Technology Strategy Board
Driving Innovation

# The Future UK Life Sciences Manufacturing Landscape

## Opportunities and Challenges for High Value Manufacturing in the Pharmaceutical and Biopharmaceutical Sectors

A Consultation for the Technology Strategy Board

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# Contents



Knowledge Transfer Network

HealthTech and Medicines

## Acknowledgments


This report was prepared on behalf of the Technology Strategy Board by the HealthTech and Medicines Knowledge Transfer Network and IfM Education and Consultancy Services Ltd, based at the University of Cambridge Institute for Manufacturing.

Grateful thanks are due to those who participated in the workshops for each of the sectors. The names of those involved are listed in the Appendix. Further thanks are extended to ABPI and the Chemistry Innovation KTN for their support and sponsorship of the workshops.

# 1. Executive summary

This report follows on from a study into the future of High Value Manufacturing (HVM) in the UK commissioned by the Technology Strategy Board and published in February 2012. One of the HVM study recommendations was that particular manufacturing sectors should be explored in greater depth. This report presents the findings from studies of the pharmaceutical and biopharmaceutical sectors. Workshops were held for each sector attended by representatives from industry, government bodies and the research community. The aims were to:

- identify the needs and capability gaps to achieving innovation in manufacturing in each sector through to 2025
- determine priority actions to meet these needs and build capability to enable innovation in manufacturing in each sector over this time scale
- better define the HVM landscape with additional data from the Life Sciences sector.

Strategic roadmapping techniques were used to help participants explore each sector's key trends and drivers; the novel products, processes and services which could be developed in the future; any technologies and capabilities required to support these opportunities; and the enabling factors that would help the sector respond successfully. The list of potential new products, processes and services was prioritised to identify key areas where it was thought the most valuable opportunities for innovation exist. A 'case for action' was developed to justify further work in each area, outlining the potential benefits, critical gaps and steps required.

This report covers the pharmaceutical sector within Life Sciences, with separate attention given to the specific manufacturing requirements for pharmaceutical and biopharmaceutical sectors.

## Key areas in pharmaceuticals manufacture

In the pharmaceutical sector the study identified a need for **more flexible production facilities** and early consideration of manufacturing needs. These could significantly cut costs and development times as well as delivering a better service to patients. **Manufacturing for personalised medicines** that tailor therapies to the needs of each patient could improve patient outcomes, as well as reducing healthcare costs. **Novel methods for how drugs are given to patients**, combined with 'smart' technologies, could integrate formulation, packaging and delivery to ensure prescribed treatments are followed more closely – improving results and reducing waste. **New developments in formulation design** could minimise use of valuable resources and maximise shelf life. **Reconfiguring the supply chain** could support radically new business models based on patient needs and wellbeing. These exciting developments all raise multiple, new manufacturing challenges.

## Key areas in biopharmaceuticals manufacture

In the biopharmaceutical sector the study identified the need to provide **new, low-cost routes to market** including manufacture for innovative therapies so that value can be retained in the UK. **Improvements in analytics** would enable products to reach the market more quickly through greater process knowledge, and therefore at lower cost and with reduced waste. **Increased understanding of biopharmaceutical formulations** could help to develop more stable and effective medicines, and improve delivery to patients. **New approaches in biological production technology** could enable individually tailored treatments to be produced more quickly and cheaply.

## Next steps

There is already evidence that the challenges facing both sectors are stimulating some innovative responses and generating a real appetite for change. The UK is in an excellent position to take advantage of these opportunities. Many of the world's major pharmaceutical companies are located and manufacture here, while at the same time the sector benefits from hundreds of small, highly innovative businesses. The existence of an open regulatory body is another important enabler for change. This study highlights the vital importance of close collaboration between industry, government and the regulatory authorities to support new manufacturing developments and to enable their impact on industry and the regulatory framework to be identified as early as possible.

**Feedback** on the findings of this report is invited from industry, policy makers and academia. Information on how to provide feedback is given on page 16.

## 2. Purpose of this report

This report follows on from a study of High Value Manufacturing (HVM) in the UK commissioned by the Technology Strategy Board and published in February 2012[1]. It describes further development of a future landscape for the medicine and healthcare field, particularly in relation to the HVM opportunities in the pharmaceutical and biopharmaceutical sectors.

The report is an interim document summarising the outputs from a series of workshops involving representatives from the pharmaceutical and biopharmaceutical sectors. It is being launched for circulation at the 9th Annual bioProcessUK Conference on 28-29 November 2012, and will be available more widely through the Knowledge Transfer Networks in order to gather feedback on its findings from a wide circle of stakeholders across industry, government and academia. Details of how to provide feedback are given on page 16.

The original HVM study involved a broad consultation exercise with industry, academia and government in order to develop consensus on the trends, drivers, challenges and opportunities for UK manufacturing over the next 15-20 years.

The HVM study created a framework – a high value manufacturing 'landscape' – against which industry and government can review their future strategies and policies. The material was collected in a structured and systematic way allowing the analysis to be constantly refreshed to reflect changing circumstances.

The study identified five, crosscutting strategic themes as well as the key national competencies required to meet future challenges. Its findings are being used to help inform public policy, investment and research in order to build and sustain UK manufacturing competitiveness across a broad range of industry sectors.


***The five strategic themes that emerged from the HVM study***

[1] 'A landscape for the future of high value manufacturing in the UK. A study conducted for the Technology Strategy Board.' February 2012

# 3. Sector studies

The HVM study recommended that particular sectors should be explored in greater depth using the framework created. One key area is Life Sciences which forms a major part of the UK's manufacturing capacity. This report presents the findings from a consultation exercise within Life Sciences, focused on the specific manufacturing requirements of the pharmaceutical and biopharmaceutical sectors.

A roadmapping workshop on a third sector in this field, medical technologies, is due to be undertaken by the end of 2012. These three sectors were among those identified in the HVM study as fast-growing, R&D-intensive areas with significant technological advantages for the UK.

## 3.1 Objectives

The aims of the studies described in this report are to:

- identify the needs and capability gaps to achieving innovation in manufacturing in each sector through to 2025
- determine priority actions to meet these needs and build capability to enable innovation in manufacturing in each sector over this time scale
- better define the HVM landscape with additional data from the Life Sciences sector.

## 3.2 Approach

Workshops were held for each sector attended by representatives from industry, government and academia and facilitated by IfM Education and Consultancy Services with the HealthTech and Medicines Knowledge Transfer Network (a full list of participants can be found in the Appendix of this report). The workshops used the IfM roadmapping methodology, a graphical, interactive approach to strategy development that allows participants to capture a wide range of interconnecting issues and to identify their linkages and dependencies.

### 3.2.1 Stage 1: Generating a sector landscape

In the first stage participants developed a high-level, sector 'landscape': a schematic on which the sector's opportunities, challenges and needs were identified in terms of four areas:

- key trends and drivers likely to affect the sector
- novel products, processes and services which could be developed
- technologies and capabilities required to support these opportunities with a focus on manufacturing challenges
- any enabling factors that would help the sector to grow and innovate

These areas were derived from the HVM landscape framework ensuring that the findings can be directly mapped onto the national competencies and strategic themes identified by the HVM study, as well as used to update the original HVM data.

The full landscape chart for each sector is shown in the Appendix.

### 3.2.2 Stage 2: Focusing on the emerging priority areas

In the second stage participants reviewed the novel products, processes and services identified for each sector and ranked them in order of importance to create a list of priority areas. These were discussed in detail to:

- develop a 'case for action' to justify further work in each area
- identify critical capability gaps and key actions required

## 3.3 Feedback and next steps

The outputs from the workshops were circulated to participants for review and any further comments have been incorporated into this report where possible. It was agreed to undertake a wider consultation exercise in relation to the emerging conclusions. We are therefore seeking feedback from interested parties in industry, government and academia with the aim of:

- achieving consensus concerning the emerging priorities and gaps
- contributing further data to build into our evolving understanding of the HVM manufacturing environment
- developing the identified actions proposed

Details of how to provide feedback are given on page 16.

# 4. The pharmaceutical sector

The UK pharmaceutical sector forms a significant part of the UK economy comprising some 365 companies, with nearly 79,000 employees and a combined turnover of £31.8bn. Of the top 50 global companies, 37 have sites in the UK. The sector is dominated by large companies with 89% of the workforce employed in firms with more than 250 employees. The company size may be a reflection of the age of the sector which has grown rapidly since the early 1900s to become one of the world's major industries[1].

## 4.1. High-level landscape

Workshop participants identified the sector's opportunities, challenges and needs in terms of the four landscape areas (trends, products, technologies and enablers). An outline of the findings that emerged is given below. The full landscape can be found in the Appendix of this report.

### 4.1.1 Key trends and drivers

Participants considered the trends and drivers they thought would affect the sector in the short, medium and longer term (up to 2025).

- Smaller lot sizes delivering tailored, more effective treatments
- Complexity of supply chains increasing as manufacturing moves offshore or closer to point of use
- More collaborative approach to product development involving partnerships with other companies or research centres
- Building quality control into the design stage (Quality by Design) requiring more responsive regulation
- Tailoring drugs to individual genetic signatures requiring complex therapies and formulations
- Lower prices, higher cost of development/ quality/goods
- *Patent cliff - reduced revenues and increased competition when product patents expire*[2]
- *Evolving healthcare needs of ageing population*[2]
- *Wealth creation for the UK*[2]
- *Time to market for new therapies*[2]

### 4.1.2 Novel products, processes and services

The (value adding) new products, processes and services that could be developed were identified as:

- More flexible production facilities located to support responsive, adaptable manufacturing capability
- Design for manufacture: Designing products for easier production
- Manufacturing for personalised medicines (diagnosis and drug treatments tailored for each patient)
- Integrated healthcare and treatment to create complete service package
- Making products to order in response to individual patient need and to reduce inventory
- Improved formulations and product platforms to increase responsiveness and minimise waste
- Future drugs and therapies for currently unmet medical needs as scientific understanding and new manufacturing processes develop
- Drug delivery: new ways in which drugs could be administered to patients
- *Low volume*[2] and 'smart' packaging e.g. technologies to enable monitoring of patient usage
- Better use of existing and new data and better understanding of customer needs through data.

### 4.1.3 Key technologies and capabilities required

The workshop participants then considered which technologies and capabilities would be required within the sector to enable the products, processes and services they had identified.

- Multifunction equipment with quick turn around: one plant for multiple products
- Continuous processing across a variety of platforms and unit operations
- Appropriate process controls and associated software and measurement to allow quality control, flexibility and small batch, complex processing

[1]Source: 'Strength and opportunity 2011. The landscape of the medical technology, medical biotechnology, industrial biotechnology and pharmaceutical sectors in the UK'.

[2]Items in italics have been added or modified during post-workshop consultations and do not appear on the sector landscape.

- Single-use components to speed-up product changeover and cleaning validation
- Better construction materials for components used in labs and production to reduce breakdown and improve equipment design
- Multi-dose/multi-pack formats for medication to be reconfigured according to required dose
- New approaches in synthetic biology to create both existing and new molecules
- Electronic prescribing data to reduce lead-time for drug manufacture following patient diagnosis
- Improved knowledge sharing and knowledge management to support new business models; open innovation and incubator facilities
- Improved supply chain design to manage complexity and encourage co-location of facilities
- *Generics supply chain addressing cost reduction and sustainability*[1]
- *Green technologies*[1]

### 4.1.4 Enablers

Finally, participants discussed the factors that could enable these innovations to take place.

- Better sustainability metrics to inform manufacturing options
- Greater engagement with other process sectors to promote knowledge transfer
- Improved communication between scientists, business and regulators to enable regulatory issues to be considered from an early stage
- Overcoming the manufacturing funding challenge
- Early engagement between researchers and industry to support better technology transfer from applied basic research to robust manufacturing development and commercialisation
- Fully understanding how patients take their medication
- *Driving innovation through the supply chain*[1]
- *Skills*[1, 2] and improved links between industry skills groups
- *Financial incentives for manufacturing*[1]

## 4.2 Links to HVM framework

The national competences identified as part of the original HVM study acted as a prompt for the workshop participants to ensure that all relevant areas were considered.

The outputs from the workshop were mapped onto the framework created by the HVM study to create a comprehensive linkage chart for the sector. Relating the sector findings to the HVM framework in this way enables the original data to be refreshed and updated to take account of new ideas and developments.

The linkage chart created for the pharmaceutical sector can be found in the Appendix.

## 4.3 Priority areas for further investigation

Participants reviewed the outputs identified as important for the sector and ranked them in order of importance to create a list of priority areas for further development.

The key areas agreed for the pharmaceutical sector were:

- Flexible production facilities
- Design for manufacture
- Improved formulations and product platforms
- Manufacturing challenges of novel drug delivery and smart packaging
- Manufacturing for 'personalised' medicines
- More integrated supply chain driven by patient demand

A 'case for action' was developed to justify further work in each of the priority areas. Participants also identified any critical gaps, barriers and enablers, as well as the key actions required to take the ideas forward.

The detailed case for each priority area is given overleaf.

[1]Items in italics have been added or modified during post-workshop consultations and do not appear on the sector landscape.

[2]Separate skills gaps analyses undertaken by Sector Skills Council, Cogent and SEMTA http://www.cogent-ssc.com/research/Publications/LSPReport.pdf. http://www.cogent-ssc.com/research/Publications/SEMTA_COGENT_report.pdf. http://www.cogent-ssc.com/research/Publications/Cogent_life_science_KETspaper.pdf

## 4.4 Priority areas: making a case for action

### Flexible production facilities

| The need | Drivers | Actions to deliver |
|---|---|---|
| • More responsive, faster production capability at a lower cost via flexible/modular factories<br>• Reduced risks arising from high costs and complex technology transfer | • Rising production costs<br>• Older population with unmet needs<br>• Rising development costs<br>• Products required in smaller volumes<br>• Current configuration not tenable/fit for purpose | • Define value proposition by mapping benefit to product types<br>• Close technology gaps via open collaborations, research, testing, feasibility<br>• Close skills gaps through training, recruitment<br>• Provide enabling regulatory framework |

Rising costs, the need to create products in smaller volumes and the growing requirements of an ageing population are driving the need for more flexible, responsive and lower-cost production facilities. The vision is for smaller, modular factories using standardised processes, to reduce capital and operating costs, and to lower the risks involved in complex technology transfer.

While this model is starting to occur in an isolated way, a more integrated approach is required. This will need to be supported by changes to the regulatory framework, improved skills and the development of new technologies and processes. It will also entail greater understanding of the fundamental science underpinning technologies required for such developments as continuous processing and Quality by Design.

Key to enabling more widespread change will be to demonstrate the value of this new business model including enabling companies to learn from the experience of those who have already adopted new approaches. Barriers to their adoption include the risks perceived in making the changes involved.

### Design for manufacture

| The need | Drivers | Actions to deliver |
|---|---|---|
| • Opportunity for the UK to develop a world-leading position by delivering better medicines at lower cost through the integration of design and manufacturing activities | • The necessary skills, capabilities and ambition to achieve this already exist in industry, academia and funding bodies<br>• Proven track record of collaboration and innovation | • Encourage new mindsets to move away from current business models<br>• Transfer lab-based concepts and processes into predictive, commercialised technologies<br>• Develop mechanisms to provide better customer data |

The UK has the opportunity to develop a world-leading position in the delivery of medicines that provide a better outcome for patients, at a lower cost with shorter development times and reduced wastage. A more sustainable approach is required with less dependence on critical raw materials. Such changes could be achieved by integrating the needs of manufacturing into the design stages of development to achieve more predictable, commercialised technologies and more flexible, responsive manufacturing. Some examples of this kind of approach exist but there is a need to demonstrate its strategic value in order to encourage wider adoption and reduce the dependence on current business models. More robust technologies and processes need to be developed to ensure critical quality attributes are included in the final product.

A more fundamental understanding of chemical and formulation technology is required, building on the UK's proven track record in successful academic collaboration and innovation and supported by the Technology Strategy Board and Research Councils. Closer relationships between the industry and its regulators need to be developed from an early stage to allow regulatory issues to be considered in parallel with manufacturing advances.

## Improved formulations and product platforms

| The need | Drivers | Actions to deliver |
|---|---|---|
| • Improve the design of medicinal formulations based on a better understanding of science | • Respond more quickly and effectively to new and growing markets<br>• Cut costs, minimise use of resources and reduce waste<br>• Maximise shelf life of drugs and chemicals | • Build UK capacity and capability in formulation research<br>• Address regulatory issues |

Formulations – how active and delivery ingredients are combined in different ways – have a critical part to play in medicinal products. There is an urgent need for a better understanding of formulation science, to support manufacturing as well as how formulations interact with human systems. Improved formulation design could, for example, enable the creation of products that remain stable without the need for refrigeration, thus reducing costs and waste and maximising the shelf life of drugs. A more effective approach to formulation design could also help bring new products to market more quickly and efficiently.

Significant improvement in simulation and modelling (molecular but also process flows, interactions between particles) is key to achieving a better understanding of formulations. Currently it is limited to single entities and is not predictive. Other critical gaps in our understanding include a lack of physical data required to understand formulated systems, the link between drug structure and immunogenicity, the polymer structures that could enable controlled and sustained release of active ingredients and fuller understanding of the effects of drugs on the human body. In the future, we can envisage water free systems, disease-based formulations, stability at (global) ambient temperatures and model formulation platforms.

An important step to achieving these greater levels of understanding would be to build the UK capacity and capability in formulations (a dedicated formulations research centre), together with active support from funding bodies to encourage further R&D (science and manufacturing). Particular barriers that will need to be overcome include any regulatory issues that may arise as well as the challenge of dealing with product-specific IP.

## Manufacturing challenges of novel drug delivery and smart packaging

| The need | Drivers | Actions to deliver |
|---|---|---|
| • Improve ways of monitoring a patient's health<br>• Increase patient compliance with treatment | • Monitoring of patients is poor with long cycle times between measuring and intervention<br>• Compliance with treatment of chronic conditions is very poor | • Repurpose existing consumer electronics (e.g. smart phones) for monitoring<br>• Develop diagnostics to automatically monitor patient health<br>• *Develop physical pack standardisation and on line printing as enabling technologies/capabilities*[1] |

Patients often fail to follow prescribed treatments, particularly for chronic conditions. Patient compliance could be improved by developing technologies to monitor whether a medicine is being taken correctly. Integrating drug delivery and smart packaging as part of the overall manufacturing process, could provide for overall cost savings (reduced waste) and improved health outcomes (greater compliance). More standardisation of the medicine product form (tablets, powder, liquids etc) and universal cartridges, together with smart delivery and communication devices, could provide for more streamlined manufacture to the patient, with opportunity for full feedback on patient use. A closed loop system can be envisaged, where rechargeable delivery devices with diagnostics and consumer electronics (i-phones) enable consumer/patient prompts and responses and feedback into the manufacturing process. The visionary concept is the 'one device for all'.

[1]Items in italics have been added or modified during post-workshop consultations and do not appear on the sector landscape.

Some of the technology required to achieve these innovative new approaches may already exist, but there will need to be selection of appropriate cartridges (able to replenish dry substances) and formulations (e.g. mini-tabs into capsules) to determine proof of concept. Consumer electronic devices such as smart phones could be repurposed to monitor whether patients follow their treatment (linking to the assisted living sector). Energy harvesting for self-powering of the cartridges remains a technical gap and will require development.

Such radical new approaches would inevitably have an impact on patients and it would be important to take their views into account if these new ways of delivering drugs are to be introduced successfully. Understanding and communicating the potential impact of the changes both in terms of patients' health and of economics would be important to ensure success. It would help drive a full life cycle manufacturing approach, giving manufacturers new connections to their customer base, and requiring more standardised but more responsive manufacturing to meet patient need/demand. Population models would provide data which could be linked to the design of medicines and the level of stratification possible. This in turn will inform manufacturing strategies.

It would be essential to involve the regulatory authorities at an early stage to identify any issues in relation to regulations and standards.

### Manufacturing for personalised medicines

| The need | Drivers | Actions to deliver |
|---|---|---|
| • Tailor medicines for individual patient needs | • Reduce side effects and improve patient outcomes<br>• Reduce healthcare costs<br>• Manage growing needs of ageing population | • Develop adaptable delivery systems<br>• Improve and integrate material and formulation science<br>• Build industrial collaboration across life sciences sector and regulatory buy in |

Medicines are not equally effective for all patients and ideally treatments need to be adapted to suit sub-segments of a population (stratification) or personalised to each individual. Tailoring or targeting therapies has the potential to decrease costs and waste as well as reduce side effects and improve outcomes for patients. The vision is to standardise many parts of the drug manufacturing system (bulk drugs, carrier, delivery system, release system, with appropriate quality controls), then tailor at point of care through a 'pick and mix' approach, as in the 'Dulux' paint mixer.

While this is an exciting prospect offering significant potential benefits for patients and the economy, some radical new developments would be required to achieve it. Some of the robotics technology required currently exists, but more integration and automation would be needed. Better understanding and development is needed of the material/formulation science including API/carrier optimisation, combining different APIs, and nano-screens to separate incompatible actives. A range of technologies lending themselves to new devices/delivery systems, compatible with the broader range of standardised drugs, can be foreseen. Industry-wide collaboration (bringing together pharmaceuticals, devices, delivery systems and diagnostics) would be needed to enable this degree of change, together with support from regulatory authorities. New business and reward models would be essential to encourage this cross collaboration which has not happened anywhere before at this scale.

The workshop noted the strong cross-over to the previous case, 'Manufacturing challenges of novel drug delivery and smart packaging'.

## More integrated supply chain driven by patient demand

| The need | Drivers | Actions to deliver |
|---|---|---|
| • Supply of medical treatments and products to be driven by the needs of patients | • Current business model not sustainable due to expense, waste and slow service response<br>• Work towards system where payment to drug companies is based on successful treatment of patients | • More flexible supply chain with local distribution systems, based on patient need<br>• Smaller, flexible, more integrated manufacturing operations |

There is growing consensus that the current supply model operating in the pharmaceutical sector is not sustainable, involving as it does huge costs to the health care service, high-inventory and excessive waste, combined with slow response.

Instead, supply could be linked more directly to the needs and well being of patients, based on real patient data. More flexible, local distribution systems are required to reduce inventory levels and lead times. In addition, more agile manufacturing operations will enable companies to respond quickly to patient demand. Ultimately we need to work towards a system where pharmaceutical companies are paid according to the success rate of their products.

To achieve these changes will require new developments in manufacturing technology as well as the introduction of more flexible, controllable processes and systems (e.g. continuous processing). The supply chain needs to become more integrated, supported by improvements in IT.

Barriers include the challenge of changing long-established structures. Regulatory frameworks may also present a barrier if they are not aligned with the needs of a demand-led supply chain.

# 5. The biopharmaceutical sector

The UK biopharmaceutical sector comprises over 250 companies that are part of the supply chain involved in research, development and manufacture. Companies offering specialist services are the dominant business segment in this sector.[1] It is forecast that eight of the top ten blockbuster drugs by 2016 will be biopharmaceuticals rather than small molecule, new chemical entities.[2] The pharmaceutical industry has therefore made a concerted effort to put resource into building biopharmaceutical capability and manufacturing of biopharmaceutical products.

## 5.1 High-level landscape

Workshop participants identified the sector's opportunities, challenges and needs in terms of the four landscape areas (trends, products, technologies and enablers). An outline of the findings that emerged is given below. The full landscape chart and associated landscape element linkages can be found in the Appendix.

### 5.1.1 Key trends and drivers

Participants considered the trends and drivers they thought would affect the sector in the short, medium and longer term (up to 2025).

- Lack of significant manufacturing investment in UK biopharmaceuticals by industry or Government
- Partnerships with regulatory authorities and improved consensus between regulators and organisations making biopharmaceuticals in the UK
- Potential threat to UK pharmaceutical activity from off shoring and overseas competitors
- Chronic shortage of experienced bioprocessing professionals including engineers and other life science skills relevant to manufacture of biopharmaceutical products
- Growing importance of analytics and process knowledge in the development and manufacture of biopharmaceuticals

### 5.1.2 Novel products, processes and services

Potential new products, processes and services were identified:

- Biopharmaceuticals for neurodegenerative diseases
- New vaccines and innovative delivery systems for emerging diseases
- Enabling manufacture on demand (just-in-time) for smaller but more frequent batches
- Products to improve patient compliance
- Improve accuracy and speed of genomic sequencing and diagnostic tests to enable stratification of patient sub-populations, leading to challenges in flexible manufacturing strategies
- Biosimilars and biobetters – subsequent versions by other companies of patent-expired biopharmaceutical products
- *Secondary manufacture and supply of biopharmaceuticals generating possible new IP*[3]

### 5.1.3 Key technologies and capabilities

The workshop participants then considered which technologies and capabilities would be required within the sector to enable the products, processes and services they had identified.

- Reducing the reliance on conventional cell production systems and the potential move to increased cell free protein production and synthetic expression technology
- Integrated continuous processing strategies and technologies of multiple products for upstream and downstream stages
- Standardising protocols and processes for different kinds of pharmaceuticals within a Quality by Design framework
- Process analytical technology (PAT)/QbD to improve manufacturing success
- Formulations that remain stable at ambient temperatures reducing reliance on cold supply chain
- Capability to manufacture thermally stable products or ingredients able to survive high temperatures in developing world

[1] HealthTech and Medicines KTN.

[2] Evaluate Pharma Market Report 2010.

[3] Items in italics have been added or modified during post-workshop consultations and do not appear on the sector landscape

- Non-surgical stimulation of endogenous (internal) cell repair using biopharmaceutical products

### 5.1.4 Enablers

Finally, participants discussed the factors that would enable these innovations to take place.

- Government policy to support biopharmaceuticals manufacturing sector
- Industry and academia to collaborate on skills development through funded opportunities
- Continued funding of skills provision e.g. apprenticeships and industry facing research such as the Bioprocessing Research Industry Club (BRIC)[1] or equivalent strategic activity
- Access to expert centres for training and pilot scale manufacture opportunities
- New regulatory approaches to clinical trials to meet the needs of complex therapies
- *New commercial manufacturing support services (e.g. testing, analytical or validation services)*[2]

## 5.2 Links to HVM framework

The national competences identified as part of the original HVM study acted as a prompt for the workshop participants to ensure that all relevant areas were considered.

The outputs from the workshop were mapped onto the framework created by the HVM study to create a comprehensive linkage chart for the sector. Relating the sector findings to the HVM framework in this way enables the original data to be refreshed and updated to take account of new ideas and developments.

The linkage chart created for the biopharmaceutical sector can be found in the Appendix.

## 5.3 Priority areas for further investigation

Participants reviewed the products, processes and services identified as important for the sector and ranked them in order of importance to create a list of priority areas.

The key areas agreed for the biopharmaceutical sector were:

- Improved manufacturability of current and future biopharmaceuticals pipeline
- Analytics and characterisation
- Biopharmaceutical formulations
- Innovation in biological production technology.

A 'case for action' was developed to justify further work in each of the priority areas. Participants also identified any critical gaps, barriers and enablers, as well as the key actions required to take the ideas forward.

The detailed case for each priority area is given overleaf.

[1]http://www.bbsrc.ac.uk/bric.

[2]Items in italics have been added or modified during post-workshop consultations and do not appear on the sector landscape

## 5.4 Priority areas: making a case for action

### Improved manufacturability of current and future biopharmaceutical pipeline

| The need | Drivers | Actions to deliver |
|---|---|---|
| • Agile, rapid manufacturing capability supporting smaller batches to enable more value to be captured and retained in the UK | • Wide range of UK biopharmaceutical therapeutics requiring more rapid manufacture at lower cost<br>• UK has the second largest biopharmaceutical pipeline but lags behind competitors in manufacturing capability | • Improve collaboration between companies and also between business and academia<br>• Introduce more vocational and academic training<br>• Provide facilities for product development and technology assessment |

There is a need to create a low cost route to market for individually tailored or stratified medicines, capable of being rapidly manufactured in small batches. Many UK biopharmaceuticals companies are developing innovative ideas and technologies for new therapies but the UK is not regarded globally as a strong place to manufacture. Additional infrastructure is needed to help advance manufacturing technology innovation, building on what already exists in companies and academia.

The aim would be to provide new processes for product development and technology assessment which are migratable to the commercial base. A range of regulatory-approved products and processes could be developed supported by increased funding for industry and industry/academic collaborations. An asset register would help to identify what facilities are currently available. Critical gaps to support these developments include an understanding of which process innovations might accelerate manufacture and a lack of appropriately skilled people.

Barriers include the current regulatory framework, which does not support such evolutionary developments although more generally the UK has a favourable regulatory environment with biopharmaceutical experience. There may also be resistance from service providers to the biopharmaceutical manufacturing value chain who could need to be persuaded of the benefits of such an approach.

### Analytics and characterisation

| The need | Drivers | Actions to deliver |
|---|---|---|
| • Develop effective analytical tools to support the manufacture of biopharmaceuticals products and to drive towards fully characterised products | • Effective analytics and characterisation are essential for product quality and safety. They enable products to get to market faster, at less cost, and with reduced wastage, contamination and risk | • Enable improved access to cutting edge tools<br>• Lower cost analytical tools such as sensor development<br>• Predictive models based on the analytical tools |

Analytical tools to ensure the quality and safety of products are vital for the biopharmaceutical sector where the purity and structural integrity of samples must be constantly checked at each stage of the process. More effective analytics would enable products to reach the market quickly, at a lower cost and with reduced waste and be more akin to a Quality by Design approach. To create more effective analytics we need to identify the complex biopharmaceutical products and processes requiring innovative analytics. Predictive models need to be created building on process data, and a range of cost effective analytical tools developed.

Critical gaps in our current capabilities include low cost and rapidly accessible sensors, immunoassays and biomarkers to support more biopharmaceutical manufacture. It is also important to establish facilities and partnerships to enable organisations to gain easier access to these new developments, as well as high-cost capital equipment, expertise and skills. The regulatory environment can play a key role in supporting change with closer collaboration needed to adapt regulatory frameworks to support these new developments.

## Biopharmaceutical formulations

| The need | Drivers | Actions to deliver |
|---|---|---|
| • Stable and effective biopharmaceutical formulations to enable targeting of the disease more effectively<br>• Better integration with manufacturing processes rather than a traditional silo approach | • More effective formulation design for a wide range of therapy types to improve drug efficiency and life, increase manufacturability and yields of active drug substance and reduce costs | • Develop formulations to support range of new treatment delivery options<br>• Better formulations of biopharmaceutical products enabling reduced reliance on cold supply chain |

Biopharmaceutical formulations – the process in which different chemical substances, including the active drug, are combined to produce a final medicinal product – remain something of a 'black art'. There is a need to develop more stable and effective formulations to increase the effectiveness of treatments, improve manufacturability and reduce costs. The vision is to develop a formulation 'toolkit' to potentially create formulations at manufacture and also at the point of care, reducing the need for cold storage in the supply chain and delivering the medication in a patient-friendly form.

Some capability already exists in molecular modeling and formulation design. However, much still needs to be done including developing techniques for formulation characterisation, understanding precisely how formulations work and why, and building a successful formulation design kit to support accelerated stability trials. Factors that would support this include improved adjuvants and stabilisation techniques, and new business models to deliver pre-competitive technology to market. Liaison with the Technology Strategy Board Formulations Special Interest Group may be important as long as it meets the needs of the biopharmaceutical community. A barrier may be the industry's unwillingness to depart from current practices.

## Innovation in biological production technology

| The need | Drivers | Actions to deliver |
|---|---|---|
| • New cell culture systems to exploit synthetic biology<br>• Simplifying manufacture of individually-tailored treatments | • Creating drugs that can be easily reconfigured as medical need changes<br>• Reducing time between diagnosis and drug delivery<br>• Decrease costs and failure rates | • Build links with Technology Strategy Board Synthetic Biology Special Interest Group<br>• Provide dedicated funding to improve collaboration across the supply chain |

Synthetic biology is a new area of biological research and technology that combines science and engineering. Its goal is the design and construction of new biological functions and systems not found in nature. Synthetic biology can be used to create new cell culture systems for biopharmaceuticals, which in turn can support the manufacture of individually tailored treatments. This may help to reduce the reliance on more conventional cell production systems currently seen across the industry and enable a more rational design of biopharmaceuticals should technology be developed. New biological production systems would enable tailored products to be produced more rapidly and at lower cost. The drugs production strategy may also be easily reconfigured as medical needs change. The move to larger scale manufacture using such radical production strategies would demonstrate a step change.

Post genomics tools are already being used to understand cell production systems, but significant development is still required. Mammalian cell production systems are used routinely but a move back to microbial is starting and GM plants are now becoming more evident. Companies spend significant time and money on cell production systems and future IP implications are uncertain. Critical gaps that need to be addressed include more effective models for cell systems, platform production processes for vaccines, and the development of knowledge and skills for cell-based manufacture. Key to success will be close involvement of the Technology Strategy Board Synthetic Biology Special Interest Group and dedicated funding to improve collaboration across the supply chain.

# 6. Conclusions

This report has highlighted both significant manufacturing challenges and exciting new opportunities currently facing the pharmaceutical sector in the UK, for both existing small molecules and the growing large molecules markets. Key examples include: dealing with an increasingly ageing population with growing healthcare needs, providing therapies tailored to suit individual patients, reducing unsustainable development costs, facing up to the so-called 'patent cliff' by which expiring patents result in plummeting revenues, and developing a more adaptable, responsive regulatory framework.

These challenges are already stimulating some innovative responses across both areas with evidence of a real appetite for change. To a great extent manufacturing approaches in the pharmaceutical industry are still stuck in the past, following long-established practices that are ill suited to the needs of the 21st Century. There are now real opportunities for radical change and improvement.

The 'case for action' for each of the priority areas outlined in this report provide an insight into some of the benefits such change could achieve across a range of areas. Manufacturers are starting to move away from traditional batch processing and introducing more responsive, continuous production with the potential to reduce costs, speed up delivery and ultimately provide better service to patients. Step changes in the way drugs are made and delivered to the patient alongside personalised medicines, tailored to meet each patient's individual needs, could dramatically improve treatment outcomes. New research to improve the design of drug formulations could help to cut costs and the use of valuable resources whilst at the same time enabling the sector to respond much more quickly to new markets. Reconfiguring the industry's supply chain to focus on actual patient needs learnt in real time could result in big cost savings and smaller, more responsive operations.

The UK is in an excellent position to take advantage of these opportunities. Many of the world's leading pharmaceutical companies are located and manufacture here, while at the same time the sector includes hundreds of small, highly innovative businesses that can contribute new approaches and technology. The UK also boasts excellence across life sciences and manufacturing with particularly commitment to drive up skills and cross fertilisation. The existence of an open regulatory body, the MHRA, is another important enabler for change. This study highlights the vital importance of close collaboration between industry, government and the regulatory authorities to support new manufacturing developments and to enable their impact on industry and the regulatory framework to be identified as early as possible.

## 6.1 Next steps

This report is being launched for circulation at the 9th Annual bioProcessUK Conference on 28-29 November 2012. It will also be available through the Knowledge Transfer Networks and other relevant organisations in order to gather feedback on its findings from a wide circle of stakeholders across industry, government and academia. Once these responses have been incorporated the findings will be used to help identify where resources can best be invested to meet the challenges and opportunities that have emerged.

## 6.2. How to provide feedback on this report

We invite feedback on the findings of this report from all interested parties. This will be collated by the HealthTech and Medicines Knowledge Transfer Network.

Please send your comments on any aspect of the report via the following weblink:

**www.healthktn.org**

**Deadline for submitting feedback**

19 December 2012

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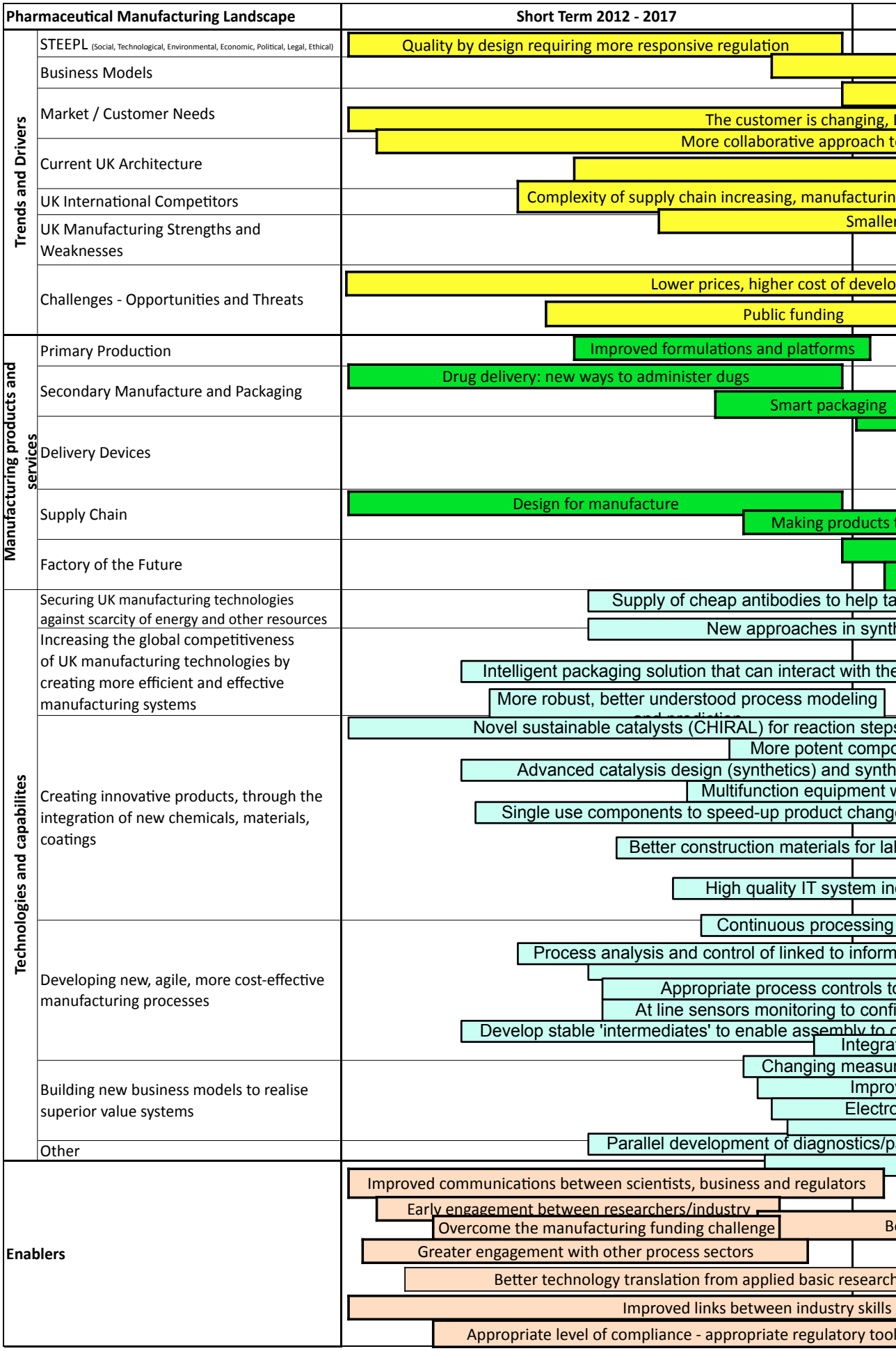
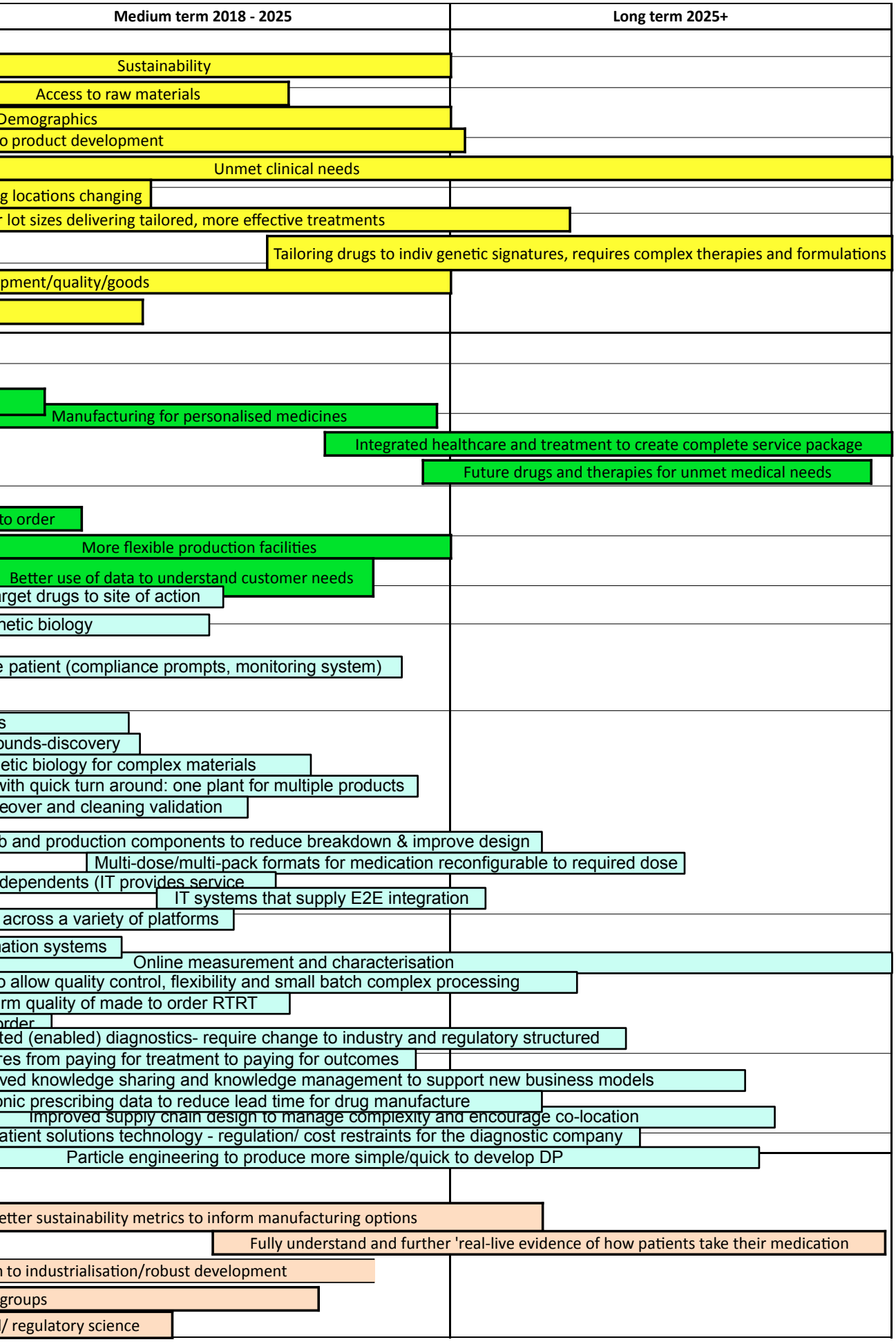
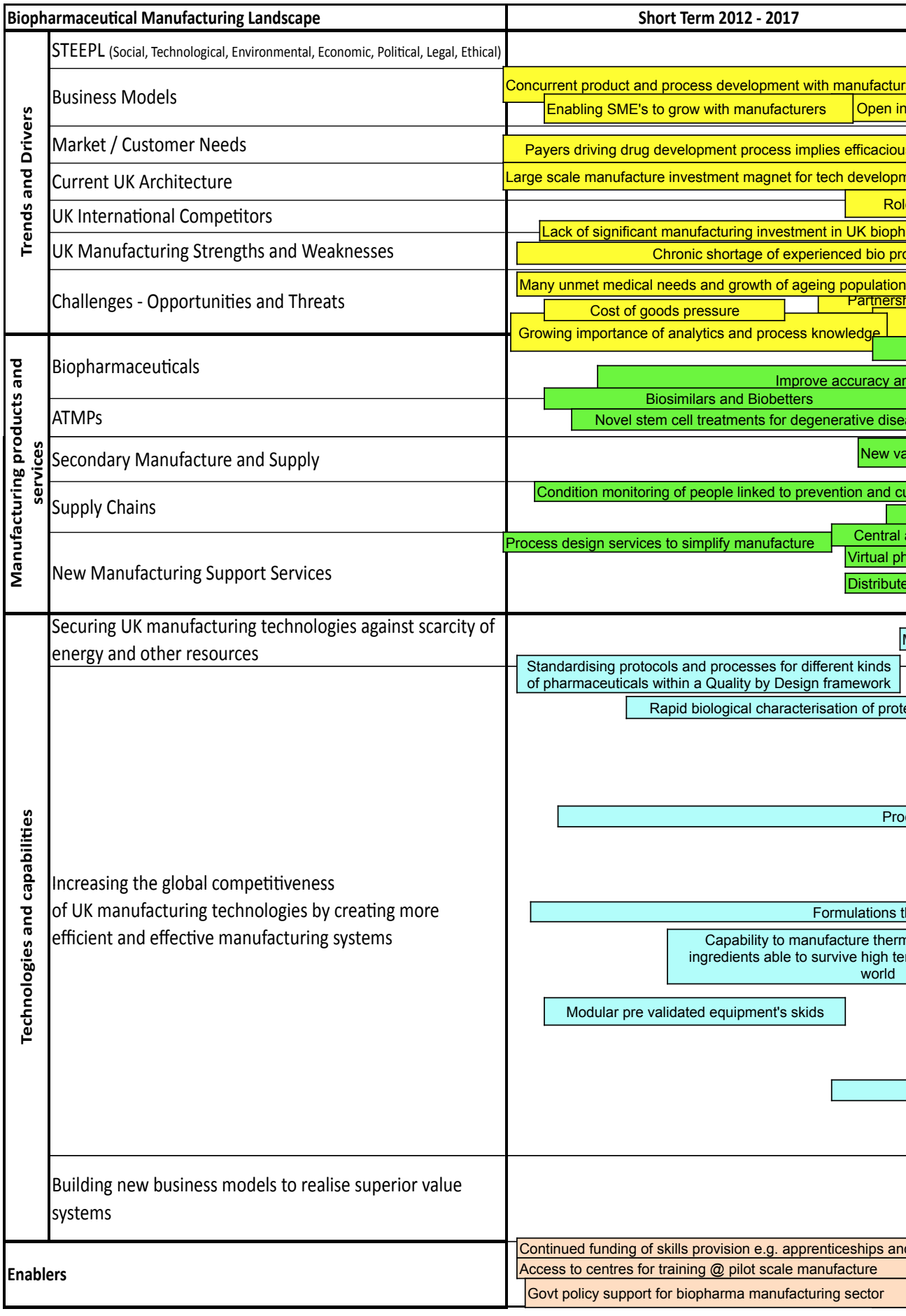
Further contributions and comments were received as part of a post-workshop validation exercise from Astra Zeneca, AMRI Global, Carroll Pharma Consulting, CMAC and the National Skills Academy.

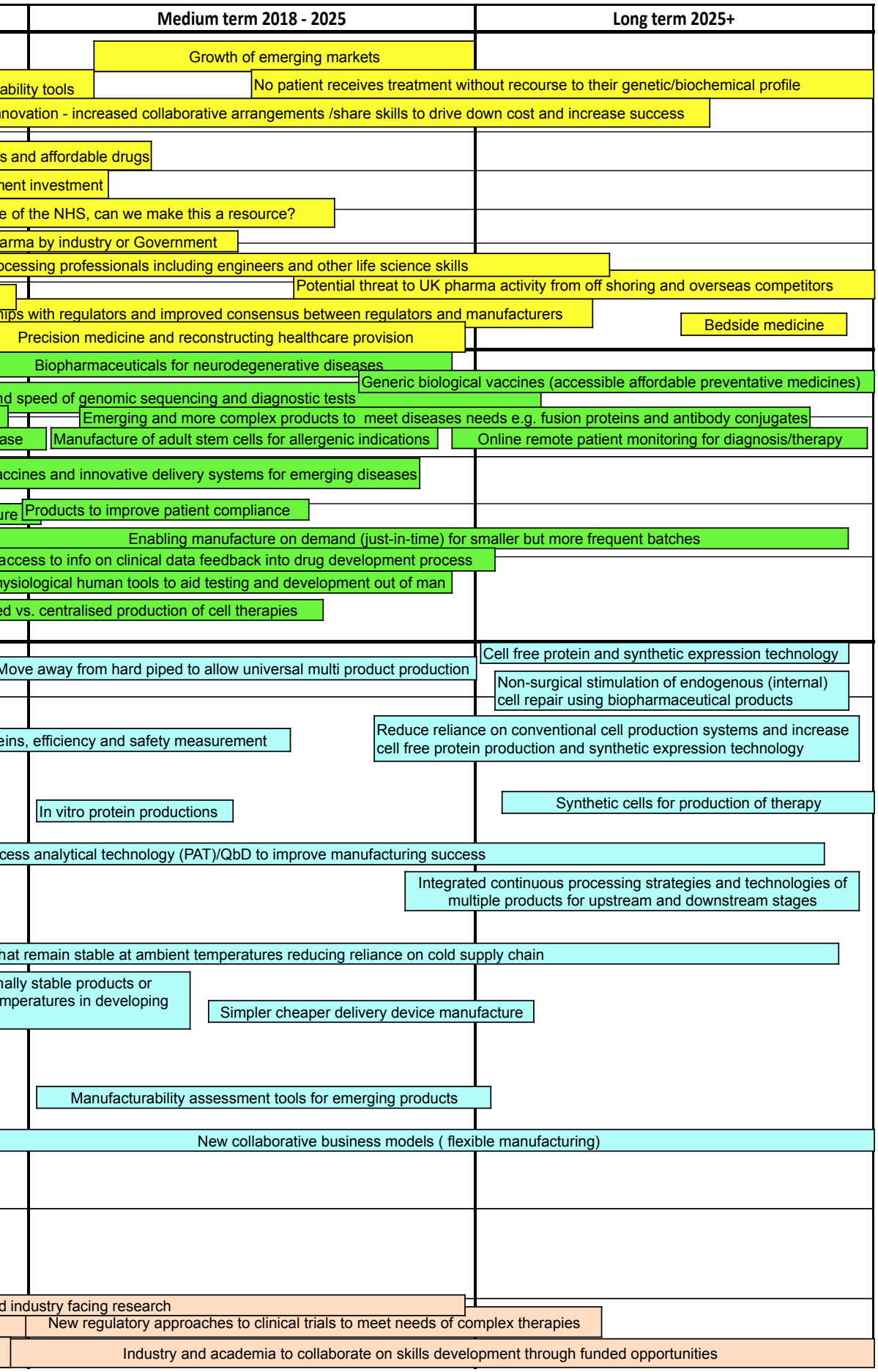
# Appendix: High-level Landscapes



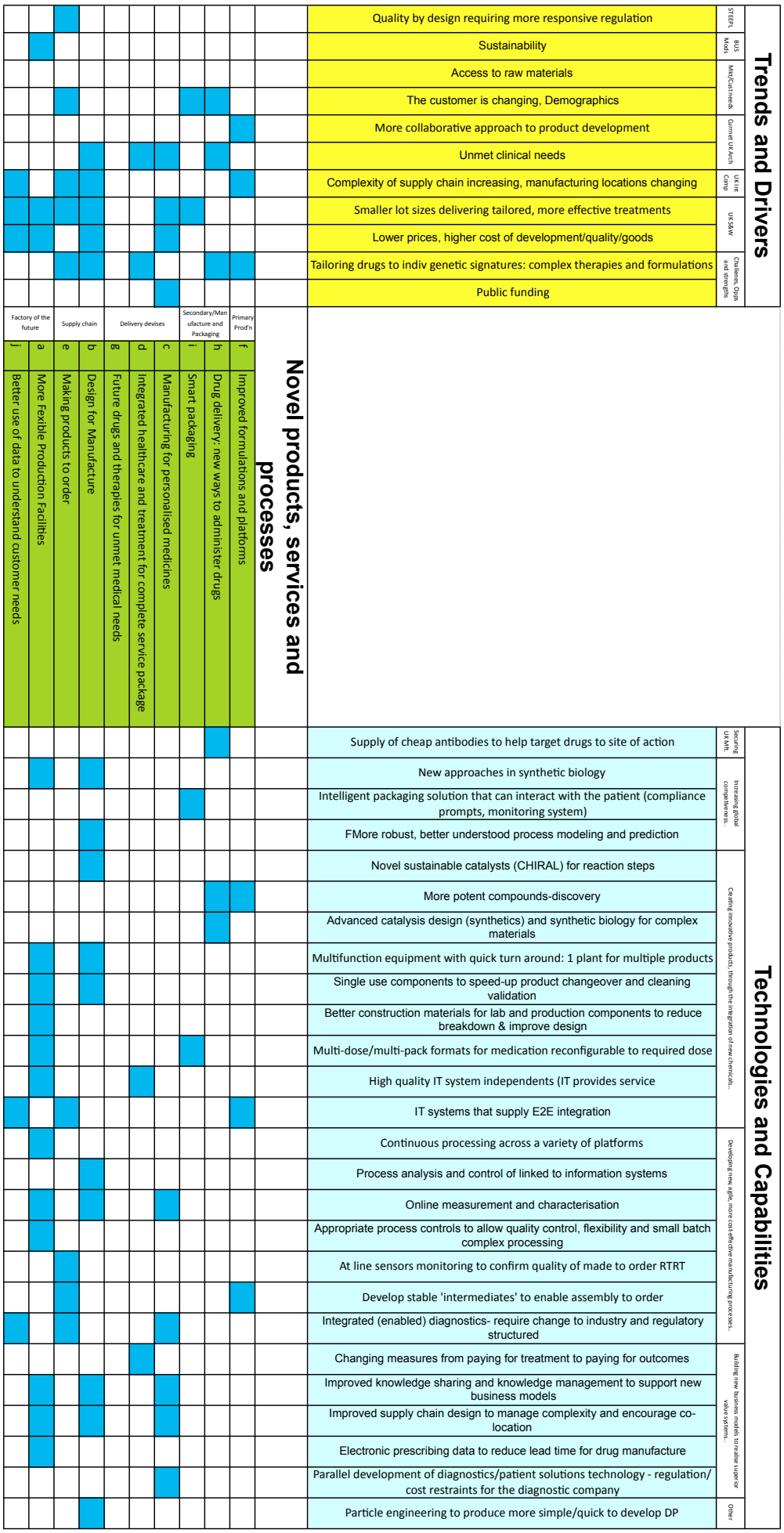

Medium term 2018 - 2025
Long term 2025+
Sustainability
Access to raw materials
Demographics
o product development
Unmet clinical needs
g locations changing
r lot sizes delivering tailored, more effective treatments
Tailoring drugs to indiv genetic signatures, requires complex therapies and formulations
pment/quality/goods
Manufacturing for personalised medicines
Integrated healthcare and treatment to create complete service package
Future drugs and therapies for unmet medical needs
to order
More flexible production facilities
Better use of data to understand customer needs
rget drugs to site of action
netic biology
e patient (compliance prompts, monitoring system)
s
ounds-discovery
etic biology for complex materials
with quick turn around: one plant for multiple products
eover and cleaning validation
b and production components to reduce breakdown & improve design
Multi-dose/multi-pack formats for medication reconfigurable to required dose
dependents (IT provides service
IT systems that supply E2E integration
across a variety of platforms
nation systems
Online measurement and characterisation
o allow quality control, flexibility and small batch complex processing
rm quality of made to order RTRT
order
ted (enabled) diagnostics- require change to industry and regulatory structured
res from paying for treatment to paying for outcomes
ved knowledge sharing and knowledge management to support new business models
onic prescribing data to reduce lead time for drug manufacture
Improved supply chain design to manage complexity and encourage co-location
atient solutions technology - regulation/ cost restraints for the diagnostic company
Particle engineering to produce more simple/quick to develop DP
etter sustainability metrics to inform manufacturing options
Fully understand and further 'real-live evidence of how patients take their medication
n to industrialisation/robust development
groups
l/ regulatory science

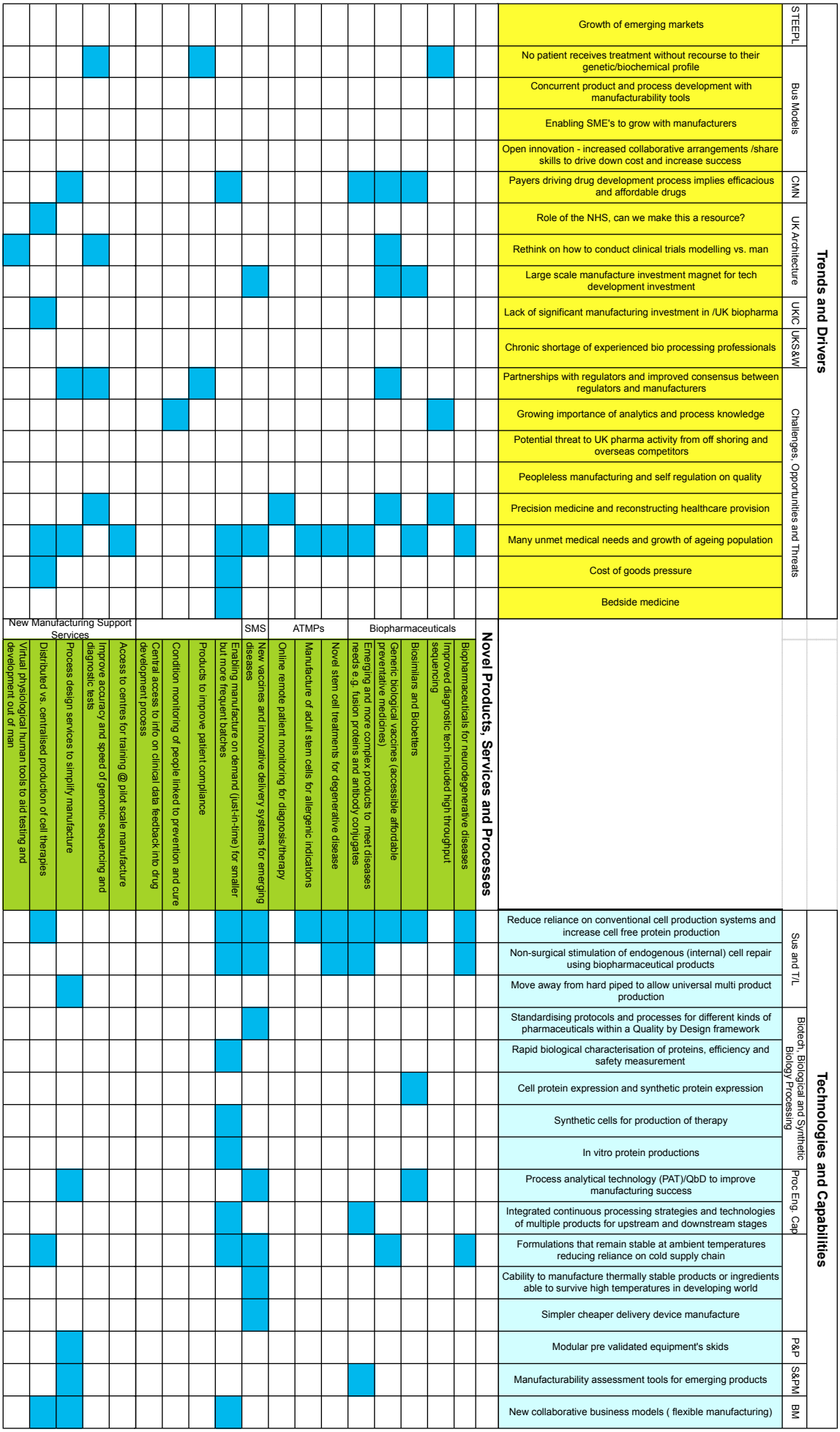
# Appendix: High-level Landscapes




Medium term 2018 - 2025
Long term 2025+
Growth of emerging markets
ability tools
No patient receives treatment without recourse to their genetic/biochemical profile
novation - increased collaborative arrangements /share skills to drive down cost and increase success
s and affordable drugs
ent investment
e of the NHS, can we make this a resource?
arma by industry or Government
ocessing professionals including engineers and other life science skills
Potential threat to UK pharma activity from off shoring and overseas competitors
ips with regulators and improved consensus between regulators and manufacturers
Bedside medicine
Precision medicine and reconstructing healthcare provision
Biopharmaceuticals for neurodegenerative diseases
Generic biological vaccines (accessible affordable preventative medicines)
d speed of genomic sequencing and diagnostic tests
Emerging and more complex products to meet diseases needs e.g. fusion proteins and antibody conjugates
ase
Manufacture of adult stem cells for allergenic indications
Online remote patient monitoring for diagnosis/therapy
ccines and innovative delivery systems for emerging diseases
ure
Products to improve patient compliance
Enabling manufacture on demand (just-in-time) for smaller but more frequent batches
access to info on clinical data feedback into drug development process
ysiological human tools to aid testing and development out of man
d vs. centralised production of cell therapies
Cell free protein and synthetic expression technology
Move away from hard piped to allow universal multi product production
Non-surgical stimulation of endogenous (internal) cell repair using biopharmaceutical products
eins, efficiency and safety measurement
Reduce reliance on conventional cell production systems and increase cell free protein production and synthetic expression technology
Synthetic cells for production of therapy
In vitro protein productions
cess analytical technology (PAT)/QbD to improve manufacturing success
Integrated continuous processing strategies and technologies of multiple products for upstream and downstream stages
hat remain stable at ambient temperatures reducing reliance on cold supply chain
ally stable products or mperatures in developing
Simpler cheaper delivery device manufacture
Manufacturability assessment tools for emerging products
New collaborative business models ( flexible manufacturing)
d industry facing research
New regulatory approaches to clinical trials to meet needs of complex therapies
Industry and academia to collaborate on skills development through funded opportunities

# Appendix: Pharmaceutical Linkage Chart




Trends and Drivers
STEEPL
Bus Models
CMN
UK Architecture
UKIC
UKS&W
Challenges, Opportunities and Threats
Growth of emerging markets
No patient receives treatment without recourse to their genetic/biochemical profile
Concurrent product and process development with manufacturability tools
Enabling SME's to grow with manufacturers
Open innovation - increased collaborative arrangements /share skills to drive down cost and increase success
Payers driving drug development process implies efficacious and affordable drugs
Role of the NHS, can we make this a resource?
Rethink on how to conduct clinical trials modelling vs. man
Large scale manufacture investment magnet for tech development investment
Lack of significant manufacturing investment in /UK biopharma
Chronic shortage of experienced bio processing professionals
Partnerships with regulators and improved consensus between regulators and manufacturers
Growing importance of analytics and process knowledge
Potential threat to UK pharma activity from off shoring and overseas competitors
Peopleless manufacturing and self regulation on quality
Precision medicine and reconstructing healthcare provision
Many unmet medical needs and growth of ageing population
Cost of goods pressure
Bedside medicine
Novel Products, Services and Processes
New Manufacturing Support Services
SMS
ATMPs
Biopharmaceuticals
Virtual physiological human tools to aid testing and development out of man
Distributed vs. centralised production of cell therapies
Process design services to simplify manufacture
Improve accuracy and speed of genomic sequencing and diagnostic tests
Access to centres for training @ pilot scale manufacture
Central access to info on clinical data feedback into drug development process
Condition monitoring of people linked to prevention and cure
Products to improve patient compliance
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New vaccines and innovative delivery systems for emerging diseases
Online remote patient monitoring for diagnosis/therapy
Manufacture of adult stem cells for allergenic indications
Novel stem cell treatments for degenerative disease
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Generic biological vaccines (accessible affordable preventative medicines)
Biosimilars and Biobetters
Improved diagnostic tech included high throughput sequencing
Biopharmaceuticals for neurodegenerative diseases
Technologies and Capabilities
Sus and T/L
Biotech, Biological and Synthetic Biology Processing
Proc Eng. Cap
P&P
S&PM
BM
Reduce reliance on conventional cell production systems and increase cell free protein production
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Process analytical technology (PAT)/QbD to improve manufacturing success
Integrated continuous processing strategies and technologies of multiple products for upstream and downstream stages
Formulations that remain stable at ambient temperatures reducing reliance on cold supply chain
Cability to manufacture thermally stable products or ingredients able to survive high temperatures in developing world
Simpler cheaper delivery device manufacture
Modular pre validated equipment's skids
Manufacturability assessment tools for emerging products
New collaborative business models ( flexible manufacturing)

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