INDUSTRIAL BIOTECHNOLOGY FOR IMPROVING THE PRODUCTION OF HIGHER VALUE CHEMICALS:

A report on the consultation with academic and business communities on future investments

Background

The UK Chemicals industry generates £9bn GVA a year, employs 105,000 people[1], and is one of the highest energy intensive industrial sectors. There is a strong industry driver to reduce carbon emissions, and consumer demand for more sustainable products, which move away from using fossil-based carbon to manufacture chemicals. These increased drivers for sustainability mean that the industry is open to innovation that will lead to more sustainable manufacturing practices and could enable the UK Chemicals industry to return to a world leading position.

Modern bioscience technologies, and multidisciplinary approaches have the potential to enable the industry to address this challenge, through the production of chemicals via bioprocesses, and the manufacturing of bio-based chemicals from non-fossil based feedstocks. This approach could also contribute to addressing climate change and sustainability issues by reducing demands on fossil fuels, lowering the energy costs of traditional chemical process, and permitting the development of novel materials with better properties such as biodegradable/bio-compostable plastics. However, for chemical manufacturers to adopt these more sustainable processes there is a need to improve connections with the bioscience research base, and address the challenges faced by industry in applying these processes in a multidisciplinary and collaborative way.

Noting this opportunity BBSRC consulted with industry and the academic research community, to better understand BBSRC's role in enabling bioscience to support the desired innovation, and building on investments in this area to date. This report summarises the responses received through the consultation and outlines the current drivers within the sector and the research challenges and barriers that need to be addressed in applying bioprocessing to improve the production of higher value chemicals. The views expressed in this report are those of the industry and academic industrial biotechnology community and are not necessarily BBSRC-UKRI's position.

Target Chemicals and Markets

Industrial chemicals fall into several different categories including speciality, performance or effect, fine and commodity chemicals. Bulk or commodity chemicals fall into a price range of \$1–3/kg and fuels \$0.5/kg. From the companies consulted speciality, fine and performance chemicals fall into a range of \$10/kg to \$1000's/kg but can fall as low as \$3/kg. In recent years, the UK has been losing share of total sales by the EUs chemical industries. This is due to a decline in output of some bulk chemicals and hides the growth in UK speciality chemicals[2].

Speciality/fine chemicals produced using bioprocesses are used across multiple sectors including pharma/ healthcare, personal care, household, food ingredients and agrochemicals. Examples include surfactants, polysaccharides, micronutrients, natural flavour and fragrances, silks and next generation adhesives, chelates, butanol acetone for esters and solvents, active pharmaceutical ingredients (APIs), pharmaceutical intermediates and antibiotics.

Current UK Strategies relevant to the sector

Several UK strategies published in the last 12 months are relevant to the application of biotechnology to the manufacturing of higher value chemicals. Industrial biotechnology can be applied to priorities outlined in the BEIS Clean Growth strategy 2017[3]; low carbon innovation, clean energy innovation, energy efficiency, carbon capture usage and storage and zero waste by 2050. Growing the bioeconomy: a national bioeconomy strategy to 2030[4], published in December 2018, outlines the vision that in 2030 the UK is a global leader in developing, manufacturing, using and exporting bio-based solutions. There is unprecedented demand on global resources and a thriving bioeconomy will produce innovative products, processes and services that rely on renewable biological resources instead of fossil fuel alternatives. It outlines "creating new forms of clean energy and new routes to high value industrial chemicals" and "producing smarter, cheaper materials such as bio-based plastics and composites for everyday items as part of a more circular, low-carbon economy".

The revised Chemistry Council (previously Chemistry Growth Partnership) strategy: Sustainable innovation for a better world[5] states that biotechnology has an increasing role to play in the chemicals industry. Their strategy comprises of 3 work streams; Innovation, Supply Chains and Regions and Infrastructure. Under their Innovation and Supply Chain priorities are 4 themes relevant to application of bioprocessing to chemicals manufacturing:

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1. Delivering advanced materials and molecules – which includes sustainable materials for consumer products and sustainable packaging.
    - Demands on products are rising in terms of functionality and environmental profile. Developing a healthy pipeline of new, innovative materials that are renewable and sustainable is at the heart of the Chemistry Council Strategy. New sustainable raw materials, new sustainable manufacturing routes and delivering a cradle-to-cradle approach to managing products through their lifecycle are all features of this sub-programme.

1. https://lb-net.net/wp-content/uploads/2018/02/LBNet-UK-Top-Bio-based-Chemicals-Opportunities_Final_Dec2017.pdf
2. Challenging Times, Sean Milmo. Chemistry and Industry Magazine Issue 09 2018
3. https://www.gov.uk/government/publications/clean-growth-strategy
4. https://www.gov.uk/government/publications/bioeconomy-strategy-2018-to-2030
5. https://ukchemistrygrowth.com/wp-content/uploads/2019/02/Chemistry-Council_v17_lr.pdf

2. Creating a pipeline of green supply chains – which includes waste to feedstocks.
    - Innovative approaches will reduce, reuse and recycle waste at all stages in the supply chain and new sustainable feedstocks need to replace unsustainable feedstocks.

3. Supporting clean growth by rebuilding cost competitive and carbon efficient supply chains.

4. Ensuring strategic raw materials are identified and are in place to support inward investment in the UK.

Biotechnology (Industrial Biotechnology, Biocatalysis and Synthetic Biology) is one of three core technologies highlighted for development. The other two are Chemistry (green chemistry, smart chemistry and catalysis) and Process and Digital Technologies (Digitisation, Big Data and Novel Processes).

At a meeting in November 2018 the Chemistry Council launched its new strategy and invited the community to provide input to developing its innovation programme. Two areas were highlighted relevant to Industrial Biotechnology:

1. Sustainable materials for consumer products

Market Opportunity	Vision 2035	Government support required
Accelerate the development of sustainably sourced, performance focussed new ingredients / chemistries Collaborate along the supply chain, utilise existing UK infrastructure and expertise, establish new routes (e.g. Biotechnology and Synthetic Biology) and new sustainable feedstocks.	All raw materials and ingredients to be sustainably sourced and manufactured in environmentally friendly processes (reduce use of energy, water and solvents). Replace all petrochemical feedstocks with biodegradable, low aquatic-toxicity materials.	£20M pa for 5 yrs for collaborative funding, £5M for training, £20M for industrial incentives for new manufacturing sites.

2. Biotechnology and continuous flow technologies

Market Opportunity	Vision 2035	Government support required
Accelerate the application of biotechnology as a sustainable technology Increase production and use of key biocatalysts across a variety of sectors to deliver solutions to issues in the chemical-using industry.	An evolution platform that is automated and modular to utilise accelerating technologies e.g. digital predictive modelling. The evolution technology will be used to underpin future synthetic biology aspirations.	£15M pa for 5 yrs for collaborative funding, £5M capital for lab and pilot scale assets, £3M pa for 5 yrs for scoping studies, £8M for training.

Changes in the chemistry sector: key drivers for using IB

In 1998 the 12 principles of green chemistry[6] was published to propose a range of ways to reduce the environmental and health impacts of chemical production. The principles include designing energy efficient and less hazardous synthesis and using renewable feedstocks where possible. In addition catalytic reagents that repeat a reaction are superior to stoichiometric reagents (ones that are consumed in a reaction). Industry are still looking to green today's chemical manufacturing and bioprocessing can be used to address these challenges. It can be used for more efficient manufacture of chemicals from feedstocks that are both biomass and petrochemically derived. One key driver of the sector is the replacement of globalisation by sustainability as the major influence. They are responding to demands of brand owners for the development of technologies that make products suitable for the emerging circular economy[7].

Other key drivers and reasons for using bioprocesses are where specific advantages over chemical manufacture can be realised, for example, where chemistry has limited performance in product purity, functionality and in chirality. The types of molecules the chemicals sector is looking for has changed over recent years, moving away from chains of unsaturated carbons and planar aromatic molecules to three dimensional chiral molecules and those with hetero atoms (O,N) playing a greater role. Biocatalysis is a powerful tool that expands and complements the range of transformations that are possible with traditional synthetic chemistry methods and can overcome cost and efficiency barriers. Sometimes a bioprocess can be added in to an existing process to overcome a specific limitation (e.g. remove a persistent impurity) or a bioprocess may already be the standard (e.g. antibiotic manufacture) and new technologies offer potential for productivity gains through more efficient synthesis. Biological transformation also enables the use of cheap / poor quality starting materials that traditional chemistry cannot use in an impure state.

In some cases when considering the use of a bioprocess as part of/ replacement of traditional chemical processes reducing reliance on fossil fuels as feedstocks or reducing energy consumption is valued but is not the primary factor. Products made via bioprocesses with superior performance qualities or that are more economically manufactured are more easily adopted by industry than chemicals that only have an environmental advantage. These superior products can demand a higher value but still need to be in similar price brackets to their chemically synthesised equivalents to remain competitive. Manufacturers will want to drive down energy requirements of processes and hence the production costs; therefore life cycle analysis is needed to provide valuable information to industry in order to make decisions on which processes could be implemented economically.

Natural labelling of ingredients gives a product a premium and is becoming more important and more in demand. In some cases bioprocesses can be used to make natural products in a way that is more sustainable than harvesting them. Therefore IB has a key role to play in this market as it enables manufacturing of natural products in a cost effective way and does not deplete natural resources.

Other products and sectors where natural labelling is important include colourants in foods, nutraceuticals and is currently a major trend in personal care products. Furthermore, those brands with the greatest sustainability advantages and transparency are the fastest growing brands; consumers are clearly beginning to make choices based on what are perceived to be more

6. http://www.rsc.org/Education/Teachers/Resources/Inspirational/resources/6.4.4.pdf
7. Challenging Times, Sean Milmo. Chemistry and Industry Magazine Issue 09 2018

sustainable products. Transparency in communications regarding how ingredients are produced will be a major factor in the success of biomanufactured products. Whilst the ingredients may be from GM origins it may be necessary to ensure GMO-free final products as the consumer in the shopping aisle will determine their success. Engaging consumer scientists could ensure better take up of products and avoid any unforeseen pitfalls. Data from life cycle analyses will allow direct comparison of environmental sustainability to conventional materials and make sure this results in genuinely sustainable solutions being implemented, rather than clever marketing.

Case study

Benefits of bioprocessing in the flavour and fragrance market

A flavour or fragrance that is produced naturally has a market advantage over an identical product produced synthetically. This is due to consumers valuing the label 'natural'. Synthetic flavours/fragrances are typically derived either from crude oil, or the result of non-biological chemical reactions to produce a synthetic product from natural substrates. Natural products that are extracted from crops are often reliant on harvests and/or consumer trends. A flavour or fragrance can be classified as natural if it is a compound already known in nature and is manufactured from a natural starting material through enzymatic or microbiological conversion.

A recent example of bioprocessing impacting the flavour and fragrance market is through the production of nootkatone, a natural organic compound and the most important and expensive aromatic of grapefruit. Natural nootkatone is at the higher end of the flavour and fragrance market and can be sold for up to ~ $4- 7000/kg (not far off beluga caviar $7 -10,000/kg). Synthetic flavours/fragrances can be much cheaper e.g. synthetic menthol ~$20/kg. Nootkatone can be extracted from grapefruits but this is a small crop and nootkatone from grapefruit is only present in small concentrations which is why it demands such a high price. It takes around 400,000kg of grapefruit to extract 1kg of nootkatone. Supply of grapefruits is affected by disease, hurricanes and falling demand for the fresh fruit and juice. During hurricane years, nootkatone can be impossible to source. However, nootkatone can be made by converting the orange extract valencene, which has a lower price than nootkatone and is more readily available. The current chemical conversion process from valencene to nootkatone is not very efficient and is dependent on some undesirable heavy metals such as chromium and manganese, and strong oxidising agents. In addition the product can only be labelled as synthetic. Oxford Biotrans has developed an enzymatic conversion process which is more efficient than the chemical process and also has the advantage of the product being classified as natural. This research was first developed by Luet Wong funded through an EPSRC grant on the p450 enzyme reaction. This was spun-out into the company and the research has been developed further and expanded through the BBSRC NIBB business interaction vouchers capitalising on their extensive p450 chemistry and expertise.

Producing natural flavours and fragrances in this way can avoid dependence on low volume crops which are subject to greater fluctuations in availability and can also deliver a much cheaper product.

In summary, applying biological processes to the manufacturing of higher value chemicals can be beneficial in three ways:

I. **Higher quality products:** biochemistry/ biocatalysis can be used to produce chiral molecules with high levels of stereoselectivity and with low-levels of impurities giving a higher quality/ purer product.

II. **Reducing manufacturing costs: Adding in biochemistry/ biocatalysis stages in manufacturing can reduce costs by**
   - lowering energy costs as it removes the need for high or low temperatures required in chemical synthesis;
   - reducing the number of stages required in multiple stage processes and therefore labour and overhead costs could be lowered as much as ~20%;
   - downstream purification costs are reduced due to fewer impurities;
   - reducing/avoiding co-factors and/or heavy metals catalysts.

III. **Sustainability: bioprocesses can lead to more sustainable products and manufacturing methods by**
   - lowering energy consumption by reducing processing steps and extreme temperatures;
   - can recycle co-factors and recover precious metals required in catalysis;
   - reduce reliance on fossil-based feedstock by better utilising biobased/waste feedstocks;
   - can produce natural products without the need for harvesting crops that can have high environmental impact through high water consumption or land clearance.

Barriers to uptake of Industrial Biotechnology by the Chemicals Sector

Corporate responsibility will only take industry part of the way towards implementing sustainable processes but ultimately economics will determine the extent that environmental sustainability will be important in business decisions. Competing against an established optimised petrochemical business model that is difficult to displace on commercial terms requires influence over policy, consumers and regulators to drive the change to sustainable biobased manufacturing. Incentives and taxes (carbon) need to be introduced to create the change needed and make it competitive.

Timing can also be an issue: the speed at which a process can be developed and implemented could be a deciding factor in choosing what type of process to use. For some products, e.g. APIs, it is important to get the product to market first if it is to be successful. Therefore it if is going to take a longer time to develop a bio-manufacturing process industry might be required to implement a chemical manufacturing process in order to get the product to market.

Changes in regulatory frameworks depending on the outcome of Brexit are likely to lead to changes to the tolerable cost for these higher value chemicals which may influence the invention model profoundly. Extra costs of companies having to register chemicals for a UK version of REACH as well as EU REACH would be unwelcome to the sector and inhibit SMEs capabilities. Divergence from EU regulations could result in loss of business with the EU trade bloc as it will create non-tariff barriers. 60% of UK Chemistry industry exports are to the EU and 75% of its chemicals imports[8]. This may provide opportunities for bio-based and bio-process products earlier. However, to support emerging biobased value chains, many partners need to be linked together in collaboration from feedstocks to products. This involves both EU and RoW collaboration and trade. The EU with its Bio-based Industries Public-Private Partnership[9] and funding routes to a biobased society is a key enabler that the UK will increasingly find hard to access. The UK does not have all the actors and enablers to go from feedstock to products alone, with the exception of the pharmaceutical industry.

8. Challenging Times, Sean Milmo. Chemistry and Industry Magazine Issue 09 2018
9. https://www.bbi-europe.eu/

Potential expansion of product pipelines and feedstocks

Currently key targets for the chemicals sector are where higher quality products can be achieved through bioprocessing, for example those with complex chemical structures that are difficult to produce via synthetic organic chemistry e.g. natural products, where stereo- and regio-selective transformations have been evolved by nature. There is also interest in harnessing bioprocessing for high volume, commodity chemicals, where it could provide an alternative to conventional processes from oil and gas feedstocks, and significantly reduce the industry's carbon footprint. However, in most cases it remains challenging for new biological processes to compete with the incumbent technology. It is anticipated that bioprocessing will enable the expansion and commercialisation of new, cheap & highly functional molecules with molecular weights of 100–600, i.e. non-peptide compounds with biological activity. Biological processes can make these compounds with unique chiral architectures under relatively low temperatures and pressures, with very few competing side reactions. However, the scale up of these processes needs to be further developed in order to be competitive with current organic chemistry processes.

In manufacturing higher value chemicals in the pharmaceutical sector, bioderived products that use a biological feedstock, are not a key priority because the costs are in the process and not the feedstock and there is no customer demand for this in pharmaceuticals. However, for high volume products that use fermentable sugars e.g. amoxicillin, companies are now looking at alternative sustainable feedstocks including waste bread[10].

The UKBioChem10 report[11] includes some solvents used by the pharma industry on its top 10 chemicals for the UK to support. However, the pharma industry only uses these solvents in small quantities compared to the chemicals industry, therefore they are not that influential as customers but use what is available in the market.

10. http://www.biorenewables.org/casestudy/pharmaceuticals-food-waste/
11. https://lb-net.net/wp-content/uploads/2018/05/UKBioChem10_Report.pdf

Integrating bioprocesses into the chemicals industry

Bioprocessing faces strong competition from conventional chemical processes where supply chains and markets are well established and the R&D and infrastructure costs have already been absorbed over many decades. Therefore when developing biological processes consideration needs to be given to the market needs and how open the supply chains are to adopting novel processes and products, and whether it is the effects/properties of the product or the chemical itself which is important or even essential. This is likely to be case specific, therefore consultation is needed with the relevant actors from the supply chains and customers before embarking on development of new products and processes.

Pharmaceutical products are well defined and bespoke to a company, and producing novel molecules requires going through registration and clinical trials which is very expensive and slow. However, developing new processes is easier and only requires registration and toxicology testing if the impurity profiles are different; much cheaper and quicker than clinical trials. Whilst different molecules with the same effects/properties as current pharmaceuticals cannot be integrated into the market without registration and clinical trials, there are some chemicals involved in the manufacturing process where properties are more important, for example alternative solvents.

In other sectors drop-in chemicals (i.e. replacing a chemical already in the market like for like) may not be essential but can be beneficial, as it can avoid a long period of market introduction and can reach into established supply chains easily with a superior or cheaper product. Drop-in chemicals can also be beneficial where there are opportunities for large impact on carbon footprints, however drop-in replacement for existing petrochemically derived ingredients will not usually work due to the cost of the bio-route. Government legislation could have a role to play in enabling more economic models to support bio-based chemicals through a scheme similar to the Renewable Transport Fuel Obligation (RTFO): a requirement since 2008 on transport fuel suppliers to ensure that five percent of all road vehicle fuel is supplied from sustainable renewable sources by 2010. New targets were put into place in April 2018 to double the use of renewable fuels in the UK transport sector within 15 years, cutting the sector's reliance on imported diesel.

In some instances biobased processing to the exact same chemistry as derived from petrochemicals may not be appropriate when it comes to end of life considerations for the product. For example a biobased route to plastic monomers does not help if the end chemistry has the same properties of non-biodegradability. Therefore end of life and environmental impact of the chemicals should be taken into consideration in the early stages of development.

In the flavours and fragrance markets, it is a combination of the purity and organoleptic properties (taste/smell) that define products. The end effect is of paramount importance to the formulator and is therefore what drives demand.

Novel functionalities are important for widening portfolios of chemicals often needed in pharma, healthcare, general fast moving consumer goods (FMCG) and agri-chemicals. For example new antibiotics, pesticides and higher value actives for skin care benefits such as anti-ageing, anti-wrinkle and skin-lightening. Bioprocessing can often provide this more easily than traditional chemical processes and can lead to new product launches and growth of the different sectors. Development of novel products requires more activity around discovery but often needs to be done in collaboration with end users to ensure relevance to the sector markets. A key public and political driver is that of sustainability, therefore development of new products should ensure the product and process is sustainable and that the whole life cycle is analysed during the development process.

New chemical entities with novel functionality will require essential safety testing prior to consumer use and therefore safety due diligence should be done as well as financial due diligence for a new process or product. This should be taken into account as soon as possible in the research and technology development process and consideration for what testing is required e.g. where no animal testing is possible. SME's often don't have the resources to consider these.

Both approaches of "drop-in" replacement chemicals and bio-based material development for functionality are important for industry and different economic models will be used to develop and commercialise a bioprocess. Understanding the basis for any regulatory requirements e.g. product identification, purity, process are important to understand during the development of novel products and processes. Determining freedom to operate and/or whether IP can be established in the process and/or the end product will also be important in the early stages of development.

Bioscience for manufacturing higher value chemicals

The consultation revealed several key areas of bioscience research which are important for underpinning and improving the manufacturing of higher value chemicals. Chemicals that are manufactured through bioprocessing can either be produced through biocatalysis with isolated enzymes, fermentation of yeast, bacteria and algae, and potentially also through production in appropriate higher plants (e.g. tomato, tobacco).

Rapid developments in biology have made new approaches to fermentation possible, for example transferring whole pathways into new hosts. However, this is still a relatively time consuming and expensive activity to even get to proof of concept as well as having a high risk of failure. More examples will improve our understanding and give greater confidence in the success of this approach. There is still a need to improve fermentation processes through new fermentation organisms/production strains and strain engineering to enhance enzyme expression and better tools to adapt novel microbial hosts with appropriate properties e.g. temperature and pH tolerance, feedstock adaptation, dealing with toxicity.

For biocatalysis of single step transformations research is needed for new reaction chemistries to replace the least efficient chemical catalysis or for the development of novel products. Protein engineering can be used to develop new classes of enzymes or improve current enzymes/classes of enzymes to have the required properties to be used under industrial conditions.

Case study

Learnings from the success of reductive amination

A good example of a new class of enzymes being developed is the reductive amination (IRED) work discovered in 2013/14 which is now being used at kg scale. There were several reasons why this work was successful in such a short period of time:

- There was the prerequisite that the reaction was meeting a substantial need where existing methods had problems.
- Serendipity played a part in that the IRED enzymes discovered were part of a large previously unrecognised family of enzymes which allowed access to wide diversity to explore.
- The key differentiator was the existence of a large public private consortium (Chem21 sponsored by IMI) that provided funding to academic groups and engaged, informed and motivated industrial partners (GSK, Pfizer, Bayer, J&J, Orion, Sanofi) who were able to drive the direction towards implementation as well as provide the research resources.
- The dynamics of this group were critical; with openness and excellent communication from all sides which enabled rapid progress. In addition to the scale up development there have been over 20 papers so far from the Chem21[12] collaborators representing more than 50% of publications in the field, and a significant proportion of the rest from Roche and collaborators.

12. https://www.chem21.eu/

There are several other classes of enzymes that have similar promise to IRED enzymes e.g. P450s, halogenases, alcohol oxidases, carboxylic acid reductases, methyltransferases, fluorinase and nitrile reductases but still require further work to ensure these classes of enzymes have the required properties for industrialisation e.g. microbial expression, substrate specificity, cofactor recycling, optimised supply of essential metals, stability, temperature and pH tolerances. BBSRC funding through a NIBB award followed by an IB Catalyst grant has already advanced recycling of the expensive NADH cofactor by developing a flexible platform technology. By immobilising the enzyme catalyst of industrial processes on a carbon bead with two other enzymes, a hydrogenase and a NAD+ reductase, 100 % atom efficient biotransformations have been achieved[13].

Work on developing these enzymes is highly competitive but can be a slow and iterative process so technologies are needed that will speed up directed evolution processes e.g. machine learning. The UK has key strengths in this area and there is the opportunity to be the most competitive and collaborative in the enzyme discovery field. The ability to join up different enzymes for sequential/ cascades of reactions would be highly beneficial to chemical production.

13. https://lb-net.net/wp-content/uploads/2018/05/UKBioChem10_Report.pdf

Research challenges for manufacturing higher value chemicals

Many research and technology challenges were highlighted through the consultation that could improve the UK's capability in fermentation and biocatalysis for industrial manufacture of higher value chemicals. Whilst these are separated out into biological focussed challenges and those at the interface with engineering and chemistry there was a strong message from both the academic and industry communities to provide support that enables the integration of the biology with the engineering and chemistry rather than provide separate research funding schemes. Better integration of the disciplines is needed; engineering and data science can only help if there is a mutual understanding of the capabilities and tools within other disciplines and how a bioprocess works. Research challenges and knowledge gaps were also highlighted for data, modelling and lifecycle analysis.

Biological focussed research challenges:

i. Increasing yields and concentrations of biocatalytic and microbial production of chemicals in order to increase economic viability through:

- More efficient tools including synthetic biology to engineer microbes for rapid assembly and reconfiguration of genetic structures for optimal and robust enzyme/microbe activity including high-throughput engineering platforms for microbial biosynthetic systems;
- Improved understanding of the bottlenecks to increases in yield of a given product or process across a range of biocatalytic, microbial and multicellular production platforms;
- Improved cell stability in a productive homeostasis to allow longer lifetimes leading to greater output;
- Development of new tools for optimizing production strains e.g. on-line fermentation efficiency and cell performance monitoring systems;
- Improving/creating new biocatalytic processes by applying expertise in metallo-enzymes optimising and developing predictable metalation tools and engineering catalytic metal-centres;
- Ensuring tools for engineering microbial systems include diverse host/ enzyme systems suited to a range of industry process conditions, with well-defined comparative performance data. Host selection should be based on their suitability in an industrial setting.

ii. Improved integrated high-throughput platforms and processes for discovery, analysis and optimisation of bioprocesses for higher value chemical manufacture

- Screening of functionalities of individual microbial isolates or enzymes will lead to the identification of strains with increased commercial potential and reduce the time to develop new bioprocesses;
- Identification of novel chemistry could speed up drug discovery and novel functionalities for the development of new materials.

iii. Development of plant cell culture systems as an alternative production platforms for high value chemicals by

- Further understanding plant metabolic pathways;
- Exploitation of plant genome sequence information as higher plant species are sequenced e.g. Earth BioGenome Project.

iv. Scale out of biochemical processes is a key challenge in the new product discovery phase:

- Low volumes of high numbers of molecules are required for screening novel functionality;
- Scale out of fermentation systems to screen genome constructs, enzymes and microbes for industrial robustness and feasibility. This was highlighted as technology development challenge and was gap in open-access facilities for SMEs.

v. Greater understanding of mechanisms for dealing with toxicity and transport of products in fermentation processes.

Research at the interface with engineering

A key part of using industrial biotechnology in manufacturing of higher value chemicals is the integration with process engineering and reducing the costs and time of process development. Several research challenges were highlighted by the respondents:

i. Further development of process engineering and process chemistry for improving biological processes:

- Improved understanding of how unit operations already employed in conventional chemical production can be better used in the biotransformation processes is necessary; for example could transformation move from stirred tanks to flow/continuous reactors? There are benefits in combining both bioprocessing and chemical processing but this requires further collaborative work;
- Improved bioreactor designs and developing new reactor configurations and modular manufacturing processes;
- Application of biochemical engineering for dealing with different substrates e.g. viscous systems, solids, dilute solutions;
- Orchestration of synthetic biocatalytic cascades through immobilisation technologies
- Improving/ developing inline/realtime reaction monitoring technologies appropriate for biological processes;
- Detailed understanding of the operating constraints of bioprocessing and the product requirements for a feasible overall process.

ii. **Advancing downstream processing and separation science:** Addressing the challenges of product separation for biological processes, which are different to traditional chemical synthesis:
   - Bioprocessing is more effective at higher dilutions, whereas chemical processes can be more concentrated. This leads to the challenges of working with dilute systems and product recovery. Therefore there is a need to develop/improve alternative downstream technologies and approaches including new membrane technologies, configurations and minimising costs of materials and operations;
   - Purification techniques such as ion exchange columns and other resin based techniques can be difficult at larger scale, in part due to cost but also due to the problems of very large columns, which can be inefficient and challenge the physical properties of resins. There is an inherent requirement of a minimal scale which has associated resource and cost implications. Therefore there is a need to address the challenges of product purification and taking a purification process from lab to plant scale. Improved product secretion and product extraction methods for fermentations could help make bioprocesses to be more economically viable.

iii. **Some products require development of more specialised processes, for example, applied research in cultivation and processing of algae, or single use fermentation bio-manufacturing systems for higher value or GMP products.**

iv. **Development of tools and techniques to understand and exploit complex feedstocks including low value food by-products and polysaccharide-based feedstocks:**
   - extraction, purification, analysis and repurposing;
   - addressing diverse/heterogenous compositions;
   - overcoming technological difficulties;
   - understanding regulatory issues of different feedstocks.

Data, Modelling and Life Cycle Analysis

i. **The ability to process large volumes of data is starting to underpin bioprocessing technology developments. Incorporation of new and improved data technologies including process modelling and AI will lead to greater predictability of the enzyme activity, robustness and economics of processes at scale. This could lead to the better design of 'smart' libraries to speed up and reduce costs of enzyme engineering through:**
   - Further understanding of the types of datasets that are needed to enable machine learning and AI-based approaches;
   - Advances in high-throughput platform development will need to be synergistic with data management through iterative interactions between biologists and scientists with expertise in data management, machine learning and AI.

ii. **Robust metrics are needed for assessing relative performance and environmental impact of biological versus chemical processes that will provide valuable information to industry in order to make decisions on which processes could be implemented economically:**
   - Development of accessible tools for life cycle analysis and pre-translation bioprocess evaluation to provide comparative performance data, de-bottlenecking, and better predictability of bioprocess performance;
   - Life cycle analyses data to allow direct comparison of environmental sustainability of innovative processes to conventional manufacturing to ensure genuinely sustainable solutions being implemented, providing consumers with the ability to make informed choices and support future government legislation.

With respect to utilising modern AI technologies there is expertise in the UK in machine learning and computation theory e.g. on molecular dynamics. However activities are somewhat fragmented with a dissociation of the *in silico* groups from the wet work groups so computation experts often design libraries that cannot be built or screened to test the design algorithms. There is also a lack of good published fitness landscapes (i.e. sequence vs activity data for inactives as well as actives with relatively dense coverage of sequence space) for people to test their algorithms against. Concern was raised that funding is not readily available to access to the required high performance computing (HPC) necessary to carry out this type of research.

Research addressing the challenges outlined above iss happening but it was considered to be slow. Reasons for the lack of progress included a perception of a lack of priority for industrial biotechnology at a governmental level and availability of funding for the commercialisation of research where academic and industry consortia are needed to progress technologies. There is also a lack of support that enables SME access to critical academic equipment centres e.g. automation, analytics. There is a lack of venture financing in the UK in this area potentially due to development costs being disproportionate to the market value for some specialty chemicals and end-users are under pressure from overseas competition which cannot support the necessary process development. Development costs increase exponentially at scale-up, which often stalls progress. It was noted that strategies and investments in sustainable growth were not strong enough to support investor confidence.

Support requirements to address research challenges

There is an on-going need to invest in bioprocessing to de-risk bio-manufacturing and encourage end-users to invest as most manufacturers and investors remain risk averse. Growing the bio-economy will take sustained investment to deliver examples of successful application of industrial biotechnology that will drive greater private investment in the future. Many natural products such as organic acids, amino acids, antibiotics have been made using large scale bioprocesses for many years where chemistry cannot compete, however, these took decades to develop and establish. Expanding the portfolio of bio-manufactured products requires greater adaptation of bio-manufacturing systems to reach the same level of productivity that microbes readily achieve for natural products. Until reliable, scalable bio-manufacturing options become available to industry, there will be a hesitance to invest in projects that are dependent upon them.

Several different types of support were highlighted by the responders outlined below.

Funding

Industry sees value in working with academics and other partners and the proof-of-concept funds delivered by the BBSRC NIBB has been very much valued by the community in enabling small scale early investigation and helping establish and prioritise areas of interest. Underpinning excellence in research is needed to build trust and establish value chains. However, there is variability amongst the companies/sectors in their ability to invest on their own in more established projects. Therefore many saw the need for investment through all technology readiness levels (TRLs) from fundamental research to ensuring access to funding for commercial applications.

Funding gaps were highlighted between the outputs of BBSRC NIBB support activities and the start of relevant BBSRC and / or Innovate funding. The current NIBB have been very useful in testing out ideas and forming new relationships through the proof of concept and business interaction voucher funding. However, the networks cannot support projects that allow further collaborative partnerships through large consortia/ long term projects that were supported through the IB Catalyst programme. This leads to little support for process development, scale-up and late stage projects. Funding that would also enable sustained SME access to high end equipment that accelerates process development and product analysis was also highlighted as a gap. Funding needs highlighted in the responses can be grouped into four areas:

Moving research up TRLs and enabling industrial engagement

Many of the fundamental biosciences and engineering/data problems could be addressed by Research Council funding alone with advisory and in kind contributions helping direct research towards industry relevant challenges. However, meaningful industry engagement will be driven by potential for return on any cash/ in-kind investments and could be restrictive in the type of companies that may be able to engage on research projects e.g. SMEs will have less resources available in terms of cash and staff time to allocate to projects.

It was noted by one BBSRC NIBB that researchers were struggling to successfully apply for funding after a Business Interaction Voucher project because the outcomes rarely provided a complete dataset and required further optimisation to address unanticipated outcomes. Work has often stalled at this point because a second round of 'development funding' is needed. Therefore rapid, targeted small-scale funds to address these challenges before large-scale proposals can be successful would help bridge the gap. Responders suggested more follow-on type funding to translate new discoveries and the need for specific calls for the development of post-proof of concept, moving towards TRL 4 and 5.

Supporting academic – industry – scale up consortia

The majority of responders highlighted the need for multi-disciplinary - multi-partner projects where research is needed from the lab, through pilot scale and up to manufacturing. Specifically the need for funding across several TRL levels 3 to 5 was highlighted as a significant gap. It was also noted that support between TRL 6 and 7 for IB was lacking in the UK where the techno-economic risk for large scale production and offtake is not addressed at this stage. Academic-industry consortia are able to de-risk this and enable the data evidence and engagement for the end user industry to invest in a new value chain.

Enabling industry involvement on research projects from the outset provides focus on industry-relevant challenges and provides rapid translation routes. Additionally, having an established producer involved early on in the project will provide the expertise and capability to scale-up the process as ultimately they will be needed to raise the finance to adapt or build a new plant. Funding should be flexible to suit the needs of the project and the partners that need to be involved.

A specific challenge reported by some companies is finding ways to get ambitious programs off the ground where the timing appears critical and the window on specific projects can be quite narrow so there is a need to move quickly or the opportunity passes by. Often internal company investment on its own is unlikely and external funding opportunities are not readily available and may not meet the time requirements. Therefore there is ongoing need to have regular opportunities for investment in a sustained way.

Issues were highlighted for big consortia projects that span several years; the long lead in time to get moving and processed through peer review means that the science and people can move on, and/or industry strategies change direction. Therefore large consortia grants should focus on problems that are not rapidly changing and need to be managed well to keep them on track and relevant to industry needs to ensure the wider benefits are realised.

Supporting SME engagement

Smaller companies noted that shorter 12–24 month projects worked better as it is difficult to predict where the research might lead in longer projects (3+ years). Therefore, there is a need to be more flexible and have an ability to adapt the project as it develops but this is not always possible without further scrutiny for publically funded grants. It was suggested that milestone-driven progression to the next phase of funding could work to better support SMEs by follow-on projects being funded more rapidly in the event that an initial project is successful, supporting more rapid translation and avoiding projects losing momentum.

A bottleneck of lack of human resources within SMEs to undertake the R&D was also highlighted and it was suggested that support for additional people integrated into the company to develop the research would be welcome.

Access to scale up facilities

Access to facilities to support the scale-up of processes to enable the transition from lab discoveries to pilot scale was highlighted as a gap in several responses. Current UK infrastructure has relatively high barriers to access which are better suited to larger industry. Support to access the scale up facilities needs to be flexible enough to enable SMEs and academics to work together as part of a consortium to exploit their abilities to generate data required to support pre-/early translation efforts. Support for SMEs in accessing specialist kit and scale-up facilities, academic infrastructure to enable laboratory scale piloting to identify bottlenecks and for scale-facilities to collaborate on research grants would enable more efficient technology transfer and de-risk investment in early translation.

Scale-down and scale out are also important but are highly specialised. Support for developing these technologies should also be considered where appropriate.

Risk for developing and implementing new industrial biotechnology processes remains high until quite late on in the TRLs compared to other more traditional sector business models. Where UK public sector traditionally reduces its investment further investment funding needs to be secured to bring a product/process to market but this is often difficult to come by in the UK.

Evidence based reports

Business planning is key for making a strong case for developing and implementing a new manufacturing process. Understanding the markets, putting together market reports and realising the cost of the final market are all key elements in knowing whether a process is worth developing. Often market reports are either not available or are too expensive to purchase. In developing a process, an understanding of what is an acceptable production price is needed. This may equate to minimum production rate, but it is the acceptable price that is needed to work back from. Balancing what consumers want vs what they are willing to pay will be important in ensuring successful business models.

Understanding market needs is key to identifying target molecules and functionalities. Developing a product that the market wants and hence industry wants to produce will enable a much stronger position to attract investments from established manufacturers. Therefore processes need to be developed for products with a market need i.e. cheaper, new/better functionality or bringing value by solving an existing problem. Identifying and mapping chemical and food ingredients companies and suppliers that are keen to engage in research in this area and understand their product needs would be helpful in targeting research to generate impact for the UK.

Skills development

The need to support multidisciplinary teaching and training for cross-skilling and up-skilling interdisciplinary scientists and technicians was highlighted to ensure an industrially relevant research base of the future. Exposure and working at interfaces of science areas, development of teaching and learning resources for early career scientists and CPD to increase skills and awareness of IB related research challenges are all important needs.

Policy development and influence

Government policies and legislation encouraging the bioeconomy could make bioprocesses more commercially viable in the short/medium term which would help drive investment to displace incumbent technologies. Increasing public awareness of opportunities for using bioprocessing in producing sustainable products should be a priority.

There are opportunities to engage with the established chemicals industry through the Chemical Growth Partnership (now Chemistry Council) and the Chemicals Industry Association to increase awareness of the potential of IB-enabled manufacturing. The aspiration should be that bioprocessing and biocatalysis are relevant, commonly understood and accepted as technologies of first rather than last resort during process design.

Time to Impact

The research timeframe is approximately five years (one year for feasibility work, two years on developing the fermentation process and two plus years on the engineering and scale up) but this is dependent on the particular challenge. It can take a couple of years to get a process/ enzyme industrialised (or recognise that it isn't going to work) but it can then take a much longer time to build, validate and integrate a new process.

Therefore the timeframes to see impact from investment in this area is still in the medium term of 5–20 years which does not encourage private investors. However, immediate action is needed for the UK public investment in this area to remain globally competitive as capabilities are advancing right now. This should be an ongoing programme of investment.

Integrating new or alternative bioprocesses is still relatively expensive compared to the well-established chemical processes already implemented. Therefore the first targets should demonstrate the economics of bioprocessing to industry: higher value products such as biopharmaceuticals, high value chemical pharmaceuticals and intermediates that chemistry can struggle to make; high value specialty chemicals in cosmetics and consumer products. Once bio-manufacturing processes are proven and costs are reduced it will be easier to roll out to lower value products such as bulk chemicals and fuels. The success of bio-manufacturing could be measured by its progress into markets where the products have lower selling prices.

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Ability of the UK science base to deliver

The BBSRC NIBB activities since 2014 and the investment of £76M through the IB Catalyst has extensively grown the capacity and capability of the UK industrial biotechnology community. There is a world-leading community able to undertake the type of work outlined in this report and therefore there would be significant take up of any activities supported including prospective collaborative grant proposals. The academic and industry research communities are well engaged and have the ability to take advantage of support mechanisms to deliver the challenges outlined above. Some examples of where BBSRC NIBB funding has supported the development of higher value chemicals are outlined in below.

Multidisciplinary research: BioCatNet has supported projects that have brought together cross-skilled scientists and multidisciplinary projects, for example, cross-skilled organic chemists alongside biocatalyst development to address the challenges of using omega-transaminases to catalyse the conversion prochiral ketones to high value optically pure chiral amines where trials of small scale biotransformations have achieved excellent conversions. Other projects have investigated new reaction chemistries including enzyme repurposing, artificial cofactor engineering and non-natural amino acid utilisation for industrially-relevant (abiological) synthetic reactions. In addition to the possibility of manipulating chiral centres the use of these biocatalysts also removes the need to use strong acids, toxic reagents and heavy metals.

Biomanufacturing of high value advanced materials: work on electrochemical energy conversion systems are testing whether copper-containing enzymes can take the place of a platinum catalyst making methanol fuel cells cheaper and more efficient and therefore be smaller and lighter power source than a lithium ion battery.

Plant cell factories: research on plant cell cultures is using synthetic biology to differentiate cells into physiological states tuned for production of specific secondary metabolites e.g. nutritive cells and maturing xylem vessels for the production of proteins and phenolic compounds respectively.

Improving production yields of anticancer drugs: investigation of the biosynthesis regulators of paclitaxel has led to the discovery of new proteins that function as a molecular switch to turn off production of paclitaxel. This will provide new ways for enhancing production yields of paclitaxel in yew cells and will help secure the supply of this important medicine.

Natural production of essential vitamins: β-Carotene is an essential component of the human diet acting as provitamin A, the optimal precursor for retinol (vitamin A) formation. Recent legislation now prevents the use of chemically synthesised carotenoids for human consumption. Research is being conducted to demonstrate that a 'metabolon' – a mechanism for channelling metabolites in bacterial biosynthetic pathways also has useful applications in pathway engineering in plants for carotenoids.

Recycling of enzyme cofactors: a key challenge of biocatalysts in chemical synthesis is developing an efficient supply of NADH. Fundamental studies into hydrogenase enzymes has led to the development of a technology, HydRegen, to recycle the cofactor NADH in hydrogen driven chemical reactions. It has taken components from bacterial cells and fixed them onto cheap carbon beads to assemble a system for recycling NADH that could be used outside of the bacterial cell. This makes for much cleaner and efficient reduction reactions that are used.

Improving efficiency of enzymes: cytochrome P450 are an important class of biocatalysts in the synthesis of materials and medicines. However, the enzymes require heme as a cofactor which is not always fully incorporated into the protein. Work done through the Metals in Biology network has generated *E. coli* strains that have increased capacity to incorporate heme into cytochrome P450 enzymes and have generated a system that gives ~3-fold enhancement of heme incorporation into two very different 'test' heme-containing proteins.

Exploiting natural enzymes: A new class of enzyme, lytic polysaccharide monooxygenases (LPMOs), has recently been discovered that drastically increases the efficiency of biomass conversion. Work is being done through the Metals in Biology network to assess whether a second-generation LPMOs with enhanced substrate activities can be created which could improve the efficiency of biomass as a feedstock.

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MiB: Metals in Biology Network
BioCatNet: Network in biocatalyst discovery, development and scale up
CBMNet: Crossing Biological membranes Network
FoodWasteNet
HVCfP: High Value Chemicals from Plants Network
IB Carb: Glycoscience Tools for Biotechnology and Bioenergy Network