on similar centres). Includes capital equipment of £5m to £20m dependent upon scale, Industrial contribution: £10m to £30m in revenue over 5 years, Grant funded activities: up to £5m in revenue over the first 5 years.

6.2.2 Investment case 2: high value products from microalgae

The strategic case

The commercial large-scale culture of CO_2–fixing, phototrophic microalgae has been established over the last 30 years, using open ponds in areas of high solar radiation and more recently using enclosed systems with either solar or artificial illumination. Markets have been established for the associated high value products in the vitamins, health food (nutraceuticals) and cosmetics sectors, and in the aquaculture and animal feed sectors. The market value for the nutraceuticals sector is projected to reach $207 billion by 2017[15] with many opportunities for growth from microalgal products which are currently estimated at >$5 billion pa[16] including $2.5 billion from the health food sector and $1.5 billion from the production of the omega-3 fatty acid docosahexaenioc acid (DHA).

Recently, with the development of more effective algal synthetic and systems biology tools, metabolic engineering and chassis improvement methodologies, attention has focussed on a wider range of products, e.g. oil production by microalgae as intermediates to biofuels, and the production of bulk, specialty and high value chemicals. The technologies deployed in this area are varied and companies such as Muradel (Australia) and Sapphire Energy (US) use shallow ponds for growth of microalgae, while others, such as Cellana (US) have developed large-scale enclosed photobioreactors. Extracted algal oil ('Green crude') can then be used as a feedstock for conversion to biodiesel and bulk chemicals or converted into hydrocarbons by hydrothermal liquefaction.

An alternative approach, exemplified by DSM-Martek and the US company Solazyme, uses plant-derived sugars as a feedstock for heterotrophic algae grown in the dark in large bioreactors ('indirect photosynthesis'). The initial commercial targets for Solazyme were the renewable energy and transport fuel markets, and the company partnered with Chevron Oil to develop the commercialisation of algal fuels. However, more recently, in partnership with Roquette, it has developed and marketed products for the high value nutrition and cosmetic markets. The company currently operates from lab scale (5-15L), through pilot and demonstration scales to commercial production (>100,000L), with current revenues of approx. $30M pa from product sales.

The use of microalgae for the production of high value products is expanding due to the availability of effective tools, including synbio, to improve algal strains. This is an area where UK innovation and translation from early stage research can have a significant and long-term impact on the sector and deliver economic benefits to the UK bioeconomy.

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[15] 'Nutraceuticals Product Market: Global Market Size, Segment and Country Analysis & Forecasts (2007-2017) Transparency Market Research, Albany, NY

[16] Pulz and Gross (2004) Valuable Products from Biotechnology of Microalgae, Appl. Microbiol. Biotech., 65., 635-48.

The UK has a number of world leading academic research groups working on microalgae (e.g. CSAR, Swansea; UCL; PML; SAMS) and there are innovative UK SMEs such as Algenuity, Aragreen, and AlgaeCytes. There is also a BBSRC NIBB (Phyconet) that aims to develop and broaden interdisciplinary links and industry-academia collaboration, and there is UK participation in several European networks (e.g. GIAVAP - Rothamsted Research, UCL; SPLASH - Cambridge University).

In the main, activity is focused on intensive culture using photobioreactors and fermenters, which is relevant to UK-based operations. It should be noted that novel photobioreactors may be unsuitable as production systems for products in highly regulated environments such as those required for the pharmaceutical industry – instead adaptation of strains to work within standardised tanks or single use systems (e.g. bags or wave bioreactors) would be advantageous. Another important point is that most facilities currently available for microalgal production are unsuitable for use with GM organisms, and there is a clear need for test, pilot and demo scale facilities to meet this need. Innovative UK SME's in this sector are already looking abroad to scale up their processes[17].

A recent BBSRC report[18] concluded that the algal research community remains fragmented and that funding for algal research had worsened over the previous two years, resulting in missed opportunities and the UK increasingly lagging behind other countries, particularly the USA. This led to a series of recommendation to create a national strategy for algae, provide strategic funding for academic Centres of Excellence and establish a Technology Innovation Centre to take step-changing research outputs through to commercial application. Such a pipeline would guarantee high impact from UK algal research and provide direct benefit to the UK and contribute to the establishment of a sustainable bio-based economy. A recent UK Roadmap for Algal Technologies[19] reiterated the urgent need for investment in strategically positioned open access test, pilot and demonstration facilities to prove economic, technological feasibility, environmental sustainability and public acceptability of processes based on microalgae.

Future moves towards algal biorefineries, incorporating large-scale culture and processing, will enable access to attractive global markets in the food, animal feed and bioenergy sectors. Large scale microalgal facilities for production of biofuels and chemical intermediates are at a very early stage in commercial development and have still to demonstrate commercial viability. There are major challenges in both the design of large-scale culture systems and in biomass harvesting. On the other hand, the production of high value speciality materials requires microalgal culture at a relatively small scale using fully contained bioreactors with either photosynthetic (autotrophic), nutrient-fed (heterotrophic), or both (mixotrophic) growth. This makes it particularly suitable for deployment in the UK, as

[17] A. Spicer, CEO Algenuity, Personal Communication

[18] BBSRC Report 2011 'Algal Research in the UK'

[19] NERC-TSB Algal Bioenergy SIG Report 'A UK Roadmap for Algal Technologies' 2013

progress in this field will not be limited by access to feedstocks, large-scale land use or requirements for year round high levels of solar radiation, but by an excellent co-ordinated research base and the development of a supporting innovation infrastructure.

Table 8. Example companies commercialising products from microalgae

Company	Processes/Products	Status
Sapphire Energy	Large scale algal culture in open ponds, algal oil production for refining into 'drop in' replacement transport fuels	Operating in New Mexico (USA) with R&D site at pilot to 10^6L scale and beginning commercial demonstration to produce 'Green Crude' at 100 barrels per day
Cellana	Marine microalgae grown in hybrid open pond/photobioreactor to produce algal oils, protein and biomass for biofuel, nutrition, aquaculture and animal feed markets.	Demonstration facility (Hawaii, USA) operating since 2009. Commercial operations at negotiation stage.
Solazyme	Closed tank fermentation of microalgae using sugar feedstock. Algal strains selected for oil or whole algal products for wide range of industrial and high value products.	Operating pilot and demo scale facilities in USA, producing high value materials for food and speciality markets. Marketing algal protein and lipid products as food ingredients. 5 x 625,000L fermentation tanks operating in Brazil in a JV with Bunge Ltd producing lubricant oils.
DSM-Martek	Producer of high value products in the health food segment including PUFA's such as Omega-3 DHA and Omega-6 arachidonic acid	Fully commercial (US) in a number of location and with sales in excess of $450m (2010)
Algenuity	Modification and development of microalgal strains for SynBio applications. Development of lab scale photobioreactor for exploration of scale up conditions	UK SME. Working at lab scale with various growth systems including its bespoke in-house photobiorector design, but looking for access to pilot-scale GM facilities

Muradel	Marine microalgae grown in seawater open ponds are harvested and subject to hydrothermal liquefaction, yielding hydrocarbons for fractionation into liquid fuels	Demo plant operating in South Australia
Heliae	Offers a package of algal strain selection, production system and DSP equipment to generate high value products (nutrition, therapeutics, health & beauty, agrosciences).	Demo facility in Arizona, USA. Negotiating JVs with Japanese companies to produce carotenoids for aquaculture
New Horizons Global	Omega-3 fatty lipids produced from microalgae for applications including food ingredients, animal feeds and pharmaceuticals.	A Northern Ireland based company with a production site on Merseyside (UK)
Algae Tec	Growth in closed solar bioreactors. Initial products nutraceuticals (Chlorella, β-carotene), longer term focus on biomass generation for biofuels, bioenergy, animal feed markets	R & D facility in NSW, Australia producing nutraceticals, initially at 2000 tonnes/yr. Pilot scale biofuel plant under construction in India funded by Reliance Industrial Holdings.

Investment case

The area with greatest commercial potential for UK-based IB activity appears to be the development and exploitation of microalgae for production of high value materials, such as cosmetic ingredients, nutraceuticals and pharmaceuticals. These are areas where the UK already has existing interests (e.g. companies like Global Horizon) with interests in collaborative development.

In addition, there is potential for the UK to act as a provider of IP and technical expertise in other areas, such as biofuels, commodity chemicals, animal and aquaculture feeds, where exploitation may occur primarily outside the UK.

Algae also represent an important chassis for delivery of synthetic biology outcomes, which will provide a range of potential engineered outcomes where UK expertise could be developed and focussed on avenues of exploitation. Existing or new facilities will need to be brought up to the required standard to work with engineered algal strains.

There could be further opportunities for growth through the integration of microalgal processes with other technologies such as biocatalysis and AD, as well as through processes such as waste water treatment and carbon capture and cycling. The UK also has a national algal culture collection and strength in process economic modelling that should provide further advantage through integration with existing algal expertise.

Current activity and expertise in the growth and exploitation of microalgae in the UK is spread across a number of academic groups and research institutes and, apart from the Phyconet NIBB, and the Algal Bioenergy SIG, there is currently no drive to develop a coordinated approach to technology commercialisation.

One of the key needs is investment to provide the seed capital to provide a focus that can draw together the required critical mass of equipment, knowledge and expertise which can then provide the further stimulus for collation of additional capabilities in synthetic biology, process engineering, process modelling and economics to form a globally-leading competence in high-value products from algae.

Investment is currently required in relevant scale-up equipment and facilities for large scale production and extraction, focussing on high high-value production. With the aim of;

- providing a focus for R&D and industry both nationally and internationally to encourage engagement and development to build on existing expertise
- ensuring there is UK capability and capacity to exploit the benefits of synthetic biology in the algal sector by ensuring facilities are GM compliant
- bringing together complementary supporting disciplines to work on specific problems hampering development - Success requires a multidisciplinary approach, combining biological, chemical and engineering skills working at the academia/industry interface
- providing a focus for sector training and skills development
- building staff capability and ensuring retention of capability and know-how to stimulate industrial development.

The establishment of an integrated national competence could be one means of providing a 'one stop shop' for process development and technology transfer to the commercial sector. The value of this approach has been clearly demonstrated in other countries where it has proved highly successful, for example San Diego Center for Algae Biotechnology, USA; Arizona Center for Algae Technology and Innovation, USA; Algae R&D Centre, Murdoch University, Australia; AlgaePARC, Netherlands.

Facilities should provide open access to research and testing facilities to develop new process steps, combine unit operations and allow pre-market evaluation of new technologies and products. Ideally, such facilities should house a range of equipment for growth and harvesting of microalgae at laboratory (10L) to pre-pilot (100,000L) scale, and include a test bed facility for new equipment. This would cover activities across the microalgae value chain, e.g. strain manipulation and development, growth and harvesting of biomass and product extraction.

An initial investment estimated at £10M would be required to fully equip a dedicated facility, with an estimated build cost of £30M to construct premises designed to accommodate the specialized facilities for growth of microalgae.

6.3 Areas requiring support for consolidation and growth

Two areas were discussed where it was clear that existing UK capability at the academic and institutional level should be improved and/or where the narrow focus of the original assets and capability was limiting the commercial applicability.

As these areas have previously demonstrated their strategic importance, pilot scale equipment already exists which, in the majority of cases, is well utilised. The current assets frequently represent only part of the value chain however and would benefit from a broadening of capability to better enable commercial outcomes. Success requires a fully integrated approach to process development and a detailed understanding of the techno-economic challenges across the value chain.

Facilities should clearly have good capability in high usage core equipment but a bespoke item of equipment may be required for a particular project but which may subsequently have limited future use. This may be a particular issue when working on the scale-up of specialty products such as high value extractives.

There are concerns about the retention of staff (and associated know-how) as projects or other sources of funding end with the strong possibility of talent moving into different areas. It was felt that this growing know-how was fundamental and enabling in the IB space and that this should be protected and nurtured. Capability in these areas is rarely fully developed and typically embedded within a three or four year project window. The majority of expertise in the scaling up of these processes is obtained through 'learning by doing', and thus continuity is important. Overall capability is strongly dependent upon retention of skilled staff and their associated know-how. The rapid timelines required by industry necessitate that the facility staff is already skilled and able to respond quickly and effectively to a new project.

In summary, for both of these investment cases there is a requirement for consolidation (to ensure a focus for industry and academia) and/or expansion of pilot scale facilities to complement that already in place. The aim of such expansion should be to at least maintain or provide an expanded business focus to help retain the developed staff expertise.

6.3.1 Investment case 3: fermentation from cellulosic feedstocks

Cellulosic feedstocks represent the most abundant global source of biomass for conversion to value added products. Sources in the UK include wheat straw, municipal solid waste (MSW), brewery waste (DDGS), high sugar grasses, food waste, woody and other agricultural wastes. Currently, the availability and supply chain logistics make most of these feedstocks challenging to utilise in a biorefinery context with the possible exception of MSW.

Despite huge investment over the last decade, particularly in the US, commercial applications from cellulosic biomass are still limited primarily to low grade heat and electricity generation. The commercial opportunities that have been researched heavily include biofuels, particularly bioethanol from a wide range of biomass sources, and more recently the production of bulk chemicals. The challenges to commercialising technologies in this area are multiple and include:

- Deconstruction of biomass to deliver a cheap fermentable sugar stream
- Integrating the technology steps in an economically viable process
- Feedstock suitability and/or variability
- Supply chain issues
- Capital intensity and access to capital to build commercial plants

Commercial progress in this area has been slower than expected but significant opportunities still exist to deliver economically attractive outcomes. The integration of the biology and the engineering challenges with the overall process economics is fundamental to success.

We have a few excellent pilot facilities in the UK for research and development in this area including BEACON at Aberystwyth University, the Biorefinery Centre at IFR Norwich, the BDC at York, and the National Industrial Biotechnology Facility (NIBF) at CPI, Wilton. Some, like the NIBF and the BDC, are developing more generic approaches to technology platform development, whereas others might be viewed as more specialist, e.g. the Biorefinery Centre working with straw, pilot-scale steam explosion pre-treatment and access to the National Collection of Yeast Cultures. Both approaches are valid as we need breadth and depth of expertise – these are essential complementary sources of enabling know-how.

We also have a number of BBSRC NIBBs that operate in this area, particularly the Lignocellulosic Biorefinery Network (LBNet - Professor Simon McQueen Mason, The University of York, and Professor Tim Bugg, University of Warwick) and the Plants to Products Network (P2PNet - Professor David Leak, University of Bath and Professor Joe Gallagher, IBERS). Both NIBBs boast a broad membership from academia, institutions and industry and are working to boost translational research for the benefit of the UK.

Investment case

Different facilities will have differing needs to sustain and build their capability, but as an example, the asset register indicates that the UK has very few open access biomass pre-treatment and hydrolysis facilities across all scales of development. This is an essential part of the process chain and needs to be integrated with the fermentation and downstream processing steps to give a plausible commercially relevant outcome. In addition, some industrial contributors noted that access to larger scale solvent extraction facilities in the UK was difficult.

The needs in this sector are diverse and provision is required to support relatively small capital bids for pieces of equipment to add flexibility to existing facilities and/or replace equipment at end of useful life. This could for example include grants for purchase of specific biomass processing equipment, or extraction equipment.

Alternatively there may be a need for investment in larger or up-graded facilities to either accommodate expanding equipment provision, often used in parallel or in plug-and-play options that provide the required flexibility in service delivery, or alternatively to provide new or modifications to facilities to comply with health and safety requirements associated with operation of specific pieces of equipment (e.g. to deal with issues around pressurised biomass processing or solvent extraction of products).

Costs in this area are difficult to estimate given the breadth of potential scenarios, different facilities will have their own specific needs to build capability and novelty, but costs are likely to be in the order of £millions per successful application. The support could be in the form of capital grants, but other models are possible leveraging other funding sources (see case study example below for high value extractives)

6.3.2 Investment case 4: high value extractives

Production of high value extractives (HVE) from plants or other sources is an area that is at a relatively early stage of development in terms of its contribution to the UK bioeconomy. Facilities for process development at lab to pre-pilot scale, processing 1-10 kg batches of starting material, are available at the BDC with further facilities at BEACON and CPI. These are used for early stage process development and evaluation in collaborative projects with industry.

Alongside the established centres, the BBSRC-supported High Value Chemicals from Plants NIBB aims to boost interaction between academia and industry in this area. At least one UK company, Advanced Extraction Technology Ltd, is active as a provider of specialist equipment and works in collaboration with academia on the extraction of high value products from waste material.

Development of a commercially viable cost-effective extraction process requires access to a range of process choices at each step in the chain from feedstock handling and preparation, through extraction to product purification, with emphasis on scale matching. This allows selection of tailored equipment taking into consideration factors such as capital cost and flexibility in operation in addition to product yield and purity. Crucially, development of an HVE process is dependent on access to in-house analytical facilities and expertise and also to the space and services to house and trial new process equipment alongside and in combination with existing equipment.

Investment case

Centres focusing on HVEs need to ensure a balance in investment between high usage equipment, in which a good capability is essential, and equipment that is used less frequently. A suggested model would be a facility well equipped with core equipment and capabilities working with clients to acquire specialist or bespoke equipment for specific projects. This model would require fully serviced operational working space to house the equipment within the core facility for the lifetime of the project.

The ultimate UK aim should be to develop flexible, modular biorefineries for conversion of a variety of feedstocks to a range of high value products, and clearly there is potential for integration with other technology areas outlined in this report (e.g. microalgae, fermentation from cellulosic feedstocks).

The needs in this sector are very diverse and facility specific. They are therefore very similar to those for fermentation from cellulosics namely;

- There is a need to support small grant applications for capital equipment that will add flexibility to existing facilities and/or replace equipment at end of useful life.
- There may be a need for investment in larger or up-graded facilities to either accommodate expanding equipment provision or alternatively to provide new or modifications to facilities to comply with health and safety requirements associated with operation of specific pieces of equipment.

Again, costs in this area are difficult to estimate given the breadth of potential scenarios and range of equipment that could be required. Costs are likely to be in the order of a few £100,000 to £millions per successful application. The support could be in the form of capital grants, but other models are possible leveraging other funding sources (see case study example below)

Case study

The Biorenewables Development Centre (BDC) in York recently launched a capital grant scheme which allows clients from SME's to purchase pilot scale equipment up to a value of £50K, which is then part-funded by the grant scheme. The BDC are trialling this scheme with the support of ERDF finance and using an internal grant committee to assess applicant bids.

In running this scheme it has become apparent that SMEs have shown a preference for the BDC itself to host the equipment on behalf of clients, and through this permit integration with other BDC facilities and other business support services.

The BDC hopes to build on this to develop specialist hosted space for SME companies where BDC staff would be on-hand to help run processes. The aim is to develop a 'plug and play' capability to which companies can link their equipment and prove efficacy in an independent test environment.

A number of approaches are being examined to support this concept including: the aforementioned grant scheme approach; provision of low-rent facilities; providing skilled staff at preferential rates to run processes; hosting and training of staff and provision of access to other analytical or business support activities to support commercial development.

6.4 Other strategic areas

Three other areas (biologics, biocatalysis and AD) were explored either in the workshop or in supplementary discussions. The conclusion was that these areas did not currently warrant significant capital equipment investment under the remit of this study, although they may benefit from other funding mechanisms and initiatives to support greater networking and integration.

6.4.1 Biologics

The discussion about potential needs of the biologics sector occurred outside the workshop. There was one defining consensus from all of the Key Opinion Leaders that were interviewed – more steel in the ground was not the answer. Previous investments in the sector (National Biomanufacturing Centre) identified a commercial appetite for investment in such facilities, and further provision will occur from the £38m National Biologics Manufacturing Centre due to fully open in Darlington in 2015.

In addition, the production model for biologics has shifted over the last decade towards single use systems that are easier and cheaper to operate within a regulated (cGMP) environment.

The breakthroughs of the future are likely to lie in developing continuous processing methods, reducing the cost of existing processes, formulation technology, and in different models for distributed manufacturing recognising pandemics and personalised medicine. Much of this is likely to be driven by existing research and development funding routes (e.g. IB Catalyst) and collaborative actions instigated by the BBSRC NIBB's.

The firm conclusion here was that the biologics sector has been looked at before and there is no additional need for large–scale pilot or pre-commercial facilities.

6.4.2 Anaerobic digestion

Anaerobic digestion is a mature technology with widespread application across the UK for waste processing in the farm and food sectors, the water industry and increasingly for municipal waste. Process plant is readily available with a large number of UK-based suppliers of equipment and control systems. The current industrial focus is mainly on waste remediation, combined with recovery of biogas as an energy source and digestate as fertilizer. However, there is potential for improvements in process economics, for example through the use of biogas methane as a transport fuel or from the extraction of high value products from digestate.

AD research centres are already established at CPI and the BDC with additional facilities and expertise in a number of Universities, including Southampton and South Wales. The BBSRC-supported AD Network NIBB provides an academia/industry forum in the UK, and there are UK participants in several EU networks. Also, an official information portal (www.biogas-info.co.uk) provides information on all aspects of the AD process for a wide range of users and interest groups.

Future improvements in the AD process and process economics are likely to result from improved understanding and modulation of process microbiology relating to factors such as feedstock variation and environmental conditions. Improved process control, based on microbiological monitoring, is seen as a key area. For developments in the area of digestate processing there are clear overlaps with the High Value Extractives theme discussed above. Thus, future development of advanced AD systems is at an early stage and catered for by existing funding mechanisms and with existing capability.

There is no strong case for substantial investment in additional large scale AD facilities outside the commercial sector. Support for established centres through existing funding mechanisms should be sufficient to ensure translation of new research into commercial application and subsequent benefits to the UK bioeconomy.

6.4.3 Biocatalysis

This technology area is frequently an enabling step in other industrial processes. There was a consensus that there was significant opportunity in the UK to develop new technologies such as continuous processing and novel non-aqueous phase systems. These however would be new technologies at the earliest stages and could be dealt with adequately through existing funding and support mechanisms.

In terms of scale-up, discussions at the workshop and elsewhere suggested that sufficient provision already existed at lab and pilot scale albeit distributed amongst a number of centres throughout the UK, e.g. CoEBio3 and CPI 'genes to kilos' biotechnology open access service. Whilst some pre-commercial scale equipment might be advantageous, this requirement was currently being met adequately through the existing commercial framework of large and small CRD contractors in the UK, EU and elsewhere.

What was needed in this area was closer coordination of the existing distributed lab and pilot facilities - potentially through a small, dedicated management operation working through a hub and spoke approach - that could unite the UK capability and provide a more effective interface with industry. Whilst there was merit in this proposal, it was not seen as relevant to this particular study but should be considered separately. This is an area where the BBSRC NIBB BioCatNet could have a role to help assess the need for, and to facilitate greater networking interactions.

In conclusion, there was no demonstrated need at this point for larger scale assets in this sector as there were sufficient facilities to enable translation of new processes to the large pilot scale whereupon commercial operators could support final commercialisation.

7 Summary conclusions

Since the publication of the Government initiated Innovation and Growth Team report on IB, UK stakeholders have been working to realise the commercial benefits of IB, building on the acknowledged strength of the UK research base.

The technology development journey from lab scale research to commercial production contains several scale-up steps which introduce technical and commercial risk and the need for capital expenditure. The ability to access scale-up equipment and supporting competences in a cost efficient manner, thereby de-risking the commercial development process is critical to the success of companies; particularly SMEs, developing IB based processes.

The study described in this report found that overall the UK is currently well served in respect to accessible pilot equipment and competence, and is competitive with other European member states. Despite this, a number of emerging technologies were identified as areas worthy of investment, and others where some investment focused on specific established sectors would strengthen UK capability. During the study it became evident that there are concerns about wider skills retention and development in IB scale up, which are seen as important to IB sector development as investment in equipment. Much of this expertise is generated 'on the job', and there is a risk of loss of such expertise posed by intermittent or fluctuating research funding. While the latter was not a focus for this study it is highlighted as an issue that requires as much attention as investment in equipment.

The IB asset landscaping exercise gathered information from the prominent open-access IB pilot scale facilities in the UK. This identified 340 relevant individual pilot-scale assets. This included 69 assets involved in biomass pre-processing, 105 assets involved in processing (e.g. fermentation) 42 assets involved in algal cultivation and 124 assets involved in product separation.

Further work with a select group of key facilities identified that in many cases internal project work can restrict access to scale-up equipment held at universities and research institutes. Conversely, larger equipment typically had lower levels of utilisation per annum, particularly assets previously secured for specific time-limited projects. Specific equipment vulnerabilities were linked to uncertainties over the future of the commercial company ReBio, which could affect access to large scale steam explosion equipment (for biomass pre-processing) and a number of co-located large scale fermenters (6000 litres and above). The loss of any of these could degrade UK capabilities significantly.

A review of open access European pilot facilities demonstrated the range of pilot-scale equipment that is available and could be accessed at the European level. These form an additional resource base available to UK researchers and industry and should be considered when evaluating future investment decisions. Unique assets in Europe included a greater emphasis on raceway pond facilities for algal cultivation. In addition a few integrated biomass-focussed centres providing wide-ranging biomass processing and refining capabilities have been established in Europe. In many cases equipment available at these facilities matches that in the UK. However, facilities are available in Europe e.g. Bio Base Europe and the Bioprocess Pilot Facility, which offer process plant at large pilot (e.g. 15m^3 fermentation capacity) scale; these facilities can be viewed as a useful addition to the large scale fermentation capability available at CPI's NIBC. These European facilities also come with ATEX ratings to support safe working with flammable solvents and gases, a factor which has attracted some UK biotechnology companies struggling to find similar facilities in the UK.

By engaging with stakeholders to gain their view of the key areas of growth in the IB sector and the likely challenges facing achievement of these goals (particularly in terms of equipment need) it quickly became clear that investment in equipment was not the only or perhaps even the key requirement. It was commonly argued that without investment in the people and the know-how to run equipment effectively, i.e. the capability, such investment would be counter-productive to the overall goal of facilitating transition of IB processes to the market.

It was difficult to derive a clear rationale for investment in all the identified IB sectors. In some cases this was due to the nascent state of development of some sectors where the commercial status was yet to be proven. In other cases, investment in scale-up facilities had been made before but resulted in eventual commercial buy-out, or stakeholders advised that there was no need for specific investment in scale-up equipment.

The IB asset survey work and stakeholder engagement through the workshop and on a 1:1 basis, helped to identify priorities for further investment in each sector examined.

Taking account of existing UK capabilities, the developed investment cases look to add to national capability or to expand and/or consolidate it where it already exists. The cases fall into three broad categories; a) where there is a need for significant investment to effectively build new capabilities; b) where there is a need for more limited investment to address gaps in equipment that affect flexibility and capability in established areas, and c) other areas where there is little or no need for investment in equipment beyond that provided by existing funding mechanisms.

A) Investment in major UK opportunities to build excellence and leadership

There are two strategic areas, C1 gas fermentation and high value products from microalgae, where investment could have a major impact at a national and international level and where early public support could deliver potentially large benefits to the knowledge base and to the UK bioeconomy. Both of these areas share a number of broad characteristics:

- They are relatively new areas in the IB sector where technology breakthroughs could deliver significant academic and commercial opportunities.

- Commercial activity primarily represents early stage companies looking to commercialise technology.
- There has been little or no significant investment on a national scale to date.
- There is significant world class expertise in the UK.
- Commercial investment would currently be seen as a risky proposition.

In these cases, developing significant UK leadership and focused national competence would provide coordination and leadership for academia, institutions and industry nationally and internationally, and ensure there is UK critical mass of equipment, knowledge and people required to deliver credible commercial outcomes

C1 gas fermentation

C1 gas fermentation offers a significant commercial opportunity in the production of bulk and intermediate chemicals. The economics of these routes will ultimately determine their commercial success as production costs are largely dominated by feedstock costs. The size of the business opportunity is substantial and many companies can be expected to enter this growing sector.

Despite this unique opportunity the fermentation and process development capability in the UK is extremely limited and currently only exists at small laboratory-scale, which limits the ability to transition knowledge to larger scale.

Investment in open-access, flexible, modular capability is proposed, in an appropriately supported environment. Essential to this will be the development of an environment that supports business engagement and the development of early stage companies. As a guide, were the approach to be an integrated National Centre for C1 gas fermentation this might be expected to cost up to £60m if it is to include a fully integrated pre-commercial demonstration unit. If the operational scale was limited to large pilot scale (circa 500L) then the costs may be reduced significantly (circa. £20m).

High value products from microalgae

The commercial large-scale culture of CO_2–fixing, phototrophic microalgae has been established over the last 30 years and markets have been established for high value products. However, the development of more effective algal synthetic and systems biology tools, metabolic engineering and chassis improvement methodologies has increased interest in the role of microalgae as biorefineries.

The UK has a number of world leading academic research groups working on microalgae and innovative UK SMEs. However, the algal research community remains fragmented. There have been several calls to invest in facilities to help co-ordinate activities more effectively and provide a 'one stop shop' for process development and technology transfer to the commercial sector.

Investment in open-access, flexible, modular capability is proposed, in appropriately supported environments to support a range of facilities for growth and harvesting of microalgae at laboratory (10L) to pre-pilot (100,000L) scale and in GM compliant conditions. This would provide support, and a focus, for activities across the microalgae value chain, e.g. strain manipulation and development, growth and harvesting of biomass and product extraction, that could support the development of a world leading competence in high value material production from microalgae.

An initial investment estimated at £10M would be required to support a fully equipped centre of competence, with an estimated build cost of £30M to construct premises designed to accommodate the specialised facilities for growth of microalgae.

B) Investment in sector consolidation and growth

Fermentation from cellulosic feedstocks and high value extractives were identified as two areas where UK capability at the academic and institutional level should be improved and/or where the narrow focus of assets and capability are limiting the commercial applicability

Fermentation from cellulosic feedstocks

The potential commercial opportunities in this sector are significant, but there remain significant challenges to commercialisation.

More limited investment is required in specific pieces of equipment or associated facilities to increase the flexibility of existing plants, particularly in up-stream biomass processing and downstream analysis and extraction, thereby increasing overall capability.

High value extractives

This is an area at a relatively early stage of development, with a limited number of facilities providing capability for dealing with small-scale pre-pilot processing. A range of processes are required at matched scales across the processing chain.

A suggested possible model would be a facility equipped with core capabilities, working with clients to acquire specialist or bespoke equipment for specific projects, possibly supported by a matched funding mechanism.

C) Other strategic areas of investment

These are represented by the IB areas; biologics, anaerobic digestion and biocatalysis. In these cases availability of pilot-scale equipment was not seen as a barrier to development and further development of process efficiency could be catered for by existing R&D funding mechanisms. However, there may be a need for co-ordinating actions to promote industry interactions which the BBSRC NIBB's would be best placed to assess and co-ordinate.

Investment in Wider capability

Development of national competence in IB means also ensuring that there is a critical mass of knowledge and skills to complement equipment capabilities to deliver credible commercial outcomes.

In this exercise concerns were raised by stakeholders that;

a) investment in staff should complement any investment in equipment

b) in some areas there were concerns about the ability to retain skilled staff

These issues are of particular concern to larger pilot facilities with a greater reliance on commercial income. While these issues are recognised, addressing them raises questions about how long-term security could be delivered. This study did not set out to address such issues, but clearly further thought is required as to how the staff complement of new and novel facilities working in relatively risky technology areas can be supported, at least for an agreed development period. Ring-fencing aspects of existing research and development funding programmes is one possible approach, or making direct investment cases for staff support alongside capital equipment investment applications is another or potentially complimentary approach.

8 Annex 1 Interviewed case studies

BEACON biorefinery facility at Aberystwyth University

Completed in late 2012, the BEACON biorefinery facility at Aberystwyth University functions as a ‘plug-and-play’ pilot plant, with key scale-up equipment available for both upstream and downstream processing of biomass. The majority of pilot-scale equipment housed within the facility was funded via the BEACON project, which itself was part funded by the European Regional Development Fund through the Welsh Government. The facility is frequently used by third parties, predominantly Welsh-based industrial companies, largely on account that facilitation of collaborative research between business and academic organisations within Wales is a principle project objective.

This BEACON biorefinery facility is of importance to the UK IB sector as it represents one of only a few institutes in the UK that has equipment suited to the production of highly pure product streams from structurally complex biomass such as lignocellulose. The facility can be used to produce a range of chemicals of value to the IB sector, such as bioethanol, biobutanol, plant oils, antioxidants and sorbitol from biomass. While a variety of different feedstocks can be handled, grasses such as miscanthus and perennial ryegrass are most commonly used.

The facility is comprised of two separate units:

- Primary processing facility
- Secondary processing pilot laboratory

The primary processing facility is dedicated to the physical processing of wet biomass and contains a variety of screw presses and milling equipment capable of handling up to several tonnes of feedstock per day. Currently, the facility is generally only used during the harvest period mid-April to mid-October on account that it has primarily been used for handling grasses and crop feedstocks.

The secondary processing pilot laboratory is dedicated to the processing of refined feedstocks and downstream product recovery. This facility is in almost continuous use, with more desirable equipment having utilisation rates of around 70%. However, it is rare that any piece of equipment is occupied by a single project for any longer than two weeks. The laboratory contains a wide variety of equipment associated with pre-treatment, fractionation, fermentation, centrifugation and filtration. Of particular note are a steam explosion unit, pilot-scale clarifying and decanter centrifuges and two large-scale cross-flow filtration rigs.

The steam explosion unit is used in the pre-treatment of lignocellulosic biomass, allowing for extraction of fermentable sugars. It is one of only two available in the UK, the other belonging to IFR. The unit is capable of producing around 50 to 75 kg of refined fibrous material per day, across 10-15 separate runs. It is generally in frequent use, although requires downtime of around one week when routine maintenance is required.

The BEACON biorefinery facility has two CEPA clarifying centrifuges, each capable of processing up to 500 litres per hour operating in a semi-continuous mode, and a Sharples decanter centrifuge, suitable for separation of heavier solids and capable of processing up to 1,000 litres per hour operating in a continuous mode.

The facility also has two pilot-scale cross-flow filtration rigs: an ultra/micro cross-flow unit and a nano-filtration/reverse osmosis system. Cross-flow systems are considered essential for scale-up of any IB filtration process as they allow for continuous filtration of product streams, decreasing product recovery time, reducing wastage and improving economic viability. This is in contrast to dead-end filtration systems which can only be run as batches. While these filtration rigs can be utilised as stand-alone systems, they can also be consecutively in product separation processes to reduce recovery times.

While the BEACON biorefinery facilities at Aberystwyth University are available to third parties through collaborative research agreements, such agreements are only available to companies within the convergence region of Wales (covering 15 local authorities across the North, West and South of Wales). However, there are means for outside organisations to utilise the facilities via collaboration if their work directly benefits the convergence region or if the organisation is willing to adopt an address within the convergence region.

All equipment at the BEACON biorefinery facility is relatively new, with the majority of laboratory equipment developed using funding from the BEACON project and the majority of milling equipment funded via the Grassohol project (which ran from 2008-2012). However, the assets must only be used for the purposes of the project in the five years following its completion i.e. until 2020. After this point in time the future of the equipment is uncertain, although the BEACON team at Aberystwyth hope that the majority of it will remain on site. Moreover, Aberystwyth University are in the process of developing a phase 2 to the BEACON project that would enable further development of its facilities. It is therefore envisaged that the University will continue to develop its biorefining capability post-2020.

Centre for Process Innovation

The Centre for Process Innovation (CPI) is a key flagship mechanism enabling public investment in the form of assets and resources to support innovation in the process industries

CPI operates flexible business and operational models. As an independent company Limited by Guarantee, CPI can engage in a range of business models acting as partner or sub-contractor in private and/or competitive grant funded projects. This flexibility allows IPR, exploitation rights and freedoms to operate to be negotiated with clients in advance on a case by case basis.

In the last 10 years CPI has completed over 350 competitive grant funded projects worth a total value in excess of £300m and involving 275 partners (40% of project funds are competitive grant investment).

The CPI has a significant investment programme planned, and partially secured, for its National Innovation centres including the National Industrial Bioprocessing Centre (NIBC) and the National Biologics Manufacturing Centre (NBMC).

CPI provides a more holistic set of skills in process modelling and simulation, techno economic evaluation, investment and consortium building support to help deliver strategic and successful commercial outcomes. CPI has also formed a number of spin-out companies to capitalise on developed IPR.

CPI's Industrial Bioprocessing Business Unit has a turnover of £8m and employs 90+ skilled staff. £40m is being sought from National, Regional and European funders for further investment.

CPI has designed and operates four facilities to deliver our Industrial Bioprocessing services:

- Pilot Facility (est 2006) 10/20/50/750L fermenters, associated downstream processing; Flexible plug & play configuration.
- Demonstration Facility (est 2011; 10,000L fermenter; flexible upstream and downstream processing; flexible plug & play configuration.
- Anaerobic Digestion Facility (est 2010); 5,000L horizontal digester and 2x 1,000L vertical digesters; Associated pasteurising and solids and gas handling equipment.
- Bioprocessing & dedicated Gas Fermentation Laboratory: Performs ultra-scaled down to 10L process development for host strain characterisation and bioprocess development.

CPI's primary core competency is its ability to understand bioprocess development in order to design and operate large scale demonstration assets to deliver development and proof of concept test data.

CPI performs technical and commercial due-diligence on each development programme it engages in, to ensure it is at technology readiness level 3/4 or higher. This includes gaining an understand to what extent the underlying business case for the proposed development is understood in terms of the economic potential and commercial/technical risks involved to commercialise the programme.

CPI is currently engaged in strategic collaborations either supported or led by world-leading collaborative partners in each of the following technology areas:

- The valorisation of C1 feedstocks through bioprocessing.
- The economic processing of MSW.
- The valorisation of agriwastes and industrial waste streams.
- Lignocellulosic feedstocks to commodity chemicals.
- Process Development in Anaerobic Digestion.

CPI's assets are typically in use year round with some down time for plant maintenance. In some instances the assets can have multiple projects running simultaneously on most occasions single projects will require the full support of the asset staff. Projects vary in duration, in the AD Development Centre individual projects tend to be in the range of six weeks to six months. Projects within National Industrial Biosynthesis Facility typically run for periods of weeks, the simplest processes can run for 1 week, more generally they occupy the facility for 2 – 6 weeks. Large scale technology development projects can occupy the asset for extended periods of time.

CPI's services are utilised by academics, RTOs, SMEs and large companies across a range of discipline and application areas.

The Centre for Process Innovation is a private, not-for-profit company limited by guarantee. It is a Member of the UK's High Value Manufacturing Catapult, the first of the UK Catapults, set up as Research and Technology Organisations (RTOs). CPI operates on a 1/3 split basis with a target of an equal split between public core investment, private investment and public -private collaborate research grants.

The asset base is expected to be in operation for a minimum of 10 years. Regular use and maintenance of the assets will extend the operational lifetime. The asset is expected to be available for a long period as an open access centre but will need expansion, modification and upgrading over time to ensure it offers UK companies the right facilities for process and commercialisation support.

CPI is currently bidding to become one of the major 'nominated demonstrators' within Europe to support IB development in the region.

Centre for Sustainable Aquatic Research (CSAR), University of Swansea

CSAR is closely linked to the School of Engineering at Swansea University and equipment is shared and moved between sites as necessary. This provides a fully integrated cell culturing, production, separation and product extraction facility.

CSAR has a range of photobioreactors ranging from 100 litre bag type systems, thought to 100-600 litre horizontal bioreactors and a 2000 litre vertical tubular bioreactor. Several 100 litre bag-type reactors provide a cost effective means of generating inoculum cultures and provide a means of providing a flexible response to the high level of demand on the facilities.

In all cases the bioreactors are used year-round, with supplementary lighting in winter, and are in virtually continuous use. Lead times to gain access are at least a month.

The photobioreactors are used to either grow cell biomass for transfer to clients or researchers offsite, or to grow specific cell lines for extraction of oils or specific metabolites.

The wide range of scales of equipment available provides flexibility in matching equipment to the scale of either project or client demands, as uses for each are very varied and interchangeable.

Uses can include production of specific cell lines for subsequent on-site extraction of high value materials, including primary and secondary metabolites. The type of applications is very wide, ranging from examination of impacts of treating wastewaters using algae to production of high value materials. The client base is therefore equally varied.

The facility was established with funds from the Welsh government, but the Centre needs to develop projects and commercial income to maintain the facilities. Current funding is estimated to split 80:20 between project (academic) and commercial income.

With such heavy use the future of the facility is assured. The centre is also continuing to invest in facilities and is in the process of commissioning a new 1000 litre LED photobioreactor.

The Centre is looking to develop a national capability and has already taken steps to start the development of a £multi-million facility, for which funding is being sought. Integral to this will be the development of capability to deal with class 2 and 3 (HSE notifiable) GM materials, requiring specific containment measures, to take advantage of the rapid development and technical promise offered by synthetic biology, while building public confidence in the ability to safely develop such technologies.

Cranfield University

Cranfield University has recently installed an anaerobic digestion pilot plant, comprising a 500 litre mixed feed tank, a 1,500 litre primary digester and a 1,000 litre secondary digester. The plant also has a macerator for front-end feedstock processing, gas engines and ancillary laboratory facilities. The pilot plant has been designed as an open access ‘plug-and-play’ facility to enable easy integration of skid-mounted equipment. The development is still in the process of being completed, with the digesters still requiring linkage to the gas engines. It is anticipated that it will be open by March 2015 at the latest.

The facility cost over £100,000 to develop and was funded by from a range of sources; the digester tanks were donated by the Shanks Group, 40% of the other construction costs were provided by the European Regional Development fund and the remaining capital was provided by the University. The funding provided by the European regional development fund was provided to help SMEs in the East of England in developing renewable energy technologies. However, the facility is also open to collaborators from outside the region. Operational costs of the plant are largely related to man-power, with the facility requiring one technician working approximately 20 hours per week to maintain operations.

As the facility remains to be completed it is difficult to give an indication of occupancy levels. However, there has been a high level of interest so far, notably in the 'plug-and-play' capability of the plant. Once operational, retention periods of 20-25 days can be expected, meaning that the plant will be completely dedicated to a single project during that time. Moreover, a change of feedstock is expected to require the running of two provisional retentions e.g. up to 50 days, before suitable for experimentation. Therefore, the plant is likely to be dedicated to individual projects for significant periods of time, potentially as much as 6 months. Lead times to accessing the plant could consequently be significant if demand is high.

It is provisionally estimated that the plant will remain operational for at least 10 years. There are no plans to further develop these facilities at the moment, although that is not necessarily surprising given the infancy of the plant.

Croda

Croda's fermentation facility at Goole consists of two 30,000 litre fermenters, one of which is glass-lined, and a 2,000 litre glass-lined seed fermenter. In addition, the facility has significant downstream cellular disruption (chemical and physical lysis) and product purification (filtration, centrifugation, drying) capability that enables full processing runs to be undertaken on a semi-continuous basis.

This facility is of great value to the UK IB sector for a variety of reasons: it has the largest fermentation capability of any facility contacted during this project; it has impressive downstream product purification capability capable of being run as a train, and; the glass-lined nature of the fermenters are particularly suited for cultivation of marine microorganisms, thereby providing the facility with greater functionality.

The equipment is not currently suitable for handling of GM organisms. However, the laboratories at Croda have already been upgraded to be GM-compatible and it is likely that the fermentation facility will follow suit, largely on account of the rapid improvements in strain development being made in the biotechnology industry through adoption of, for instance, genetic sequencing and systems biology approaches.

The fermentation facility was constructed four years ago and was funded directly by Croda capital. It has since been used as a demonstration facility for development of speciality chemicals for skin-care actives and biosurfactant markets. Due to its scale, it could feasibly be used as a production facility for very high value metabolites, although this is not as yet an intention.

The facility been used for many in-house Croda projects, as well as various TSB-funded projects with both industrial collaborators (e.g. Unilever) and academic partners (e.g. Newcastle University). Croda also has a bioprospecting agreement with Canadian-based biotechnology firm Nautilus BioSciences, for which the equipment is in the process of being used for developing products for human and animal health markets from marine microbes.

Utilisation of the facility varies hugely, with both the run-time and frequency of projects varying hugely. However, it is estimated that on average the facility has about a 20% occupancy rate. While the glass-lined fermenter offers greater functionality, it is usually dedicated to cultivation of marine microbes. On account of this, the standard fermenter is generally in more frequent use.

These assets have a 15-year write down period, although it is envisaged that the facility will remain operational for “tens of years”. There is also further interest further expansion, the first stage of which is likely to be making the facility GM-compatible.

Institute of Food Research, Biorefinery Centre, Norwich

The IFR has a unique asset in the 2000 litre high torque solid-state fermentation (SSF) facility. This is a bespoke piece of equipment fashioned by the IFR.

It is relatively time consuming and expensive to run and to maintain in a clean state between runs. It is primarily used to confirm the findings of smaller scale 10 litre SSF tests that are quick and cheap to run and clean with steam decontamination.

It was originally built to examine compost digestion under controlled conditions. Until recently it was used almost 24hrs per day in association with a number of research projects, but now is only occasionally used perhaps once every quarter.

It is primarily used to support internal research projects.

The 100 litre liquid fermentation facilities are again regularly used, primarily to grow up yeasts for internal projects or external clients.

The IFR also has a steam explosion rig for biomass processing. There are relatively few of these in the UK. It runs at up to 40BAR and so has a long list of Health and Safety requirements attached to it and a dedicated set of trained staff to run and manage it. It is used regularly and has run over 15,000 1kg batches over the last 3-4 years, typically at a rate of 10 batches per day. There is a significant infrastructure associated with running such equipment, and a regular maintenance requirement to ensure safe operation.

The key areas of use of all the facilities is around the biodergradation and exploitation of biomass and development and testing of yeast strains for ethanol production and more recently for high value chemical production.

The majority of time the equipment is used for internal projects, but some commercial work has been undertaken for both multinationals and SME's.

Access for others is not seen as an issue, and could be granted relatively quickly given a reasonable lead-in time, which would be expected with most of the relevant project work likely to be undertaken. Work can be performed on a rental basis, utilising relevant staff, or on a project agreement sharing any relevant IP arising.

There are no specific plans for upgrading or expansion currently.

Plymouth Marine Laboratory

Plymouth Marine Laboratory (PML) has four notable assets relevant to IB scale-up processing: a 10-1,000 litre vortex bioreactor suite; 600 litre bespoke tubular photobioreactor; a 1,250 litre raceway pond and; a 180 litre (combined capacity) bubble column photobioreactor suite. These facilities are largely targeted towards algal cultivation, although the vortex bioreactor is capable of extracting and processing cellular materials from a variety of different microorganisms. The facilities at PML benefit by being suitable for cultivation and processing of genetically modified (GM) organisms – a rarity within existing UK algal facilities. Most recently, this has facilitated a collaborative research project with Rothamsted focused on achieving high DHA oil yields from GM algal strains.

The vortex bioreactor is possibly the most novel IB scale-up asset owned by PML; it is the only one available in the UK, and one of just five in the world (all which were developed at PML). The bioreactor is designed for cellular processing and disruption combined with high-efficiency extraction of cellular products. The technology is particularly suited for scale-up procedures as it allows for processing and product recovery to occur in a single vessel, minimising wastage and improving economic viability. Moreover, the process is less energy intensive than traditional cellular disruption technologies. The bioreactor was designed and patented by Manchester-based Protein Technologies Ltd in collaboration with PML and was funded through a TSB project won by a PML-PTL-UCL consortium 3 years ago. However, the equipment has been used infrequently since its development and is not currently in use. It is a high-throughput technology so even when it is "on project" it can have multiple users, with batch runs typically taking 10-15 minutes.

The tubular photobioreactor at PML was developed alongside the vortex bioreactor and was funded by the same TSB project, costing in the region of £150,000. Its primary purpose was to provide sufficient algal biomass for use with the vortex bioreactor, although since its development it has been used as a stand-alone asset for large scale algal cultivation. It is built to a very high "pharmaceutical grade" specification, constructed with high quality stainless steel components where possible. Typical projects making use of this asset typically last between two and three months, with the asset completely dedicated to the project during the period. The clean-up process between runs generally takes around three to five days. While this asset was used almost continuously for its first 2-3 years, it has not been used in the last 6 months.

The bubble column photobioreactor suite at PML currently consists of fourteen 10 litre columns and thirteen 3.5 litre columns. The suite was initially funded under the aforementioned TSB project and has been continuously developed since its establishment 18 months ago. The column reactors are comparatively simple pieces of apparatus, originally designed to produce algal inoculates for use in the tubular photobioreactor. However, their design has been conducive to achieving good algal growth rates and so they are now regularly for cultivation of algal biomass in early-stage scale-up projects. The reactors typically have a 30-40% utilisation rate.

The raceway pond at PML was self-funded and has been operational for around 3 years. In contrast to many algal raceway facilities, the asset is housed indoors. This enables better control of environmental conditions and use of GM algal strains. Batch cultures usually take around one week to grow, with the clean-up turnaround procedure taking just one day. The asset is typically used in projects for around 10-20% of the year.

All facilities at PML typically have low overheads, especially with regards to consumables, with man power estimated as 95% of operational costs. Additionally, most of the equipment has only been developed relatively recently. Therefore, PML's assets are expected to have a long lifespan and are not currently vulnerable to dismantling, despite several assets having not been used for a significant period of time.

ReBio

ReBio Technologies Ltd is a new industrial biotechnology company formed in 2014 following the administrative take-over of the facilities of TMO Renewables.

ReBio has an extensive range of fermenters ranging from 60 to 6000 litres in scale. Several scales of equipment for enzymic hydrolysis are available to match the fermentation capacities. The facility also has steam explosion biomass fractionation facilities at both 60 and 1000 litre capacity. The former is twice the capacity of any steam explosion fractionation unit at any other UK facility and the 1000 litre steam fractionation facility is considerably in excess of anything available in any other facility.

The facility was established to develop TMO's cellulosic ethanol and biofuels technology. The new management team is looking for options to support the facility.

Currently there are greater calls on fermentation equipment at the 60 litre scale than at larger scales, with current work focussed on small scale developments. The management is looking for active partners to establish Joint Venture's as well as other means of developing the business. This could potentially include the plant (particularly the larger facilities on-site) converting to small scale commercial production. Given the scale limitations this is most likely to be focussed on low-volume, high-value applications, for example lactates for biopolymer production. Other alternatives being considered include tie-ups with other facilities to build greater competence to support biotechnology projects.

The enzymic hydrolysis facilities have been used independently of the fermentation facilities to provide hydrolysate to clients as part of development projects etc.

Further investment would be required to upgrade the plant to a cGMP[20] plant if there were plans to go into production of Active Pharmaceutical ingredients (API's) and other high value nutraceutical type products.

While the centre continues to look at opportunities to secure its long-term future, it's clear that this could entail conversion to commercial production of materials which would limit or potentially exclude future access to equipment. The sell-off of equipment (steam explosion facilities) is also a possibility if sufficient demand is not found to justify upkeep. This is a worse-case scenario and the facility is currently open to discuss any opportunities to support scale up and demonstration.

University College London (UCL)

UCL has laboratories primarily targeted towards the development of vaccines and other biopharmaceutical products, typically at scale ranging from millilitres up to 7.5 litre. However, the University has recently invested in new larger scale assets that will be suitable for IB scale-up operations. Of note, a simulated moving bed chromatography unit that can be used as a separation and purification system both upstream and downstream of fermentation will be installed, alongside a 120-150 litre fermenter. The fermenter is expected to be capable of both liquid culture and solid-state fermentation while the chromatography unit benefits by being able to handle a far more heterogenous input than most other chromatography systems. The new equipment is expected to be installed by the end of 2014, with all facilities suitable for the handling of genetically modified microorganisms.

The new assets were purchased through a Research Council grant, with the proviso that they are used for synthetic biology applications. Within this remit, the range of products that could be produced is wide; alongside biopharmaceuticals, the production of both bulk and industrial speciality chemical would be considered.

[20] Current Good Manufacturing Practice and associated regulations to cover quality, safety and hygiene issues etc.

Much of UCL's facilities are utilised predominantly for its own research, although occasional collaborative projects with academic partners are conducted. However, UCL are interested in expanding their collaborative research efforts, with the new assets providing a potential means to assist with this goal. There is currently only one project planned for the new equipment, although this can be expected to increase once fully commissioned. Anticipated occupancy rate is therefore difficult to estimate, but currently good future availability exists. With regards to the smaller 7.5 litre fermenters used for vaccine and biopharmaceutical production, approximately two out of the seven owned by UCL will be typically be in use during the week. Usage of much of the other equipment, such as the 20 litre and 30 litre fermenters, is less frequent.

Given that the large scale fermenter and chromatography system are brand new and yet to be installed, these assets can be expected to exist at UCL for at least 10 years, most likely significantly longer. There are no immediate plans to expand UCL's IB facilities on account of space limitations. However, the University is currently in the process of expanding its campus, with the possibility that new science facilities could be constructed. In this eventuality, there would be interest in further development of UCL's IB capability.

Warwick University

Warwick University possesses a 270 litre fermenter that can be used for both microbial liquid culture and solid state fermentation. The asset was installed seven years ago, funded through a West Midlands Council grant. The fermenter is suitable for use with genetically modified (GM) organisms, and has been used for such in the past, as is the laboratory in which it is located.

The asset is predominantly used in its solid state for preparation of novel enzymes from lignocellulosic residual and waste feedstocks, such as straw. Often the isolated enzymes are targeted at biomass pre-treatment applications. The asset is most regularly used by Warwick University themselves, although numerous SME's have utilised the equipment in the past and Warwick are open to further collaboration.

When in use the fermenter is generally dedicated to a single project for approximately one month. On average, the asset is occupied around 30% of the time.

While the future of the asset is not under threat, Warwick has no further plans for improving its fermentation capability. However, there is interest in acquiring larger scale equipment for downstream separation and purification.

9 Annex 2 – International open access pilot plant facilities

9.1 Facilities offering broad generic biomass processing and fermentation equipment at pilot scale

		VTT Technical Research Centre
Location		Finland
Equipment	Preprocessing	Grinding units, Extruder, Steam explosion unit, High-pressure liquefaction Organosolv facilities Chemi-mechanical grinder/refiner Fibre pulping (mechanical and chemical) and subsequent fractionation unit
	Fermentation/ Bioconversion	Gasification & syngas cleaning unit Fast pyrolysis Chemical conversion pilots (based around stirred-tank reactors that can handle alkaline or acidic conditions as well as pressure). Stirred tank bioreactors; batch reactors for enzymatic conversion, mashing tanks and brewing bioreactors. Fermentation up to 1200 L
	Downstream Processing	Continuous centrifuges; Filtration/screening units; Film evaporator; Crystallisation tanks; Supercritical extraction cell separation by continuous centrifugation; vacuum- and pressure filtration; cell disruption by pressurized homogenization for release of intracellular products; product polishing by microfiltration; protein concentration by ultrafiltration and drying by lyophilisation
Expertise		Covers the whole chain from biomass fractionations, separation and purification to chemical or biotechnical methods to produce value-added products. Process chemistry pilot plant, fermentation pilot plant, food and beverage pilot plants
Services		Broad range of services to support pilot scale development and processing with links to other support services.
Comments		Chemical products, food, pharma, biobased materials
Website		http://www.vtt.fi/

		Bio Base Europe Pilot Plant
Location		Ghent, Belgium
Equipment	Logistics and storage, feedstock	Bulk solid biomass storage (55 t silo, 3X90 t bunkers) Liquid storage (vessels up to 125 m^3) Refrigerated storage room, freezers
	Preprocessing	Reactors for chemical pretreatment (suitable for acid (H2SO4, HC.), alkaline (NaOH, ammonia), sulfite, organosolv and other types of pretreatment). These can be also used for anaerobic fermentation. (500 to 5400 l, ATEX rated) Reactors for enzymatic hydrolysis of biomass (500 to 50,000 l) Mechanical pretreatment equipment Dry milling (roller crusher, knife mill, hammer mill); Wet milling (pulper, inline high shear mixing and milling); Jet cooking Filter press, belt filter press, decanter centrifuge, screw press, falling film evaporator, wiped film evaporator
	Fermentation/ Bioconversion	fermenters (batch, fed-batch, continuous), 7 to 15,000 l Anaerobic fermenters (see preprocessing) Gas fermenters: 1x7 litre (ATEX)
	Downstream Processing	High speed disc stack separator, 100-750 kg/h Screw decanter centrifuge, 100-750 kg/h; Basket centrifuge, 10 kg; Inverted filter centrifuge, up to 50 kg of product per cycle Filtration; Dead-end filtration such as plate and frame filters, Filter presses, Cross-flow membrane filtration units for Micro, Ultra & Nanofiltration Ion exchange and adsorption; Packed column units for ion exchange, adsorption or carbon treatment (30 to 800 l) Various reactors from 50 l to 4 m^3 for cooling crystallization and evaporation crystallization; Continuous evaporation units from litre to ton scale; Falling film three-effect evaporator up to 5t/h water evaporation; Wiped film evaporator, 50-150 kg/h water evaporation; Glass wiped film evaporator, 1-5 kg/h water evaporation; Spinning cone evaporator, up to 50 kg/h water evaporation Batch evaporation reactors for both water and solvent based distillation 1900 l filter dryer for solvent extraction and solids drying Glass lined reactors, 500 to 5400 l for solid-liquid and liquid-liquid extractions Continuous water-based extraction unit 5 x 1000 l GRACE small scale preparative chromatography unit; Columns up to

		500 l for batch chromatography Continuous sludge dryer, 5 kg/h; Vacuum tray dryer, 2400 l Conical vacuum dryer for water and solvent based applications, 980 l, Filter dryer, 1900 l ; Drying oven, 2000 l
Expertise		Biomass Pretreatment, Fermentation, Biocatalysis, Green chemistry, Product Recovery and Purification
Services		Scale-up, custom manufacturing, start-up assistance and process design, training
Accessibility		Commercial, open access
Comments		Chemical products, biofuels
Website		http://www.bbeu.org/

		Bioprocess Pilot Facility
Location		Delft, Holland
Equipment	Preprocessing	Pilot scale pretreatment - autohydrolysis, acidic and alkaline treatments, liquid hot water, SO2, steam explosion (catalyzed/uncatalyzed). The pilot scale unit (approximately 40 kg dry biomass per hour) enables delivery of sufficient sugar material for pilot scale fermentations (4 m^3 and 8 m^3).) Hydrolysis up to 4 m^3 is currently available.)
	Fermentation/ Bioconversion	Pilot Plant equipped with 4 x100 l, 4x 300 l, 1 m^3 and 4 m^3 stirred vessels which can be used for batch or fed-batch processes. An 8 m^3 bubble column fermenter can handle batch or fed batch type fermentations. The 300 l fermenters and bubble column are located in an ATEX (T3) zone.) ATEX (Flammable materials can be used in the designated ATEX zones (T3) of the Fermentation Pilot Plant.
	Downstream Processing	Cell disruption (The BPF has a pressure homogenizer with a maximum working pressure up to 700 bar.) Solid liquid separation (With a variety of unit operations available, such as several filter presses, centrifuges and membrane filtration.) Concentration (Such as circulation (glass) evaporators (1 to 80 l concentrate), falling film evaporator (capacity 250 l/h water evaporation) and multiple batch evaporator chemical vessels.) Purification (Including extraction, membrane filtration and several

		columns (ranging from 5 l to 170 l) for chromatography.) Formulation (including mixing, sieving and milling equipment.)
Services		Allows modular use of equipment to produce kg quantities of materials for further product testing
Expertise		Feedstocks (agricultural side streams, agricultural residues, energy crops, waste materials) Pre-treatment (aqueous, chemical, solvent, biological) Hydrolysis, fermentation, downstream processing and formulation
Comments		Chemical products, food processing, biofuels, pharma
Website		http://www.bpf.eu/

		Agro-Industrie Recherches et Développements (ARD)
Location		Bazancourt,France
Equipment	Preprocessing	Not specified "wide variety of separation equipment at an industrial scale"
	Fermentation/ Bioconversion	2x2l, 2x5l, 3x20l, 1x100L fermenters Micro and ultra-filtration Scaling up of fermentation from 2l up to 80 m^3
	Downstream Processing	filtration, ion exchange, electrodialysis, evaporator, crystalisator, centrifuges, chromatography
Expertise		plant fractionation and biorefining, white (industrial) biotechnology, green chemistry; bio-based chemistry and agro-materials; analytical chemistry; formulation.
Services		an open technological platform for the industrial scaling-up of biotechnology processes. The platform includes laboratory equipment, pilot installations and an industrial demonstration unit (BioDémo).
Accessibility		Partly-restricted access due to commercial development work of originating funding partners.
Comments		Chemicals, biobased materials, food/nutraceuticals
Website		http://www.a-r-d.fr/

		Fraunhofer Center for Chemical Biotechnological Processes (CBP)
Location		Leuna, Germany
Equipment	Preprocessing	Pulping and separation of lignocellulose components using organic solvents (capacity: 1 t biomass / week) Lignocellulose fractionation module Tanks up to 1000 L for the enzymatic hydrolysis of polysaccharides
	Fermentation / Bioconversion	Fermentation capacity ranging from 10/100/1000 up to 10,000 L Continuous gas phase reactions of 10 kg/h Liquid phase reactions up to 100 L
	Downstream Processing	Mechanical and thermal separation processes Homogenizer for cell breakdown Micro/ultrafiltration plant for concentrating Crystallization tank Chromatography column for further product purification Dry freezer and spray dryer for product preservation
Expertise		Fractionation of lignocellulose Bio-based alcohols and olefines Development of new technical enzymes Microalgae as a resource for functional substances and energy carriers Use of residual biomass by means of fermentation
Services		Implementation and optimisation of processes, products and equipment until they are ready for use and for the market.
Accessibility		Open access, work in all the application-relevant fields of expertise for contractual partners from industry and the public sector.
Funding		The Fraunhofer CBP is supported financially by the German Federal Ministries of Education and Research (BMBF), of Food, Agriculture and Consumer Protection (BMELV) and for the Environment, Nature Conservation and Nuclear Safety (BMU) as well as the State of Sachsen-Anhalt.
Comments		Chemicals, algae, lignocellulosic feedstock
Website		http://www.cbp.fraunhofer.de/

		NREL Bioprocessing Pilot Plant
Location		Golden, Colorado, USA
Equipment	Preprocessing	
	Fermentation / Bioconversion	One 20-L fermenter, Two 160-L fermenters, Two 1500-L fermenters, Four 9000-L fermenters, All equipped for anaerobic and aerobic operation largest can be operated in batch or continuous mode
	Downstream Processing	Wide range of filter and centrifuge process equipment Suite of product purification and analysis equipment
Expertise		Designed for converting lignocellulosic bio-mass to ethanol, the plant includes most fermentation and downstream processing equipment commonly used in the biotechnology industry
Services		Process development for microbial fermentation systems.
Accessibility		Available via contract or research partnerships
Funding		US DoE supported
Comments		Biofuels and chemicals
Website		http://www.nrel.gov/docs/fy04osti/34309.pdf

9.2 Facilities offering generic fermentation equipment at pilot scale

		CVG - Centre Valorisation Glucides et des Produits Naturels
Location		Dury, France
Equipment	Preprocessing	Extrusion Cooking: Line BC45 Kilo Lab hemisynthesis for 5 and 10 liters Reactive Extrusion: EVOLUM 32 reactors equipped with ultrasonic reactor subcritical water drivers of electrodialysis membrane ATEX extraction tank to filter bottom physico-chemical characterization and analysis
	Fermentation / Bioconversion	Bioreactors of 50 litres, 150 litres, 300 litres and 3,5 m3, Fermentation line of 300 litres, Fermentation line of 3,5 m3
	Downstream Processing	Splitting / separation (45m³ Installed reactors, separators, filters) concentration / purification evaporators up to 1 m³ / h , membranes up to 30 m² Atomization: Simple towers and multiple effect up to 100kg/h capacity evaporation
Expertise		Test or develop extraction and chemical/enzymatic modification processes. Studies of scale-up and production for fermentative biomass and

	metabolites
Comments	cosmetics, food ingredients, nutrition, technical additives, health, food / feed, fine chemical and nutraceutical
Website	http://www.cvgpn.com/

		Biosentrum, Stavanger
Location		Stravanger, Norway
	Fermentation/ Bioconversion	The plant offers fermentation capacities ranging from small-scale lab-fermenters, pilot productions for nonclinical development to commercial quantities up to $30m^3$.
Expertise		Microbial contract fermentation facility Process development/Optimisation/Scale up Cell construction/ Strain development
Services		Biosentrum can process a wide range of products from starter cultures to high value products, including fine chemicals and recombinant proteins The pilot facility also includes upstream and downstream equipment as well as analytical services.
Comments		High value chemicals, biobased materials,
Website		http://www.biosentrum.no

		Leibniz-Institute for Agricultural Engineering Potsdam-Bornim e.V., Dept. Bioengineering
Location		Posdam, Germany
Equipment	Fermentation/ Bioconversion	Lactic acid fermentation (continuous mode) 10 t/a
	Downstream Processing	solid/fluid transport, mixing, heating/sterilization ultrafiltration, softening, electrodialysis, ion exchange
Expertise		Processing of sugar and starchy (after enzymatic hydrolysis) materials
Services		Feedstock pre-treatment, fermenter, nanofiltration, elektrodialyse, product separation & refining

Accessibility	Partially open, (partnership)
Comments	Food, materials, energy (biofuel)
Website	http://www.atb-potsdam.de

		INETI, Instituto Nacional de Engenharia, Tecnologia e Inovação
Location		Lumiar, Portugal
Equipment	Fermentation/ Bioconversion	Fermentation from 2 to 100 L total volume;
	Downstream Processing	Solid liquid separation (disk-stack centrifuge/decanter, MF/UF filtration units) Semi-preparative HPLC; Thermochemical conversion facilities; pilot facilities for the growth of microalgae.
Comments		Biogas, biofuel
Website		http://www.ineti.pt/

		Biopolis
Location		Valencia
Equipment	Fermentation / Bioconversion	Fermenters of 2, 5, 15, 30, 75 and 300 L of capacity, with "in situ" sterilization and control software. Production of microorganisms by fermentation up to volumes of 300 l.
Expertise		Development and optimization of fermentation processes Optimization of recovery processes for biomass and microbial products. Standardized production of batches according to established procedures
Services		Agri-food, microbial biotechnology,
Accessibility		Open access
Funding		Public-private co-funding
Comments		Food, chemicals, Pharma, textiles, energy
Website		http://www.biopolis.es/en/

9.3 Facilities offering fermentation equipment at pilot scale with supporting expertise in pharma applications and/or high value chemicals

		Pilot Plant for Bioprocesses (SINTEF)
Location		Trondheim, Norway
Equipment	Fermentation/ Bioconversion	32x3 l, 8 x 1 l, 1 x 14 l; 300 l, 1500 l fermentors Cell homogeniser
	Downstream Processing	Equipment for membrane filtration and chromatography
Expertise		Strain evaluation and development, fermentation technology, product recovery and purification; process development and economical evaluation; biocatalysis (enzyme technology, immobilized biocatalysts, industrial enzymes)
Accessibility		University facility
Comments		Pharma
Website		http://www.sintef.no/

		IBET – Instituto de Biologia Experimental e Tecnologica, Oeiras
Location		Oeiras, Portugal
Equipment	Fermentation/ Bioconversion	Fermentation from 2 to 300 L working volume
	Downstream Processing	Solid liquid separation (disk-stack and tubular centrifuges, MF/UF filtration units); Homogenizer; Film evaporator; Chromatographic separations; Supercritical extraction Solid-Liquid Extraction with biocompatible solvents • Pressurized Liquid Extraction • Supercritical Fluid Extraction • Adsorption Processes (molecular imprinted polymers)
Expertise		Production of proteins, DNA, viruses, viral particles and cells under novel bioprocessing and downstream processes; Development of alternative green technologies for the isolation of natural of bioactive compounds with high added-value and application in food, cosmetic and pharmaceutical industries.
Funding		Non-profit association with public and private shareholders, but mostly public funding

Comments	Pharma, Food
Website	http://www.ibet.pt

		Fermentation pilot plant. Chemical Engineering Department Edifici Cn-Universitat Autònoma de Barcelona Bellaterra
Location		Barcellona, Spain
Equipment	Fermentation / Bioconversion	Biostat UD50 pilot scale bioreactor, 300L pilot scale bioreactor (B.Braun), Stirred tank with cooling system. Pressure and storage tanks.
Expertise		Development of continuous, batch or fed-batch processes with microorganisms either bacterium, fungi or yeast, genetically modified or not. Development of products obtained from cultures. Primary downstream stages.
Services		Design, development and optimization of bioprocesses. Growth and production kinetics. Analytical methods implementation. Culture strategies study. Scale-up development. Downstream development.
Accessibility		Open access
Funding		Public
Comments		Pharma, Chemicals, cosmetics
Website		http://www.catalonia.com/en/our-services/tecnio/PPF.jsp http://ppf.uab.cat/

9.4 Facilities offering pilot scale equipment with supporting expertise in biocatalysis and high value chemicals

		EMPA
Location		St. Gallen , Switzerland
	Fermentation/ Bioconversion	Bioreactors, high pressure reactor for two-phase solvent fermentation;
Expertise		Pilot plant facility for the biotechnological manufacture of

	valuable products, especially biomaterials / bioplastics / enzymes. Up- and downstream process development (enzymes, bioplastics, biomaterials, biofilms); enzymatic catalysis: screening, production and process optimisation; small scale production for customers; process qualifications and transfer to industry
Services	Analytical chemistry, polymer chemistry and –processing Service fermentations; Screening and characterisation of enzymes
Comments	Biobased materials, biocatalysis
Website	www.empa.ch

See also: Pilot Plant for Bioprocesses (SINTEF)

9.5 Facilities offering pilot scale equipment for phototrophic algal cultivation

		Centre d'Etude et de Valorisation des Algues (CEVA)
Location		Pleubian, France
Equipment	Logistics, storage, feedstock	Both sea and land assets to support marine and freshwater algae projects.
	Fermentation / Bioconversion	75L, 1000 L, 2500 L , 850 L, 1000 L photobioreactors and stirred tanks
	Downstream Processing	Evaporator, concentrator; filtration: vibrating screen, rotary filter, filter bell, filter press, tangential ultrafiltration and reverse osmosis, end filtration; Dryer, steamer, forced air oven, lyophilizer
Expertise		algae (macro & micro), marine plants, and marine biotechnology
Services		Support, project management, R&D
Accessibility		Open access
Comments		Microalgae and macroalgae
Website		http://www.ceva.fr

		Hochschule für Technik und Wirtschaft des Saarlandes (Htw saar)
Location		Saarbruecken, Germany
Equipment	Fermentation / Bioconversion	2 x 10m3 RAS mounted with filters and ozone flotation system 2 x 120 litre tubular PBR 3 x 25 litre flat panel airlift PBR
Expertise		Research on microalgae production using nutrients from recirculation aquaculture systems (RAS) for fish.
Services		Not specified
Accessibility		University
Comments		algae
Website		https://www.htwsaar.de/htw/forschung/struktur/forschungseinrichtungen/ipp/bvt/enalgae

		Lelystad Open pond pilot
Location		Lelystad, the Netherlands
Equipment	Logistics, storage, feedstock	2 open ponds of 250 m^2 each; open pond algae pilot connected to an anaerobic digester and a biogas engine.
Expertise		improve the management of algae production at a semi-commercial scale level, to minimize production costs, and maximize the algae yield level
Accessibility		Demonstration site
Comments		algae

		Instituto Technologico De Canarias
Location		Canary Islands, Spain
Equipment	Fermentation / Bioconversion	1200 m2 surface of open tanks. Production of 6 tonnes of dry biomass per year
Expertise		Cultivation and processing of microalgae for biomass production. Downstream processing of biomass for food production. Process optimisation.
Accessibility		Open access
Funding		Public
Comments		Algae
Website		http://www.itccanarias.org/

10 Annex 3 - Survey of interest in accessing a UK fermentation process demonstration plant

Key findings

- There were 79 responses to a survey of stakeholder interest in accessing a fermentation process demonstration unit, 42% of the responses were from industry
- 77% of respondents expressed an interest in accessing an open-access fermentation facility, with equal interest in using the process development unit and smaller pilot test rig.
  - Most interest was received from the bulk and fine chemicals sector and secondly from the biofuels sector
- When asked "how likely are you to access such equipment in the next 2 years" of the 57 interested respondents, only 10 were highly likely to access such facilities, looking to a 10 year timescale this rose to 22 out of 56 respondents.
- More detailed insight on potential user interest was gained from stakeholder interview, this identified;
  - in the main, commercial stakeholders did not demonstrate a strong interest in using the facility as an open-access facility
  - some concerns were expressed over the flexibility of the PDU to meet their needs
  - mixed opinions were expressed on the appropriateness of geographic location and access to relevant competency
- Some commercial interest was expressed in outright purchase of the equipment and for specific pieces of equipment in other cases.

10.1 Background

As an adjunct to the main study, after recognising the vulnerability of the facilities held by ReBio, NNFCC were tasked to undertake a small additional study to ascertain stakeholder interest in accessing identical facilities on an open access basis (for both the fermentation process demonstration unit (PDU) and pilot test rig) (details in following

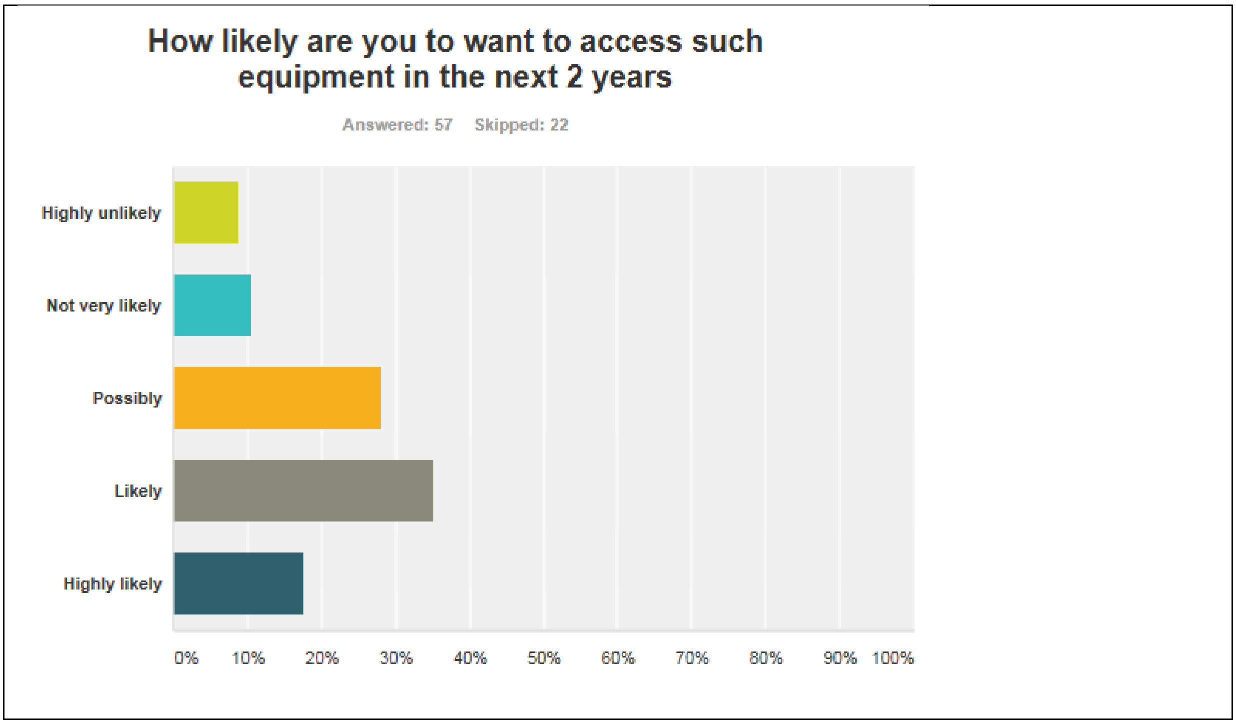
NNFCC circulated an online short survey link to interested parties and via relevant BBSRC NIBB leads to encourage participation, this also included a link to a prospectus for the facilities (which was anonymised) (see).

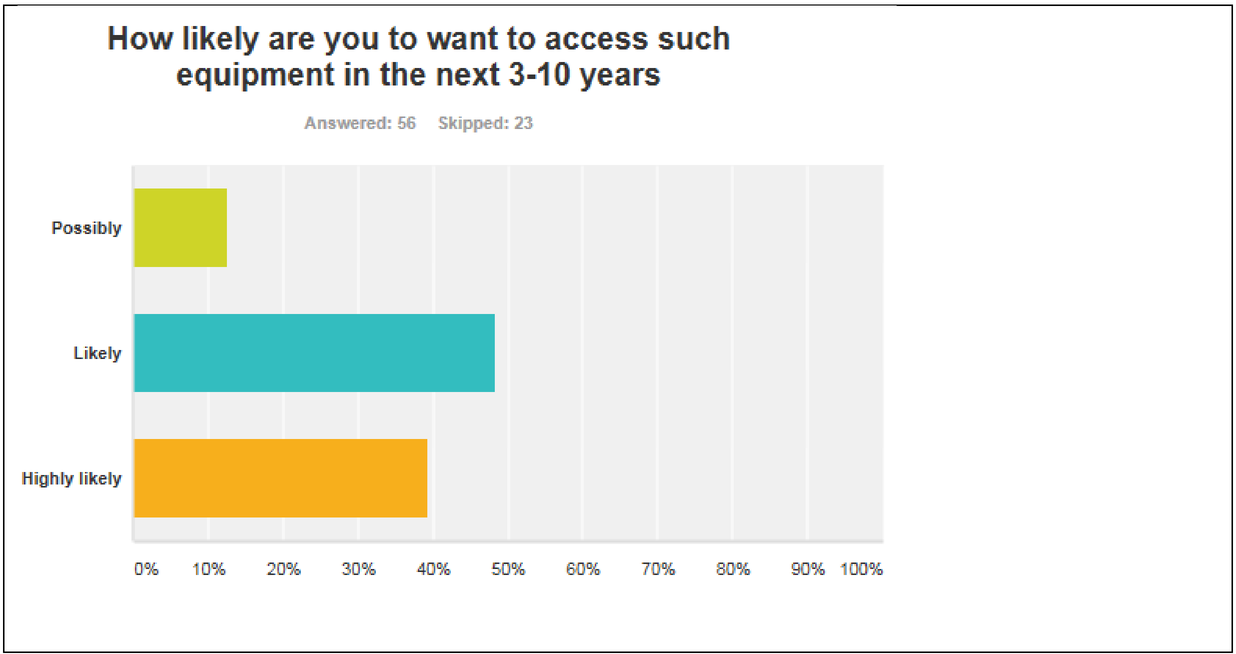
In addition, comment from several relevant IB industrial contacts was sought to add further detail and context to gain a deeper understanding of potential commercial interests in the pilot facility.

10.2 Survey results

There were 79 responses to the online survey, 42% of which were from industry, representing manufacturers or technology developers (37%) or contract manufacturing interests (5%), the rest were from academic (43%), publicly-funded or non-profit RTOs (14%).

77% of respondents expressed an interest in accessing the facility, with equal interest in using the PDU and pilot test rig. However, when asked “how likely are you to access such equipment in the next 2 years” of the 57 interested respondents, only 10 indicated that they were ‘highly likely’ to access such facilities, looking out to 3- 10 years this rose to 22 out of 56 respondents.





Of the 56 respondents with an expressed interest in the facilities, 91% had a specific interest in fermentation and 46% in biomass pre-treatment.

Most interest was received from the bulk and fine chemicals sector and secondly from the biofuels sector, which is not surprising considering the PDU and Pilot Rig were originally designed for processing of cellulosic feedstocks to ethanol.

For those not interested in using the facility, a large proportion felt they either had adequate access to scale up facilities (31%) or the plant configuration was not felt to match their needs (13%). The rest felt they had no need for, or interest in scale-up.

10.3 Findings from stakeholder interview

Short face-to-face or telephone interviews were held with 10 stakeholders representing commercial product developers and commercial contract services to ascertain interest in the identified facilities and to gain an understanding of issues that affected commercial interests as the key stakeholders looking to scale up to large-scale, pilot production as a pre-cursor to commercial development.

flexibility

A key problem expressed by some stakeholders was the bespoke nature of the plant and lack of flexibility, which would make retro-fitting to alternative uses difficult. Space limitation at the plant was also identified as an additional difficulty when looking to add to flexibility.

The facility was seen to be limited in the specific types of fermenters available (limited to common high solid (30%) and liquid fermentation). Questions were raised around the exact nature of the ATEX characterisation of the facility, as this was an important factor that could limit certain types of work using flammable gases and solvents. Similarly, there are no downstream product purification facilities, and limited capability to add these due to space limitations on the site, which also limits interest.

location

There was seen to be some potential benefit in having an accessible facility in the south of the UK to compliment other UK pilot facilities (CPI, Beacon and IFR). However, in cases where test batches would be run, location was seen to be less of a concern, and certainly not a barrier to use.

Some concerns were expressed about the potential to attract the appropriate staff capability in the South of England.

Nature of interest

It is recognised that the facility does not suit pharmaceutical (due to problems achieving GMP standards) or marine applications (high corrosion risk), which limits its appeal to certain sectors.

There was relatively little interest expressed by commercial interests in gaining access to the highlighted facility as an open-access facility in its own right. Only 3-4 commercial stakeholders expressed any interest in short-term contracting or running projects through the facility as batch tests and for product development and testing, including use of the small pilot rig alone (2 interests), where further development and scale-up would then progress elsewhere.

Some commercial stakeholders (2) were more interested in part or total purchase, which was unexpected. Accessing open-access facilities like CPI was seen to be relatively expensive (this was not quantified further) and the expectation was that the identified facility would be no different if run as an open access facility. This was seen as a driver to look to outright purchase where there was a specific interest in the facility.

In other cases there was some commercial interest expressed in acquiring at least some of the equipment, the intention in such cases was to move the equipment (or in one case to split use of equipment) to more suitable locations to meet their own specific needs. There was some interest in utilising the facility to complement existing capabilities (and further support for this approach was voiced by a separate commercial interest to help build and develop wider UK competence), though again this would be through re-location of specific equipment.

10.4 Conclusions

While there was a general interest in accessing the pilot facilities, there was a relatively low level of likelihood expressed that the facilities would actually be accessed by interested parties within the short-to medium term. This suggests that there is not currently a strong commercial demand for such additional facilities. In part this may be due to the relatively limited flexibility of the identified plant facilities and configuration.

Commercial interests were less interested in accessing an open access facility, but surprisingly some interest was expressed in purchase of the equipment for exclusive use, or for relocation to compliment other existing capabilities. There was commercial interest in accessing the small pilot rig to undertake smaller test runs.

10.5 Prospectus for an open access facility for pilot scale process development

The proposed facility provides a Process Demonstration Unit along with a 100th scale small pilot rig (Scale-through rig) for pre-trials testing.

Potential areas of interest

The facility is likely to be of interest to those with an interest in cellulosic processing and extraction of sugars from lignocellulosic feedstocks for onward utilisation in a range of market sectors.

The facilities should more broadly suit any pilot to large scale fermentation process, although any requirement for sterilisation of feeds would tie-up one of the fermentation vessels as there are no intermediary holding tanks. The facility was not designed to work aseptically so there is no formal 'sterilisation in place' (SIP) system on the largest fermenters. However, the seed fermentors (up to 1000L) have SIP capabilities rendering them capable of undertaking smaller scale process research – for example on recombinant yeasts or slow growing bacteria.

The facility is less suited to pharmaceutical and unsuited to marine applications (due to corrosion risks) and so would primarily suit work in the fuels and chemicals sectors.

Process Demonstration Unit (PDU)

Fermentation vessels in the main PDU (left) and by-product capture tank (right)

The bespoke PDU is fully automated and integrates biomass pretreatment, enzyme hydrolysis and fermentation processes. It has a flexible feedstock capability and can work with high solid concentrations (>30% w/w). It has the capability to work 24/7 for long periods in an automated fashion.

The PDU Outline Equipment List

Item	Description	Size	Comments
	External silo		Standard external silo loaded from a walking floorway, pit and elevator system adjacent to the silo. Material transported from silo to mixing reactor via bucket lift
PT01	Main Pretreatment Pressure Reactor	300kg	A non-agitated mixing tank above the main pre-treatment reactor allows dosing with water and dilute (<1% w/w) acids/alkali prior to pressurised steam pre-treatment (capable of operating up to 220 degrees C and 20bar)
EH01	Enzyme Hydrolysis Tank 1	12,000L	PT01 and EH01 are linked together enabling high solids and high viscosity operation. The tank has recirculation and agitation for mixing. It can be dosed automatically with enzymes and/or acid/base to adjust pH. Temperature control is via a heat exchanger.
EH02&3	Enzyme Hydrolysis Tank 2&3	2 x 6,000L	These tanks can take material from EH01 once the viscosity has reduced. In both cases these can be dosed to change pH or take a further/different dose of enzymes
FV01&2	Production Fermenter 1&2	2 x 6,000L	Large batch fermentors – standard agitated system with retractable DOT and pH probes.
CFV01	Production Fermenter	1,000L	Set up to run in continuous fashion.
CG11	Seed Culture Fermenter	1,000L	Usually used to inoculate the production tanks. Transfer is fully automated
CG10	Seed Culture Fermenter	100L	Medium-sized fermenter – could be used to inoculate production tanks
CG09	Seed Culture Fermenter	10L	Smallest seed culture tank – usually inoculated from a pooled flask culture by aseptic transfer
BP01&2	By-product Tank	2 x 60,000L	Non-stirred tanks to collect waste beer from the fermentors. These can be dosed with acid/base to inactivate the broth prior to collection and discharge

The PDU is also equipped with the following:

- Scrubber – to reduces volatiles in waste gases
- Energy recovery system - to allow engineers to model the energy efficiency of the plant
- Heat exchanger - for rapidly adjusting temperatures in process tanks. It can be used for any process vessel but was designed to work with high viscosity materials
- 'Clean in place' system to clean the plant vessels and pipe work. It is also possible to 'free steam' parts of the plant
- Steam boiler – capable of working up to 25bar
- Fermentation vessels are ATEX rated, providing compatibility with highly flamable substances.

The facility is equipped with a process control room which allows automated recipe control and monitoring for almost all processing on the main PDU. It also has a small micro lab with autoclave, microbiological safety cabinet and benching for production of seed cultures and monitoring in-process samples.

Pre-processing capability is limited; there is a small hammer mill, further pre-processing is currently limited to soaking and washing using equipment such as dough mixers and sieves.

The facility currently has no downstream processing capability (as ethanol separation is a well- established process) so the process stops at the generation of the "beer" ferment, which is currently disposed of after inactivation. However, there is the capability to add small-scale processing equipment (for example on skids).

Silo and conveyor system

Production fermenter 6,000 l

The Scale-through (ST) Rig

The ST system has a 30kg steam hydrolysis pre-treatment system, capable of dealing with high solids and an associated fermentation capability. However, vessel transfers and much of the process operations are manual. The system has been used frequently to assess the potential of different cellulosic feedstocks. and to generate materials for research purposes in the lab (optimising different process test conditions).

Scale-through system. To the left is the pre-treatment system (30kg) and to the right is a high solids enzyme hydrolysis tank (200L). Two 100L fermentors are covered by the blue pumps and associated pipework

Item	Description	Size	Comments
PT02	Pilot PT reactor	30kg	Manually fed. It can operate up to circa 240°C/20bar. The PT reactor is vented to a flash tank and the pre-treated contents removed at the bottom
EH11	Pilot EH Reactor	200L	This is a high solids mixing tank using stirring and/or recirculation
FV11&12	Pilot Fermenter	2 x 100L	Pilot fermenters – that can be inoculated from EH11 by overpressure.

The ST facility has its own small hammer mill and a small mixing unit for combining biomass with hot water and acid or base treatments prior to addition to the PT reactor.

NNFCC

NNFCC is a leading international consultancy with expertise on the conversion of biomass to bioenergy, biofuels and bio-based products.

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