REPORT OF THE BIOPROCESSING RESEARCH AND INDUSTRY CLUB (BRIC) WORKING GROUP ON FUTURE ACTIVITIES FOR BRIC

JULY 2009

REPORT OF THE BIOPROCESSING RESEARCH AND INDUSTRY CLUB (BRIC) WORKING GROUP ON FUTURE ACTIVITIES FOR BRIC

CONTENTS

CHAIRMAN'S FORWARD 2

EXECUTIVE SUMMARY 3

INTRODUCTION 6
Background 6
New Challenges 7

ACHIEVEMENTS OF BRIC 1 8

BUSINESS CASE FOR CONTINUING BRIC 8

RECOMMENDATIONS 11
Continuation of the BRIC network 11
Translation of research projects 11
Addressing remaining and new challenges 12
Meeting the Skills Need 15

PROPOSAL FOR BRIC 2 17

RESOURCES 18

TABLE 1 19

APPENDIX 1: BRIC WORKING GROUP 20

APPENDIX 2: WORKING GROUP MEMBERSHIP 21

APPENDIX 3: DEFINITIONS 22

CHAIRMAN'S FORWARD

It has been a privilege to chair this important Working Group (Appendix 1), reviewing the progress and achievements of the first Bioprocessing Research Industry Club (BRIC) and examining the case for further investment. I was delighted to have a particularly strong and active representation from Industry on the Working Group (Appendix 2) in addition to experienced and senior Academics and Executives from BBSRC, EPSRC and TSB, the synergistic funding partners in this enterprise. If the UK is to exploit the human and scientific outputs of BRIC effectively it is vital that this strategic and active partnership between Industry, Academe and Public Funding Bodies continues.

The recent BIGT Refresh chaired by Sir David Cooksey concluded that the UK was falling behind in its ability to translate the output from its world leading research base in fundamental bioscience into new businesses and new products, and thus to reap the commensurate financial returns. Although there are multiple factors contributing to this situation, including the challenging venture finance and entrepreneurial environment, increased attention and support must be given to all factors that could reverse this trend. Biological medicines continue to be the fastest growing sector of the world pharmaceutical market, led by novel monoclonal antibody therapies where the global market value has trebled since 2004. Improving and expanding the national capacity to invent, design and execute optimal biological manufacturing processes is one essential contributor to the UK regaining its competitive position (definitions in Appendix 3).

The provision of an expanding flux of postgraduate bioprocessing professionals who are trained to a globally leading quality and who are relevant to the needs of industry is absolutely critical. Despite the success of BRIC, and very positive interventions such as the EPSRC Doctoral Training Centres, the current flux of new postgraduates is barely sufficient to meet the current needs of industry. The recommendations made in this report require urgent attention, and given the highly competitive global market for UK trained talent, the Research Councils must be prepared to "over produce" rather than just match the forecast growth in need.

There is no doubt in my view that investment in BRIC and essential partnering initiatives such as the KTN and TSB industry focused innovation and translational projects should be renewed. However this should not be just "more of the same". The next phase must (i) concentrate on those strategic science needs of industry that were not delivered in BRIC 1, (ii) support and translate the most promising and useful outcomes from BRIC 1, (iii) deliver the skilled personnel required and (iv) find room for some real innovation!

The quality of the network and relationships that have been established by the KTN and BRIC 1 are a real UK asset that must be exploited. In the next phase industry must continue to define and prioritise its most critical science requirements clearly and through real collaboration help ensure that the multidisciplinary academic response is appropriate and readily exploitable.

I would like to acknowledge and thank all members of the Working Group for their contributions to this important report. Particular thanks go to Professor Andrew Lyddiatt, Dr Malcolm Rhodes and to the absolutely essential BBSRC Secretariat team who supported us so ably and kept us focussed on the task!

John Stageman July 2009

EXECUTIVE SUMMARY

Recommendations

1. That the BRIC programme is continued for a further 5 years to ensure maintenance and growth of a vibrant bioprocessing community in the UK training skilled professionals and delivering industry-led strategic research which enable wealth creation for UK-plc.

2. That the synergistic partnership between BBSRC, EPSRC and TSB that so successfully linked BRIC 1, the KTN and TSB co-funded industry innovation projects be continued.

3. That the extended programme should enable the most promising research areas already started to be further developed to the point that they can be utilised by companies in commercial processes.

4. That the critical research challenges that were not addressed sufficiently in BRIC 1 should be addressed by workshops and commissioning activities to stimulate academic and industry researchers to design multidisciplinary projects that have high value and economic impact.

5. That all projects funded under the extended programme should address at least one of the six industry value drivers described in the high-level Business case contained in this report.

6. That an expanded capacity-building programme to train additional bioprocessing researchers at masters, doctoral and post-doctoral level is essential to meet the forecast needs of industry by 2015. This programme should include increasing the number of PhD level biochemical engineers and those in scarce industry-relevant research fields such as animal cell-culture, microbial physiology, large-scale protein purification and analytical technologies. The current UK provision of modular MSc courses should be reviewed and stronger elements of training designed to provide graduates with direct industry experience at both Masters and Doctoral level should be introduced.

7. That bioProcessUK, with BRIC industry members and the BBSRC take immediate steps to provide a better estimate of the skills needs of a successful and expanding biotechnology sector and generate UK targets for the type and flux of professionals.

- Bioprocessing is recognized as a key sector for the success of the UK biotechnology industry and is pivotal to the development of future medicines, vaccines and diagnostics.
- In order to underpin the sector the Bioprocessing Research Industry Club (BRIC) established in 2005 has funded 25 research projects totaling £13.3M through three calls for proposals in two broad areas:
    - Bioscience underpinning bioprocessing; which includes understanding, controlling and manipulating metabolism in microbial fermentation and mammalian cell culture, growth of stem cells *in vitro* and understanding of the properties of functional proteins
    - Improved tools for bioprocessing; which includes high-throughput process technologies, analytical methodologies and improved down stream processing
- BRIC has created an exciting and effective bioprocessing network and reenergized the bioprocessing research sector by encouraging deeper, more relevant and more enthusiastic engagement of industry as well as academics.
- BRIC has made excellent progress in addressing some complex research problems, but several important challenges still remain.
- Better and more predictable bioprocesses will reduce the cost of biopharmaceuticals and some of the high risks inherent in their development. This will directly help both large and small biotech companies and make a greater number of life saving therapies available and affordable.
- There is a strong national business case for sustaining and enhancing the support for specialist research and training in the processing, formulation and manufacturing of functional biological products. This should be strategically prioritized in terms of industrial need and be enabled by positive mechanisms to ensure rapid and effective translation of the knowledge, tools and skilled professionals so created.
- It is therefore recommended that the BRIC programme be continued for a further 5 years to ensure further growth and sustainability of a vibrant bioprocessing community in the UK which will enable wealth creation for UK plc.
- It is also recommended that the synergistic partnership between BBSRC, EPSRC and TSB that has been so effective thus far, is fully sustained in the next phase
- The conclusions and recommendations of the Working Group have been made in the context of a preliminary BBSRC evaluation of the progress and outputs of the current BRIC extant since 2005. The general tone of the evaluation was very positive with some of the main conclusions being given below:
    - BRIC is an effective and timely scheme that is achieving its objectives and is on-track to deliver future impact.
    - BRIC is supporting high-quality research that is of broad relevance to the UK bioprocessing industry.
    - Training of post-doctoral researchers within BRIC is good, although there is scope to improve the level of industry relevant transferable skills.
    - BRIC has strengthened the UK bioprocessing community and is promoting partnership links between academic and industry.
    - BRIC is very strongly supported by relevant companies and they believe that it will deliver valuable and transferable research outputs & skilled individuals.
- The Working Party's vision for the result of the continued and collaborative investments by BBSRC, EPSRC and TSB will be to create a sustainable critical mass of leading bioprocess science and engineering research in the UK that will lead to:

- *The education and training of a sustained flow of professionals required by an expanding and diversifying biotechnology industry.*
- *The rapid development and design of predictable, modular and intensive processes that support delivery of the next generation of complex biological medicines.*
- *Data-rich development approaches that incorporate principles of "quality by design" that lead to decreased time to market. This will increase probabilities of success and contribute to robust manufacturing processes and consistent products which address unmet medical needs and bring value to patients.*
- *The continued invention and development of analytical technology that will determine the full composition, structural and conformational integrity of complex biological products, ideally in real (or short) time.*
- *The creation of processes that are significantly less costly, that utilise recyclable and disposable units to a greater degree and that are much more rapid to establish and validate.*
- *The design of product forms in which the desired exquisite biological functionality is faithfully reproduced and is fully stable to the most demanding criteria for storage, transport and delivery.*
- *The support of a unique collaborative relationship between specialist HEI centres and Industry that underpins the UK as a international location of choice for leading bioprocess development and inward investment.*
- *A substantial and demonstrable return to UK Plc by 2015.*

INTRODUCTION

Background

1. In the BIGT (Bioscience Innovation and Growth Team) Report "Bioscience 2015" published in 2003, bioprocessing was recognised as a key sector for the UK that was pivotal to the development of future medicines. Over one third of all drugs now under development by pharmaceutical and biotechnology companies are biological medicines.

2. In 2003 there were 703 biological medicines in development globally (pre-clinical to registration); in 2008 this had grown to 845. 94 biological medicines have been licensed in the USA since 2003, and the top 20 accounted for $82billion of sales worldwide in 2008 (total pharmaceutical sales were $740billion approx), compared with $33billion (total pharmaceuticals $499billion) in 2003 [source IMS Health]. Traditional medicinal chemistry based companies such as Pfizer and AstraZeneca have purchased biologics companies in multi-billion dollar deals in order to gain access to this rapidly growing sector of the industry.

3. However in the material it contributed to the recent BIGT Refresh working party, bioProcessUK found that the relative proportion of biological medicine development projects coming from UK based companies in comparison to the rest of the world has declined from about 12% in 2003 to about 9% in 2008. In stark contrast the total global market for biological medicines continued to grow faster than that for small molecule drugs with an average CAGR (Compound Annual Growth Rate) across the same period of approximately 10%. In summary, despite a national annual investment in leading fundamental bioscience research that exceeds £3bn and the positive interventions implemented since the first BIGT report, the UK is heading in the wrong direction.

4. There is a real need to expand academic research that underpins the development of bioproducts and processes to ensure support for a rapidly growing biological medicine industry that matches the quality and potential of the UK's bioscience base. The challenge is not only to address the current need to accelerate the development of robust, predictable and intensive processes but to rise to the challenge of inventing future processes that will reduce the cost of goods by one or two orders of magnitude.

5. In order to address these challenges the Bioprocessing Research Industry Club (BRIC) was established by BBSRC, EPSRC and Industry in 2005 with the aim of supporting industrially relevant research into bioprocessing and to reinvigorate the respective academic and industrial communities.

6. Since its launch BRIC has been successful in four major areas.

    - Calling for and funding high quality industrially-relevant scientific proposals in the area of bioprocessing
    - Increasing the range of academic talents focussed on bioprocessing
    - Establishing a framework for a bioprocessing network that links academics and industry
    - Helping catalyse vibrant and effective engagement of academia and industry through the network

7. The Club has funded 25 research projects totalling £13.3M through three calls for proposals that fall broadly into two areas:

    - Bioscience underpinning bioprocessing; which includes understanding, controlling and manipulating metabolism in microbial fermentation and mammalian cell culture, growth of stem cells in vitro and improved understanding of the properties of proteins

- Improved tools for bioprocessing; which includes high-throughput process technologies, analytical methodologies for bioprocessing and improved down stream bioprocessing

8. The research aims to make an impact on bioprocesses at all scales of operation, from the small amounts required for preclinical studies through to post-license bulk manufacture. In addition it will help to reduce the bottleneck in the development of biotherapeutics and contribute to the continued development of a vibrant bioprocessing community, creating wealth for UK plc.

9. Dissemination of research findings and networking between BRIC company members and funded academics are key aspects of the club and are carried out through twice-yearly dissemination events. These events have been highly successful in galvanising the academic and industrial sectors, bringing them together as a single community that can share the research challenges faced in the field and jointly develop solutions.

10. Alongside these activities BRIC has also supported the training of PhD studentships in bioprocessing, through BBSRC's Targeted Priority Studentship competitions, to ensure the UK has both academic and industrial researchers with the right skills to take this sector forward.

11. All the funding available through BRIC 1 has now been awarded, although established research projects, disseminations and networking activities are set to continue until 2012.

New Challenges

12. The research challenges BRIC set out to address are complex and multidisciplinary, and, although BRIC has made excellent progress, significant further research still remains to be done to support the needs of industry.

13. In 2009 the Review and Refresh of Bioscience 2015 was published. It welcomed the developments that have taken place since the original report was written but observes that high drug prices are now one of the most important issues facing the biotechnology and pharmaceutical sector if new therapies are to be accepted by healthcare providers with finite budgets. This increases the pressure to innovate and increase the efficiency of bioprocesses. The Review acknowledges the progress made by BRIC in addressing this long-term vision of developing Centres of Excellence and goes on to recommend as follows:

    Relevant Research Councils and Knowledge Transfer Networks along with the Technology Strategy Board and industry should build on the success of the Bioprocessing Research Industry Club to develop a set of follow-on activities. New funding must be in place for distribution in 2009 and onwards to build capacity for multidisciplinary bioprocessing research and training to 2015. The growth in capacity should make the emergence of new centres of excellence possible, and be sufficient to meet the needs of academic and industry recruitment.

14. The potential for more cost effective biosimilar drugs has become of increasing interest and challenge to the industry since the launch of BRIC. Delivering the promise of more affordable but equally effective treatment by biological medicines will require significant process innovation and intensification to reach a much lower cost of goods. The UK needs to be at the forefront of such developments.

15. The rapid advance of Stem Cell research and the exceptional promise of regenerative cell based therapies brings with it a vital requirement to develop bioprocesses that are safe, cost-effective and consistent. It is absolutely essential that a relevant and competitive academic research community is established and expanded in collaboration with this new industry.

ACHIEVEMENTS OF BRIC 1

16. BRIC has succeeded in encouraging academic bioscientists to research topics of relevance to industry. It has:

- called for and funded good quality science programmes, through three funding calls focussed upon the underpinning science and new tools for bioprocessing.
- facilitated a flow of material outcomes from funded research including technical exchange with BRIC industrial members, conference presentations, peer reviewed journal papers and patent applications.
- posted BRIC outputs on a secure Web Portal specifically established for the benefit of industrial and academic members.
- encouraged grant holders from the first funding call to seek follow-on funding to advance their findings toward commercial adoption by BRIC Industrial Members
- engaged new academic players with valuable cross-disciplinary skills in contemporary bioprocessing within Heriot-Watt, Strathclyde, Newcastle, Durham, Birmingham, Kent, Warwick, London, Nottingham and Southampton Universities.
- re-energised and refocussed some previous community players, and encouraged new partnerships between institutions (Bath-Southampton, Loughborough-Nottingham, Cambridge-Nottingham, Cambridge-KCL, Kent-UCL, Warwick-UCL, Edinburgh-Heriot-Watt)
- created an exciting and effective bioprocessing network, linking industry and academia, through 6-monthly Dissemination Events wherein all funded researchers are required to present recent work in oral and poster mode to peers and representatives of the industrial members. These events now regularly attract in excess of 120 delegates and match the very best of academic-industrial conferences in terms of quality research findings, collaborative opportunities and networked sources of skills and know-how. Interim evaluation confirms that such managed dissemination has accounted for significant growth in technical, material and skill exchange between academic and industrial BRIC members.
- organised additional events, such as speed-dating, interactive workshops, industrial presentations and confidential consultations, which have ensured that the BRIC community has visibly matured into a confident and coherent whole.
- facilitated academic and industrial site visits and seminar presentations by key technical personnel which have stimulated significant additional activity including new funding applications to TSB and the Research Councils for related collaborative work at postdoctoral and postgraduate level. Increased uptake of Industrial CASE Awards has been particularly indicative of community growth.

BUSINESS CASE FOR CONTINUING BRIC

17. The general business or “impact” case for continuing the investment in BRIC rests on six main drivers:

a) The considerable commercial opportunity presented by recovering and expanding the overall UK position in the growing global market for biological medicines that was worth $80bn in 2008.
b) The indirect support of a major cluster of UK based high-technology companies (i.e. approximately 50 companies of all sizes developing biological medicines and about 200 other companies supplying technologies, products and services in support) many with significant growth potential.

c) The creation of a vibrant and highly skilled bioprocess community of professionals that will facilitate new business start-ups, remove 'access to skills' growth constraints on existing companies, facilitate inward investment and encourage companies to stay in the UK even if they are acquired.
d) The direct commercial and competitive value to existing companies from decreasing the time, cost and risk of product development.
e) The reduction in capital investment magnitude and risk to existing companies coming from the ability to design intensive, modular and predictable processes that inherently embrace 'quality by design'.
f) The decrease in risk of product development delays imposed by Regulatory Authority concerns about process and product integrity and reproducibility.

18. There is no doubt that biological medicines are becoming increasingly important.

- According to a report from Evaluate Pharma, published June 2009, 50% of the top 100 drugs will be biological medicines in 2014, with 7 of the top 10 drugs (by sales) being biological medicines. Pharmaceutical company investment in this sector continues to grow, attracted both by the scientific opportunity and by the current robust forecast CAGR of 13% for biologics compared to 1% or less for small molecules.
- Roche is the leading Big Pharma player in the biological medicines market. It holds an extremely strong position in the antibody market thanks to its merger and recent full acquisition of Genentech. Roche is forecast to record the highest sales growth rate to 2010 within the peer set, equal to an increase in annual company sales of $14bn.

19. The UK based pharmaceutical companies are also moving into biologics. AstraZeneca has acquired both Cambridge Antibody Technology, a leader in antibody technology and discovery, and the US firm MedImmune, with a number of biological medicine products already on the market, to expand rapidly its capabilities in biological medicines. From the AstraZeneca report to investors, June 2009:

- *Biological medicines are a strategic necessity against a changing industry science base*
- *The target is for 25% of development compounds to be biological medicines*
- *6 biologic IND's (Investigational New Drugs) per annum will be filed*
- *The objective is to gain one new biologic approval per annum from 2013*

20. GSK has purchased Domantis, a UK domain antibody technology company and has a large collaboration with GenMab, to develop an antibody Danusomab which is currently in Phase III clinical trials. The GSK annual report 2008 states that 6% of their current drug development pipeline is biological medicines. They plan to grow this figure.

21. Pfizer has also acquired a substantial portfolio of biologics as a result of its acquisition of Wyeth.

22. Within the field of biological medicines, stem cells are forecast to be a particular growth area. Pfizer is carrying out significant levels of stem cell based development in the UK. GSK has also made a substantial research investment in this area in Boston. There is clearly an opportunity for the UK to seize the leadership position in stem cell bioprocessing.

23. It is clearly difficult, without a full professional study, to quantify the return to the UK on the investments proposed in this report, however it will be driven by increasing the

chance of projects reaching the marketplace (decreasing development attrition), decreasing the time to marketplace and helping to increase the size of the “national project portfolio”. A typical biological drug can be expected to hit peak sales at approximately 7 to 10 years after approval. By improving the process development, and hence the manufacturing process, prior to approval (rather than after as happens with many drugs) it may be possible for the peak sales to be brought forward by 5 years. For a drug that has annual sales of $1Bn (i.e. a modest blockbuster) then this equates to an increase in lifetime value of $1.6Bn (10 years to peak sales: NPV = $2.9Bn; 5 years to peak sales: NPV = $4.5Bn: Delta = $1.6Bn) (Transforming Industrialisation – a new paradigm for pharmaceutical development, IBM Consulting 2006).

24. A study conducted in 2008 for bioProcessUK estimated that the number of biological medicine projects under all stages of development by UK owned companies was about 160. Even to recover its relative ‘national portfolio’ position in 2003 there needs to be an additional 50 projects. Another way of looking at the proposed investment to extend BRIC is to compare it directly to what it costs Pharma to acquire a promising Phase 2 monoclonal antibody being developed by a small biotech company. It equates approximately to the cost of ONE such acquisition.

25. Driven by strong commercial and competitive time pressures, there is always a tendency to fix on ‘an adequate’ process rather than one which is fully optimised, predictable and understood. Clearly there needs to be a careful balance on not doing too much process development work until clinical data is positive, however fixing a process early so that it is merely adequate can store up issues that are only revealed at higher scales of operation and contributes adversely to the cost of manufacture. More effective and predictable process invention and development will reduce the cost of biological medicines and make a greater number of life saving therapies available and affordable.

26. Another important concern is that with the current low intensity technologies, the very significant investment for Phase 3 clinical development and commercial manufacture sits firmly on the critical path to market. The difficult choice is either to delay the investment until critical clinical proof of concept data is available or commit to stay on the fastest path to market at considerable financial risk.

27. Global Regulators are demanding more and more scientific evidence that companies understand the processes they have developed, understand how to control and analyse the quality of biological medicine products made and understand why and how they made design choices that lead to good product quality. They are building concepts such as ‘Quality by Design’ into regulatory frameworks and require evidence that the latest knowledge of conformational or compositional issues that might affect the specificity, functionality or safety of the bio-molecule have been addressed.

28. Overall this description provides a summary of the key factors that contribute to the business case for the BBSRC, the EPSRC, the TSB and the existing family of pharmaceutical and biotechnology companies to support strongly the proposed investment in this critical and most innovative sector. It is also particularly noteworthy that it was industry that proposed the BRIC programme initially to the Research Councils, and it has now has requested continuation, without a time gap, so as to maintain momentum in the progress that has been made.

RECOMMENDATIONS

Continuation of the BRIC network

Recommendation 1: That the BRIC programme is continued for a further 5 years to ensure maintenance and growth of a vibrant bioprocessing community in the UK training skilled professionals and delivering industry-led strategic research which enable wealth creation for UK-plc.

29. Funding bioprocessing research through BRIC as a coordinated initiative has facilitated the creation of a coherent bioprocessing community. This coherency would not have been achieved through a portfolio of separate Research Council responsive mode grants. The appointment of an external programme manager and an industrial coordinator have been key to this aspect. The interim evaluation demonstrates that this is seen as one of the major successes of BRIC and will help ensure that the UK has a world leading and innovative bioprocessing sector. The benefits of this network are felt wider than just those who are members or funded by BRIC, embracing those who attend open events such as call workshops. Many academics who have not been subsequently funded by BRIC have been able to use the contacts made to initiate participation in other programmes.

30. It is therefore key that this coordination and the active network is sustained. Continued support will allow BRIC 2 to expand further and go beyond its traditional boundaries to engage with other disciplines that are needed to move the research agenda forward.

31. In considering how the network should be sustained the Working Group recommended that the successful model of the dissemination events should be continued as this had proved a most effective way to bring the community together. To allow for more inclusive networking with companies and academics outside of BRIC it will be important that wider bioprocessing focused meetings, such as the bioProcessUK annual conference and the ESACTUK meeting continue to be held and that BRIC participates in them.

32. In terms of expanding the network, the Working Group considered that there would be benefit in the closer involvement of stem cell companies and technology based companies through becoming members of BRIC. Many of the issues that will be faced by stem cell companies in the development of a bioprocess for stem cells will be similar to those already experienced in the development of bioprocesses for protein based therapeutics and there could be significant benefits to them gaining from this experience.

Translation of research projects

Recommendation 2: That the synergistic partnership between BBSRC, EPSRC and TSB that so successfully linked BRIC1, the KTN and TSB co-funded industry innovation projects be continued.

Recommendation 3: That the extended programme should enable the most promising research areas already started to be further developed to the point that they can be utilised by companies in commercial processes.

33. The research supported through BRIC has aimed to underpin the long-term needs of industry and to build capacity. In most cases the expected output from the funded research will be published, whilst unpublished data and knowledge will assist companies by underpinning their own in-company applied research and development.

34. Whilst it is still early days in terms of research outputs, the interim evaluation shows that 43% of BRIC grant holders reported that new products, processes, resources, tools or technologies have arisen from their research projects and 14% had made patent applications as a result of their grant to date (57% claim they are likely to apply to secure IP). Alongside this to date two disclosures of commercial opportunities arising from BRIC projects have also been made to and are currently being considered by the company membership. It is therefore timely that mechanisms are put in place that will allow research outcomes to come to fruition for the benefit of the bioprocessing industry and prevent them from being lost. A key part of this process will be to ensure engagement of company members to ensure only those outcomes that are likely to have a significant impact on the industry are taken forward. To ensure potential opportunities are identified from BRIC projects, a close-out meeting will be carried out towards the end of each project by the programme manager and with the involvement of company members. This will provide an opportunity to highlight research outcomes that are of interest to the company membership and opportunities for where further research would be of direct relevance to the bioprocessing industry.

35. To enable research outcomes to be taken forward the Working Group recommended that support be available through two mechanisms. The first mechanism should provide financial support, through the established BRIC 'process', for further research projects to take forward the findings of BRIC projects where there is a high likelihood of benefits to industry from doing this. The second mechanism should support Knowledge Transfer activities from BRIC funded projects where the outcomes are directly applicable into industry. Examples of activities that would be supported through this mechanism could include opportunities for post doctoral researchers to spend time in industry transferring their research findings. The Working Group noted that there are currently a number of schemes that such knowledge transfer activities could be supported through (for example KTP's, BBSRC's Industry Interchange Programme, support available to universities from EPSRC's KTA scheme or the Research Councils Follow-on Fund) and recommended that there needs to be a way by which the BRIC Steering Group could influence the funding available through these schemes.

36. There is also a role for the Technology Strategy Board in taking research outcomes closer to industry through calls for Collaborative R&D. Data provided by the Technology Strategy Board shows that translation of bioprocessing research is already taking place through the TSB Collaborative R&D scheme. The Technology Strategy Board have funded 15 bioprocessing relevant projects through collaborative R&D competitions, ten of which include academic partners of which six are BRIC funded groups. Thirteen out of the 18 company members are also participating in these projects.

Addressing remaining and new challenges

Recommendation 4: That the critical research challenges that were not addressed sufficiently in BRIC1 should be addressed by workshops and commissioning activities designed to stimulate academic and industry researchers to design multidisciplinary projects that have high value and economic impact

Recommendation 5: That all projects funded under the extended programme should address at least one of the six industry value drivers described in the high-level Business Case contained in this report (paragraph 17a-f)

37. The funding already awarded through BRIC 1 has enabled significant progress in rebuilding the bioprocessing capacity in UK HEIs and has begun to address key challenges faced by the industry. However, as stated above, not all challenges have been resolved or even addressed by BRIC 1, and since its launch new research needs have emerged. In order to achieve the long-term vision for the future of UK bioprocessing, further research is required in a number of areas. A survey of the BRIC industrial membership has identified key areas for continued and newly commissioned work. These areas may be distilled into the following headings that are not exclusive but offer clear opportunity for synergistic proposals from academic researchers and productive industry collaboration.

Bioprocessing Research Challenges for Protein Products

38. Fundamental biochemical and biophysical understanding of protein form and structure is not yet sufficient to enable useful predictions of protein behaviour in bioprocesses. A key economic requirement is prediction of manufacturability of biological medicine discoveries at the earliest possible stage of development – particularly where structural variants (e.g. monoclonal antibodies engineered from a common molecular scaffold) are to be manufactured by established template bioprocesses. Issues of unexpected activity loss, proteolytic sensitivity, molecular aggregation, insolubility and losses through surface adsorption, all arise from the effect of variable physical and chemical environment on protein 3-D structure.

39. Understanding of relevant protein chemistry is critical to advancing the effective expression of native, folded protein products in established and newly developed host cell lines with higher expression capability.

40. The physico-chemical impact of the environment in common unit operations of product recovery and purification (e.g. centrifugation, microfiltration, chromatography and ultrafiltration) upon the molecular integrity of protein products or impurities is poorly understood. Operational lifetimes of chromatographic media are strongly predicated upon degrees of protein fouling and the effectiveness of cleaning regimes. Proposed alternatives to chromatography such as selective precipitation, crystallisation or aqueous solvent extraction are constrained by lack of mechanistic understanding of the effect of novel bioprocessing environments upon the structural integrity of products.

High-throughput bioprocess development

41. Automated, ultra-scaled down, high throughput technologies are required for the rapid development and selection of productive cell lines, as well as the selection and optimization of other unit operations. This approach is not only applicable to existing process (e.g. therapeutic protein production) but also emergent processes for products appearing on the horizon such as antibody fragments, nanoplexes and cell-based therapies. It should embrace the effective integration of upstream and downstream operations of manufacture as well as the establishment of compatible solvent and excipient conditions from fermenter to formulation. It should also include the development of analytical techniques that allow for real-time measurement of parameters in a non-invasive manner or with negligible analyte consumption.

Effective modelling of whole bioprocesses

42. There continues to be an important requirement for robust modelling procedures that are applicable to whole bioprocesses. These should exploit early data flowing from scale-down process measurements, facilitate the evaluation of alternative process routes and allow confident prediction of behaviours at the manufacturing scale. Improved models must be based upon, and be validated using industrial bioprocess datasets which may be limited in size and quality.

43. Modelling approaches that could link (i) high throughput discovery, (ii) native product expression, (iii) optimised fermentation and (iv) downstream recovery and purification in an integrated fashion would accelerate development and reduce the need for expensive pilot studies. The capacity for such modelling approaches exists in UK academia, but is not currently applied to industrial bioprocessing. It should be a goal of BRIC 2 to catalyse greater collaboration and generate highly competitive proposals in this area.

Robust and effective analytics for bioprocessing

44. There continues to be a need for the development of improved analytical methods and tools for the design, analysis and control of both present and future bioprocesses. The scope of these methods should embrace product structural homogeneity, molecular integrity, functionality, stability, product and process contaminants and shelf-life evaluation. It is highly desirable that new measurement technologies are robust enough to operate near-plant on real process fluids, ideally in real-time or rapidly off-line. Given the highly regulated environment for bio-manufacturing it is also essential that the techniques selected are capable of full GMP validation.

Bioprocessing Research for Cellular Products

45. Cell therapy products are commonly produced by larger, non-optimised versions of laboratory scale methods. More robust and practical large-scale manufacturing processes need to be developed along with scaled down versions that facilitate predictive process evaluation and new non-invasive (or low sample consumption) analytical methods for monitoring & control. As the development of active cell based products is in its infancy further research must also be conducted to define the minimum set of markers that can be used to define such products for clinical use.

46. The Working Group considered the mechanisms by which the research should be supported. For a number of the areas that industry still considers key (e.g. biophysical studies and modelling of protein structure and properties, whole process modelling) it proved difficult to obtain suitable high quality applications in BRIC 1. For these areas the Working Group recommended that a collaborative commissioning process should be adopted to assemble the necessary skills to address the research and to develop innovative proposals. For these and other research areas, open calls supported by workshops and interactive proposal management should be adopted in the manner proven successful in BRIC 1.

Meeting the Skills Need

Recommendation 6: That an expanded capacity-building programme to train additional bioprocessing researchers at masters, doctoral and post-doctoral level is essential to meet the forecast needs of industry by 2015. This programme should include increasing the number of PhD level biochemical engineers and those in scarce industry-relevant research fields such as animal cell culture technology, microbial physiology, large-scale protein purification and analytical technologies. The current UK provision of modular MSc courses should be reviewed and stronger elements of training designed to provide graduates with direct industry experience at both Masters and Doctoral level should be introduced

Recommendation 7: That bioProcessUK, with BRIC industry members and the BBSRC take immediate steps to provide a better estimate of the skill needs of a successful and expanding bioprocessing sector and generate UK targets for the type and flux of professionals required over the next decade.

47. The provision of a strong and consistently expanding flow of internationally recognised skilled professionals is vital for the growth of the biotechnology and bioprocessing sector in the UK. Recent informal surveys among existing companies in the sector highlight that the hiring and retention of appropriately experienced and trained staff is top of the list of non-financial factors constraining business expansion. Similar clear messages are contained in the recent ABPI STEM survey and the 'BIGT' 2015 Refresh report and analysis that underpinned the SEMTA Bioscience Skills Agreement.

48. In 2007, bioProcessUK informally surveyed UK bioprocessing companies to determine their need for PhD level researchers for jobs in process development. In summary, the total annual requirement was estimated at about 60/year. It was estimated that UK universities in 2007 produced about 30 PhDs per year with some relevant bioprocessing training. Clearly supply is not meeting demand, as many of the 30 do not choose to join UK companies. The global biological medicine sector is growing at around 17% annually, and so if the UK merely wishes to hold its own, there is a vital need to expand training capacity.

49. All the evidence shows that there has been a chronic shortage of people with bioprocessing research training since the early 1980s. This gap has been filled by companies training fresh bioscience PhDs on the job themselves or by recruiting from overseas. The 60 new PhDs / year needed includes about 45 bioscientists and 15 engineers with skills in one or more of the technologies described above. Potential growth rates for the biopharmaceutical industry suggest that this requirement for skilled professionals could double by 2015. The BRIC programme has started the necessary process of growing the relevant UK academic research and training capacity but this needs to continue. Some of the postdocs trained in BRIC should soon be offered academic positions to build this capacity, and they should be concentrated in a few centres in complementary teams of specialist academics.

50. Since 2007 bioProcessUK and BRIC company members have worked to increase the supply of PhDs by increasing the number of Industrial CASE studentships taken up facilitated by additional BBSRC funding. This has probably increased doctoral numbers by around 10-20 per year, but as it takes 3-4 years to graduate, the PhD graduates have not emerged yet. BRIC2 needs to build on this excellent start. bioProcessUK and BRIC

are also holding careers events to encourage the graduates to seek jobs in bioprocessing.

51. The Working Group considered the capacity, type and training curriculum necessary for the future. The new EPSRC sponsored Doctoral Training Centre (DTC) at Newcastle and the additional funding of the existing UCL DTC were a welcome development. However, their capacity to train industrially aware PhDs was insufficient to meet the forecast of demand for sector expansion by 2015. It is therefore essential that a number of bioprocessing specific studentships continue to be available for BRIC 2. The Working Group considered that there may be benefit in aligning some of these with the EPSRC funded DTCs.

52. It was also considered that there was a need to review the provision of modular Masters level training to serve as a post graduate step into the sector or on the job training. BRIC 2 will be uniquely placed to add significant value by using the BRIC network to develop multi-centre Masters training bringing together the specialisms of a number of academic centres. A very strong message from the industry was the vital importance of introducing more practical and industry relevant experience into existing and new academic training curricula. Therefore opportunities for in-company research experience should be built into this training with member companies providing experiential opportunities to enable the best young researchers to develop the relevant skills.

53. By incorporating taught masters level modules and industrial placements to doctoral training a Bioprocessing Professional Doctorate should be established to help meet the industry need for bioscientists and engineers equipped to work in company research and development labs and manufacturing plants.

54. The Working Group also discussed the provision of fellowships to support academic careers and industry collaboration. It was recognised that there were already Research Council and Royal Society schemes in existence to support fellowships within bioprocessing and that BRIC support would allow the development of talented high quality PDRAs that would be able to compete for these fellowships.

55. Working Group also recognised that certain specialised skills (at an internationally competitive level) are currently in very short supply (as highlighted by the ABPI Sustaining the Skills Pipeline Report 2008). Examples of these, for biological medicines are: microbial physiology, fermentation technology, mammalian cell culture technology, protein separation technology, safety and toxicology; pharmacokinetics and biological fate; bioprocess and product advanced analysis; product formulation, stability and delivery. In addition business and enterprise training is also needed to ensure that some of the researchers are equipped to become the future business leaders of the industry. The Working Group recommended that where relevant BRIC should ensure the engagement of its members in wider activities, including the Leadership Programme under development by the BIA.

56. The Working Group endorsed unanimously a challenging vision for what was necessary to develop the UK as a leading international hub for bioprocessing research and training by creating an environment:

    - That generates a consistent flow of the best researchers globally at all levels who can take up employment in the UK
    - Encourages UK companies to become actively engaged in the academic training curricula and have access to the best recruits

- Provides a clear career pathway where personal development is actively encouraged through modular training packages and assisted opportunities for academic-industry exchange
- Offers proactive mechanisms for international collaboration and exchange delivering training and experience with the best centres in other countries across the world
- Facilitates an expanding national and international alumni network and an active return of talent from overseas

PROPOSAL FOR BRIC 2

57. The BRIC programme should be continued for a further five years to ensure the growth and establishment of a vibrant bioprocessing community in the UK which will enable wealth creation for UK plc.

58. The Key features of delivering BRIC 2 will include:

- Overall management of the BRIC 2 programme by BBSRC's Business and Innovation Unit, working in collaboration with EPSRC and TSB to ensure all funders and their communities are engaged and opportunities for aligned funding, as envisaged by the business case, are secured.
- Activities to enhance the BRIC Network, developing collaborations and supporting the interface between companies and the academic community and ensuring effective dissemination will be delivered through an external Programme Manager working in collaboration with bioProcessUK. This is particularly important to ensure the expansion of the network, build on success of BRIC 1 and address the technical challenges articulated by companies.
- Translation of research outcomes will be delivered through a range of mechanisms. These will include funding earmarked specifically to undertake further technical development of BRIC 1 project outcomes where industry has identified a benefit in funding further research (BRIC 'Follow-on Projects') and support through relevant wider KT mechanisms offered by the Research Councils and TSB. It is envisaged that the TSB Collaborative R&D programme will help engage companies that are leading in technical expertise that can contribute to delivering the complex industrial research challenges that BRIC 2 will address.
- BRIC 2 will support a small programme of research projects to address ongoing research challenges. This programme is likely to be delivered through call(s) for proposals/research competitions. In addition, research challenges not previously addressed through BRIC 1 have been identified by companies. These new or unaddressed challenges are unlikely to be addressed through standard calls for proposals and therefore new approaches will need to be developed. These are likely to include consortia building workshops to bring new expertise and collaborations together to address the research challenges.
- The provision of skilled individuals is critical to the ongoing success of the bioprocessing sector. BRIC 2 will build on the increased capability developed through BRIC 1 and recent investments such as EPSRC funded Doctoral Training Centres at University of Newcastle and UCL. BRIC 2 will be uniquely placed to add significant value by using the BRIC network to, for example, develop Masters level training which in combination with experiential opportunities within member companies and PhD training can for the basis to develop a professional bioprocessing doctorate targeted to the best young researchers. PhD studentships will be targeted to the BRIC 2 Programme with further opportunities provided through CASE/Industrial CASE.

59. BRIC 2 will continue the valuable evangelism for the bioprocessing sector to alert academics to the contemporary science and technology needs and continue to draw in a committed and collaborative industrial membership. Bioprocessing is deeply multidisciplinary so it will also be necessary to attract inputs from all science and engineering disciplines through pro-active commissioning of joint proposals aligned to the strategic industrial needs.

RESOURCES

60. BRIC 2 coordinated 5 year programme of activities described in this report is estimated to require a total budget of £13.25M contributed jointly by BBSRC, EPSRC and TSB. A summary of the proposed allocation of this funding to the component activities of the BRIC 2 programme is described in Table 1. This outline budget has not yet been agreed by the funders and is subject to the following assumptions:

    - Industry will contribute a total of £1M to this funding pot through subscriptions from company members.
    - BBSRC would contribute funding to support 66% of the BRIC 2 translational and 50% of the BRIC 2 research projects where the relative contributions to these activities reflect the nature of the science undertaken.
    - EPSRC would contribute funding to support 33% of the BRIC 2 translational and 50% of BRIC 2 research projects where the relative contribution to these activities reflects the nature of the science to be undertaken.
    - TSB will contribute to enhancing the network through continued support of bioProcessUK and also co-fund KTPs and Collaborative R&D projects to deliver translational activities under the BRIC 2 programme through existing activities.
    - Further resources would be aligned to the BRIC 2 programme through BBSRC and EPSRC KT schemes such as Industry Interchange, Follow-on Fund, Industrial Partnership Awards and CASE/Industrial CASE through existing budgets for these schemes.

TABLE 1. PROPOSED RESOURCE ALLOCATION UNDER BRIC 2 PROGRAMME.

NOTE: The table identifies resources required to deliver all of the activities highlighted by the working group. Contributions in this table have not been agreed by funders

ACTIVITY	£M					Total	Contributions*		
	Year 1	Year 2	Year 3	Year 4	Year 5		EPSRC	TSB	BBSRC
Enhancing the Network	0.35	0.35	0.35	0.35	0.35	1.75		0.25 (0.05 p.a.)	1.5
TRANSLATION									
▪ BRIC 'Follow-on' Projects	0.5	0.5	0.5	0.5	0.5	2.5	0.85 (0.17 p.a.)		
▪ KT Activities (e.g. KTP, Collaborative R&D, Industry Interchange, BBSRC Follow-on Fund)	Funding allocated through separate scheme budgets. Will include support from TSB through relevant schemes.							1.65	
RESEARCH									
▪ Ongoing Challenges	1.0	1.0	1.0			3.0	1.5 (0.5 p.a. over 3 years)		
▪ New Challenges	2.0	2.0	2.0			6.0	3.0 (1.0 p.a. over 3 years)	1.5	
					Total	13.25	5.35	0.25	7.65
SKILLS	Number of Studentships							3.0	
PhD Studentships	10	10	10	10	10	50 PhD Student ships			
BRIC Facilitated Masters training		10	10	10	10	40 Masters Student ships			

* Contributions would be reduced proportionately to reflect £1M contribution from industry

APPENDIX 1: BRIC WORKING GROUP

BRIC was launched in 2005 as a partnership between BBSRC, EPSRC, Industry and bioProcessUK. The club supports research that is aimed at helping the bioprocessing industry address the challenges it faces in terms of the efficient production of biological medicines and the development of an effective academic and industrial bioprocessing community within the UK.

In 2008, following the commitment of all existing funds to research, the BRIC Steering Group asked that a Working Group be set up to ensure the impact of the funding already awarded and activities held through BRIC to date are maximised for the benefit of the bioprocessing sector. The Working Group comprised members of the Steering Group, Company Members and grant holder representatives together with non-BRIC companies and academics not funded through BRIC (membership is attached in Appendix 2.) It was asked to consider whether further support was required for the bioprocessing sector from Research Councils and the Technology Strategy Board and, if so, to consider potential activities and to develop a case for support. More specifically the Group was asked to focus on:

The activities that are important to ensure the success and impact of BRIC research outputs on the bioprocessing sector, taking into account:

- *Education and skills needs and capacity of UK to train high quality researchers;*
- *Whether research areas from the original BRIC remit require further funding or if new research areas that were not included in the original BRIC remit should be included in future activities;*
- *The translation of the outputs of the grants funded to date through BRIC to industrial application.*

The group met on 22 February 2009 and 21 March 2009 to develop a set of recommendations on the future of BRIC that would be submitted to BBSRC, EPSRC and the Technology Strategy Board (TSB) as a case for further support.

In addition the Steering Group asked that an interim evaluation of the progress that had been made by BRIC in meeting its aims and objectives be commissioned that would form part of the case for any continued support. This evaluation has been carried out as a separate exercise by BBSRC's Corporate Policy and Strategy Group.

APPENDIX 2: WORKING GROUP MEMBERSHIP

Position	Representative
1. Chair	John Stageman (AstraZeneca)
2. Industry Steering Group Representative 1	Carol Marshall (GlaxoSmithKline)
3. Industry Steering Group Representative 2	Mark Carver (Avecia)
4. Industry Steering Group Representative 3	Brendan Fish (MedImmune)
5. Academic Steering Group Representative	Elaine Martin (Newcastle)
6. BRIC Grantholder	Alan Dickson (Manchester)
7. BBSRC/ EPSRC funded research scientist not receiving BRIC funds	Andrew Livingston (Imperial)
8. Industry representative not a BRIC member	Roger Benson (ParOS Ltd)
9. Industry representative not on BRIC Steering Group 1	Rocky Cranenburgh (Cobra)
10. Industry representative not on BRIC Steering Group 2	Tim Allsopp (StemCellSciences)
11. International representative – Academic/ Industrialist	Joaquim Cabral (Univerisdade Tecnica de Lisboa)
Specialist Advisors	Andy Lyddiatt
	Malcolm Rhodes

APPENDIX 3: DEFINITIONS

“Bioprocessing” here-in is defined as those activities enabling the design, development and production of biological medicines both in bulk product and final dosage form. This breaks down into stages/unit operations: cell line development, cell banking, fermentation process, recovery and purification process, chemical modification (conjugation, PEGylation), formulation process, dosage form, storage and stability, analytical methods for in-process, final product and stability testing.

“Biological medicines” or “biologics” includes recombinant proteins of human and non human origin e.g. cytokines, antibodies and antibody derived materials, IgG, Fab, ScFv, single domain antibodies scaffolds etc, enzymes, subunit vaccine antigens, viruses, virus-like particles, DNA, RNA, human cells, bacterial cells. Currently 90% of marketed biopharmaceutical products are proteins, of which approximately 25% are antibodies.