MANUFACTURING VISION
FOR UK PHARMA

FUTURE PROOFING THE UK THROUGH AN ALIGNED TECHNOLOGY AND INNOVATION ROAD MAP

Medicines Manufacturing Industry Partnership

abpi BIA Innovate UK Knowledge Transfer Network

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TECHNOLOGY AND INNOVATION (T&I) ROAD MAP

EXECUTIVE SUMMARY

The primary purpose of this road map is to set out recommendations on how to protect and grow the respected UK 'Pharmaceutical Brand' with a specific focus on Technology and Innovation (T&I). Historically, the UK has excelled at early innovation in medicines platform research and development, but has lost out to other countries for the final manufacture of these high value products. A plan of action is described via the road map to define how we can build on existing medicines platforms and through strategic technology investment to prepare the UK for the very latest step change opportunities in Advanced Therapies and Complex Medicines and their associated manufacturing requirements. The creation of GMP capable innovation centres is proposed to serve not only as 'test beds' where ideas can be accelerated from the bench to the clinic but also provide an efficient route onto commercial manufacture as required. Collaboration between academia, industry (small and large) and government is needed in order to achieve this vision.

The proposed road map is not only driven by the goal of pharmaceuticals (Pharma) being a key industry in leading UK economic production but it could also enable an improved healthcare service. The latter will extend into a partnership with more effective and connected diagnostics and dispensing and the intent would be to offer healthcare that is more predictive and personalised but also participatory and this integrated model could be part of a timely solution to manage some forms of healthcare more efficiently. With a projected £120.6bn NHS spend in 2017[1] investing a small percentage of this in these synergistic technologies is a core recommendation.

For simplicity 'Medicines' throughout this road map have been split into several areas and each is at a different point in its respective lifecycle. MMIP focuses on three strands of medicines manufacturing that build on the UK's global competitive advantage in research and development:

- **Future Treatments** (for example, cell and gene therapies)
- **Complex Medicines** which the UK is not making the most of (ADCs, Oligonucleotides, viral vectors, new vaccines)
- **Established Medicines** (Small molecules, mAbs, traditional vaccines, therapeutic proteins), including those increasingly outsourced, where the application of process innovation (e.g. continuous processing, digital manufacturing, synthetic biology) creates a strong opportunity for the UK.

1 http://www.nhsconfed.org/resources/key-statistics-on-the-nhs

CONTEXT

The global Pharma Industry is comprised of companies engaged in researching, developing, manufacturing and distributing medicines for human use. New medicines have an enormous positive influence on global health, prosperity and economic productivity by saving lives, increasing life spans, and shortening hospital stays. Advances in medicine have eliminated deadly diseases and have brought other life threatening conditions under control. Drug therapy is now an integral part of every facet of healthcare and new breakthroughs continue to revolutionise the treatment of non-communicable diseases. The UK is a substantial force in this global market with over 1300[2] companies directly involved in medicines manufacture.

Encouraging and fostering the UK as an innovative and technology led industry is critical to the future of the UK economy (current Pharma exports are £25.8bn[3]). As growth rates slow in traditional markets there is now even more focus needed to maintain and grow this successful sector to drive new solutions to new opportunities and challenges. The UK has a track record of early innovation in all aspects of medicines development. The solid academic foundations coupled with external investment, a strong skills base and targeted Government funding and fiscal incentives encourages both large and small companies to focus their R&D capabilities in the UK. The UK's ability to innovate early in a collaborative way sets it apart in what is an ever increasingly competitive market.

Historically, translating this early innovative development into actual scaled up medicines production physically in the UK has not been so successful. Examples of lost opportunities include:

- The UK was a leader in biological drug development and its manufacture moved to the USA, Japan, Singapore, Switzerland and Ireland.
- API manufacturing capability has been off-shored to the Far East over the last 10-15 years, drawn to lower cost locations at times at the expense of consistent quality/compliance and supply chain security. Two persistent problems for API manufacturing in these locations have been high staff turnover and challenges satisfying the requirements of global regulators for supply back to major markets (i.e. USA, Europe).
- We manufacture very few packaging components that are needed for all medicine packs. This can result in medicines manufactured in the UK being exported to other markets for final packaging into "patient ready" form. This results in the UK losing out on export value as exports of unfinished products are less valuable than finished products.

2 http://www.mmlandscape.ktn-uk.org/

3 http://www.efpia.eu/uploads/Modules/Mediaroom/figures-2015-key-data.pdf

All of these examples mean that the UK imports more materials and finished goods, we are less self-sufficient and more vulnerable to supply shortages and we ultimately lose high value jobs and manufacturing know how and skills. The importing of key medicine components and materials will undoubtedly be made more complex post Brexit.

There is a sea change however, and the UK Pharma Industry is now at a pivotal point (especially with the scope offered by Advanced Therapy Medicinal Products and more 'Complex Medicines'), and there are global challenges and opportunities to regain the UK's position as the leading country for medicines development and manufacturing. With a focus on not only these new molecules but also the novel associated manufacturing technologies to better meet the needs of our patients, there is also the opportunity to improve and re-engineer existing manufacturing processes using innovative emerging technologies, tools and techniques to reconfigure and extend the current chemistry of 'established' medicines. This involves the whole end to end supply chain and integrates various parallel 'game changers' including digital, automation and advanced diagnostics and analytics.

This wider vision will be realised by the UK's uniquely collaborative capability, including other recently announced Industry Challenges and also the partnership with key stakeholders such as the MHRA and NHS. This alignment and timely initiative is vital to secure manufacturing investment now as there are key technologies that have the potential to integrate, enhance and disrupt the traditional manufacturing model for medicines. This integration can only happen if the various stakeholders work together and have a clear end goal, which has to be driven through by anchoring the UK as the country for all medicines innovation and manufacturing investment.

A key lever in delivering forward growth is the ability to get medicines into the clinic early; this will primarily benefit patient access but also crucially accelerate investment making this an important 'sticky' industry. By default innovation drives intellectual property and the UK patent box opportunity complements this drive from early development to eventual commercialisation.

WHY A TECHNOLOGY AND INNOVATION (T&I) ROAD MAP NEEDS A STRATEGIC END GOAL: THE GRAND CHALLENGE

We know the UK is a respected world leader with regards to T&I. The Pharma Industry is part of this success but it now needs an aligned T&I strategy that is appropriate, targeted and delivers against real defined needs. A key ask from the Technology and Innovation Futures 2017 paper (*Technology and Innovation Futures 2017 Govt Office for Science: P18*[4]) was that with any disruptive technology strategy the most valuable ones should be where the *'UK can achieve the greatest gains in increasing economic productivity and improving delivery of public services'*. This ask is particularly pertinent with healthcare where there are two clear 'Challenges'. These are inter-related but have different end 'customers':

- For Industry: The T&I strategy must lever the UK as the destination of choice for investment in development and manufacturing. It must not only offer simple mechanisms to accelerate investment decisions (including fiscal and skills) but also encourage a collaborative environment with academia, other industry platforms, key stakeholders and SMEs. The availability of translational funding and 'test beds' where bench to clinical to commercial timelines are leaned by aligned T&I strategies is imperative. For internationally mobile investment, speed along with cost, service and quality are a competitive advantage.

- For Health Services and Patients: An effective T&I strategy will ultimately secure access to better and more affordable treatments for all patients, however it has to do more than this. Health systems are coming under pressure due to not only an aging population but also as the burden of chronic diseases is soaring[5] - this is exacerbated by dietary changes and more sedentary lifestyles. This situation is not sustainable and there has to be a disruptive technology driven collaboration that tackles this 'big challenge' head on, and quickly. It will undoubtedly involve Pharma as the opportunity is to ensure that companion diagnosis[6] and disease measurement is more predictive and the subsequent healthcare management is more personalised and participatory. As such it will include technologies in MedTech and digital but it will also challenge the way we undertake clinical trials beyond Phase I. The new paradigm will look to optimise medicine dispensing based on more informed trials using 'bigger data' and this will extend to larger 'real world' outcome trials. This approach will set new standards for healthcare management and set the UK as a genuine healthcare leader[7]. This vision is evolving and it can be realised by the recommendations laid out not only in this enabling technology road map but also those detailed in the Accelerated Access

4 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/584219/technology-innovation-futures-2017.pdf
5 WHO Preventing Chronic Disease – A vital investment (2005)
6 Deloitte: Global Life Sciences Outlook 2016 (p11)
7 http://www.bioindustry.org/newsandresources/bia-news/uk-is-on-track-to-build-the-worlds-third-global-biotech-cluster/

Review[8] and in the NHS Five Year Forward View[9]. The common thread in these recommendations is patient centricity coupled with added value, and the target is to ensure the right technologies are invested in at the right time.

A clear T&I road map for the UK must address these two 'Challenges'. They are inter-related and they will be enabled primarily by T&I platforms all working together. This vision will only be successful if investment is targeted and managed and stakeholders are true partners. Only the UK can deliver this due to its unique connection between industries, the healthcare system, regulators, academia and a skilled technical workforce. Some of the individual pieces are already in place, and other opportunities have been identified in this road map, and they now need to be aligned more and funded appropriately.

In defining the road map there was consultation with multiple stakeholders (see acknowledgements in Appendix) through workshops, meetings and interviews and extensive literature research carried out to understand the core inputs and outputs for a recommended strategy that the road map structure would be created around. A wider understanding of the capabilities and restrictions of various existing UK facilities including the CPI and Catapults was built and this was coupled with identified technology gaps.

ROAD MAP PROPOSAL

From the research and insights into 'needs' and 'manufacturing gaps' there is the opportunity for **Centres of Excellence** in the following areas:

- To further develop the current capabilities in continuous manufacturing at CMAC through the creation of the Medicines Manufacturing Innovation Centre (MMIC) which will be capable for clinical supply.
- To support the creation of an open access facility capable of manufacturing complex medicines for clinical supply (and the ability to handle high potency medicines) from API production through to fill/finish (patient ready).
- To support the development of the next generation of packaging technology and associated Smart devices required for new medicine platforms (including specialist packaging needed throughout the processing and manufacturing supply chain).
- Provide innovation support for advanced therapies manufacturing, as laid out in the 2016 Advanced Therapies Manufacturing Taskforce[10].

8 https://www.gov.uk/government/organisations/accelerated-access-review
9 https://www.england.nhs.uk/ourwork/futurenhs/nhs-five-year-forward-view-web-version/5yfv-exec-sum/
10 http://www.bioindustry.org/home/

These 'centres' would crucially be GMP capable with a focus on making suitable clinical supply (through to Phase III), be a 'test bed' resource for various users, they would share common technology platforms and have their own specific technical capabilities and would complement facilities currently offered by the Catapults and CPI facilities. Their end goal will be one of accelerating clinical supply delivery to meet this technology and innovation 'Grand Challenge' for patients, the pharmaceutical industry, government and ultimately UK plc.

Inputs: Who would typically use the Centres of Excellence?

- **Academia -** Provide a 'test bed' for Universities to access and develop specialist manufacturing equipment and also offer additional capacity (including high containment as required) and training.
- **SMEs -** Provide a 'test bed' to experiment with developments and tie in with academia. The GMP capability would accelerate clinical supply capability, especially lacking within their own vertical capabilities. Training packages could be tailored for these potential clients on top of offering a clinical manufacturing service.
- **Partner Industries -** Suppliers of materials/API could utilise facilities, again as a 'test bed' through to clinical supply, of value especially to players from areas not traditionally connected (or just starting entry) to the biopharmaceutical space.
- **MedTech -** Integration between companion diagnostics and digital with medicines is a more recent opportunity and one where with this potential interface/'test bed' could identify and provide technical support.

Capabilities: What technology opportunities would these Centres of Excellence offer?

- **Medicine Manufacturing Innovation Centre (MMIC)**[11] - Build on the current proposal for continuous manufacture, initially for established medicines. The UK leads in continuous manufacturing research. This manufacturing process development platform can be extended to other molecules and importantly the MMIC will be a GMP facility.

Note: A consideration for antibiotics was reviewed but this is catered for by the AMR research facility at Alderley Park. If antibiotic manufacture was to be required to be included in the MMIC proposal, then a separate capability would most likely be needed.

11 https://www.cmac.ac.uk/files/media/CMAC_Brochure_2015.pdf

- **'Complex Medicines' Centre of Excellence -** The need for a GMP ready facility that can (for example) manufacture a range of larger molecules has been identified. It would focus on sterile production for clinical supply and also have the unique capability for high potency products. It would have a fill and finish capability to be 'patient ready'. It could if desired be specified to meet any future UK vaccines development and manufacturing strategy.
- **Packaging and Device Centre of Excellence -** This capability would design, develop and produce optimised packaging (including materials) and device solutions for medicines and the medicines supply chain. It would also integrate smart packaging technology and provide scale up material to enable timely clinical supply (including disposables as appropriate). Other industries could use this packaging research facility if required but it would have a focus in the first instance on Pharma and the interface with MedTech, Digital, and Automation and Robotics initiatives.
- **Specialist Cell and Gene Therapy Manufacturing Operation -** The ATMPs will have the added support from the above centres as required and in the proposal the intent is that the existing Cell and Gene Therapy Catapult (CGTC) capability for ATMP manufacture complements the UK's 'one stop shop' principle. The ATMP taskforce proposal for the UK: Government to establish competitive funding to support viral vector capability growth within two years. The Taskforce proposes the development of a specialist manufacturing operation leveraging where possible, existing infrastructure. The operator(s) should be mandated to work with academic groups to supply viral vectors and therefore gain exposure to cutting edge developments, whilst at the same time industrialising the academic processes.

Essentially, with this capacity proposal, the UK would be ready to approach any medicine platform to the clinic using this unified and collaborative technology ready model. This would connect all of the relevant UK discovery, development and manufacturing capabilities and give the country a unique 'one stop shop' responsibility.

<u>Output</u>: Who would benefit from the centres?

- **UK plc -** Anchoring of both the development and manufacture of a range of medicines platforms. Having this broader 'one stop shop' capability with associated shared specialities with a clinical supply focus would make the UK an attractive country for investment. Clinical trials would ideally be supported through the UK's unique partnership bodies such as the National Institute for Health Research. Having a well-connected capability could reduce timelines substantially.
- **Healthcare and patients** - Improving delivery of medicines (and healthcare) through earlier intervention, providing a focussed world leading clinical arena for access to medicines and evaluating longer term 'real world' opportunities. This can extend from new medicines to

companion diagnostics to trial. An example of this already starting is technology combinations and the NHS is opening up this capability with innovation 'test beds'[12].

- **Academics** - the processes and 'know how' developed can further update our level of understanding of applied and basic science, optimizing training practices and optimizing direction of ongoing research projects in real time.

What would this model look like?

The intent of the T&I road map is to build a model that lays out how the UK's new and existing capabilities can get access to technology and technology expertise to drive innovation through to an end point. Ultimately, this is into the clinic and it is well understood that this involves getting all these innovation links in the development process made and thoroughly tested long before getting to patients.

The model has been created **(Fig 1)** and highlights the core Centres (MMIC/complex medicines) where there will be a focus on clinical product being made and packed (working in parallel with the Pack CoE as required). These Centres are supported by shared 'technology strands' (13 identified to date). With this aligned approach Pharma would have the capability to lean its technology readiness with any medicine platform with a focus on patient access and commercial readiness.

Note: that the cell and gene therapy catapult has already been initiated and this is where some ATMP capability can be placed in the future.

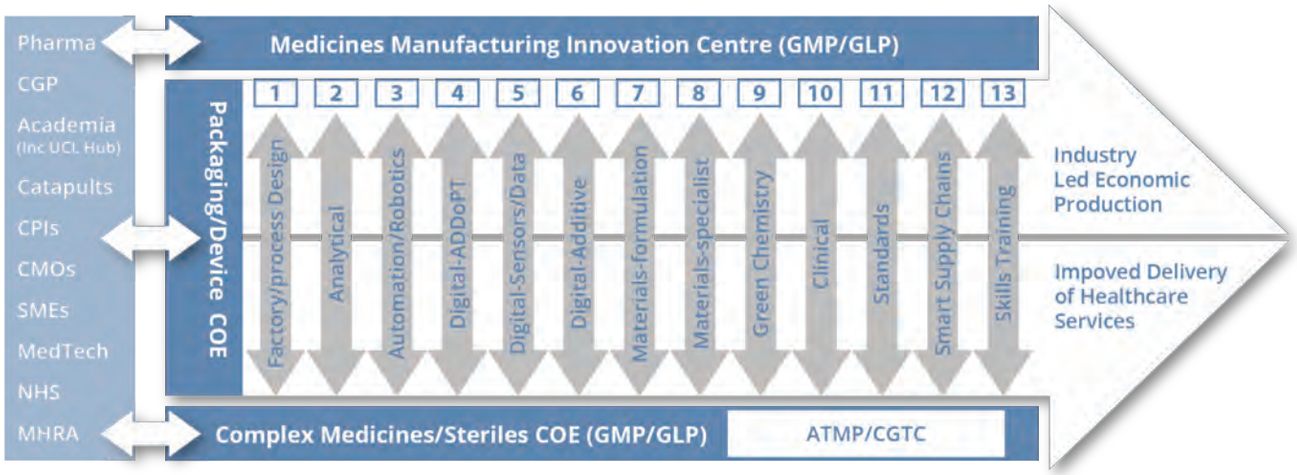


Fig 1: Model for delivering clinical trial capabilities for medicines platforms in the UK

12 https://www.england.nhs.uk/ourwork/innovation/test-beds/

HOW THE CENTRES WOULD BE ALIGNED AND SHARE TECHNOLOGIES

This distinction between various medicines platforms has been made previously as they have different manufacturing methods with different challenges and opportunities. Where they can share common 'technology strands' are of particular interest, and these shared 'technology strands' are where the UK can create additional competitive advantage by adding real value to the whole end to end supply chain. The proposal to share 'technology strands' improves efficiencies and encourages shared learning so maximising benefits as they cut across all the centres. This sharing of 'technology strands' essentially optimises investment and reduces duplicity. 'Technology strands' identified were:

- **Factory/Process Design -** The factories that make our new medicines will be different. They will need to be fully flexible/adaptable scalable (both 'up' and 'across') and fully integrated. Factory of the Future concepts will be incorporated into the manufacturing capability within these centres. They will share similar platforms and as part of the build plan, the infrastructure for equipment and processes will need to be defined to ensure that there are no additional overlaps with existing offerings. They will also create 'test-beds' for various manufacturing hubs including fully modular units that incorporate relevant technologies. These smaller more flexible modular units could be built within the CoEs and evaluated. This approach is unique but one that would be important as some manufacturing becomes more 'boutique' and potentially portable.

  Several specific 'technology strands' have been highlighted as core to Factory Design. These include:

  - **Analytical Equipment -** Fully integrated Process Analytical Technologies (PAT) that offer real time in line analysis and inspection
  - **Automation Equipment that include the use of Robotics -** 24 hour labs/sterile manufacture/ fully connected and flexible capability/closed systems
- **Digital -** Digital is too over-arching a definition and this has been broken down into several separate strands as each has its own technology requirements. These digital areas include:
  - Fully integrated systems
  - Sensors – Data
  - Additive technologies
  - Smart devices - Diagnostics /Apps

- **Materials**
    - API manufacture (plan to bring more onshore and enhance with UK expertise)
    - Novel packaging materials and coatings for both packaging, devices and process equipment

- **Green Chemistry -** Build on UK expertise to clean processes and reduce production waste
- **Clinical Supply -** Scale up capability with automated assembly and analytics using the GMP facilities and aims to tackle clinical supply issues that may arise with new medicine platforms
- **Regulatory Standard and Guideline development -** Through MHRA, NIBSC and British Pharmacopeia, the UK is respected as a lead in standard setting, and as such this is a value added asset
- **Supply chains -** optimise end to end supply chain solutions for future medicines
- **Training -** ensure UK has facilities to train at all academic and technical levels using up to date equipment and processes

Note: this model takes into account the Advanced Therapies Manufacturing Action Plan[13] requirements and builds on them. It has to be pointed out that where there are also common 'technology strands' that these too would be shared and one of the key technology challenges is with viral vector manufacture and this will be part of the Cell & Gene Therapy Catapult capability which will be GMP compliant.

This list of 'technology strands' is not exhaustive by any means but it clearly shows that there are many shared technology challenges and the more that they can be aligned the more value will be added. The key opportunity is to ensure that each area plugs potential technology gaps in the manufacturing end to end supply chain. There are some established complementary facilities for technology development within the UK network (primarily the Catapults, including the National Biologics Manufacturing Centre and CPI) but they have a limitation in that they are not all GMP approved so cannot manufacture medicines for clinical use nor can they handle highly potent products. They can however be used for exploratory research and have an important part to play in the development of certain platforms and as such these would complement this proposal to offer the UK as a complete service provider for medicines discovery, development and manufacturing.

The facilities would not only act as 'test-beds' to optimise processes, they would also exchange technology platform knowledge. Skills training would also be undertaken as a service. The facilities estimated cost and build time have been drafted below:

13 http://www.abpi.org.uk/our-work/mmip/documents/advanced-therapies-manufacturing-taskforce-report.pdf

Who	What	When	Cost
Medicines Manufacturing Innovation Centre (MMIC)	**Process innovation in all small molecules and established medicines – into clinic**	**3 Yrs (new build)**	**£56m**
Complex Medicines (Sterile) Centre of Excellence	**Process innovation in larger molecules (with HCF) – into clinic**	**3 Yrs (new build as HCF and fill/finish capability)**	**£58m (tbc)**
Smart Packaging and Device CoE	**Pack/device/supply chain and material innovation**	**2-3 Yrs Could be earlier if existing facility used**	**£26m (tbc)**
Specialist Cell and Gene Therapy Manufacturing Centre/Operation	Advanced therapy innovation and production	Q4 2017	Underway

The intent would be that the MMIC and Complex Medicine CoE would have specific skill sets and some clearly defined differences but both have the capacity and capability for GMP manufacture of new medicines. As pointed out they complement the existing CGTC and recently requested ATMP investment plans. The estimated spend for the innovation centres is £140m and this will need further confirmation but for the intent of this road map latest cost models have been used. They will provide a 'fee for service' for access to technology resources (both equipment and expertise) and this will be needed to ensure ongoing sustainability post initial funding/investment. These capabilities have been recommended because if there are not the facilities or the experts to drive technology in a cohesive way then the road map will essentially fall apart. If the UK is to take this bold step to ensure that medicine manufacture for all platforms can move nimbly to the clinic it has to not only invest but invest wisely and ensure that the operating model is well managed (centrally) and has clear measureable outputs. Only then can industrial and societal objectives be delivered.

These proposed technology centres will allow for more open T&I development with a focus on ensuring that there is this capability to ultimately enable clinical supply. The sharing of common technology platforms and the connection between product, process and pack are the unique proposition and would complement current facilities positioning the UK as a 'one stop shop' technology hub for all forms of pharmaceutical research, development and manufacture. The timing to implement this strategy is dependent on funding approval and some initial proposals would be prioritised based on their current evolution and ease of implementation.

The 'Technology Strands' would be funded through the initial CoE set up but also from other traditional funding routes to ensure sustainability. The intent is that these could also be virtually led (as well as be

established entities, or built from existing programs such as AMSCI) and would include representation from industry, specialist suppliers and academia. Work on these 'Technology Strands' is already underway (such as Green Chemistry at Nottingham University and Digital Manufacture -ADDoPT) and this is where alignment with technology to molecule development can be enhanced and fully explored and validated. The road map recommends that the setting up of the 'Technology Strands' could be initiated early on once the principal is agreed.

'What will be up and when?'

An estimation of programme timings is shown in **figure 2**. This assumes Q3 approval of recommendations made in this road map.

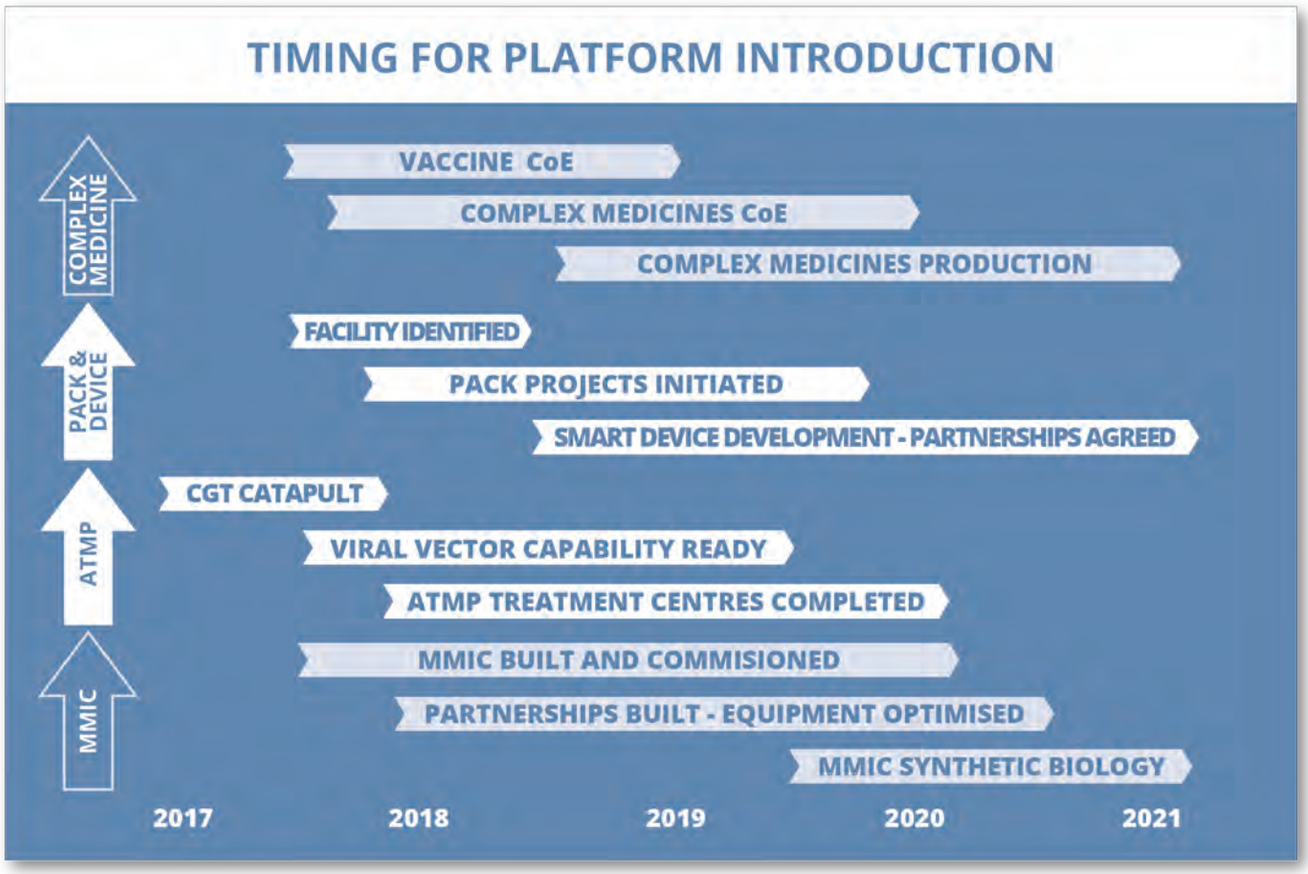


Fig 2: As estimation of programme timings

Alignment of the Pharma T&I Road Map with the Government's Industrial Strategy and Challenge Fund

The Government's Industrial Strategy[14] has identified ten "pillars" which are critical to the success of UK based industry and for which new policies and priorities will be developed.

14 https://www.gov.uk/government/consultations/building-our-industrial-strategy

The above proposal relates to all these pillars but in particular:

- Investing in science and innovation
- Developing skills relevant to the future
- Encouraging trade and inward investment
- Affordable energy and clean growth
- Driving growth across the whole country
- Creating the right institutions to bring together networks and places

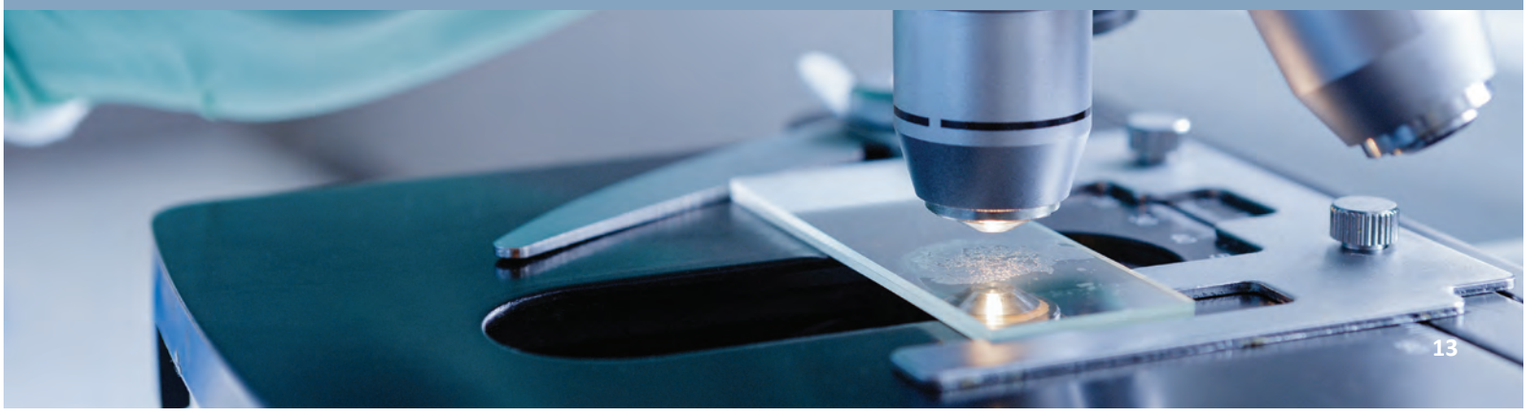
The proposed centres will enable accelerated development with a particular focus on clinical supply as a first intent, whilst also optimising manufacturing processes early on in the development cycle. This clinical focus is key as it is often a critical catalyst for increased inward investment. Having the infrastructure to then commercialise this will be enabled by the network of UK manufacturers across the whole range of medicine platforms, including CMO's who would ideally be linked into the centres to ensure lean scale-up and commercial launch.

Associated with the Industrial Strategy, the new Industrial Strategy Challenge Fund, overseen by UK Research and Innovation, will support a number of priority technologies and help the UK build on existing strengths in research and development.

The proposed new centres are relevant to a number of the technology challenges but in particular:

- Leading Edge Healthcare and Medicine
- Robotics
- Manufacturing processes and Materials of the Future

The 'Leading Edge Healthcare and Medicine' challenge is a fundamental driver for our T&I road map recommendations for small molecule enhancement, advanced therapies and complex medicines.



RECOMMENDED ACTIONS FOR WIDER TECHNOLOGY AND INNOVATION ROAD MAP

Re-enforce and secure the UK as the leading technology and innovation hub for Medicines development and manufacturing using fiscal and intellectual property levers:

- Build on the UK's strength as a fiscally attractive country for investment with specific incentives for innovation (including R&D Tax credit system/Patent Box).
- Continue to target research and innovation investment through existing channels such as the Biomedical Catalyst, Innovate UK CR&D and Research Council Funding.
- Support and connect SMEs with available technology funding and incentives (Tech loans/grants and access to experts and bodies such as MMIP and the proposed technology centres).
- Offer Intellectual Property support with patents and know-how and also offer litigation funding. Fast tracking of patent preparation should be considered as a potential lever.

Identify, prioritise and mitigate technology gaps and opportunities:

- Within medicines development and manufacture there are currently key technical challenges. These vary depending on the specific platforms and this road map has highlighted areas for technology focus. In an ever changing environment, gap analysis will have to be frequently undertaken but with this proposal managing the current technology gaps through the technology strands it strengthens the capability providing a robust technology path through to clinical supply for new medicine platforms. Further clarity is needed to look for opportunities and it would be advantageous to identify if there were any technology synergies that could be factored in further during the Industry Strategy Challenge fund review.
- Mitigating technology gaps will ultimately enable more efficient manufacture with improved robustness to meet customer expectations. There is a real sense of urgency needed with this challenge as the next 1-3 years is a critical time due to increasing competition.
- Universities must continue to collaborate with each other and with industry in a structured way to maximise funding and also focus on the core gaps and challenges. There is a need to sustain and increase the process engineering research undertaken in the universities. This approach will deliver the innovative manufacturing technologies required which will ideally be scaled up in the facilities that have already been invested in (those proposed in this road map). This potential will

be reinforced by initiatives identified by ongoing ISCF workshops.

- The ongoing gap analysis must consider the whole supply chain. Logistics, packaging and storage challenges are all opportunities for the UK and are included in the manufacturing scope. In this first full road map the whole end to end supply chain has been considered.

Accelerate Technology through targeted and aligned hubs and Centres of Excellence:

- The opportunities offered by these new medicine platforms localising centres of excellence in the UK would enable technologies to be developed faster with the intent of bringing together academia and industry into an environment where, for example, Quality by Design (QbD) could be factored into the early design stage. This could be offered as a value added service. These CoEs would be set up under a similar model to the Catapult and CPI with part funding and this funding percentage would be positioned once the principle is agreed. Centres will share knowledge (where appropriate) and again this is a capability that can position the UK as a technology led country that can accelerate from the bench to the clinic as these facilities will have a GMP capability. The Centres would offer the unique GMP capability and they would be located/integrated to ensure that there was no doubling up of facilities. As such a detailed review of existing UK capabilities would be undertaken as a priority to avoid any duplication and confirm this approach. This aligns with existing university hubs e.g. UCL.
- Centres of Excellence would connect to specialists in other areas of manufacturing to integrate platform technologies such as novel materials (including packaging), robotics, automated analytical testing and digital. The convergence of other key technologies will transform the future of medicines and drive growth. These centres must be made to work in partnership with clearly defined expectations laid out and defined business cases agreed with core customers such as the NHS. Funded technology projects must be based on real needs.
- With the expectation for smaller more flexible manufacturing methods, these centres could act as pilot sites and realise a ‘Factory of the Future’ where innovations and technologies could be assessed and optimised by experts.

That the UK offers a unique and well defined ‘route to market’ for T&I implementation:

- Innovation is valueless unless it can be applied. In medicine development the ultimate goal is to move from the bench to the clinic to commercial in a timely manner. To enable this there has to be a partnership between the stakeholders/payers/manufacturers and the UK offers this potential opportunity by bringing together representatives from the NHS/NICE/DoH/OLS/MHRA.

The unique environment that the UK has with these groups offers a powerful collaboration to rapidly develop, test and ultimately commercialise innovation. Note: nearly one third of respondents stated in a report[15] on innovative products and services in Pharma that these are co-created with external partners so multiple partnerships need to understand the clear advantages of UK plc.

- Existing initiatives such as the Accelerated Access Review, NICE modelling and NHS specialist commissioning will help pave the way to the use of new technologies and these will range from the introduction of ATMPs to the use of patient data with 'smart devices'. The added value is that the UK is noted for its approach to technology adoption whilst at the same time setting 'gold standard' requirements.
- With the development and convergence of technologies such as sensors and monitoring coupled with digital capability, clinical evaluation will become more accurate and more data informed. This could accelerate development time and ultimately optimise dosing and adherence. The current clinical model is somewhat cumbersome and there is an exciting opportunity for the UK to challenge the existing model and enhance the personalised medicine model which could ultimately ensure that the patient gets the exact dose that they require.
- With the advent of ATMPs it will be critical to work with the government (including the NHS) to site Cell and Gene Therapy Treatment Centres and these will incorporate a range of technologies. The design and build of these centres will be innovative in themselves and should become 'anchors' in their own right. Facilities will enhance patient care and optimise the management and dispensing of these new medicines and ensure 'total cost' value.

Create Technology and Innovation platforms that are developed and launched with appropriate global standards that where appropriate are endorsed by the UK Regulator:

- Although there is an understandable priority for ATMP manufacturing innovation, using technology to improve existing processes must also be a focus to ensure that the UK stays competitive globally. If standards can be created around technologies during development this will enhance and re-enforce the UK's technological lead. The MHRA has set up the Innovation Office and this unique capability can assist in driving out these standards early. The Regulatory bodies could be part of an inclusive team during early new medicine development within the CoE model.
- Standards are fundamental in defining the quality expectations and controls for products, processes, equipment and even services. With new technologies comes the need for new standards and the Government should continue to support and recognise the challenges in standard setting but also the potential benefits that they can bring.

15 https://www.pwc.com/gx/en/pharma-life-sciences/assets/pwc-managing-innovation-pharma.pdf

- Align with the recommendation regarding identifying technology gaps. There is a particular opportunity on ATMPs with the MHRA, NIBSC and the BP leading a series of stakeholder engagement meetings. These would be held with industry, SMEs and academic innovators to review different aspects of cell, gene and viral vector materials as well as their manufacturing processes and products.
- Government must resource the MHRA to support the evaluation and approval of new standards to advance manufacturing efficiencies.

UK must retain and grow its skill base across a range of technologies to support both research and manufacturing capability:

- Without a skilled workforce (from post-doctoral to technicians) there will be no technology or innovation advancement. The UK has to continue to invest in science and engineering at all levels and target research and manufacturing skills. The gap analysis on the whole medicines supply chain will help with skills identification and all stakeholders must be involved in this planning. The SIP 2016 report[16] is a basis to work from.
- The centres would be open to offer 'hands on' training using the very latest equipment and science, in a GMP capable environment (as would be expected in an industrial setting). Bridging academic experimentation and the latest manufacturing technologies to keep the UK ahead across various production platforms must be factored into the centres' ongoing deliverables. Training could be a revenue generator to ensure centre sustainability. A similar model for training/skills development has been highly successful for biologics manufacturing at NIBRT in Ireland.
- With the increase in digital and complex upstream (and downstream) technologies; software, production and automation engineers are key skills. With limited higher education in these areas the UK will have to consider leveraging existing training capability (including apprenticeships) and also continue to look abroad for these skills in the short term.
- Some skill areas such as validation could be pooled and offered to SMEs with Government support. This could be a service added to capabilities that are currently offered by organisations such as the Catapults and CPI who could double up as training providers. Moreover, the level of demand for and the strategic use of QPs will need consideration.

16 http://www.scienceindustrypartnership.com/media/529053/5202fd_sip_skills_strategy_2015_final_low.pdf

1.0 INTRODUCTION AND BACKGROUND

The UK Technology and Innovation (T&I) road map has been developed to define how the Pharmaceutical industry should approach a transition to a patient centric future, using road mapping as a policy tool. It shows how road mapping helps create the foundations to support the emergence of new medicine innovation and technology levers in what is a very complex environment. The industry has some large 'blue chips' but is also collaborates heavily with academia and SMEs and as such there is distributed decision making. The UK is now facing real challenges on how best to maximise the benefits that medicines discovery and manufacturing technologies bring and there is a need to introduce a co-ordinated strategy tool, hence this road map. It is designed to be inclusive and drive out a wider consensus on setting out priorities for the discovery, development and manufacturing of world leading medicines in the UK. Historically, the UK has excelled in the discovery and development field but then lost out on the high value manufacturing, with much going abroad.

The road map is structured to give an overview of the UK Pharma Industry and recent trends in R&D manufacturing investment. It details the rationale for Government intervention and also the external drivers. The report also pulls on wider recent policy interactions such as the key 2017 Industrial Strategy work being undertaken by OLS[17].

2.0 THE UK PHARMACEUTICAL SECTOR

The UK has a strong and well established Pharmaceutical industry, composed of a mix of domestic companies (e.g. anchors like AstraZeneca and GSK) and inward investors. Over the last decade the industry has evolved with small biotech's being spun out of universities and these include companies developing advanced therapy medicinal products and therapeutic proteins. The sector is characterised with significant direct investment with high exports[18] - £25.8bn but this is essentially neutralised by Pharma imports of £28.7bn, this negative trade balance is the challenge to change. The sector has, for the purposes of this report 'pharmaceuticals /drugs/ medicines' being referenced to as innovative and generic products that are chemically or biologically derived:

17 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/586626/building-our-industrial-strategy-green-paper.pdf

18 https://www.ons.gov.uk

- **Future Treatments** (for example, cell and gene therapies)
- **Complex Medicines** which the UK is not making the most of (ADCs, Oligonucleotides, viral vectors, new vaccines)
- **Established Medicines** (Small molecules, mAbs, traditional vaccines, therapeutic proteins), including those increasingly outsourced, where the application of process innovation (e.g. continuous processing, digital manufacturing, synthetic biology) creates a strong opportunity for the UK.

Note: Advanced Therapies are medicinal product for human use – gene and cell therapy or tissue engineered.

This has been done as they are different: they have different manufacturing methods, are at different stages in their lifecycle and they have different challenges. Where they can share common technology platforms is of particular interest and these areas will be highlighted throughout this road map.

The UK is a global centre of excellence for medicines discovery and development and is supported by class leading academia and an array of creative SMEs who provide scientific and engineering innovation and technology development in close collaboration with customers. The sector however has more recently faced a gradual slowdown in GVA - £16 to £11bn from 2009 to 2014[19] and this has been attributed in part to the fact that although the UK excels in molecule discovery and development it loses out when it comes to commercialising and manufacturing them. Other factors have also included skills gaps, fiscal constraints, competitor countries increasing their efforts to attract investment from global industry and an increasingly cost competitive external landscape coupled with patent expirations.

The sector has the opportunity to challenge this slowdown and with recent changes such as: improved fiscal incentives, a skills review, earlier collaboration with regulators and potential funding, there is the real possibility to not only reverse this slowdown but also to then rapidly accelerate it. New medicines such as ATMPs and step change technologies (across all areas of the medicine supply chain) could help ensure that the Pharma Sector remains anchored in the UK.

The section below has been included as ATMPs as a distinct science already have a Cell and Gene Therapy Catapult that has a plan in place to complement the UK's research capability with a GMP manufacturing offer. For simplicity this model has been included within the proposed Complex Medicines CoE. T&I 'strands' will (where appropriate) be shared across all CoEs to encourage collaboration and re-enforce the message that the UK is ready for new medicines development, from research through to clinical (and most importantly) commercial supply.

19 UK Office of National Statistics

2.1 | ADVANCED THERAPIES

Advanced Therapy Medicinal Products (ATMPs), including breakthrough cell and gene therapies, offer unique promise for the long term management and even cure of disease, particularly in areas of high unmet medical need. They are a new paradigm in healthcare and the UK currently has a leading position in ATMP discovery and development that is supported by academia, innovation hubs (Cell and Gene Therapy Catapult), SMEs and now big Pharma focussing research in the UK. To position the importance of the opportunity that ATMPs offer, 939 clinical trials were underway in Q1 2016[20] and nearly 10% of these were carried out in the UK.

The challenge is to translate this early research and development into manufactured products more consistently and at commercial scale therefore positioning the UK as a world leader. A plan of action to meet this challenge was published in the ATMP Manufacturing Taskforce November 2016 Report[21]. Within its specific recommendations for T&I it highlighted the need to invest in viral vector manufacturing infrastructure capacity and capability as there is a global shortage and the UK has the assets and expertise to mitigate this situation if funding is made available. Although the Cell and Gene Therapy catapult is on target for completion this year there will be continued technology challenges to drive down viral vector costs and optimise production control, whilst maintaining efficiencies and ensure the quality of product. This has to be carried out within a window of two years to ensure effective 'early technology anchoring'. Making sure that the UK can make and research in this area in a timely manner will position the UK as a potential leader of this medicines platform. The proposal of the ATMP Manufacturing Taskforce is that the operator (with assistance from government funding) will work with academia to supply viral vectors and build knowledge and know-how, all the way through to commercial supply.

With the ATMP focus being on viral vector supply, associated manufacturing technologies covering specialist tools such as automation, advanced analytics and digital will be invested into. Where possible these technology platforms will be shared to avoid duplication and help with prioritisation.

There has been a recent gap analysis carried out with the ATMP space to ensure 'weak links' in the manufacturing chain are identified first (KTN Gene Therapy Workshop). Over 100 delegates attended and the outcome highlighted the following technology gaps:

- Manufacture and scale up technologies lagging behind – increasing yield and titres is a key target

20 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4846788/

21 http://www.abpi.org.uk/our-work/mmip/documents/advanced-therapies-manufacturing-taskforce-report.pdf

- Little vector specific technology developed - especially downstream processing
- Lack of rapid analytics – slowing manufacture and impacting product life
- Limited 'off the shelf' solutions for GMP manufacture and academic awareness on scale-up requirement is constrained
- Characterisation impact during manufacture of products/vectors needs more understanding
- Opportunity for further knowledge sharing between industry and academia

Technology opportunities highlighted for ATMPs included:

- Flexible production - Creation of platform technologies that cover multiple products that overcome process complexity
- Higher efficiencies enabled by single use technologies and continuous processing
- Development of associated analytical technologies
- Low shear operations and pack formats that protect product through the supply chain
- Parallel development of optimised delivery devices/systems

Technologies can only be realised if there is a partnership between industry communities. Connecting academia, manufacturers, regulators and customers is of particular importance with ATMP. For example, the use of standards in this new field (including characterization, comparability, potency and stability assays) will require the creation of reference materials, the generation of stable cell lines and funding availability to create GMP materials of importance for vector characterisation and analytics.

The ultimate goal for integrating the technologies will be to increase reproducible production, offer flexibility through scale up (and scale across), maintain the highest quality which will all enable cost reduction. Targets could be set for longer term cost reduction driven down by the cumulative improvements made in process technologies.

The output from this report, the Advanced Therapy Manufacturing Action Plan coupled with the recommendations noted in the National Cell Manufacturing Consortium clearly highlights the urgent necessity for a joined up technology strategy for ATMPs. Some of the technology platforms have a cross-over with other medicine manufacturing processes.

2.2 | VACCINES

At an Innovate UK-hosted Workshop held on 24th April 2017, certain gaps and opportunities regarding vaccines were identified and discussed in detail. The scope of the Workshop included vaccine discovery, manufacturing process technology development and final manufacture of vaccines in the UK. A key objective was to get industry, academia, research councils and government to agree on a set of common goals for UK vaccines development capability and capacity (including Technology and Innovation). The whole supply chain was considered and included various scenarios from large commercial to the capability to develop a response to a pandemic crisis (10000's of treatment scale). Conclusions included:

- The UK has a very limited capability for the scale up (development and manufacturing) of vaccines at GMP. For the current high volume vaccine capability, Europe has considerable capacity and has historically made substantial capital investment. This would not necessarily be an ideal short/ medium term strategy for the UK.
- Vaccines research in the UK is excellent. The ability to scale up manufacture however is limited especially when taking new medicines to the clinic, where GMP capability is needed at this early phase along with a robust and timely fill & finish facility. Lean process development at this stage would be an added advantage and these could help define new standards, as appropriate.
- When working with epidemics (such as Ebola) or pandemics, there is the opportunity to have the proposed capability to manufacture a GMP supply where speed to patient is paramount and capacity for any facility was estimated to be adequate at a maximum of approximately 100K doses (from 50ltrs). It would not be a commercial enterprise, more an emergency supply one. An infrastructure where new vaccines and any new technologies could partner together would be of particular benefit and enhanced by a flexible manufacturing mentality. The 'Centre of Excellence' would be focused on driving discovery through development and ultimately manufacture; optimising the making of vaccines and biologic medicines is a fundamental need.
- Support to have this cutting edge vaccine 'centre' where there would be a collaborative model to develop these new platforms (i.e. cell based vaccines, thermo-stable medicines etc.) beyond the bench. Open access for various stakeholders would be a unique proposition and partnerships would extend from academia to industry where a UK centric vaccines 'community' could accelerate development.
- It was noted that the UK does not have many vaccines component suppliers and this could be a future opportunity especially when new medicines are being developed (this would also extend to the filling process and the end to end supply chain).
- Any UK scale-up or scale-out capability would involve a thorough review of existing UK assets to

avoid any duplication and maximise technologies with the intent of immediacy to plug current production limitations. GMP clinical supply (with a high containment capability) is a priority ask.

- Development tools including initiatives such as QbD enhanced processing, PAT etc. would be parallel services that would be supported in the 'centre' to ensure that scale up and transfer from clinical to commercial supply could be optimised.
- The 'centre' would also be used to train and enhance skills in vaccines discovery, development and manufacture.
- As an aside, the 'centre' could consider extending its capability to veterinary products.

The road map is aware of the Future Vaccine Manufacturing Research Hub (Vax-Hub) and there is the opportunity to work as a 'Project Partner' with the Vax-Hub and a sharing of capabilities with a focus on scale up of certain products and this could optimise investments. This partnership would have to be defined but the logic is there and there could be great synergies.

3.0 TRENDS IN THE PHARMACEUTICAL SECTOR

The UK biopharmaceutical sector forms a significant part of the UK's economy comprising some 1,948 companies, with nearly 107,000 employees (65,000 in pharmaceutical) and a combined turnover of £39.7bn. Of the top 50 global companies, 37 have sites in the UK. The sector is dominated by a few large companies with 89% of the workforce employed in firms with more than 250 employees. The GVA per employee is estimated at £330, 000[22].

- Interestingly, the digital health sector is an emerging one and an estimated 7,400[23] people are employed with a turnover of £886m, growth in this sector for employment is 23% over the last 5 years
- Genomics activities employ 1,364 staff with a turnover of £164m
- The landscape is evolving and although small molecule manufacture is prominent (82% of UK Pharma are employed making these) the highest growth regarding turnover is advanced therapies (35%) and therapeutic proteins (16%). This matches global trends.

There has been a shift from traditional chemical small molecules to more innovative asset designs, however small molecules still play a crucial role in medicines access and have opportunities to be enhanced, including their manufacture. Although relatively young, cell and more recently, gene-based technologies have globally treated many thousands of patients over several decades, and their potential is far from being fully realised. This move to more complex molecules opens up exciting opportunities and they have their own associated challenges:

With small/medium drug molecule development, trends include:

- Complexity of synthesis steps
- More highly potent products (Oncology/Respiratory)
- Antibody Drug Conjugates (linked small and large molecules – make the small molecule and link)
- Increasing importance of physical form

22 https://www.cmac.ac.uk/files/media/16-780_cmac_brochure_v3.pdf

23 http://www.abpi.org.uk/our-work/library/industry/Pages/Open-for-Innovation-ABPI-Sourcebook-2016.aspx

- Smaller volumes required
- More products licenced/brought in at Phase III (e.g. SME origin)
- Growing asks for patient-targeting and advanced packaging solutions and devices (including electronics)

High Potency designed solutions for disease areas are increasing, most today are predicted as needing parenteral delivery (typically infusions/injections etc.), and trends here now include:

- Smaller quantities required especially for stratified patient groups
- Increased use of combination therapies
- Antibody Drug Conjugates – requiring high containment
- Oligonucleotides – ideally close to the chemistry, simple formulation
- Large Synthetic Peptides
- Modified RNAs
- Polymer/dendrimer conjugates
- Less stable formulations which require protective device/packaging
- Polymer nanoparticles
- Egg free vaccines (e.g. cell based)

The technology challenges with these more complex molecules is ultimately the GMP manufacture of them to get them into the clinic early. Accelerated development tools are needed as many of these new chemical entities will require novel processing. The intent is to offer the appropriate facility for the developer (whether academic/SME/Pharma) and to have clinical manufacture capability. The flexibility, in-house expertise and drive to get from the bench to man will be enabled by having the clinical ready GMP capability proposed in the road map. Increased requirements for new product development and clinical to commercial manufacture are:

- Guaranteed high quality and scalable processing. QbD designed early (expertise could be CoE ‘service’).
- Minimise costs during development and ongoing commercial supply to ensure competitive “UK” cost base. Cost modelling undertaken as part of the service to ensure ‘total cost’ is taken into account.

- Minimise supply and revenue exposure risk during manufacture (capacity at CMOs is limited for sterile manufacturing – especially with high potency formulations). CoEs will add to current GMP capability, note that the UK currently only has 22 cell and gene therapy GMP facilities[24]. As technology advances (e.g. standards) are evaluated and implemented these could be shared more widely. A 'Fee for Service' will be available, again to ensure that facilities are more sustainable in the longer term, and this is a fundamental target. Building a sustainable long term business plan is a requirement of any facility to ensure longevity.
- Security of component supply to commercial supply – enabled by the need to manufacture as many critical components as possible in the UK from API to packaging materials.
- Flexible capacity in larger Pharma to ramp up/down quantities quickly as products succeed (or fail) and to effectively manage with demand uncertainty.
- Ability to quickly industrialise and commercialise products from small biotechs – Responsive business processes that are aligned and supported using shared 'lean' development know how.
- Regulatory expectations (i.e. sterility assurance). Facilities to GMP / GLMP including HCF to complement current UK GMP capacity and capability.
- Accelerating the development process (potential co-location benefits) reducing overall discovery to revenue cycle time. Location is important, and the infrastructure in the UK is excellent. Localisation of component suppliers will simplify supply chains.
- Analytical and legislative requirements are becoming more challenging and sharing solutions to meet these will leverage the speed to market, standards and ultimately product quality.
- Minimising environmental impact. Green chemistry will be a common thread throughout.
- Managing high containment for highly potent molecules.
- Incorporating a focus on novel vaccine development with this factored into a capability with suitable fill/finish suites.

The core challenge in any medicines development is the move from the bench 'craft' making to clinical and commercial manufacture. The UK's strength is early research and the T&I platforms would be primarily focussed on scaling up to supply the clinic, whatever the molecule and whatever the process. The sharing of technology platforms would lean this capability. Having the unique proposition where the UK could be a research and clinical 'one stop shop' with a manufacturing scale up capability would undoubtedly help leverage any future investment decisions and anchor early funding especially with complex medicines.

24 https://ct.catapult.org.uk/sites/default/files/01_GMP-report-2016.pdf

3.1 PROCESS TECHNOLOGY OPPORTUNITIES TO MEET NEW CHALLENGES

Small/Medium molecules

Potential areas include:

- Continuous Manufacturing (flexible capacity) for some stages of some molecules
- Barrier Technology (handling of potent materials)
- In-Line Process Analytical Technology and real time release
- Particle size engineering
- Disposable and 'clean in-place' plant
- Modular Plant
- Digital Factory concepts (Automated/Robotics/Analytics/Connected devices etc.)
- Explosion protection
- Quick product change overs (parallel development to enable efficient scale up production)
- Synthetic Biology
- Improved Catalysis
- Green Chemistry
- Excellence in Route Development

Biopharmaceuticals

For biopharmaceuticals, opportunities include:

- Continuous Manufacturing (flexible capacity) for multiple products/release – build on small molecule process knowledge

- Streamlined industrialisation to launch path (including MHRA partnership)
- Barrier Technology (handling of potents and sterility assurance)
- In Line Process Analytical Technology including contamination inspection
- Real time release
- Disposable plant and single use systems coupled with pack and device enhancements
- Agile, Modular Plant
- Digital Factory concepts (Automated/Robotics/Analytics/Connected devices etc.) to take full advantage of Industry 4.0
- Data sharing protocols and feedback and feedforward control capabilities
- Pilot to full scale production when using the proposed high potency GMP facility
- Polymer chemistry advances
- Digital twin technology
- Sterilisation approaches
- Green Chemistry
- Higher efficiency cell culture systems and cell free systems
- New formulation techniques (combination products and improved stability)
- Point of care / bedside manufacture and delivery of personalised medicines
- Scalable single-use technologies tailored to ATMPs and biopharmaceutical vaccines and proteins
- Novel characterisation assays especially for ATMPs
- Real-time tracking, traceability and monitoring across the supply chain especially for Advanced Therapies and personalised medicines

The road map has split these 'process' challenges as although there will be obvious shared technologies (as seen above) there will also be differences between them. Complex Medicines will present new green chemistry challenges and some processing will obviously be more complex. Again, if these additional potential 'blockers' are tackled in parallel to offer 'total solutions' this will stand the UK in a strong position offering facilities that consider the complete impact of any new processes. This more commercially aligned way of working will focus on scale up/production readiness and risk mitigation. It will be vital to prioritise these opportunities and the road map will be updated to reflect the changing landscape.

4.0 GLOBAL AVAILABILITY OF FACILITIES TO MEET NEW MANUFACTURING REQUIREMENTS

Small/Medium molecules

- Limited capacity in current CMOs for low or flexible volumes
- Large Pharma companies have gaps in internal assets and will need to invest
- SMEs have limited assets and ability to fund new assets/research

High Potency Medicines

- Currently limited global capacity in current CMOs for sterile manufacturing (including radiation capacity). Limited GMP HCF capability within UK to handle high potency medicines
- Sterile manufacturing and combination product assembly and fill/finish capability limited
- Complexity of sterile manufacture can result in GMP issues at CMOs
- Large Pharma companies have gaps in internal assets and will need to invest
- SMEs have limited assets and ability to fund new assets/research

There are currently technology and manufacturing capability gaps and these are the drivers behind the road map recommendations coupled with those made by the Advanced Therapy Manufacturing Action Plan. The newer ask of a steriles facility (with HCF) is an output from discussions with stakeholders and

this would enable the UK to facilitate innovation with complex medicines. The MMIC would allow the UK to maintain its lead in the research and development of continuous manufacturing with the emphasis on scale up of small molecule clinical supply, and beyond.

UK Opportunity - Strengths for discovery, development and manufacture of new medicines. The UK has excellent capabilities and these include:

- Strong academic base in Chemistry, Chemical, Engineering, Device Engineering, Pharmacy, Pharmacology and Clinical Pharmacology, Biochemistry, Biomedical Sciences, Genetics, Materials Science and Analytical Research
- CMAC/REMEDIES and other collaborations are technology platforms to build from/leverage
- Established non Pharma Chemical Manufacturing Industry collaboration
- A current manufacturing/development asset base in the UK across large Pharma, SMEs and CMOs. These assets could complement capability and offer clear differentiation if further investment is strategic and aligned
- Building on current parenteral development capability in the UK linked with commercial manufacturing of existing complex sterile products such as Zoladex, Bydureon
- Research collaboration and funding by companies like AstraZeneca (AZ) / GlaxoSmithKline (GSK)
- Building links with upstream supply chain, cycle capabilities and skills/skills training
- Having the MHRA as a progressive Regulator, with NIBSC developing the majority of global standards for biological medicines

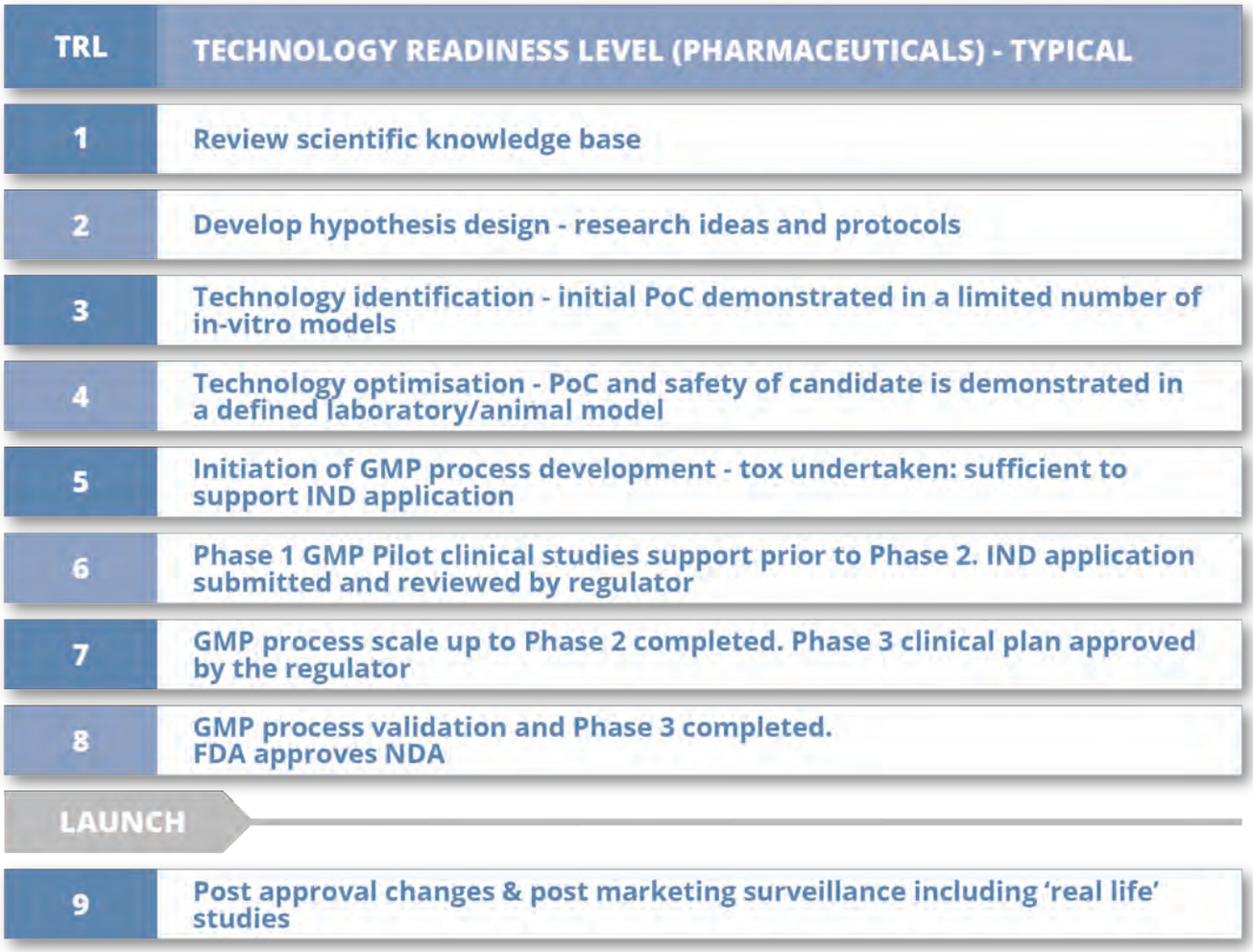
The UK has class leading research and it now needs to leverage and connect its current capabilities and plug the identified technology and facility gaps that will position the UK as a 'one stop shop'. The CoE proposal completes this technology capability circle. Sustained and increased university process engineering research would be recommended to support the investment already made into the Catapults and those planned for the CoEs (including suppliers). To ensure that there is clarity on how facilities are connected and the right facilities used, the intent would be to provide 'account managers' to support investors.

5.0 TECHNOLOGY AND INNOVATION - FILLING AND FUNDING THE CAPABILITY GAPS

This road map has been driven from an analysis from discussions across the industry and also from Workshops that have been held as part of the KTN wider initiatives (including gene therapy, viral vectors and therapeutic vaccines through to packaging). Funding models will need more detail and the focus of the road map is to identify the technology opportunities and how to align them, however these will obviously need this funding to not only initiate technology investments but also to ensure that they are sustainable.

5.1 TECHNOLOGY READINESS LEVELS (TRLS)

TRLs are used across various industries to describe where technologies are in their development journey from early research to launch, and beyond. They can be used to position funding and act as stage gates. There is not currently a single UK agreed 'Pharma TRL' so for this road map we researched existing TRLs from various sources and simplified it down to the levels shown in the diagram below. It has been endorsed by MMIP/ABPI/Innovate UK and will be updated as the road map is up-issued, if required.



5.2 SMALL AND MEDIUM MOLECULES – MEDICINES MANUFACTURING INNOVATION CENTRE:

- Continuous Manufacturing further developed as a platform process and the MMIC would be funded to deliver this capability, starting with 'established' medicines
- Aligned Technology development (Innovate and Research Council funding)
- Flexible funding to support Investments – fee for services (based on contribution)

5.3 ADVANCED BIOPHARMACEUTICALS/ COMPLEX MEDICINES FACILITY:

- Highly Potent Sterile Facility capable of clinical and potentially commercial scale supply, set up as a consortium
- Aligned technology development (Innovate and Research Council funding)
- Flexible funding to support Investments – fee for service based on contribution
- It could have an associated vaccines development and limited fill/finish scale-up (to manage diseases like Ebola)

'Technology strands' shared between the two centres where active product will be processed and these will be complemented by the Packaging and Device CoE. The 'technology strands' will have shared funding and the detail of this will need further discussion and agreement but the intent is to ultimately provide value for money and an avoidance of repetition whilst encouraging collaboration and shared synergies. It is important to point out that strong account management to work with potential investors should cut across all facilities and this support could be from early discovery through to transfer of full commercial manufacture with the added attraction of the UK offering a 'one stop shop' with technology support. A 'Fee for Service' model to access the facilities and expertise will be expected but this option needs further detailing and agreement as part of the next steps for road map implementation and this approach is aimed at ensuring the centres are sustainable.

An aligned skills strategy to support the attraction, training and retention of highly qualified staff is recommended with the intent being that these Centres will be used as a platform to enable hands on training at all levels (technicians to post-doctoral).

5.4 TECHNOLOGY INNOVATION SHARED AREAS

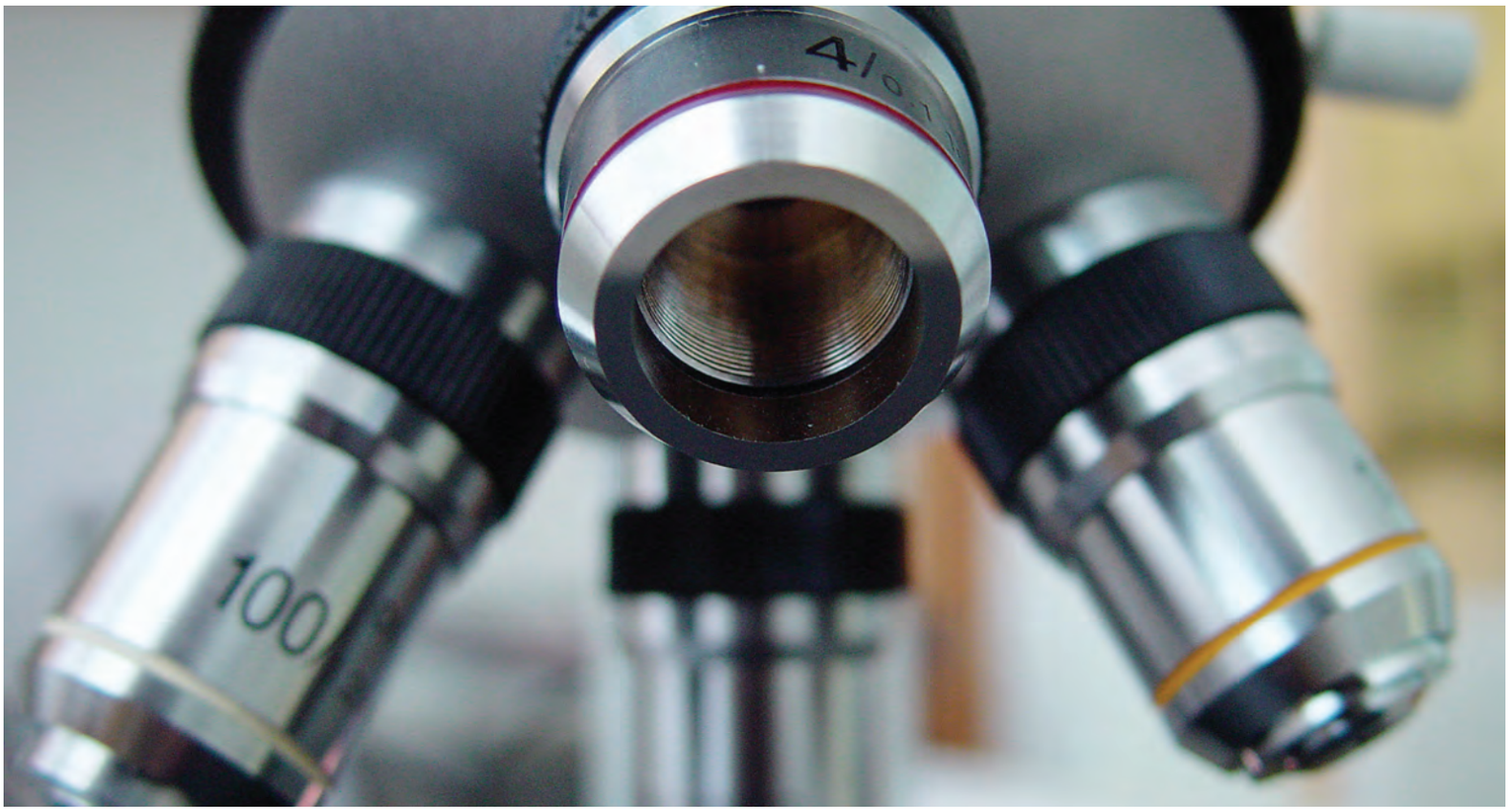
The concept of the shared 'technology strands' is driven by the opportunity to optimise resources across CoEs to increase added value and accelerate know how. These shared strands have been identified through discussions with stakeholders and the intent is that they will be resourced from existing platforms (such

as ADDoPT) or from teams brought together with explicit sets of objectives based on real technology needs. These needs will be prioritised and teams will be funded from a centralised budget. The teams can be virtual and would comprise of technology experts with input from, for example academia, pharma industry and suppliers. 13 strands have been defined and these are not exclusive, they can be added to or as initiatives are completed teams can be re-appropriated. A programme management system would be put in place to ensure that these areas are effectively managed and delivering against customer needs and targets. Each area is described in more detail below:

5.4.1 | FACTORY/PROCESS DESIGN

The 'Factory of the Future' concept is set out to accelerate adoption of emerging and novel manufacturing technologies and transform chemical/pharmaceutical manufacturing by enabling certain areas to be focussed on enabling the UK to:

- Create a physical infrastructure and capability for radical and disruptive innovation in chemical/pharmaceutical manufacturing
- De-risk investment in new technologies
- Attract resources to coordinate and drive chemical/pharmaceutical manufacturing innovation
- Provide a support structure for Academia/SMEs and start-ups to innovate and grow
- Provide thought leadership to the chemical/pharmaceutical innovation community
- Provide the latest infrastructure (building design) to enable flexible/modular manufacture conceptualisation and testing
- Develop modular design across build and facilities to optimise design and build costs and shared input early on will future-proof these investments
- Provide the latest equipment and also be a 'test bed' for equipment development. The UK lacks in equipment manufacture for Pharma and this needs more focus. Early development scale up/out
- Connect Digital platforms - all the way through the supply chain and especially with end to end manufacturing and these principles would tested and validated
- Drive standards – the more standardisation that the UK can implement across facilities the more integrated our processes will become
- Ensure factory would run digital management systems – electronic notebooks/digital collaboration etc.



- Factory would have to have a secure high quality wireless infrastructure

The Factory of the Future will have connected/integrated equipment to research, make and measure, underpinning this there will have to be a total 'digital platform' that will support deployment of advanced technologies in this IT and OT rich environment. The flexible manufacturing environment will need an appropriate digital and data infrastructure and supporting service (especially as new technologies are added to the CoEs). The FoF principle will align with the wider industry 4.0 initiative and act as a conduit of expertise across pharma and tiered suppliers.

5.4.2 ANALYTICAL DESIGN FOR MANUFACTURE (IMPROVED YIELDS AND OPTIMISED PROCESSING)

Manufacturing flexibility in both scheduling and capacity for rapid production scale up is especially vital for cost effective[25] commercial success of medicine supply (identified as a core requirement in cell and gene production) and will be primarily driven by the use of more process automation.

25 http://www.bioprocessintl.com/manufacturing/cell-therapies/designing-the-most-cost-effective-manufacturing-strategy-for-allogeneic-cell-based-therapies/

The Needs and Drivers	Actions
• Develop Analytical technologies that enable high throughput that meets required quality standards • Data management – establish and implement Standards and specifications for data analysis • Use data more – build data libraries - develop common software platforms • Integrated and process robustness knowledge – use predictive technologies • Minimising contamination - technology need for optimised in line real time inspection/release • Robust and timely measurement. Different processes will require different measurements - need to prioritise and connect with other industries to share needs/knowledge • Standardisation where possible (equipment / methods etc.) • Define and assess Critical Quality Attributes early in development • Use of detection systems (such as imaging, cytometry) • Fully integrated, non-destructive process (important with high value products)/ small batch and patient derived • Cost must be reasonable and consider 'total cost benefits' – less waste/high quality/speed • Ultimately enable access to all patients including emerging markets and the FoF must consider flexible scaling to provide this capability	• Identify the technology gaps – prioritise and set a plan with academia/suppliers/industry • Use data driven modelling where possible to improve process robustness • Develop suitable real time equipment/ sensors (disposable/reusable) – test and validate • Share more and also work with equipment providers early (know how is as important as IP) • Collaborate with imaging experts and use other sectors, i.e. engineering • Automate and consider scale up requirements in early clinical development - ease of analysis • Apply analytical innovation and technology to heritage processing where possible/ feasible

Analytical tools to ensure the quality and safety of products are vital for the pharmaceutical sector where the purity and structural integrity of samples must be constantly checked at each stage of the process. More effective and accessible analytics[26] would enable products to reach the market more quickly, at a lower cost and with reduced waste and this needs to be applied to all medicine manufacturing formats, including continuous. To create more effective analytics we need to identify the complex pharmaceutical 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. These tools would be integrated to complement appropriate QbD and PAT initiatives (especially when dealing with low dose medicines).

The use of process technologies that can monitor and control will ultimately facilitate increased knowledge generation and robustness of these sophisticated manufacturing processes. The supportive use of effective and higher capability analytical measurement equipment that could in parallel offer real-time decision making that will maximise efficiencies. Ultimately fully automating this 'make/monitor/correct' principle early on means it will then continue to be imperative as scale up opportunities evolve to ensure transferable control and consistent quality in commercial supply.

The analytical strand would work with specialist suppliers to identify best practice opportunities, as well as develop new methods and tools to measure more at scale up, for example; biomarkers, purities, potency, characterisation etc. This again will all enhance product quality and will be particularly pertinent with ATMPs.

There is the risk of contaminants all the way through the pharmaceutical manufacturing process and detection of these is important at each stage. Advanced visualisation systems are used effectively in manufacturing in other sectors building on these learnings. Pharma could identify and validate suitable imaging technologies to mitigate risk and ensure effective quality. Imaging systems can also be used to measure processing conditions. Packaging and processing materials can be specified to enable optimised visioning and the development and specification of these need consideration (and standardisation).

Better predictive tools need to be developed and implemented to improve manufacturing process

26 https://iscmp2014.mit.edu/sites/default/files/documents/(NEW)%20ISCMP%202014%20White%20Paper%205%20-%20Equipment%20and%20Analytical%20Companies%20Meeting%20Continuous% 20Challenges.pdf

efficiencies with process design space understood in greater detail. Well planned stability tests set up early in development can optimise pack and materials and increase product knowledge. Measuring and monitoring throughout the manufacturing process will ultimately lead to improved quality and coupled with well-defined scale up volumes, costs should then be reduced.

The ability to quickly but accurately measure Critical Quality Attributes (CQA) for new medicine platforms will be key, and ensuring consistency in their quality will be vital - this is where in line monitoring will be a valuable target along with correction capability. The data required to continually deliver this through the process (and the predictive modelling) should be shared more widely as some of these (by default) are still at the early part of their lifecycle and the more data that is collaboratively shared (and effectively analysed), the more we (as UK Pharma) will learn how to improve manufacturing through having a better understanding of 'predicted vs actual'.

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 respective 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. The MHRA Innovation Office[27] is a unique enabler regarding ongoing regulatory support and they will be an important stakeholder with new analytical developments.

Reproducibility in characterization/analytical science, particularly in the emerging biological sciences, is an ongoing challenge. Low reproducibility rates that undermine the replication of data and cumulative knowledge generation leads to unnecessary delays to research and development, and are unhelpful to effective translation and conversion to new and more effective products. The solutions to this problem should be intended to enhance the rigorous application of biological science.

The largely accepted principal cause of the low reproducibility rates is the highly technical nature of the detection of very minor changes to ever-smaller components of complex biological systems. Laboratories often use different standard protocols, sophisticated instrumentation, different origins and 'brands' of reagents, low statistical power and different scientists with variable expertise. The smaller the measurement, the more error can impact it and the more likely it is that variations in experimental protocols or analyses can lead to differing results and interpretations.

The root causes of irreproducibility highlight more significant categories that align with the typical stages

27 https://www.gov.uk/government/groups/mhra-innovation-office

of study development, these include: Biological reagents and reference materials, Study design and Data analysis.

The solution is establishment of a more robust characterisation/analytical ecosystem framework for life sciences going forward and this is proposed in this strand. There is the opportunity for the industry to work in partnership with the national measurement laboratory and designated institute/academics for chemical and bio-analytical measurement. These opportunities include bringing stakeholder communities together through the three pillars of i) measurement research, study design, data analysis and reporting; ii) biological reagents and reference materials and iii) training, to strengthen scientific quality and reputation. This approach can enhance increased competitiveness and ultimately increased positive economic impact. It will minimise wastage of resources (increasing productivity), enhance skills and reduce health risks (decreased disease burden/improved patient outcomes and decreased NHS costs).

5.4.3 AUTOMATION-ROBOTICS (CLEAN ROOMS/HIGH SPEED SCREENING/ CELL MANUFACTURE/24 HR LABS)

Automation of complex manufacturing processes is going to be a fundamental lever if the UK wants to be in a position where it can scale up. With platforms like ATMPs there has to be a move away from it being a 'craft industry' to one where it can manufacture effectively and efficiently with competitive costs, speed, flexibility and quality.

The needs and drivers	Actions
• Agile, faster production capabilities with end to end monitoring and fully closed systems • Equipment integrated and capable of moving process from highly manual to a more automated approach • More efficient separation/screening/ selection/ sterilisation methods	• Join up automation technology gaps (integrating technologies through manufacturing – Pharma should challenge the UK automation industry to map out gaps and set out a collaborative plan of action on how to get this first challenge defined)

• Scale-up/scale-out using modular systems (an area where the UK lags) • Cost and reproducibility • Improved capability and data management - need to integrate with digital platforms • Ability to accommodate ever increasing manufacturing complexity • Technologies and value chain anchored in UK (unfortunately many control and sensor suppliers and equipment assemblers are currently not based in the UK) • Service models – equipment and automation needs associated service packages - could we determine operating efficiencies and standards between UK facilities? • Equipment designed with production in mind - e.g. optimising line clearance and cleaning and also energy efficient. Note that greener chemistry is covered later.	• Prove efficacy/reliability throughout automated manufacture • Application of automation to all platforms (continuous / sterile / analytics) • Joint development and partnership with digital providers (there will be considerable opportunity to generate data and its effective analysis is where the value added will come from) • Develop funded collaborations between industry and academia

With process equipment more automation with robust integrated closed loop systems are needed to ensure reproducibility through the manufacturing process. Industry 4.0 will need to be fully exploited to enable controls with complex production[28] and validated IT systems will have to support this and the increased use of sensors. The analysis of the data they collect will provide chemists and engineers with the opportunity to work together with a goal to design optimum systems that are agile with the prime intent to make clinical supply and pave the way for commercial scale up.

There is also a need for cross-fertilisation of technology between industries, including learning from those sectors which understand how to implement scale-up manufacturing methods that require tight controls for product consistency and the setting of 'control space' parameters.

Whilst this is an exciting prospect offering significant potential benefits for patients and the economy,

28 http://insights.bio/cell-and-gene-therapy-insights/wp-content/uploads/sites/2/2016/07/Farid-Branke.pdf

some radical new developments beyond manufacturing will be required to achieve it. These include identifying potential gaps in the infrastructure of the industrial base to the delivery of the cycle of care including service packages.

One specific area for immediate focus is that of viral vectors. Current capacity is restrictive to perform both early and commercial scale trials from the UK due to constraints in upstream and downstream, fill finish, quality control, supply chain challenges and access to scalable and industrialisable platforms. There is a need for new tools, technologies, assays and materials to be developed more rapidly. There is a request in the Advanced Therapy Manufacturing Action Plan to focus on meeting this urgent technology need.

5.4.4 | DIGITAL – INTRODUCTION

Digital is an all-encompassing word and it impacts different industries in different ways. Digital will be important in medicine making, it already is and it will continue to shape and influence not just how medicine is discovered, developed and made but also how patients are diagnosed and managed. The digital landscape will become more and more of a closed loop where it will learn and predict with increased accuracy and continue its rise as a powerful service tool. Pharma is represented on the Digital Engineering and Manufacturing Leadership Group[29] and this enables an informed connection with other industries and also ensures that we not only have a voice at the table but also understand more about potential opportunities that digital can bring to not only make incremental improvements but also offer step change platforms. These include:

5.4.5 | ADDoPT

The ADDoPT (Advanced Digital Design of Pharmaceutical Therapies) project is addressing the pharmaceutical industry's desire to deliver medicines more effectively to patients[30]. The intent is for

29 https://hvm.catapult.org.uk/news-events-gallery/news/digital-technologies-manufacturing-leadership/

30 https://www.cmac.ac.uk/files/media/16-780_cmac_brochure_v3.pdf p36

ADDoPT to use advanced digital design techniques that eliminate non-viable drug candidate formulations early on, therefore streamlining the development process. Its research challenges in partnership with CMAC include:

- Precise control in manufacturing of solid particles using continuous technologies
- Control and exploitation of nucleation and growth of particles via crystallisation under continuous flow
- Continuous crystallisation platforms: process analytical tools and strategies for particle engineering
- Understand key particle properties for enhanced formulated product performance
- Manufacturing operations and supply chain management
- Optimise manufacturing industries operations and supply chain to enable the effective adoption of continuous manufacturing

The focus on high throughput, modelling impact assessments and stretching manufacturing process knowledge is key with any step change innovation. This capability will be leveraged with new tools and approaches using data analytics to both qualitative and quantitative modelling and this research is leveraging the potential of the digital factory and has already begun with ADDoPT's AMSCI funding which runs through to 2020. Looking ahead, the ability to digitally manage complex predictive models will reduce development lead times (by for example challenging the use for real time performance testing). The potential for big data in formulation to enable better prediction will without doubt offer an opportunity to speed up development and optimise integrated and automated manufacturing processes whilst ensuring the highest quality products are produced, and this will include all companies within the pharma supply chain. The principles behind both data collection analysis must be shared not only amongst all manufacturers (to ensure provenance) but also in the proposed Centres of Excellence.

5.4.6 DIGITAL - HEALTH AND DISEASE DETECTION AND DIAGNOSTICS

The potential for digital technology to help measure, maintain and improve health and wellbeing through preventative approaches and supported health management is considerable. Digital 'lifestyle' devices are a global phenomenon (e.g. FitBit) and they are evolving rapidly into more complex tools, in parallel to these being successfully launched, connected clinical devices are now starting to being used in trials to

collect more and more data. A core functionality is gaining acceptance and opening up new possibilities:

- Devices are increasing in capability and data generated is more rich
- Data analysis is getting smarter and more informative with intervention possible
- Data is ultimately being personalised and can enhance patient centricity
- Data can assist with Pharma gaining a real-life understanding of how patient's lives are improved through longer term studies where various end points are monitored over time

If we could leverage this potential seen in digital lifestyle devices from 'fitness/wellness' to one of more self-care (especially in chronic conditions), this could enable valuable insight into effective measuring, monitoring, medicating and ultimately motivating patients to optimise their disease management. Safety and efficacy will need to be demonstrated but continued confidence in both early and ongoing trials would shape this opportunity. This 'Fitbit 2' concept would not be a 'gizmo' it would have to be a well-designed patient centric tool with easy to use functions, proven sensors and reliability and a secure and meaningful data interface. This MedTech coupled with effective medication could revolutionise healthcare as we know it by helping to manage chronic conditions more effectively allowing the acute ones to be focussed on. Essentially, digitally driven technology could become part of the therapeutic package. This mobile health/telecare will involve a wider industry engagement and a new vision from the regulator, payer, patient and healthcare professional. The NHS has pledged to foster several regional test beds to experiment with these digital innovations over the next five years so this journey is already beginning.

Using this digital interface platform the UK could become the healthcare innovation lab for the world, by offering a rapid and efficient way to generate more data on existing medicines but also build a clear model about how new products are effective in real-world settings and the patient outcomes that result. The data generated would help companies and the NHS determine with more precision the value the product delivers, which patients should be targeted and how the system should best deliver that treatment. If this data was available early enough, it would be very valuable to companies to support launches in other

countries. In addition, it would offer UK patients quicker access to innovative medicines. Technology companies would develop alongside the infrastructure to provide the necessary support and this would be managed ideally by the Packaging and Device CoE. Device platforms that would enable monitoring could be UK manufactured and the supporting data service could also be UK focussed. The UK would thereby offer a unique value proposition to attract private investment whilst delivering benefits to patients, the NHS, academia and to companies. **Note:** deals in companion diagnostic devices have gone from 8 in 2009 to 226 in 2013[31]. The potential for the integration of digital as a patient tool is detailed further in a recent report from DHealth[32].

Digital - Cyber-security – Security of data is a global challenge across all industries but one that could be a real risk in healthcare if automation, diagnostics and analytics are to become more prevalent. It is an issue that government needs to support along with data owners and providers. There will be no one clear solution to this, but for this road map digital security will remain a sub topic that will have to have robust and secure solutions in place, especially if there is to be transfers of data throughout the supply chain all the way through to the patient. Security standards and appropriate encryption technologies are needed and there is an expectation that this challenge would be integrated into the wider 'quantum' challenge being undertaken by government.

Digital - Artificial Intelligence – Artificial Intelligence will be enabled by the ability to quickly analyse large data sets such that automated intervention will be triggered. Learning systems have their limitations and any AI system will have to be fully validated and risks defined. AI will be a technology that Pharma will align with and it will be applied in manufacture but also through to patient care, its pace of acceptance will also depend on regulatory approval. CoEs will be used as 'test beds' and the integration of AI will involve partners that can handle and analyse data. Ultimately, AI could reduce the time for a medicine to reach the market and it is a digital technology platform that the life sciences sector should invest in as a global program.

5.4.7 DIGITAL - ADDITIVE MANUFACTURING TECHNOLOGY

Additive Manufacturing (AM) is a key enabler in HVM with potential benefits such as smarter supply

31 https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-healthcare-and-life-sciences-predictions-2020.pdf

32 http://www.dhealth.co.uk/news/4233954

chains, digital manufacturing flexibility and design freedom. These are transforming the way products and components are designed, manufactured and supplied and the technology is still early on in its lifecycle. AM is gradually being applied commercially in MedTech component supply (e.g. hip and knee replacement) and Pharma has used AM as a development tool to create prototypes and for modelling. AM is still restricted by being only ideal for low volume production and with a limited pallet of materials, it is not suited to very high volume production (needed with much of Pharma). However, AM continues to evolve and grow, the market value is estimated to reach £69bn by 2025[33] and the recommendation in this road map is to ensure that there is a sector champion that will continue to technology scan and identify specific AM opportunities for the industry. An example for this is AM could be used to produce one off pieces for disposables to reduce development time.

Apps

Healthcare Apps have grown exponentially over the last few years with 165,000 available on the Apple Store[34]. They are a digital platform and are at present unregulated when stand alone, however when an App is aligned with a device they do have to be approved and in 2016 the FDA approved only ten. The value in Apps is the fact that they can be associated with MedTech devices and there is, as noted, associated regulations required for this application.

In the not too distant future Apps will need to be controlled more and standards set especially as there could be potential risks to patients. The use of Apps with medicines has to be carefully considered and a recommendation is for the Life Sciences to build on the current MHRA[35] recommendations (in partnership with the NHS) to define a potential regulatory strategy for Apps noting that there could be wider European (and even Global) requirements. This road map recognises the power of Apps and the fact that they will be a valuable healthcare tool in the future and its worth is considerable with the global health market projected to grow to nearly $21.5 billion by 2018, with a five-year compound annual growth rate (CAGR) of 54.9%. Europe is the fastest moving segment in this market with a CAGR of 61.6%[36].

33 Additive Manufacturing in the UK (Sept 2016) HVC
34 https://www.ft.com/content/ed3268f2-e620-11e5-a09b-1f8b0d268c39
35 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/564745/Software_flow_chart_Ed_1-02.pdf
36 http://www.bccresearch.com/pressroom/hlc/global-mHealth-technologies-market-projected-to-reach-nearly-$21.5-billion-2018

5.4.8 | MATERIALS - API/FORMULATION

With Biopharmaceutical Formulations - the process in which different chemical substances, including the active drug, are combined to produce a final medicinal product - there is a continued 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 more patient-friendly form.

Some capability already exists in molecular modelling 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. The additional use of digital modelling for stability testing as a technology could have significant benefits in shortening launch times[37].

Production of API chemicals and materials for pharmaceutical manufacture have over the last 10-15 years moved offshore. With recent issues with quality, security of supply and variable demand the UK is in a position to re-shore these materials. The UK still has a robust and capable chemicals industry and it could benefit from the opportunities offered by complex medicines and small molecule enhancements (including processing). Potential UK synergies (through the Chemistry Growth Partnership) would be built from offering access to the MMIC and complex medicines capability. With early collaboration, examples of how the relationship could be enhanced by T&I include:

- Supply Chain integration and closer collaboration across all aspects of the API supply using smart labels to ensure effective inventory/demand/protection through to delivery. Localisation would reduce cross border supply and any reduction in timing will accelerate not only development but also commercial supply. REACH implications will also be a consideration with supply chain management.
- Supply of chemicals / materials in flexible, modular manufacturing units (including, perhaps, single-use, disposable vessels) with quick turnaround capability. Shared learning and development on process design and appropriate automation will ensure an effective and aligned end to end manufacturing process.
- Closer collaboration between suppliers of chemicals / materials and their customers in the pharma

37 G. Cruickshank, Moving from art to science: The Chemical Engineer, Feb 2017, p39-41

- industry in terms of sharing analytical data on particle properties and the impacts of their raw materials on the pharma manufacturing process; in addition, analytical methodology will need to be developed to support the move towards continuous manufacturing. The provenance of raw materials will be better controlled ensuring more opportunity for optimising quality. QbD can be designed into materials and components at the onset.
- Developments in the Biologics supply chain (including analytics and metrology). API and raw material suppliers will work with fill/finishers to optimise distribution packaging and also if a process has specific demands (high containment etc), raw material providers can help ensure that safe and effective transfer methods are introduced into production.
- Novel materials and design solutions for Medical Packaging (including self-indicating, self-cleaning materials; innovations such as real-time reporting, anti-tamper solutions, etc.).
- Innovations in cleaning, sterilisation, biocides, disinfectants and detergents (e.g. self-indicating materials which show bacterial presence).

The partnership opportunities above are all designed to minimise development time and reduce new molecule development.

Synthetic biology is a new emerging area of biological research and technology that combines science and engineering and is viewed as providing a step change in cell line engineering in the future. Its goal is the design and construction of new biological functions and systems not found in nature.

New cell culture systems for biopharmaceuticals, which in turn can support the manufacture of individually tailored treatments will be important moving forward. In the future this may help to reduce the reliance on more conventional cell production systems currently seen across the industry (platform processes) and enable a more rational design of biopharmaceuticals. New biological production systems would enable tailored products to be produced more rapidly and at lower cost. The 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 real 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 here will also be dedicated funding to improve collaboration and innovation across the supply chain.

Note: The road map classes medicines with a target being for human use. This also encompasses the use of these for paediatrics and infants. These are critically important patient groups who will require specific product dosing and pack formats. They must be considered within any development.

5.4.9 PACKAGING MATERIALS - MATERIALS TECHNOLOGY AND INNOVATION IN PHARMA

All medicinal products need to be protected throughout the supply chain and these have to meet a range of standards and specifications. With the complexity of packaging materials and the technical nature of medicinal products, manufacturers are challenged with performance expectations and production capability. Materials must be stable and offer acceptable shelf life and protect against:

- Environmental influence
- Biological contamination
- Physical damage

The pack must also offer security, patient acceptance and hold the correct information and identification.

More pack standardisation will be needed as pharmacies (and the supply chain) become more automated and this will impact more medicines pack platforms.

Historically, packaging materials have evolved as the pack format has. Quality standards have improved organically as process developments have increased, but realistically the Pharma industry is not known as a pack or pack material innovator. This is primarily due to legislative restrictions, existing manufacturing capacity and a certain reluctance to explore formats – especially primary pack materials. Glass/foils/PVC/commodity polymers have been around for many years and there is scope on several fronts for the UK to grow its expertise and opportunities in this area including:

Pack/Device Supply - Most primary packaging materials are imported into the UK and this makes UK Pharma more vulnerable to not only longer delivery timelines and currency fluctuations but also with a future need for smaller batches (especially with advanced therapies) potentially making supply of pack components at a reasonable cost and in time more challenging. The UK could strategically invest in localising supplies of key packaging components whilst having the added advantage of procuring the latest production equipment. A robust supply chain is imperative, and stock outs and variable quality of incoming components can slow down development and supply.

Pack and Device Technology & Innovation - The UK already has expertise in advanced material science through facilities such as the CPI. In Pharma there are opportunities to meet challenges such as extending product shelf life with new materials and material coatings. Enhanced features and technologies including anti-counterfeiting could also be incorporated. The UK is not a leader in this ever-important technology and further expertise could be shared with other industries to ensure enhanced pack security and provenance.

Where medicines are 'combination' products - i.e. medication is incorporated into a device such as inhalers and injectors - there again is the opportunity to have the primary and secondary components designed, developed and manufactured in the UK. Future 'smart' pack formats will extend to include printed electronics research is already underway with the REMEDIES project[38] and these platforms will be an enabler for digital. This will be detailed further under the Pharma device section.

With over 85,000 jobs in the overall packaging Industry and £11bn sales[39], packaging plays a vital part in the UK economy. 'Smart' Pharmaceutical packaging is high value and technically

38 https://www.cmac.ac.uk/files/media/16-780_cmac_brochure_v3.pdf
39 http://www.packagingfedn.co.uk/

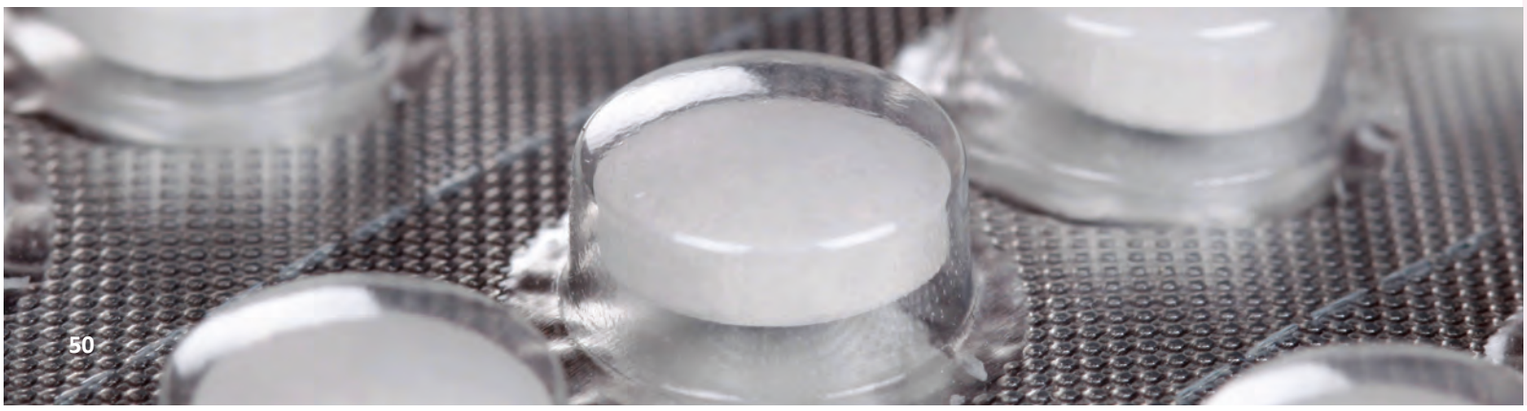
demanding but it has the potential to carve a specific niche and also support and differentiate the new medicines being developed. Smart packaging would not only enhance a packs technical performance but it would be designed to ensure secure transportation and tracking. This capability will be more critical as we move towards more high value personalised medicines. As such there is a proposal in this road map to site a Packaging Centre of Excellence that would serve Pharma but also share its capability across other industry sectors. This proposal would form part of the wider technology strategy for Pharma and it fully integrates with it. This is a competitive landscape and setting up a research facility with a focus on packaging could be a real asset for UK plc.

Single-use Equipment - The implementation of single-use equipment is evolving into an established industry primarily around Complex Medicines and is utilised more frequently with high value medicine manufacture. The advantages are that it reduces the risk of contamination, speeds up change-over time and minimises cleaning processes. It has become a speciality and many suppliers are based outside the UK. Often the design of the disposables is bespoke and during process development having disposable lines designed and made can take many weeks. If there could be a high speed capability in the UK this could reduce timescales and this would be another remit for the packaging CoE. The use of additive (3D printing) could be an ideal application to accelerate development. This is also an area for standards development.

Packaging in Supply Chains - Smart Labels for Track and Trace

Having a robust global supply chain (SC) that is fully scalable is fundamental with any industry. With Pharma, manufacturers must have a SC that provides complete control and is fully capable with the potential to expand as volumes increase. These factors will ensure end to end quality and that production efficiencies are maintained.

Effective tracking of components and finished products throughout the SC is vital. Close collaboration is needed with the Pharma community (along with logistics providers and customers) to standardise where feasible, and also continue to drive innovative SC solutions to ensure medicine supply is optimised



through minimising inventory (often a hidden cost and management of this is more critical, as shelf life can be short with some components and finished goods) and as importantly having clear and accurate demand signals. With the imminent implementation of serialisation and the advances in data management coupled with print (and print recognition) technology SCs can be leaned. This will save on inventory investment and reduce stock-outs and also potential product write offs. This is a considerable opportunity, especially if we are to become an even greater exporter, and post Brexit supply chains could become more complex. Avoiding waste also has an obvious positive environmental impact too.

As such, reliable SC optimisation and tracking is a given and being able to scale up this capability and fully integrate and digitise IT will be a future challenge. A particular focus should also be given to cold chain supply too. There is the opportunity to develop pack formats and 'smart' labels needed to optimise the SC and consider partnering with manufacturers and service providers to develop and make these in the UK. Smart labels are already being developed and tested as part of the REMEDIES project[40]. The ultimate intent of this project is to provide a standard format for Pharma that could be supplied for both clinical and commercial product tracking (including all input materials thus ensuring full provenance). Pack security is an ongoing technology challenge and in the EU serialisation is to be introduced in 2019 to enhance medicines' security. However, as counterfeiting is a global issue there is an opportunity for the UK to take more of a lead in this area.

Personalised Packaging - With the new paradigm of personalised medication (small batch production) there is inevitably going to be the associated need for 'personalised packaging' (both primary and secondary). Control of labelling (including instruction leaflets) will be needed along with other required data such as serialisation marking. Pack sizes and formats will need careful consideration due to the advent of more automation in the supply chain. Technology platforms such as late pack customisation, digital printing on line and phone technology are all tools that can come together to enable this vision. It will be able to supply both clinical and commercial volumes and must have this flexible capability. The Packaging and Device CoE would have the remit to optimise Personalised Packaging and this service would be offered in parallel to medicine development to minimise time to the clinic and ultimately the market.

Digital Solutions to enable patient centric design such as digital leaflets and guides will become more common and there is already a project underway through REMEDIES to digitise patient instruction leaflets onto mobile devices. This is a medium term technology enabled vision that will require collaboration between Pharma and other key stakeholders. It will increase patient benefit through adding value to how information is provided and will improve safety for example, by updating immediately if there are adverse effects. The Packaging and Device CoE will work with partners on technology projects like this to

40 https://www.uk-cpi.com/news/cpi-leading-consortium-to-develop-world-class-near-field-communication-packaging-capability-for-the-uk/

ensure ideas can be developed, tested and verified.

Devices – Dispensing Devices in Pharma are typically re-useable or incorporated with the primary pack - referred to as combination packs. There is, as such, a crossover between devices and packaging in Pharma but for the sake of this road map devices will be defined as secondary packs and include combination products, mini-pumps, auto-injectors, inhalers etc. and include 'sensors' (e.g. incorporating hardware/software with or without digital capability). The UK has a world class device engineering and design consultancy sector and like our research capability, we are good at intellectualisation but often fail to take through to full manufacture in the country. The Packaging and Devices CoE would support the device development sector by offering expertise in device manufacturing, it would connect specialist component suppliers, moulders and assemblers. A long term vision would be a 'Green Field' park for device and packaging component manufacture.

MedTech - MedTech platforms are different in that they would not include medication but they could have diagnostic (and measuring) capabilities and these are included within this road map as they are a fundamental enabler for not only early diagnosis and measurement platforms but they could enhance, for example compliance and adherence and be linked digitally to healthcare providers. With this early use in drug development, clinical trials could be enhanced and medicines optimised. MedTech Devices connected with dispensing devices could revolutionise healthcare through this digital association. Certain common chronic diseases could become preventative, predictive but also personalised and participatory.

This road map acknowledges that this technology is still in its infancy but with the acceleration of digital and electronics it is achievable within 2-4 years, much quicker than any drug development. There are regulatory hurdles as there are with any new technology platform, but the UK has positive and forward thinking relationships with bodies such as the MHRA. The recent value added seen with 'real world' effectiveness trials with medicines will need this connected MedTech and 'big data' capability.

5.4.10 | GREEN CHEMISTRY

The needs and drivers	Actions
• Minimise environmental burden of medicine manufacture – through the API and formulation supply chain • Complex Medicines will require new approaches to reduce environmental impact - early intervention is key • Waste in process is not good for the environment, and cost of goods disposal is expensive • REACH – Ongoing challenge for the whole industry – need for new materials	• Design in 'Green Chemistry principles' early on • Ensure chemical engineers work with chemists to minimise process environmental impact • Use tools such as lifecycle analysis throughout development to aid decision making and understand impact • Technology challenges needed and standards evolved to 'green' manufacture latest Complex Medicines

In a recent paper by Industry it is recommended in early development to focus on multi step syntheses required for API and build on the 12 principles for green chemistry[41] and that this should be applied across all medicine manufacturing platforms. Materials and processes must be measured to define environmental impact and where possible life cycle analysis carried out when choosing/deciding on technology routes. Logic states that if a process is being leaned to reduce cost by default it will be greener (through reduced material waste/increased capacity).

Early intervention and collaboration between chemists and engineers will drive out effective solutions. Technology advances are in areas such as continuous processing and LED photo catalysis which are enhancing improvements in synthetic methodology. With the non-classical therapeutic agents such as oligonucleotides, peptides, antibodies and polymer conjugates (along with current small molecules) a new set of challenges are facing the pharma industry. As part of the T&I proposal the innovation centres must factor in the environmental impact of these new agents and strategically work to minimise process waste. The advantage of doing this is not only a sustainability one but also potentially a value added cost benefit. Again, with these new platforms, standards to improve Green Chemistry should be shared and this is another strength that the UK could offer. The environmental impact of any new technology should be one of reduction and that should be by default.

41 https://bit.ly/2cFRNOH

5.4.11 CLINICAL TRIAL MANUFACTURE AND SCALE UP

The needs and drivers	Actions
• How to tailor medicines more for individual patients (including potential for dose banding) • How to speed up the preparation/ packing/ storing/distribution of clinical supplies • Small scale production with ability to scale out and up • Access to GMP (a basic requirement) facilities and potentially HCF for high potency products • Data capture and therapeutic effect analysed more efficiently - could medicines efficacy be more effectively measured and dosing optimised. This could be measured through Phases II to IV with 'real world' follow ups being a real asset for the UK (including a collaborative partnership with the NHS) • Data capture and analysis	• Standardise pack formats where possible for clinical trials • Automate clinical trial production and packaging where possible (design into facilities) • Utilise track and trace technology to manage inventory • Review REMEDIES recommendations for reducing timescale for clinical production • Evaluate the technology challenge for connected measurement tools to optimise clinical trial data collection and the sensor development needed along with the data analysis. These will vary for different diseases • Speed and quality of data output and analysis will be invaluable and clarity and agreement on what is measured must be endorsed by all stakeholders. This will be a new paradigm and it could be part of the positioning of an outcomes model

The importance of technology to enable effective clinical evaluation and manufacture cannot be underestimated. It is the fundamental stepping stone to commercial supply. Manufacturing models are changing and plant design has to evolve quickly to meet new medicine manufacture. Continuous production for small molecules, sterile manufacture for Complex Medicines and Advanced Therapies manufacture are key drivers for the industry to rethink the clinical to commercial supply model. Another important factor is the reduction of timescales that could be implemented if the clinical supply chain is optimised.

The need for GMP facilities that can transfer to commercial supply from clinical will become more common as new therapies are discovered and developed. The UK, as noted earlier, has limited GMP facilities, so managing demand through these is important and creative ways to optimise capacity will be needed, including the possibility of freeing up lower value work in NHS aseptic units. A challenge is where these GMP facilities are and how the cost of manufacture is fairly managed. This will have to be determined as part of the Industry Strategy but as clinical supply needs to be made in a GMP facility, having an infrastructure that is connected/localised will undoubtedly simplify these trials. Technology targets will be to ensure that facilities are flexible, capable and the quality of product can be scaled up quickly. It would be logical that if production moves to commercial scale in CoEs then this is done at a market price. This point is out of scope for the T&I road map as it is a fiscal one but it does highlight the fact that the proposed facilities should be capable of both clinical and small scale GMP production. This 'intermediate' commercial capability needs further discussion but it would ensure effective and efficient technology transfer with smaller volume products.

5.4.12 | STANDARDS

The needs and drivers	Actions
• New Technology needs appropriate standards as the industry evolves – across whole supply chain • Robust reference materials are needed • Standards that are appropriate for the space and are aligned • Standards that drive common procedures and specifications	• Initiate Gap Analysis for new medicine and advanced therapy standards • Work closely with Regulators (MHRA/NIBSC) • Strong industry partnership when setting standards • Make the UK a leader in Standards setting and compliance globally • Develop reference materials • Consider the opportunity for digital standards

The need for standards in the Life Sciences is important primarily due to the variabilities that can occur in the manufacturing process, as well as the performance of novel technologies and products.

The more complex the process, the more critical it is to have effective standards (and procedures).

To reduce the risk of inconsistencies (and quality) of products, materials, emerging processes and technologies manufacturers and developers will work together in the CoEs to create common standards and control methods (where they can) and input on guidelines and CMC regulations that could impact the manufacturing processes. This includes materials, methods, testing and storage. This will ultimately improve safety and drive defined quality control and be a useful asset that could add value to UK Pharma manufacturing especially with new technologies and innovations. This could be accelerated using the existing relationship with key stakeholders such as the MHRA/NIBSC and the NHS.

The UK's MHRA is renowned for its progressive thinking and leading role in the regulatory space, both in Europe and internationally. This is epitomised by approaches like the Early Access to Medicines scheme (EAMS) that is paving the way for the accelerated adoption of innovation by the NHS.

Another of the unique assets of MHRA is the National Institute of Biological Standards and Control (NIBSC). Working with industry and other regulators, it is currently developing and producing more than 90% of the international standards for biological products, also carrying out foundational research to ensure the safety, efficacy and quality of biologics. NIBSC is also the UK's Official Medicines Control Laboratory, responsible for testing biological medicines within the framework of European Control Authority for Batch release.

Advanced Therapies involves the development of novel manufacturing processes and supply chains and the MHRA has a wide range of contact points to help companies streamline changes involving the introduction of new facilities, processes or tests. The MHRA's 'Specials' is also a flexibility that the UK has used to allow the supply of advanced therapies where suitable authorized products are not available.

However, the advanced therapy development and manufacturing sector in the UK is still largely up-and-coming, with the majority of new platforms and processes being small-scale. As in every fledgling space, advanced therapy regulatory requirements are still driven by technological developments, posing persisting challenges to the regulators and calling for a sustained capacity to adapt standards, specifications and assessment frameworks to emerging knowledge and technologies.

Standards are to be applied to both clinical and commercial supply and they should be implemented wherever possible in the supply chain. As part of any road map there should be a longer term vision for new standards and they will be constantly introduced and existing ones should be updated as required.

5.4.13 FLEXIBLE PRODUCTION FACILITIES AND ADAPTIVE SUPPLY CHAIN (SC) HANDLING, LOGISTICS AND PRESERVATION TECHNOLOGIES

The needs and drivers	Actions
• Supply of medical treatments and products to be driven by customer needs • Robust control of end to end supply of raw materials to finished goods • Effective control throughout the supply chain and measurements to support this • Secure Tracking – building on the control need, a capability to identify patient personalized product is fundamental especially with products like advanced therapies • Complex, cost effective and robust supply chain needed – note: including frozen • Class leading preservation technologies needed in the supply chain for advanced therapies • Close tracking history of product/ components - know where it is and what environmental conditions it has been in • Increased integrated automation - currently much is manual. Early demand signals are key • Smarter use of digital platforms to reduce expensive inventory and risk of stock outs	• Creation of standards within the SC includes: storage/tracking/components (etc.) • End to end analysis of current SC infrastructure gap analysis and consider wider shared community opportunities (hubs etc.) – flexibility enhanced by connected digital technologies • Early mapping out of potential SC supported by CoEs and expertise shared plus 'pinch points' highlighted and de-risked in parallel with product development to speed time to clinic • Learn from other 'personalised' supply chains blood/organ to automotive. Do not re-invent the wheel - focus on safety/ security, especially with advanced therapies • Look to future preservation technologies and impact on product quality • Does the industry need to contract out some of the SC? • Risk analysis on supply chain deviations and mitigation plans • Potential use of shared hubs to lean logistics and utilize capital investment/inventory

	• UK GMP capacity to be mapped out and NHS aseptic suites freed up of lower value SKUs to enable better utilisation for new medicines

Supply chains for medicines need to be lean and flexible. 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.

Personalised medicines will lead to small batches (Personalised Packaging) and the capability to manufacture 'at bedside' is an important target. Acceleration of clinical to commercial will drive adaptive SC models and they must be considered early on in the development process and CoEs will support customers in SC design. Standards will simplify this but with Complex Medicines potential 'pinch points' should be identified and design solutions proposed, built and validated. This process will inevitably include the Packaging and Device CoE. Early SC solutions will lean launch times.

Having a robust SC that is fully scalable is fundamental with any industry. With ATMPs, manufacturers must have a SC that provides complete control and is fully capable with the potential to expand as volumes increase. These factors will ensure end to end quality and that production efficiencies are maintained (including any analytical testing required within the SC, such as components and raw materials).

Effective tracking of components and finished products throughout the SC is vital and close collaboration is needed especially with the ATMP community (along with distribution partners/logistics providers) to standardise where feasible and also continue to drive innovative SC solutions. ATMPs do have a short shelf life and the control of storage and distribution is fundamental. As such, reliable supply chain optimisation and tracking is a given and being able to scale up this capability and fully integrate and digitise IT will be a future challenge. There is the opportunity for the UK to develop associated pack formats, 'smart' labels and equipment needed to optimise the ATMP SC.

Better knowledge within ATMP manufacture is needed on product viability and the impact of preservation techniques in processing is an area for more ongoing specialist innovation. With storage in the ATMP SC being complex there is the ability for wider collaboration with manufacturers and stakeholders to drive efficiencies using a range of technologies (both existing and new) and these will be targeted due to the unique needs required by ATMP manufacturers.

Advanced Cryopreservation and Alternative Preservation Technologies have been proposed as areas of future focus. Increased understanding of the importance of controlled preservation will drive new equipment development (and manufacturing procedures). As this knowledge grows, production efficiencies will be enhanced. Having industry wide research into this area will benefit the wider UK ATMP manufacturing base. This wider collaboration should be considered synergistic. As ATMPs and complex medicines evolve the SC infrastructure will enable better supply and demand management and this will involve new models and ways of working (including supply hubs) and it will involve a mixture of technologies that will ultimately improve safety and quality through improved control and tracking.

Supply Chain challenges and expertise could reside in the Packaging and Devices CoE and it is an ideal opportunity for the UK Pharma industry to target technology and innovation challenges. The supply chain is rather academically unloved but its importance and relevance in these new medicines' platforms is crucial as it influences cost, quality and inventory. Expertise here could also be extended to partners such as the NHS.

5.4.14 | SKILLS AND TRAINING

The needs and drivers	Actions
• Advanced Therapies/Complex Medicines are at the forefront of Life Sciences – background education needs to keep up with accelerating pace of development/ science • New technologies require new generation of experts. Future proof AT with a strategic need to have specialists ready to create and leverage novel manufacturing technologies	• Develop appropriate training and professional development courses • Utilise Centres of Excellence as training grounds for not only graduates/post docs but also for apprentices. CoEs must be learning and training facilities as well as 'making' ones.

• Specialist skills needed along discovery/ development/manufacture journey • Potential skills shortages in new technology platforms and attraction of other industries (pay/career) • Early engagement on identifying (and filling) skill gaps could leverage UK opportunities to anchor these Complex Medicines in the UK and by achieving a critical mass continue to attract a sustainable succession process • On technical level training the biopharmaceutical and ATMP industries still require people with higher level of specialized skills ranging from undergraduate, masters or doctoral level degrees based on complexity of processes, often involving the combination of several fields and disciplines • Appropriate apprenticeships in AT manufacturing required • Apprenticeships will be required across all technical areas as we move into more complex manufacturing and these should be connected to academia and CoEs	• Focus on research and manufacture. UK needs to enhance the image of manufacturing (including Pharma) • Engage industry in offering 'internships' and placements for graduates and this must extend to SMEs too • Introduce Complex Medicines into other academic subjects (chemistry, engineering, IT etc.) • Encourage cross fertilisation with other industries (especially with application of new technologies, such as the use of Adaptive manufacture etc.) • Work with Universities to help educate schools on a variety of lesser known degree programmes and careers where there are skilled people gaps in the industry e.g. Biochemical engineering • Subsidies and funding for degree programmes, Centres for Doctoral Training (CDT) and Engineering Doctorate programmes is essential to build a pipeline of skilled people in this sector • Support and resource for universities offering CPD courses to reach a wider industrial audience and thus support the rapidly evolving bioindustry to upskill / reskill staff, particularly where there are options for a part time Masters level degree

With any new and rapidly evolving industry there is always the need to support its growth with a suitably skilled workforce that cannot only create the hardware needed to manufacture the product but also develop and manage the subsequent quality and consistency of this product from small laboratory scale to full commercial supply. Historical knowledge will need to be built from and although complex

medicines and processes will pull from certain existing professions and sciences these areas will need to be complemented to meet new technology challenges.

There will need to be well designed courses developed with a curriculum that needs to be shaped by industry and academia. The synergy (or network) is there to crossover with other core areas of science in the UK's prominent education system to strengthen our anchoring potential. Courses will range from undergraduate to post-doctoral and constantly be updated in this fast moving field. Subjects like engineering will be extended to enhance the complex medicines technology opportunities that include analytics and automation. Again, there is the expectation that technology gaps identified by the industry will drive areas for further academic focus.

For the short term the Advanced Therapies Manufacturing Action Plan Skills paper has highlighted specific targets for skills training in the UK and it forms a guideline for next steps. Industry must take the lead with support from multiple stakeholders including academia, higher education, Innovate UK and research bodies, to create and implement an end-to-end talent plan for the sector. The plan will encompass integrated strategies to develop the talent pool at multiple entry-points. These range from Manufacturing Technicians through to post-doctoral and professional levels.

The growth of the sectors such as ATMPs in the UK will crucially rely on a commensurate growth in the available talent pool. A conservative estimate is that 400-600 additional skilled staff will be required over the next two years for ATMPs alone. Currently the advanced therapies sector in the UK is in a nascent stage. Products are mostly in the experimental phase and manufacturing processes are largely under-developed and small-scale. As a result, the skills and knowledge requirements currently associated with advanced therapies are highly specialised (often post-doctoral) and multi-functional. As the industry matures and begins to commercialise products, the highest growth in skills and knowledge demand will not be in this highly expert group but increasingly in competent technicians or operators capable of reliably running routine manufacturing operations. In addition, specialised roles such as Qualified Persons and Regulatory professionals will grow.

The risk of an acute skills shortage is not unique to the advanced therapies sector. There are a number of science-based industry sectors that recognise a common need around themes such as attracting young people into STEM careers, promoting vocational training and linking academia to industry needs. The SIP, an industry-led group, recently published a report entitled Skills Strategy 2025[42], which made a number of proposals regarding increasing the capability and capacity of the UK science talent pool to meet the identified needs of the industry over the next decade.

42 http://www.scienceindustrypartnership.com/media/529053/5202fd_sip_skills_strategy_2015_final_low.pdf

5.4.15 GENOMICS - OVERARCHING OPPORTUNITY AND A FUNDAMENTAL FUTURE BUILDING BLOCK

The recent explosion in the development of Gene therapies has spearheaded an unanticipated increase in the demand for plasmid DNA, as well as viral vector generation; either GMP or non-GMP. A vast array of players, including cell/gene therapy developers, research institutes and contract manufacturing organizations are playing a critical role in the development of this expanding space, exemplified by a striking growth in the number of spin-outs globally. The current plasmid capability has real limitations:

- **Genetic engineering:** extreme variability in vector types and constructs
- **Cloning:** scalability remains an issue - large scale is needed for commercial production
- **Bacterial cells:** cannot amplify complex sequence – capability to amplify complex sequences is key, whereby crossing with synthetic biology can be pivotal
- **Fermentation:** slow - real need to accelerate the process to avoid bottlenecks
- **Lysis and Purification:** Expensive - significant CoGs reduction required
- **Current facilities limited -** too few vector types and production types, restricting collective knowledge of new/advanced designs
- **A number of critical analytics and technology platforms still missing:** safety, stability, purification, scale-up, potency, identity, comparability

With the ATMP space in its early stages, naturally the demand is still mostly geared towards the research and clinical grade, compared to commercial grade vectors. However, looking ahead the target is to enable supply of high yield, high fidelity, high purity product, while adding favourable attributes, i.e. elimination of antibiotic resistance.

However, the development of commercial scale facilities for vector production for most SMEs is prohibitive and usually remains limited to product-directed vector types and technologies, led by their specific clinical trials.

Specialized Cell and Gene Therapy Operation: The Advanced Therapies Manufacturing Taskforce in particular, has recommended that the UK Government establish competitive funding to support viral vector capability growth within two years. The Taskforce proposes the development of a **specialist manufacturing operation** leveraging where possible the existing infrastructure. The operator(s) should be mandated to work with academic groups to supply viral vectors and therefore gain exposure to cutting edge developments, whilst at the same time industrialising the academic processes.

Expanding the scope further, there is the potential opportunity for a broader specialist development and supply of engineered DNA either through the partnership with government or grant funding (the former has the advantage that it could help anchor firmly a suitable site in the UK). The manufacturing facility would be GMP and have at its core the capability of in vitro amplification to capture the next generation of DNA medicine platforms (including preparedness for vaccines). Genomics could easily become one of the 'Technology Strands' defined in the road map model **(Fig 1)** and this requires further discussion.

6.0 CONCLUDING REMARKS

The Technology and Innovation road map has been written to inform the wider Life Science community (and all those who supply and service it) about the strategy for anchoring new technologies and innovation for medicines manufacture. It has considered the potential for not only advanced therapies and complex medicines but also small molecules. The reasoning behind this is that by the UK covering these areas it captures future medicine opportunities, but the strategy also recognises the considerable scope for enhancing the current capability to ensure that the UK Pharmaceutical Industry is fit for the future. It has been created from in-depth workshops and discussions with stakeholders.

To complement the 'manufacturing anchor' the UK has class leading academic foundations that will continue to partner with industry to ensure that there is an ongoing and appropriate supply of skilled staff to support all aspects of development and production. Identifying the technology needs for the next decade is a fundamental output from the road map and it must inherently link with academia to ensure that research is focussed on real step change programmes.

The road map has proposed a clear model that highlights the facilities (centres) needed along with a detailed set of shared technology strands that when integrated will accelerate development from the bench to the clinic and ultimately to the patient at the end of the supply chain. By identifying and covering these existing technology gaps this should position the UK for inward investment. The UK Life Science industry must continue to identify further 'technology gaps' as this is a fast moving industry and plan to fill them, and it should also reach out to different industries to understand where additional shared knowledge and opportunity can encourage identified synergies. These areas are multifaceted and include: automation, digital, modelling techniques, process engineering, supply chain design. All of these specialities can enhance and enable robust and cost effective scale up of all manufacturing aspects across the Life Science value chain.

With the foundation established and clear priority centres identified there is the need to engage stakeholders on an on-going basis. These stakeholders will provide coordinated governance, economic support (including fiscal) and guidance to ensure that the road map is delivered. The UK Regulator (MHRA) will be a core partner as will collaborations with bodies such as the NHS to drive through clinical evaluation and accelerate and implement technology driven access to novel medicines. Government will be imperative in setting on-going fiscal opportunities and also endorse initiatives to target resources onto

technology, innovation and skills and this will set the UK as the country to invest in. With this investment for the Life Sciences comes inevitable economic growth in this important High Value Manufacturing Platform.

The Future Vision for 2025 is that the UK anchors and maintains its global position as a leading country for investment in the Life Sciences. A strong and enduring academic, manufacturing, regulatory and skilled workforce will complement the fiscal advantages and business attractiveness offered by the UK.

The UK has a class leading **academic base** that produces the required talent pool of high quality graduates and research projects that consistently spin out new assets, processes and operations. Research often creates the need for new technology and ultimately adds considerable increased value when it transfers from the bench to scale up. The step change in medicines manufacturing that this road map proposes will require sustained and increased support of the academic base.

The unique **partnership between academia and Industry** is one that drives this innovation and the capability to industrialise research is one of the UK's core strengths. Another strength that accelerates innovation is the connected SMEs across the UK that deliver (and often create) technology solutions. The UK has a proud engineering and production background that supports T&I initiatives and these direct and indirect companies also benefit from inward investment. This power base must not be underestimated.

Next steps will be agreement in principle for this model to be endorsed and then medicine platforms would have targeted technology specifics mapped out in exact detail. There has to be an agreement on the identified opportunities first. Timelines for the model to be in place are dependent on this agreement to support. Where some parts will take 2-3 years (primarily any 'new builds') others could start immediately assuming that they are resourced and suitable space identified in existing facilities (certainly in the short term). A central body should be considered to manage the complexity of this vision to ensure resources are aligned and optimised and they could also help co-ordinate the proposed 'account managers' that will be charged at ensuring our new medicines remain in the UK.

7.0 | INITIATIVES, ACKNOWLEDGEMENTS, ABBREVIATIONS AND HYPERLINKS

Existing Initiatives which support Life Sciences Manufacturing (in alphabetical order)

Since the start of the road mapping exercise, a number of new or extended initiatives have been launched, some in part informed by this exercise. These and their direct relevance to HVM are highlighted below.

AMSCI (Advanced Manufacturing Supply Chain Initiative) - AMSCI was a BIS (now BEIS) initiative in support of their Industrial Strategy and set out to provide a flexible package of support (grants and loans) with the aim of helping existing supply chains grow and achieve world class standards while encouraging major new suppliers to set up and manufacture in the UK. This programme has been developed over recent years to make it increasingly applicable to businesses in the Life Sciences sector. It completes in Q4 2017.

BBSRC BRIC - This initiative has provided £26m of funding for industry-driven academic research and will continue to operate until 2017. It has currently 15 industry members and has been viewed by the sector as a leader in terms of quality, outputs and industry interaction. It has also enabled 28 BRIC PhD studentships to be aligned and taken up by the industry members. The KTN has also been key in ensuring industry engagement and latterly overall programme management. The establishment of the biopharmaceutical bioprocessing (BioProNet) enables further interaction from academics and industry in wide ranging research challenges.

Biomedical Catalyst - This joint initiative between the existing Technology Strategy Board and MRC has been pivotal is moving early stage products and technologies into or towards the Clinic.

National Formulation Centre - Provides access to industry trained experts and open access facilities which enable the formulating industries to develop and scale up advanced formulated products productively, efficiently, and with less risk. CPI's National Formulation Centre provides a joined up approach to the development of next generation formulated products and their applications across markets such as healthcare and pharmaceuticals.

MISG - This Ministerial Industry Strategy Group is tasked with developing a shared understanding

across key stakeholders of the existing support available and challenges for industry and proposing a cohesive strategic vision for medicines manufacturing in the UK. It will cover issues relating to the manufacturing of all types of medicines including small molecules (pharmaceuticals), biologics and advanced therapies sectors (such as cell and gene therapies), both for clinical trial and licensed product manufacture.

MMIP - The Medicines Manufacturing Industry Partnership represents the voice of the medicines manufacturers in the UK. It was established jointly by Government and the biopharmaceutical industry in 2014 to ensure that the UK is recognised by the global medicines industry as a world class advanced centre for medicines manufacture.

MMTSG - This Ministerial Medical Technologies Strategy Group is similarly (to MISG) tasked with developing a shared understanding across key stakeholders of the major issues facing the medical technologies sector and how support mechanisms can be optimised to enable a responsive and competitive sector. Amongst other things, it addresses issues related to manufacturing across all sub-sectors and the supply chain and is aligned with the MMIP.

Catapult Centres - Catapult Centres are an Innovate UK product and were launched to address the need to transform the UK's innovation potential in key areas where a critical mass of expertise is required coupled with an enabling and high cost infrastructure which has some form of open access to large and small businesses.

- Two Catapult Centres are particularly relevant here: High Value Manufacturing and Cell and Gene Therapy.
- The former comprises seven core centres. The important new Centre within this is the National Biologics Manufacturing Centre.
- The Cell and Gene Therapy Catapult addresses a part of this road map, but will also form its own manufacturing road map and is a major contributor to unblocking the commercial and clinical realisation of cell and gene therapies.

Cogent - £25m pilot scheme for the Science Industry Partnership (SIP) led by GSK. The SIP is a proposed national, skills and education focused Partnership for the science-based sector to develop ambitious end-to-end skills solutions for the industry. SIP recommendations published in March 2016.

EPSRC - EPSRC supports basic research and skills development in a range of manufacturing and physical science technologies. Of particular note are their Centres for Innovative Manufacturing for which one already exists in Medical Technologies, one in Emergent Macromolecular Therapies, one in Regenerative Medicine and to address skills there are new Centres for Doctoral Training which aim to develop post-graduate engineers with strong commercial awareness alongside academic excellence.

Knowledge Transfer Network - The KTN is the UK's innovation organisation and works with Innovate UK. KTN was established to foster better collaboration between science creativity and business with specialist teams covering all sections of the economy.

Innovate UK - The UK's innovation agency and its goal is to accelerate economic growth by stimulating and supporting business-led innovation. The Innovate UK has a Life Sciences and HVM team that are responsible for calls directly related to these areas. The HVM team have released relevant competitions that have been informed by this road map as well as other inputs.

Europe (EU) – the aim of the EU investment in health research is to improve the health of European citizens, to address global health issues and to boost the competitiveness of European health-related industries. In the area of Life Sciences including HVM the Horizon 2020 for Health is the EU's new programme for investment in research and innovation, is expected to include more than 7 billion EUR for the 'Health, demographic change and wellbeing' challenge. There are also other EU wide schemes running that relate to this sector.

With Brexit in Q2 2016 there will be an ongoing need to update the road map depending on timings for Article 50 and the impact that this will have on future UK plans, opportunities and threats within the Life Sciences.

Trade Associations – The main Life Science Trade Associations of the BIA (The BioIndustry Association), the ABPI (Association of the British Pharmaceuticals Industry) and the ABHI (Association of British Healthcare Industries) have been highly supportive of this road mapping exercise and the process has strongly engaged their members.

7.1 | ACKNOWLEDGEMENTS

This road map was authored by Gregor Anderson (Technology and Innovation work-stream lead for the MMIP) with the support of the extended MMIP Team, the ABPI/BIA and is an output of an industry wide discussion for which we are grateful to all. The roadmap is intended to be built upon, revisited and updated on a regular basis due to Pharma being an ever changing industry . It is there also to align many of the opportunities that the UK offers to anchor the country as the medicines 'one stop shop' from discovery through to manufacture, no matter what the platform.

We would like to thank all the following contributing organisations for their input into this process.

3M

Advanced Manufacturing Research Centre (AMRC)

Amcor Flexibles

Association of the British Pharmaceutical Industry

AstraZeneca

BioIndustry Association

BSI

Centre for Process Innovation

Cisco

CMAC

Consort Medical

Department for International Trade (DIT - formerly UKTI)

Digital Health - DHealth

Eisai

FUJIFILM Diosynth Biotechnologies

GE Healthcare Life Sciences

GSK

Innovate UK

Lonza

Medicines Manufacturing Industry Partnership

Molins

Office for Life Science

Owen Mumford

Oxford BioMedica

Pfizer

ReNeuron

Rockwell

Science Industry Partnership

Symbiosis-Pharma

The Knowledge Transfer Network (KTN)

Touchlight

University College London

University of Limerick

University of Loughborough

University of Nottingham

7.2 | ABBREVIATIONS

AAR - Accelerated Access Review

ADC - Antibody Drug Conjugates

ADDoPT - Advanced Digital Design of Pharmaceutical Therapeutics

AI - Artificial Intelligence

AM - Additive Manufacture

AMR - Antimicrobial Resistance

API - Active Pharmaceutical Ingredient

ATMP - Advanced Therapy Medicinal Product

BIA - BioIndustry Association

BP - British Pharmacopoeia

CGP - Chemical Growth Partnership

CGTC - Cell and Gene Therapy Catapult

CMAC - Continuous Manufacturing and Crystallisation

CMO - Contract Manufacturing Organisation

CoE - Centre of Excellence

CPI - Centre of Process Innovation

CQA - Critical Quality Attribute

EAMS - Early Access to Medicines Scheme

FoF - Factory of the Future

GLP - Good Laboratory Practice

GLMP - Good Laboratory Manufacturing Practice

GM - Genetically Modified

GMP - Good Manufacturing Practice

GVA - Gross Value Added

HCF - High Containment Facility

HVM - High Value Manufacturing

ISCF - Industrial Strategy Challenge Fund

IP - Intellectual Property

IT - Information Technology

KTN - Knowledge Transfer Network

LED - Light Emitting Diode

MHRA - Medicines and Healthcare Regulatory authority

MMIC - Medicines Manufacturing Innovation Centre

NIBSC - National Institute for Biological Standards and Control

OLS - Office of Life Science

OT - Operation Technology

PAT - Process Analytical Technology

PVC - Polyvinyl Chloride

QbD - Quality by Design

QP - Qualified Person

REMEDIES - Re-configuring Medicines End-to-End Supply

SIP - Science Industry Partnership

SME - Small Medium Sized Enterprise

STEM - Science Technology, Engineering and Mathematics

UK CR&D - UK Collaborative Research and Development

7.3 | HYPERLINKS

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