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Profile and Importance of the North East Pharmaceutical Manufacturing Sector:

Growing Its Contribution

North East Local Enterprise Partnership

FIRST FOR PHARMA
North East England Pharmaceutical Community

cpi

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A special thank you to the industrial partners for their time and knowledge shared which was fundamental to this report's construction.

1. Foreword

I am pleased to have been involved in developing this report on the history and current status of pharmaceutical manufacturing sector in the North East of England.

The North East of England has a long and strong heritage of pharmaceutical manufacturing, capability and expertise. Significant facilities were established in the 1960s and 1970s by UK and American owned parent companies in response to the sector growth in innovative medicines and the favourable environment in the UK for manufacturing and marketing of pharmaceutical products. Facilities included capability in the manufacture of Active Pharmaceutical Ingredients (APIs) and in formulation and packaging, primarily for UK markets. This established the North East as one of three major areas for pharmaceuticals manufacturing in UK together with the Home Counties and the North West of England.

These facilities grew in capability and performance and were able to adapt to the needs of global customers as the first of several phases of globalisation, expansion and then consolidation took place in the pharmaceutical industry with added manufacturing capacity in tax advantageous countries and emerging markets. The continuing evolution of the market and the development of blockbuster products enabled these facilities to hone their performance in terms of quality cost and reliability of supply. They contributed powerfully to UK economy, adding significantly to the UK's balance of payments and enhancing the UK's reputation in regulatory compliance and manufacturing process development, where it operates consistently at a very competitive global level.

Many changes have occurred in the region in the last 20 years and the North East sector has evolved successfully. All the North East facilities established in the 1960s and 1970s remain in operation, several with different ownership and with different technologies and a changed product portfolio. The sector has grown further through the addition of biotechnology companies, contract manufacturers and supply chain companies. And strong, supportive academic institutions have develop a global reputation for research excellence in leading areas of life sciences.

Together they have established the region's pharmaceutical manufacturing as globally competitive - vibrant, viable and valuable. This has been achieved despite a challenging outlook globally, with favourable economic conditions in several competing countries resulting in spare capacity and adding to pressure on UK companies through threats of reduced product portfolio and pricing pressures. For the North East manufacturing plants this challenge has been met through deep knowledge of global business conditions and effective response to global competition. Many capabilities have contributed to this response. Areas critical to the industry's success over a sustained period include lean working practices, upskilling, reducing or mitigating costs and ever increasing quality, compliance and supply agility. Much credit must be given to leaders and their colleagues in these organisations who have adapted and utilised the strengths of the region, including the region's significant modern manufacturing capability in other sectors which has been encouraged and enabled by several government initiatives.

This long history of success in a rapidly changing global environment provides confidence of a future for employees and for the local and national economies. Continuing success will require efforts both locally and nationally at Government level in a challenging and uncertain world to

ensure all parts of the sector remain strong, viable and valuable to owners, investors, customers and regulators. This report aims to provide quantitative and qualitative evidence for the sector's success and illustrates some of the factors that have contributed to past achievements as well as providing confidence in the sector's future. Providing the correct strategic path is taken and the sector is appropriately supported, the sector will continue to remain viable and globally competitive whilst adding substantial productivity to the UK's economy during and after the process of leaving the European Union.

Martin Inskip
MSD Cramlington Site Head (2004–2015)

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2. Executive Summary

This report has been produced by the Centre for Process Innovation (CPI) and First for Pharma (FFP), supported by the North East Local Enterprise Partnership.

It has been researched and produced at a time when the UK Government is preparing plans to leave the European Union and is framing a new UK Industrial strategy. It follows on from the process of refreshing the North East Strategic Economic Plan published in March 2017.

Each of these processes references the importance of life sciences and advanced manufacturing to the UK and North East economy. In this context, FFP members agreed that there was priority to improve the profile and understanding of the North East pharmaceutical manufacturing sector and to identify opportunities for growth.

Key aims of this programme of work were therefore to:

- Evaluate and demonstrate the economic profile and impact of the North East's pharmaceutical manufacturing sector.
- Identify the sector's opportunities to maintain and grow its international competitiveness and to continue to contribute significantly to the UK's productivity growth.
- Draw out views and insights of senior business leaders about the challenges facing the sector and identify the support needs of businesses.

The report provides a summary of the findings of this work and sets out conclusions and proposals for the North East sector, regional partners including the North East LEP, and UK Government and its agencies.

Profile of the North East Pharmaceutical Manufacturing Sector

In preparing this report the researchers surveyed and interviewed the majority of key businesses in the NE sector which is arranged across Northumberland, Tyne and Wear and County Durham and includes both UK and internationally owned businesses of different scales, ranging from 50 to 1000 employees.

The sector includes a range of business models including business services, technology ranges and scales of production. Despite this diversity, the sector is well established and benefits from a global reputation for business resilience and regulatory reliability.

As a collective the sector is unique in UK terms and includes a number of contract development and contract manufacturers, key supply chain companies and large multinational drug developers. Taken together, the region's pharmaceutical manufacturers have full capability to develop drug manufacturing processes for clinical development and commercial supply of tableted medicines.

2.1 Summary of Key Facts

- There are 15 pharmaceutical manufacturers in the North East of England sector including a diverse range of business models, ownership arrangements and relationship structures with the regional and UK economy.
- Five pharmaceutical manufacturing sites in the North East are internationally owned. Owners include US, Japanese and Indian companies and individuals.
- Overall direct, indirect and induced GVA contribution to the UK by the regional sector surveyed is estimated to be between £0.73 billion and £1.28 billion.
- Pharmaceutical manufacturing sites in the sector export an average of 86% of their products with 64% of exports going to the United States.
- The sector's value chain contribution to the pharmaceutical manufacturing chain is very high at between 20 to 50 fold.
- The sector is growing and expecting to recruit additional jobs to its current manufacturing and research workforce this financial year (2017-2018).

Trade, imports and exports

The sector is strongly connected to international markets for the import of raw materials and processing equipment and the vast majority of manufactured products are exported.

Manufacturers reported that they imported lower cost raw materials, chemicals and reagents from Asian markets such as China and higher value processing equipment and specialised raw materials from North America, other parts of the UK & Ireland, and mainland Europe.

Between 55-100% of the outputs from the different companies is exported to international markets. The United States is the largest recipient of finished products with approximately 64% of all exports going to the US market.

6 out of the 9 businesses involved in the interviews operated an outsourced logistics model.

Skills

Of the 3500 people directly employed in the companies surveyed, about 66% are male and 34% female. Almost 2000 of the employees are in research or manufacturing roles with the largest cohort aged between 31 and 50 (49%), 22% are aged under 30 years old and 29% are over 50.

The quality and stability of the employees in the local labour force is one of the North East's

competitive advantages in hosting these businesses and the regular circulation of staff is seen as positive leading to sharing of ideas, best practice and a sense of a career structure. There is an expectation of growth and additional demand for key personnel.

However, the businesses identified a number of key issues with regards to expertise and education within the region with external recruitment often required for senior-level leadership and strategic-level employees, and in key research and analytical roles although graduate level staff can usually be recruited locally. The businesses are intending to be proactive looking forward and will use the apprenticeship levy to help recruitment planning and the moulding of staff. The ability to recruit internationally was also mentioned in most interviews.

Funding and Reinvestment

There are different approaches to funding and capital investment evident, dependent on the structure of the business and its relationship with owners and position in the supply chain. In general terms, however, the North East sector has been successful in attracting inward investment globally from the United States, Japan, India and mainland Europe, as well as the UK.

Some companies had considered the possibility of using private equity finance as a means of raising capital, but this was the least preferred option for acquiring capital due to the equity stake expected by the private equity companies in return for funds.

Regulatory issues

A uniting feature across all of the interviews was the ability to operate globally in an increasingly competitive industry. The businesses in the sector rely heavily on the ability to import materials and export their products and looking forward, interviewees identified the potential to attract business from international clients as core to the continued success of this industrial sector.

An underpinning core common theme identified in all interviews was the importance of the UK's regulatory environment. This was regarded as central to the sector's success and had the characteristic effect of providing a non-tariff barrier that has formed to the sector's advantage due to the high quality manufacturing standards alongside a reputation for delivery on time and on budget.

In this context, a key theme identified during the interviews was a concern about the possible impact of the vote to leave the European Union. Interviewees reported that the devaluation of Sterling has eased exchange rate pressure on export heavy industries and feedback suggested that this is likely to be positive for the sector over the longer term. However, the possibility of regulatory disruption created through the process of exiting the European Union was viewed as a significant threat to the sector, particularly with the strengths that the UK's regulatory framework provides the industry through Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Agency (EMA) guidelines.

Sites who form a part of a global manufacturing network also reported specific concerns

regarding potential supply chain disruption due to changes in customs procedures that may reduce the ability of a global manufacturing supply chain to efficiently include UK sites within the process. In discussion, arrangements equivalent to the Swiss-EU arrangements were seen as a minimum viable outcome required from the negotiations.

Economic Impact

The North East pharmaceutical manufacturing industry employs between 4,300 and 5,300 in the region and contributes £450 to £790 million to the region's Gross Value Added (GVA). Including indirect and induced effects, the North East pharmaceutical manufacturing industry supports between 18,800 and 23,500 jobs across the UK and £0.73 and £1.28 billion to the UK economy.

Key opportunities and challenges

Interviewees identified key opportunities and challenges for the North East sector going forward:

Profile

- Ensuring that the profile and the sector needs were fully understood at national and regional level, taking opportunity of processes envisaged in the Industrial Strategy Green Paper
- Ensuring that the North East sector, its capabilities and needs are fully reflected in the forthcoming life sciences sector deal
- More active engagement in processes in the North East to support skills, business growth and innovation development

Industrial Development

- Strengthening the sector's pharmaceutical supply chain integration through combined utilisation of the North East's manufacturing sites
- Strengthening collaboration with science and research assets in the region and with other advanced manufacturers to develop new products and explore improved processes. Three future capabilities were seen as particularly important; ultra-high potency manufacturing, continuous manufacturing processes to deliver more efficiency and higher productivity and smart packaging and delivery. The proposals to invest in the MMIC and Smart Packaging Centre were welcomed.
- Strengthened knowledge base on global best practice and continuing benchmarking.
- Opportunities for improved linkages across Advanced Manufacturing sectors in the North East should be explored including automotive and energy to consider key process development such as industrial digitisation and low carbon manufacturing.

Human Resources

- Action to ensure that the ongoing need to continue to recruit senior and strategic roles continued and that the Apprenticeship Levy was an opportunity to shape a future skills supply.

The Brexit process:

- Ensuring that the regulatory framework derived from the decision to leave the EU was conducive to continuing competitiveness, avoided additional impediment to integrated global supply chains for raw materials, intermediates or finished products by import or export resulting in an increase for operational complexity, lead times and costs.
- Mitigating any knock on impact on investment decision making from owners.

2.2 Key recommendations from the report:

Development of a supply chain and logistics strategy: Detailed work should be undertaken between the regions businesses to understand opportunities to strengthen the supply chain in the region and identify opportunities for improving the logistics support, including taking advantage of the North East growing digital capabilities.

Innovation: Strategies should be developed to foster the following innovation opportunities in the North East, or within the UK to support the performance of manufacturers based in the region, taking advantage of existing regional capability:

- The following future capabilities; ultra-high potency manufacturing; the application of continuous manufacturing for drug manufacturers; smart pharmaceutical delivery including packaging, sensing and new formulations including monitoring capabilities
- Incremental process developments including application of digital, robotic and low carbon technologies.

Skills: In response to the current demographic and policy environment, the sector should work with the North East LEP develop a clearer analysis of current skills gaps and potential future needs and to inform the content of these initiatives.

Regulatory Environment: The continuing importance of the regulatory environment should be promoted and concerns about the impact of the vote to leave the European Union should be communicated during the current period of consultation on the negotiations.

Co-ordination: The implications of this work for ongoing co-ordination between North East pharmaceutical leaders and other partners to take these recommendations forward should be discussed.

3. Introduction

Background and purpose

For a seven month period starting in January 2017, the Centre for Process Innovation (CPI) and First for Pharma (FFP), supported by the North East Local Enterprise Partnership, (North East LEP) progressed an industry engagement programme with senior managers and executives in North East pharmaceutical businesses.

This work followed on from discussion within the FFP network that, at a time when the UK Government is developing its plans to leave the European Union and framing a new UK Industrial strategy, and following on from the process of refreshing the North East Strategic Economic Plan, there would be benefit to clearly describe and project the capability, opportunities and needs of North East pharmaceutical businesses in the context of global trends affecting the sector.

There was a general belief amongst the sector's businesses that the North East pharmaceutical manufacturing sector is not understood at national or regional level in a manner which is commensurate with its economic impact and industrial standards and that opportunities for growth are therefore not realised. A number of reasons for this were identified, including a sense that the sector had been successful and had not required external engagement or support, and a sense that the structure of the businesses themselves meant that the value and capability of the capacity within the North East was not accurately accounted for in UK data.

Taking forward the engagement and reporting process

FFP partnered with the CPI, the process industry arm of the High Value manufacturing Catapult, supported by the North East LEP, to undertake this work.

Businesses within the FFP network were consulted on the project and agreed to respond on an anonymous basis to both provide detailed information about their activities and key operational and financial data and to provide thoughts and insights about key issues and opportunities facing the sector derived from economic, industrial or policy trends.

The methodology used for the study was as follows:

- A survey questionnaire was prepared seeking access to key industry data and setting out a series of lines of discussion. This was circulated to North East pharmaceutical manufacturing sector, regional supply chain companies and small and medium enterprises (SMEs) from FFP's membership list and CPI contacts.
- A programme of face-to-face interviews was scheduled with senior managers or executives who answered the questions and more broadly discussed key topics areas.
- Data from a further 3 businesses was accessed from published reports.

Leaders from the following organisations took part in these interviews; Aesica Pharmaceuticals, Arcinova, Biosignatures, Fujifilm Diosynth Biotechnologies, GlaxoSmithKline, Glythera, High Force

Research, MSD, Orla Protein Technologies, Piramal Healthcare, Sterling Pharma Solutions, Wasdell.

The interviewees have been open with both information about their business as well as their views and concerns about the issues and opportunities for them in this environment. As agreed at the outset, information provided has been treated on a confidential basis. The research team would like to record their thanks to those individuals who took part for their time and input. With the benefit of the data secured from the engagement process, the drawing in national data and in consultation with staff from national statistical authorities, an economic analysis of the North East sector was then developed.

This report:

- Reports findings from the engagement process, draw together a number of conclusions about the profile and structure of the sector in the region and some opportunities and challenges.
- Provides a summary of data estimating the economic value and impact of North East pharmaceutical manufacturing.
- Provides a group of recommendations to a number of audiences about key next steps to further support North East pharmaceutical manufacturing.

Alongside these estimates a fuller discussion of the data and some technical issues is set out in a technical annex in appendices.

4. Findings from the research

Manufacturing Metrics

Selected facts and figures from North East pharmaceutical manufacturing output:

Capacity

- Over 9.85 billion tablets are produced from 4 of the sector's sites per year, with 4.8 billion being manufactured by one site.
- The sector holds manufacturing contracts on 153 drugs in preclinical/clinical development, approximately 2-3% of the overall 7000 global drugs in development .
- The sector manufacturers 90+ clinically approved drugs and commercialised products.
- A multinational drug developer manufacturers 5 out of its top 11 products within the region including its top selling drug which generates ~$6 billion revenue per annum and works across 12 product families.
- A multinational drug developer produces over 30 products, with 1500 stock keeping units (SKUs) and distributes these to 140 countries worldwide.

Capability

- Efficiency was cited as a key driver for performance for the sector's pharmaceutical manufacturing sites with one site reporting 50% increase in profit per full time equivalent over the last 4 year period. Techniques such as lean six sigma were reported as being used by one internationally owned site some time before the practice became heavily utilised by the global pharmaceutical manufacturing industry.
- Depending on scale, the raw material costs per batch are between 25-40% of overall batch value. Sterling devaluation will have an impact on raw materials purchasing, but this may be balanced by the value of a weaker currency in export markets.
- A regional SME noted that a drug development company can progress an antibody drug conjugate (ADC) to complete a Phase I trial and beyond through services available from companies North of York.

4.1 Profile of the North East pharmaceutical manufacturing sector

The North East pharmaceutical manufacturing sector has a diverse range of business models, technologies and capabilities which can present challenges in fully understanding the sector profile. It has a broad spread across the region, with some concentrations of businesses in South East Northumberland and Newcastle, but with other major employers in County Durham and northern Northumberland (see map 1). There are a wider network of supply chain companies and SME's across the region.

The researchers interviewed 12 companies in total; 7 of these were CDMOs/CMOs, 3 supply chain companies or SMEs and 2 large multinational drug developers. The glossary of terms (see

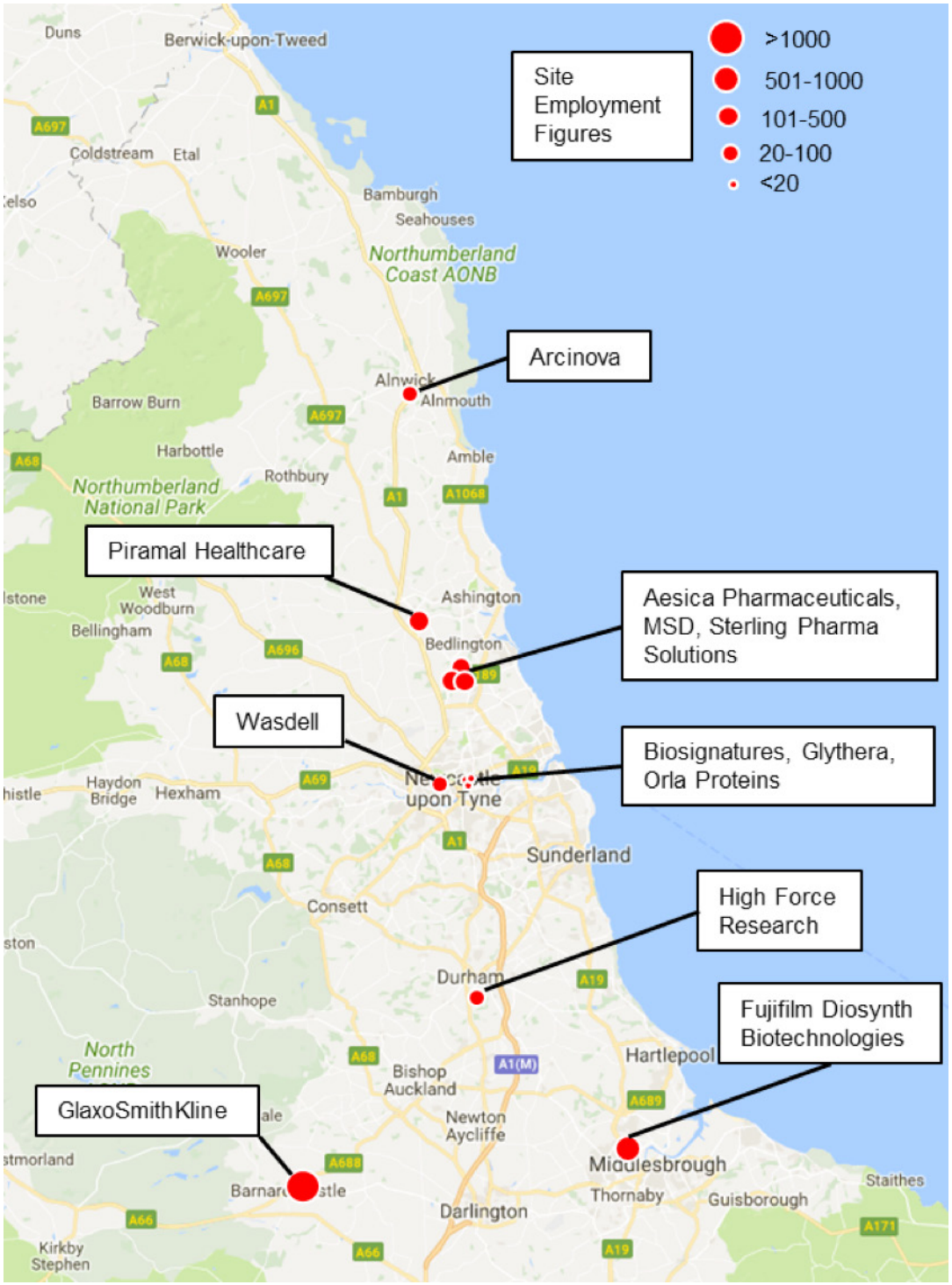
appendix 1) identifies how both the large multinational drug developers and the CDMOs/CMOs are encompassed under the term pharmaceutical manufacturers, which gives a total of 9 sites.

The following pharmaceutical manufacturers and supply chain companies/SMEs participated in the study (see table 1). These provide a good cross section of the existing manufacturing base.

Company Name	Location	Company Type	Employees on site	Ownership
Aesica Pharmaceuticals	Cramlington	CDMO/CMO (pharmaceutical manufacturer)	101-500	UK (Subsidiary)
Arcinova	Alnwick	CDMO/CMO (pharmaceutical manufacturer)	20-100	UK (Independently owned)
Biosignatures	Newcastle	Supply chain company or SME	<20	UK (Independent, has VC-backing)
FUJIFILM Diosynth Biotechnologies	Billingham	CDMO/CMO (pharmaceutical manufacturer)	501-1000	Foreign (Asia; Subsidiary)
GlaxoSmithKline	Barnard Castle	Large Multinational Drug Developer (pharmaceutical manufacturer)	>1000	UK (Part of a manufacturing network)
Glythera	Newcastle	Supply chain company or SME	<20	UK (Independent, has VC-backing)
High Force Research	Durham	CDMO/CMO (pharmaceutical manufacturer)	20-100	UK (Independently owned)
MSD	Cramlington	Large Multinational Drug Developer (pharmaceutical manufacturer)	101-500	Foreign (USA; part of a manufacturing network)
Orla Proteins	Newcastle	Supply chain company or SME	<20	UK (Independent, has VC-backing)
Piramal Healthcare	Morpeth	CDMO/CMO (pharmaceutical manufacturer)	101-500	Foreign (Asia; Subsidiary)
Sterling Pharma Solutions	Cramlington	CDMO/CMO (pharmaceutical manufacturer)	101-500	Foreign (Asia; Independently owned)
Wasdell	Newcastle	CDMO/CMO (pharmaceutical manufacturer)	20-100	UK (Independently owned, but has other UK sites)

Table 1: Summarises general company information such as company name, location, company type for this study's purposes, an employee range for the site and ownership information.

Location of North East Pharmaceutical Manufacturing Sites with Employment Figures



Map 1: Map showing the distribution of pharmaceutical manufacturing sites interviewed within the North East region with approximate employment figures per site.

FFP and CPI estimate that this combination represents approximately 75% of the North East pharmaceutical manufacturing sector with a further 3 companies listed in the region as undertaking manufacturing work in the same SIC codes. As detailed in table 1, Biosignatures,

Glythera and Orla Proteins are not classified as pharmaceutical manufacturers.

Linkages to wider North East Life Sciences and Manufacturing assets

Pharmaceutical manufacturers have existing connections and interactions with businesses and other organisations from related sectors in the region and there are opportunities for strengthening collaboration across these sectoral boundaries in the context of supply chain development, research and innovation and skills issues. These include:

- Life sciences research and business organisations represented in the North East Life Sciences Steering Group.
- The wider chemistry oriented sector in the North East and the Tees Valley.
- Other North East and UK Advanced Manufacturers and the supporting supply chain.
- Innovation hubs, networks and agencies including the Catapults.

These opportunities have particular relevance in the context of the emerging UK Industrial Strategy and the North East Strategic Economic Plan and there are potential opportunities to highlight these connections linked to the development of the UK Life Sciences strategy and the Local Industrial Strategy process which is envisaged in the Industrial Strategy Green Paper.

Stories of the Sector

Whilst companies may own relatively similar equipment and have comparable plant scales, the way in which these are utilised by different sites depends on the nature of business. North East sites have varying developmental histories. Many are typically a part of a global drug manufacturing network or operating as part of an internal company multinational supply chain or through outsourcing to other clients who are often internationally-based. This diversity means that the core focus and nature of the company operations' is often unique to each specific site.

These varying business models can hinder the sector's ability to co-ordinate or present itself as a united, integrated sector. When this is combined with varying financial and accounting practices that often attribute economic impact away from the North East, the challenge of representing the sector's impact or supporting its development is increased.

Understanding these issues formed a key part of the face-to-face interviews and helped to frame the conversations about the profile, needs and perspectives on future opportunities and pressures facing individual businesses and the sector as a whole. It became very apparent that each site has its own unique past with some sites changing owners and business models multiple times throughout their history in which the ability attract inward investment has been vital; other sites have maintained their purpose for which they were built decades ago.

Case Studies of North East Pharmaceutical Manufacturing Sites: Diverse Histories and Profiles

Contract Development & Manufacturing Organisation

The site currently operates as a CDMO, but started under an American drug developer who initially commissioned the site in 1969. The site then ran under this name for 19 years, before the company was purchased by an American imaging company who inherited the site as part of the acquisition in 1988. In 1992, the site's capability increased with the commissioning of a biological water treatment facility and in 1994 the North East site was acquired by a large French pharmaceutical company. This was a challenging time for the site and in 1996 due to supply chain rationalisation, a management buyout along with private sector investment to enable facility upgrades led to an independent company forming. As the investors looked for an exit, the site was sold to a French specialty chemical company in 2000 who operated the site until 2006 when a Japanese company bought out the site. Nine years later in 2015, the Japanese company merged with an Indian company and again, due to rationalisation, a management buyout was facilitated through an independent Indian investor who is now setting ambitious targets and growth expectations for the site. The company's management are optimistic given the site's new ownership and looking forward to meeting the new targets.

The site's story is one of resilience through rounds of rationalisation, it has continued to operate effectively and attract international business. With the site's new ownership the site is now strategically targeting new international markets and focusing on capability build through either organic or inorganic means.

Large Multinational Drug Developer

This site is part of a global drug manufacturing network and has been in operation since World War Two. Its isolated location was selected due to it being a non-importance area for Luftwaffe strategic bombing. The site's original purpose was as a penicillin plant during the war and up to the 1960s when the site started to manufacture creams and ointments. Since the 1980s further capability was added to the site as it was selected to produce 2nd and 3rd generation antibiotics from which the active pharmaceutical ingredients were transported from another UK site to the North East for processing. The owner company continues to invest in the site, with a £100 million aseptic fill facility soon to be commissioned.

The brand of the site's owner is held in high regard due the quality of medicines manufactured which is a direct result of the high standards expected and maintained at the North East site.

Supply chain companies or SMEs

This innovative SME was founded in 2007 through private sector investment funding for intellectual property developed from a south west based University. Since 2007, the company has secured further investment from equity and non-diluting grant-based sources. The company debated numerous avenues in which to commercialise the intellectual property, but decided to progress along a drug development path in which they are currently looking to reach the clinical in 2019. The company works closely with both regional Universities and a large American antibody drug conjugate company showing the benefits of an integrated approach across separate research and industrial sectors.

4.2 Key capabilities and position in the value chain

Taken together, the sector's pharmaceutical manufacturers have full capability to develop drug manufacturing processes for clinical development and commercial supply of tableted medicines.

There are three main manufacturing steps in the processing of initial raw materials through to a product that is suitable for clinical and commercial supply; these are:

1. API Manufacture/Bulk Drug Substance – This step involves the process of taking the initial raw materials needed to make the active pharmaceutical ingredient (API) material, this product is not a tableted form at this stage. For biopharmaceuticals, the equivalent of manufacturing API is manufacturing the bulk drug substance.

2. Formulation & Tabletting – This step takes the API manufactured in step 1 and formulates the API with other excipients to form the drug product which the patient will eventually use. The output of this step is the finalised tablet, cream, ointment or liquid in their correct dosages.

3. Packaging for commercial/clinical supply – The tablets from step 2 are packaged into their correct format needed for varying global geographical regions and distributed; some sites provide one and some two of the steps.

Figure 1 shows how the sites pharmaceutical manufacturers (comprising large multinational drug developers and CDMOs/CMOs) cover the three main manufacturing steps from initial raw materials through to the final packaged product being introduced into the global supply chain. Depending on the size of the organisation, the research identified that manufacturing output can range from 20kg batches for preclinical supply to mid-sized supply capability of approximately 150 tonnes per annum through to large scale supply of 0.5 million packs produced per day with 100s tonnes of API production. The integrated regional capabilities range from niche small-scale process development, preclinical clinical research organisation analytics, full primary and secondary manufacturing, tableting and packaging for global commercial supply. The large multinational drug developers who have sites in the region form part of a global manufacturing network who export their finished products to other locations in mainland Europe, Asia or the Americas for further processing closer to the destination markets.

These sites have extremely high levels of production and an individual site can formulate approximately 4.8 billion tablets per annum ranging across multiple products lines and product families. For these individual sites, the logistical challenge is substantial. As an example, one company can service over 140 countries worldwide from a single site for which labelling needs to be bespoke for the destination market, meaning that a product range comprising 30 products can demand over 1500 Stock Keeping Units (SKUs) when varying destinations and drug doses are considered.
Sites enter and leave the overall manufacturing process at defined value chain steps, meaning the number of sites within the sector able to service a particular value chain step varies from step to step. When a company does not have capability within a value chain step, the product at that point is either exported or transported off site as shown in the diagram. Key observations from this figure are:

- Both the sector's large multinational drug developers do not manufacture API and this is imported largely from the EU and the Americas
    - One site receives between approximately 70% of its API from the United States & China and the additional 30% from the EU & Middle East each year. This is either from other CMOs or from other sites within the company's internal manufacturing network.
    - The other site is a part of a 74 sites global manufacturing network and imports or receives API from a number of these sites.
- One of the large multinational drug developer sites has the capability to package formulated & tableted drugs for supply into the global supply chain, but the other site exports the formulated & tableted product to packaging sites in Holland, North America and Asia.
- For CDMOs/CMOs, there are six sites with API manufacturing capability, which drops to three in the next value chain step (formulating & tableting).
- The packaging for commercial/clinical supply value chain step gains an extra site with this capability, but loses two sites.
- There is one site in the overall sector that has integrated capability across all three key value chain steps which spans the ability to process initial raw materials through to a packaged product for commercial/clinical supply.

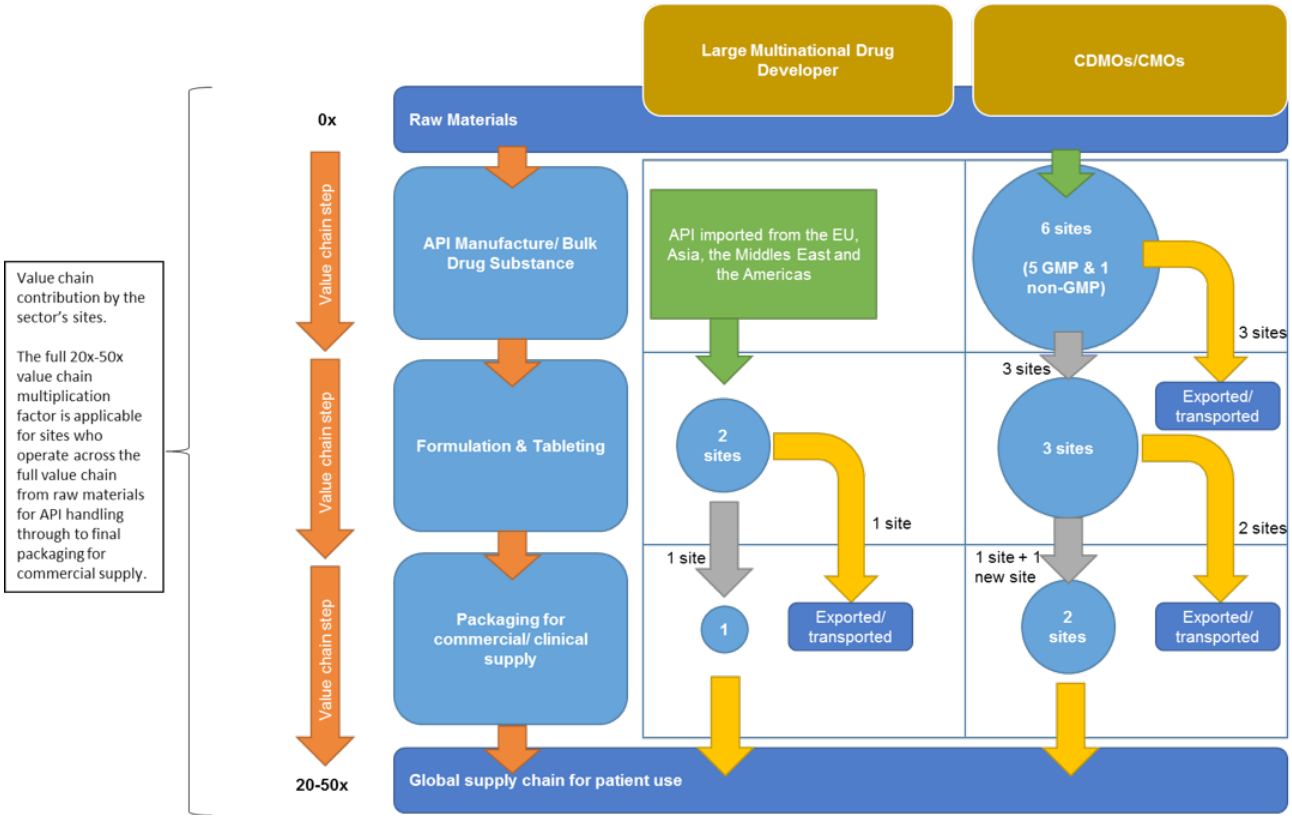


Figure 1: Shows where within 3 value chain steps an aggregated number of sites within the sector operate. This breaks down the value chain contribution by large multinational drug developer and CDMOs/CMOs.

Value Chain Overview

As the sector is a key part of the pharmaceutical supply and value chain, the value it creates through the processing of delivered or imported raw materials is a good indicator of its value contribution to the global pharmaceutical industry.

The sector's value chain contribution on the drug product ranges from 20 times as a typical measure, up to 50 fold for drugs that are targeted at higher value markets often with lower disease prevalence.

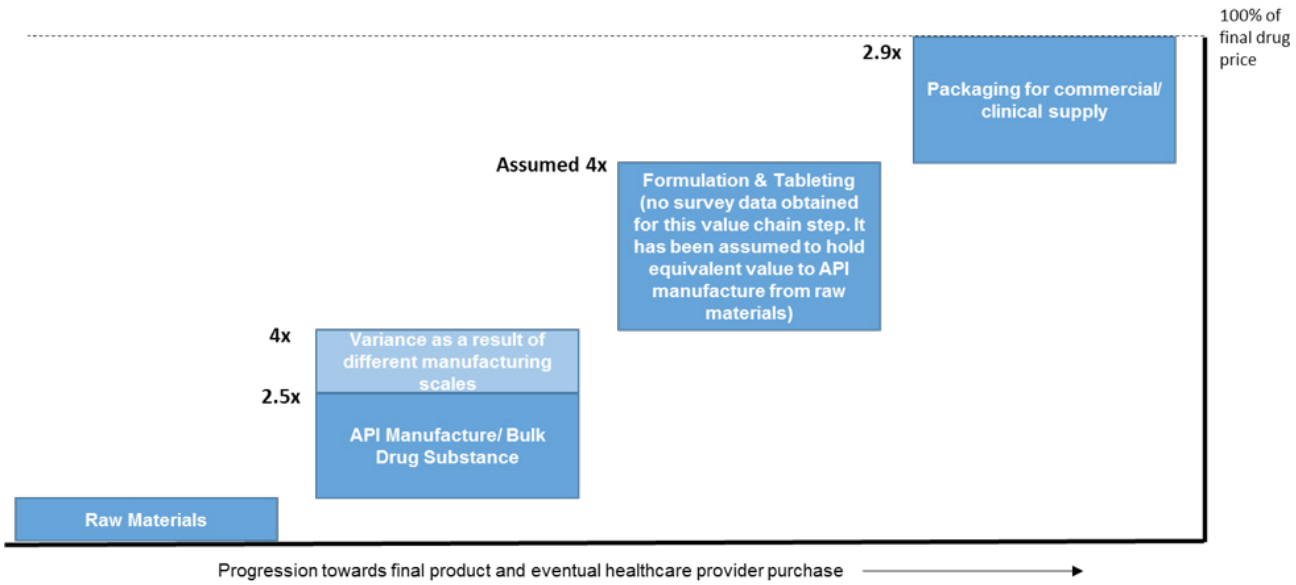


Figure 2: Shows an illustrative waterfall chart showing the value chain multiplication factors at each of the three key value chain steps within the pharmaceutical manufacturing process from raw materials through to a final packaged product for patient/clinical use.

The following notes and assumptions are associated with figure 2:

- The figure utilised data from CDMO/CMO companies who are focused on separate value chain steps, therefore there may be scope for efficiencies with an integrated sectoral approach.
- For the formulation & tableting value chain step, there was no survey data attained to support the value chain multiplier factor and this is an assumption based on the API manufacturing value chain step.
- Any value chain multiplier factors do not include employee costs associated with the value chain steps and only considers materials needed to complete the value chain step.

Calculation of the API Manufacture/Bulk Drug Substance value chain multiplier

- For a £1M batch of API, the raw material costs for the sector sites answers ranged from 25-40% of the overall batch value. The difference is related to varying scales of production.
- Therefore, a simple division calculation gives a figure of between 2.5 and 4 as a value chain multiplier for this step.

Calculation of the Packaging for commercial/clinical supply value chain multiplier

- For a single batch of packaged drug product for commercial/clinical supply, a sector company in this value chain step stated that approximately 35% of overall unit costs are for materials.
- Therefore, a simple division calculation gives a figure of approximately 2.9 as a value chain multiplier for this step.

In terms of overall contribution to the regional and national economy, the value chain multiplication factor of between 20-50 which is identified for the pharmaceutical sector occurs

once the whole drug product has been manufactured and it is ready to be distributed in its final packaging for clinical/commercial distribution to the end users which are generally healthcare providers, insurance companies and patients.

It should be noted that not all of the sector's sites have the capability to import the initial raw materials for API manufacture and process this through to a final packaged product ready for clinical/commercial distribution.

Understanding North East value chain position: An example of one site's value chain contribution

1. A drug compound that is manufactured within the North East is sold on the United States market for $22 per pack
2. Within the pack there is a total of 6 grams of drug product
3. The North East site manufactures ~75 tonnes of this product per annum. This is the equivalent of 12.5 million manufactured packs per annum
4. Assuming all packs are sold against demand, this will generate $275M
5. Using the North East manufacturing company's average cost per kilogram to this client, the revenue generated by the North East manufacturer is ~$12M per annum.

Therefore, the drug product manufactured in the North East generates ~23 value chain multiplier when sold to the healthcare provider or insurance company against raw material value.

4.3 Trade: Imports & Exports

The Medicines manufacturing supply chain is integrated and complex and the businesses in the North East are strongly connected to other parts of the world, in particular the United States in order to import raw materials and to export products to key markets and partners. The interviews identified the importance of continuing to maintain and develop vital trading relationships and to continue to remove barriers to better services, new business models and emerging markets.

Figure 3 provides a visual representation on how the sector operates in its micro-environment and sets out some of the factors influencing its macro-environment discussed in this report.

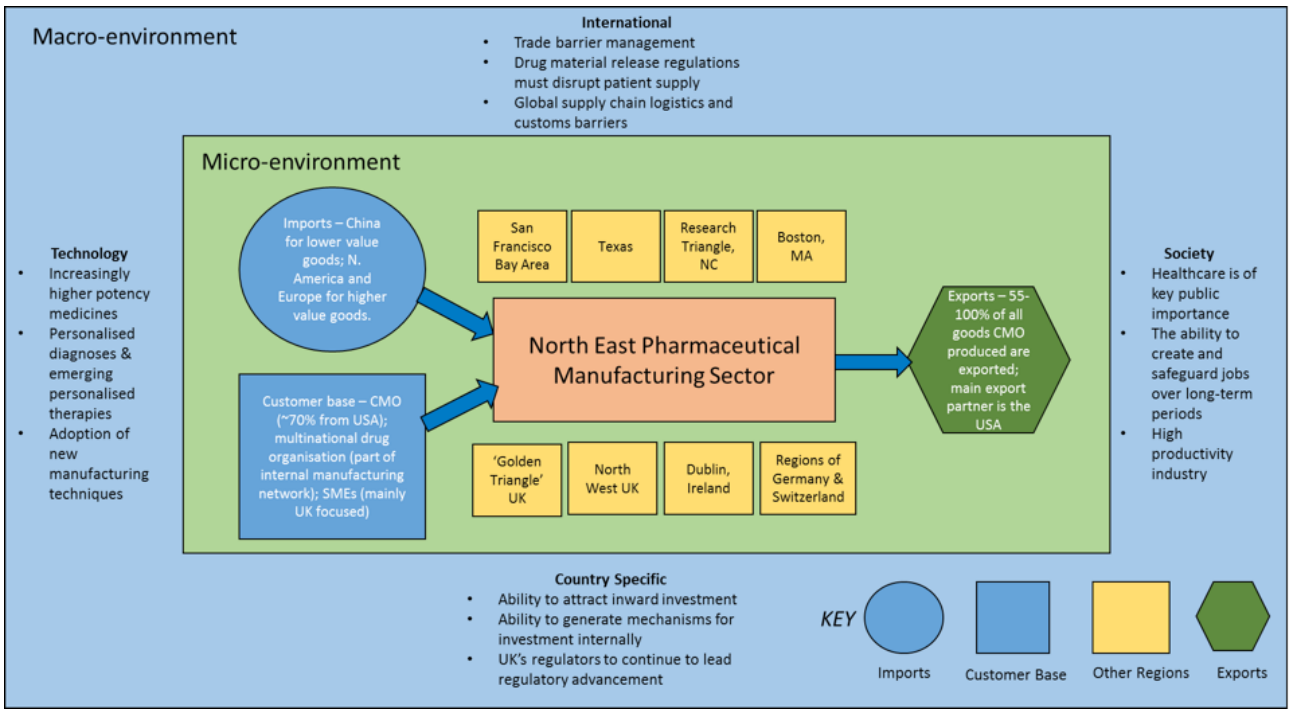


Figure 3: Visual representation of key drivers and dependencies in the micro and macro-environment for the North East pharmaceutical manufacturing sector.

Imports

Observations identified in the research include:

- The ability to procure raw materials and processing equipment from foreign suppliers is key to the success of businesses in the sector. A common import theme highlighted was the importing of lower cost raw materials, chemicals and reagents from Asian markets such as China and higher value processing equipment and specialised raw materials from North America, the UK & Ireland, and mainland Europe.
- Import strategies and models varied substantially depending on business model and company type. Some generalised patterns can be identified:
  - Large multinational drug developers operate centralised procurement services where cost and on time supply are the key drivers.
  - CDMOs/CMOs & SMEs operate processes where individual sites are responsible for procurement practices. Cost and on time supply are of high importance but some sites have consciously chosen higher cost UK and Irish suppliers due to quality and culture alignment and the ability to overcome any potential supply chain disruption or quality issues.
  - Sites operating as part of a multinational drug developer's global manufacturing network imported materials and APIs from other sites within the manufacturing network. This could be from the UK & Ireland, Eastern Europe or the Americas.

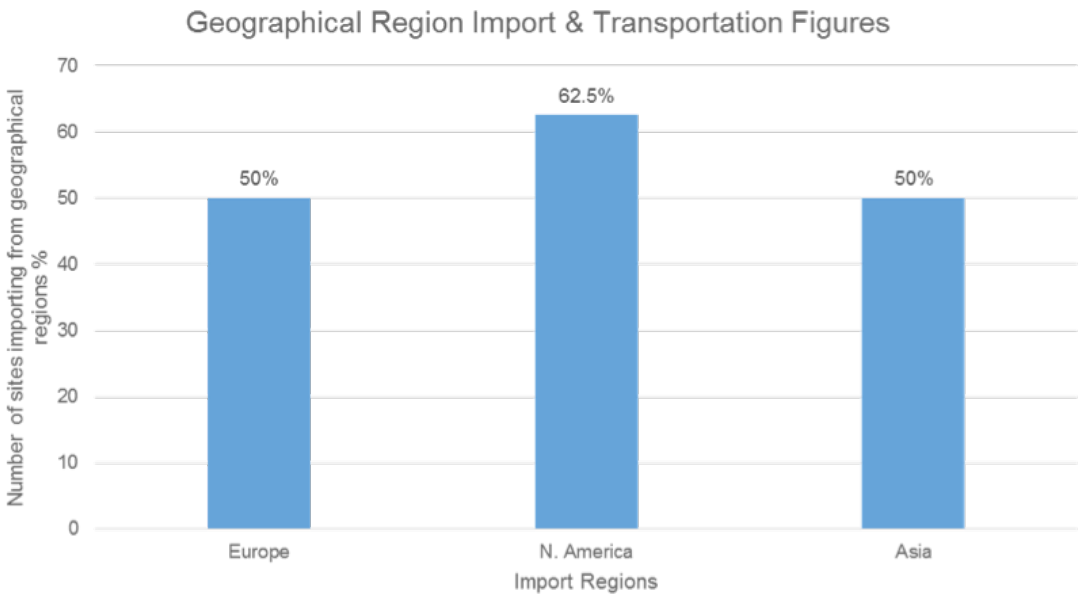


Figure 4: Data showing the geographical regions globally in which the sector's sites either import or transport raw materials and equipment from.

Exports

Observations identified in the research include:

- 55-100% of all material produced by pharmaceutical manufacturers is exported per annum; of this 64% goes to the United States making maintained free or low tariff trade vital to this industry.
- For pharmaceutical manufacturers surveyed, the average sectoral export figure was 86% each year (see figure 5a).

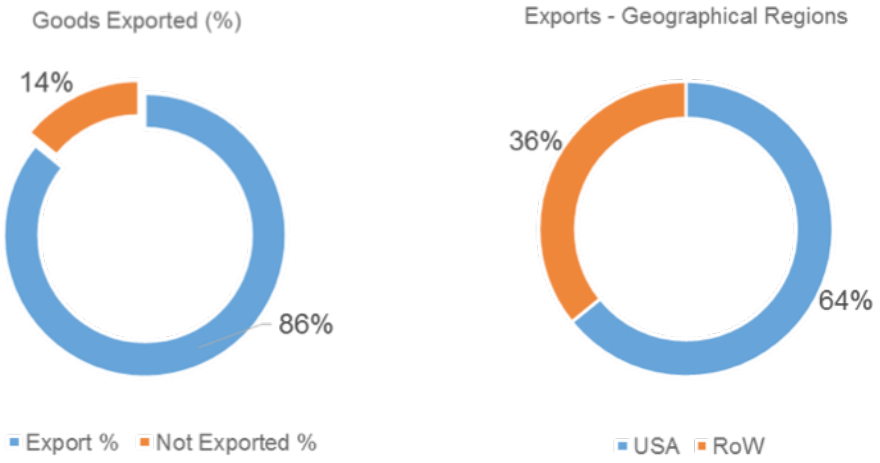


Figure 5a (left): Shows the average amount of goods globally exported each year as a percentage across sites surveyed; **Figure 5b (right):** Shows the sector's export statistics each year between the USA and the rest of the world (RoW)

- Export transportation used all three typical modes across the sector's sites: road, shipping by sea and air freight. Air freight, although a higher cost when compared directly with shipping by sea per quantity transported, can offer substantial inventory savings throughout the supply chain due to handling efficiencies and reduced volumes at the receiving destination.
- Transportation method is dependent on the final destination; for a UK destination, road was unanimously used, but for foreign destinations it was a combination of shipping and air freight as appropriate against required delivery date and shipment size.
    - 6 out of the 9 pharmaceutical manufacturers interviewed utilise an ex works logistics model whereby at the site's gate product responsibility is relinquished and is passed either to an external courier on to a customer's internal logistics division. The remaining three sites offer logistical supply chain handling services which can aid customer retention for CDMOs/CMOs.
    - Figure 6 shows export logistics by site; 4 sites utilise all 3 export methodologies, 1 site utilises air and shipping, 1 site utilises road and shipping, 1 site only uses road and 1 site only uses air. Site 9 in figure 6 totally relinquishes responsibility at the gate and did not state an answer, but stated all products are initially transported away by road.

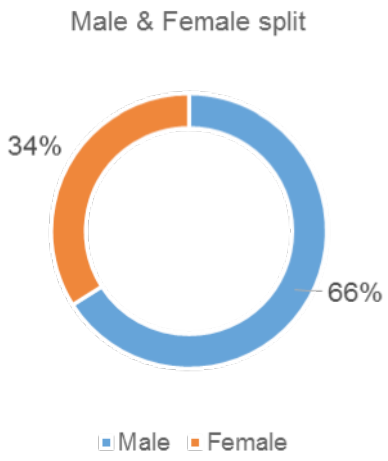
Figure 6: Shows the preferred export logistics methods by site comprising of air freight, shipping and road transportation.

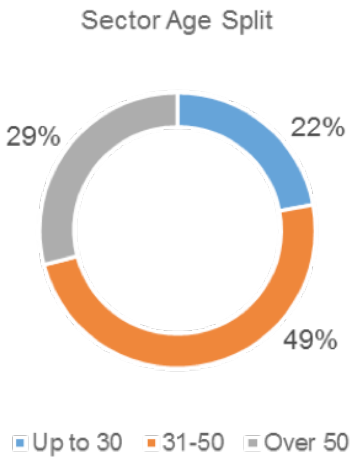
4.4 Skills

The availability of skills and a quality workforce was reported to be of high importance for the businesses in the North East and the region has particular features in terms of future business needs and succession planning.

Interviewees said that having a healthy circulation of employees through companies regionally is positive for the sector as a whole as it allows for new ideation and good practices to become common throughout the sector. Companies in the sector have varying strategies on how to address skills recruitment which can range from international recruitment campaigns through to school leaver and apprenticeship schemes.

Workforce Statistics Obtained during the Survey[1]





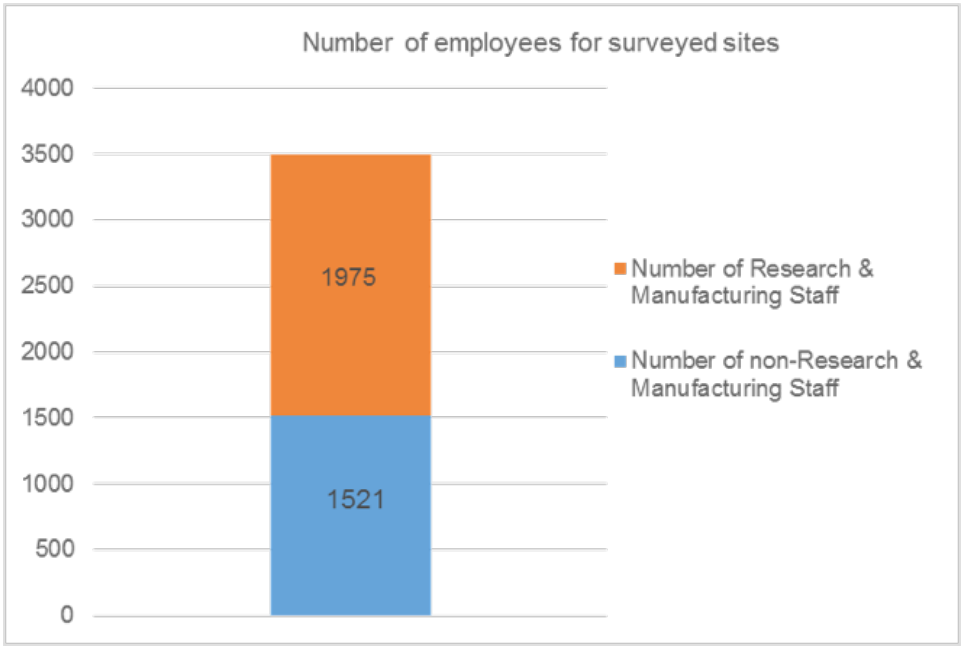


Figure 7a (top left): Male & female employee split from the surveyed sites; **Figure 7b (top right):** Age split of employees from surveyed sites split into 3 categories; **Figure 7c (bottom):** Number of direct employees for surveyed sites.

[1] The ONS estimate of the North East's pharmaceutical manufacturing industry's GVA is £711 million, within the range of £450 to £790 million. This would seem to suggest that current official statistics provide an accurate estimate of the GVA of the sector in the North East.

The sector identified a number of key trends with regards to expertise and education within the region:

- Senior-level leadership and strategic-level employees are often sought from outside the North East region from other regions within the UK and abroad. Companies have generally been able to recruit successfully into these roles.
- Within research areas, high quality scientific analysts and formulation scientists are more difficult to recruit, whereas technicians and manufacturing operator positions have typically shorter recruitment cycles, largely sourced within the region.
- Graduate-level employees are attracted to the region or can be recruited locally, but PhD-level candidates often require national or international recruitment campaigns.
- Many sector companies have either utilised or are planning to utilise the Apprenticeship Levy funds directly. Most cited recruitment planning and the ability to mould employees as the key reasons for choosing to regard the levy as an opportunity.
- Recruitment tactics play a key role in the ability to attract applications; one large company in the region stated that a role advertised solely on the company's own website would attract 10-12 times fewer applications than by using professional networking sites for advertisement.

4.5 Funding and Investment

The ability to reinvest in manufacturing facilities and research infrastructure was reported as paramount when competing in a global market and in continuing to attract trade to the sector.

The ability to acquire capital and reinvest varies across the sector and is dependent on whether the site acts as an independent legal entity, is part of holding company but is expected to run as a profit centre, is part of holding company and is financially supported or is part of wider manufacturing supply chain network. The key behaviours and themes associated with the sector's reinvestment capability are below:

- The sector has attracted inward investment globally throughout its history and continues to draw significant investment from countries such as the United States, Japan, India and the EU as well as the UK.
- Capital investment or reinvestment is largely done through budget allocation from a larger umbrella company or debt financing.
- CDMOs/CMOs often rely on debt financing to reinvest in assets. Access and affordability of debt finance is dependent upon their holding company's core country. The nationality of the holding company is key in determining the likelihood of the use of debt financing and is impacted on in particular by the circumstances of that trading environment. For example debt financing obtained from a Holding Company domiciled in a developing nation may be acquired at double digit interest rates which adds significant costs, but may be balanced by the practice of some Asian banks in developed nations especially which make the capital easier to service when measured against UK rates and inflation. Recent examples of large, often Asian, foreign investment within the North East for the automotive and rail transportation industries demonstrates the North East's ability to attract significant, long-term investment.

Some companies had considered the possibility of using private equity finance as a means of raising capital, but this was the least preferred option for acquiring capital versus debt or grant funding due to the equity stake expected by the private equity companies in return for funds.

4.6 Regulatory issues

As discussed above, interviewees identified multiple factors that define the structure, character and future direction of the individual sites in the sector. However a uniting feature across all of the interviews was the importance of the ability to operate globally in an increasingly competitive industry.

The sector's pharmaceutical manufacturers rely heavily on the ability to export their products and on the ability to import raw materials as well as other materials required for products. Looking forward, interviewees identified the potential to attract business from international clients as core to the continued success of this industrial sector.

An underpinning core common theme identified in all interviews was the importance of the UK's regulatory environment. This was regarded as central to the sector's success and had the characteristic effect of providing a non-tariff barrier that has formed to the sector's advantage due to the high quality good manufacturing practice (GMP) standards that sites have adhered to which, alongside a reputation for delivery on time and on budget, reflects a significant competitive advantage for the region.

There are numerous planes of competition and performance within the industry such as supply reliability, expertise, regulatory adherence and cost; interestingly there has been a strong reversal of an earlier trend for drug development companies to use countries with lower cost bases, such as India, for outsourced manufacture. There are number of issues with these lower cost regions behind this, including degree of expertise, regulatory shortfalls and poor quality standards. This trend reversal places a much increased amount of value on the outsourced manufacturers in the more developed world and shows that the manufacture of drugs is not a commoditised market. The sector is aware of increasing investment and upskilling in India as the country adapts to the regulatory and industrial feedback it has received, so even though this trend has reversed in the short-term, there is still a possibility this will return.

Industry engagements show that between 55-100% of all material produced by pharmaceutical manufacturers is exported with 64% going to the United States each year. This represents a key market for the sector and the ability of the North East to continue to attract North American customers will be crucial.

One key theme identified during the interviews was the impact of the vote to leave the European Union. Interviewees reported that the devaluation of Sterling has eased exchange rate pressure on export heavy industries and feedback suggested that this is likely to be positive for the sector. However, given the importance of the regulatory environment as a competitive advantage, the possibility of regulatory disruption created through the process of exiting the European Union was viewed as posing the largest sector threat, particularly with the strengths that the UK's regulatory framework provides the industry through Medicines and Healthcare products

Regulatory Agency (MHRA) and European Medicines Agency (EMA) guidelines.

When compared with the US Food and Drug Administration (FDA), for example, the MHRA/EMA place more emphasis on the quality standards of raw material manufacturers from which manufacturing sites procure materials and equipment used to manufacture pharmaceutical products. This provides the sector's pharmaceutical manufacturing clients with a much stronger regulatory framework to adhere to, but it ultimately is very effective at guaranteeing supply for the clients as compared to other developed nations and especially those in the developing world. This framework is perceived to be acting as an effective agent aiding the security of the drug developers' supply, but also limits the potential to switch sites once a site in the sector is chosen for manufacture.

Sites who form a part of a global manufacturing network also reported concerns regarding potential supply chain disruption due to changes in customs procedures that may reduce the ability of a global manufacturing supply chain to efficiently include UK sites within the process. Any increase in customs barriers will be working directly against company ambitions to fully manufacture and release a drug within 90 days. With current timeframes currently between 12-18 months, further barriers will be viewed disadvantageously should a need for global supply chain rationalisation occur.

Interviewees emphasised the importance of the UK's regulatory strengths being maintained during and beyond the transition to leaving the European Union. The MHRA's reputation as at the forefront of industry regulatory innovation both in Europe and worldwide must be maintained into the future. There are a number of models as to how this can be achieved but in discussion it was suggested that the Switzerland-EU pharmaceutical trading partnership should be regarded as a minimum viable outcome from the Brexit negotiations (see Appendix 3).

The general framework is based on the WTO's 'Zero-for-Zero Pharmaceutical Initiative' of which the EU, United States, Japan, Canada, Switzerland, Norway and Macao are included. Within this there are mutual recognition rules on product inspection, batch certification and certification of manufacturers are laid down in Chapter 15 of the EU-Switzerland Mutual Recognition Agreement (MRA) of 2002. Should the UK join the EEA it would automatically be subject to the provisions of the EU-CH MRA. But should it stay out of the EEA there is nothing preventing the conclusion of a separate EU-UK MRA. The EU-Swiss agreement(s) is as close to Internal Market membership as is possible and is managed through a series of bilateral agreements, and essentially includes all 4 freedoms. It is complex and not popular with the EU as all the agreements are conditional on each other (for example the free movement agreement was called into question by a referendum and the EU retaliated by halting the Erasmus+ agreement). It is understood that the EU would prefer a general agreement rather than a patchwork model.

5. Economic Impact

One of the key aims of the research was to understand the economic impact of the pharmaceutical manufacturing sector in the North East and its opportunities in the context of wider life sciences assets in the region. At a time when the UK Government is developing a new Industrial Strategy and the North East and Tees Valley Strategic Economic Plans are supporting areas with the potential for future productivity growth, industry leaders in the North East pharmaceutical manufacturing sector felt the economic contribution and potential of the sector was not widely understood and that there would be value in both understanding the contribution in more detail and sharing this with key policymakers and company decision-makers.

The research team from CPI/FFP identified 15 pharmaceutical manufacturers in the North East region (covering the North East and Tees Valley Local Enterprise Partnership (LEP) areas) and has interviewed 9 of these companies. In addition, company accounts are available for 8 North East pharmaceutical manufacturers through Bureau van Dijk's (BvD) Fame and MintUK databases – including 3 that have not been interviewed. This chapter summarises the findings from both the interviews and desk-based research on economic impact of the North East pharmaceutical manufacturing sector, including assessing the contribution of the sector to the North East economy as a whole and to the UK pharmaceutical manufacturing industry. In addition, the research team has interviewed a number of companies within the pharmaceutical manufacturing supply chain. The contribution of these companies to the North East economy is discussed towards the end of the chapter.

To provide context for the research findings, official statistics for the sector are set out in the box below.

Overview of Pharmaceutical Manufacturing Sector in North East

Employment

- Employment in 2016 – **2,500** (Source: Business Register and Employment Survey (BRES)).
- Employment in 2016 in 'biopharma' – **4,000** (Source: The Office for Life Sciences and Department for International Trade Bioscience and Health Technology Database)[2].

GVA

- Gross Value Added (GVA) in 2015 – **£711 million**. (Source: Regional Gross Value Added (Income Approach)).
- This is equivalent to 5.6% of UK pharmaceutical manufacturing GVA, with the sector having a location quotient[3] of 1.88. Only two industries in the North East have a higher location quotient than pharmaceutical manufacturing[4].

Exports

- Exports in 2016 – **£292 million** (Source: HMRC Regional Trades Statistics).

Definitions used for calculating these figures are given in Appendix 2.

Employment

One of the major contributions that the pharmaceutical manufacturing industry makes to the North East economy is creating employment opportunities.

- The 9 interviewed pharmaceutical manufacturers employ 3,500 individuals[5] at sites in the North East.
- The 3 pharmaceutical manufacturers that were not interviewed but for which Fame/MintUK data is available employ 800. It is not possible to determine whether all of these jobs are in the North East – but our understanding is that these companies are all either solely or primarily based in the North East.
- Combined, the 12 pharmaceutical manufacturers that data is available for employ 4,300 individuals.
- There are 3 pharmaceutical manufacturers for which no employment data is available (as they have not been interviewed and data is not available for them through Fame/MintUK). If an assumption is made that the 12 pharmaceutical manufacturers for which we have data are representative of the sector as a whole, total employment across the 15 pharmaceutical manufacturers can be estimated at 5,300. Given that the 3 pharmaceutical manufacturers for which there are no available data are thought to be among the smaller companies, this can be considered the upper boundary and is likely to be an overestimate.

[2] Biopharma is broader than pharmaceutical manufacturing but is included here as this is definition and dataset used for the advanced medicines manufacturing 'area of opportunity' in the North East Strategic Economic Plan (SEP).

[3] Location quotients measure the geographic concentration of industries.

- A value of 1 means that the area has the same share of GVA in the industry as its share of national GVA.
- A value greater than 1 means the region has a higher share of GVA in the industry than its share of national GVA.

[4] Data for all industries are given in Appendix 2.

The North East's employment of 4,300 to 5,300[6] is equivalent to:

- Between 0.4% and 0.5% of North East employment and between 3.8% and 4.7% of North East manufacturing employment.
- Between 12.0% and 15.0% of Great Britain's[7] pharmaceutical manufacturing employment (defined as 'manufacture of basic pharmaceutical products' and 'manufacturing of pharmaceutical preparations'). The proportion of manufacturing process will be higher as the Great Britain employment figure includes all activities undertaken by pharmaceutical manufacturers.

As well as creating employment opportunities within their own organisation, pharmaceutical manufacturers can also support additional employment opportunities:

- In their supply chain. These are known as indirect or Type I multiplier effects.
- Through the expenditure of their employees and the employees in their supply chain. These are known as induced or Type II multiplier effects.

Using the multipliers for pharmaceutical development and manufacturing employment provided in the PwC report[8,9,10,11], the North East's pharmaceutical manufacturing sector supports:

- 9,100 to 11,400 jobs in their supply chain.
- 5,400 to 6,700 jobs through the spending by their employees and their supply chain's employees.

Combined this means the North East pharmaceutical manufacturing sector supports 18,800 to 23,500 jobs across the UK.

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[5] This figure differs from employment data presented in Chapter 3 as this section focuses on pharmaceutical manufacturers only. In addition, the employment figures throughout this chapter are rounded (to nearest 100).
[6] The estimate of 4,300 to 5,300 is above the official estimates (from BRES and the Office for Life Sciences and Department for International Trade Bioscience and Health Technology Database). This suggests that the scale of employment in the pharmaceutical manufacturing sector in the North East is currently *underestimated* in official statistics.
[7] BRES employment data are not available for the UK.
[8] No specific multipliers for the pharmaceutical manufacturing sector in the North East are available.
[9] The PwC pharmaceutical development and manufacturing employment multipliers are: Type I – 3.14; Type II – 4.4.
[10] The PwC report used a broad definition of pharmaceutical development and manufacturing. It is not possible to assess whether the inclusion of 'manufacture of other inorganic basic chemicals', 'manufacture of other organic basic chemicals', 'manufacture of other chemical products not elsewhere classified' and 'wholesale of pharmaceutical products' in their definition will have led to a higher or lower multiplier than if a narrower definition was used.
[11] Rounding means total employment may not equal the sum of direct, indirect and induced employment.

GVA

Gross Value Added (GVA) measures the contribution to the economy of each individual producer, industry or sector in the United Kingdom. Two sources provide ratios for the relationship between GVA and employment for the pharmaceutical manufacturing sector and these are used to calculate the GVA of the North East pharmaceutical sector[12].

As outlined in the previous section, the North East pharmaceutical manufacturers are estimated to employ 4,300 to 5,300.

- Using the ABS ratio, this suggests these companies collectively have a GVA of £450 to £560 million
- Using the ratios from the PwC report (using the small companies ratio for those with fewer than 250 employees), this suggests these companies collectively have a GVA of £630 to £790 million.

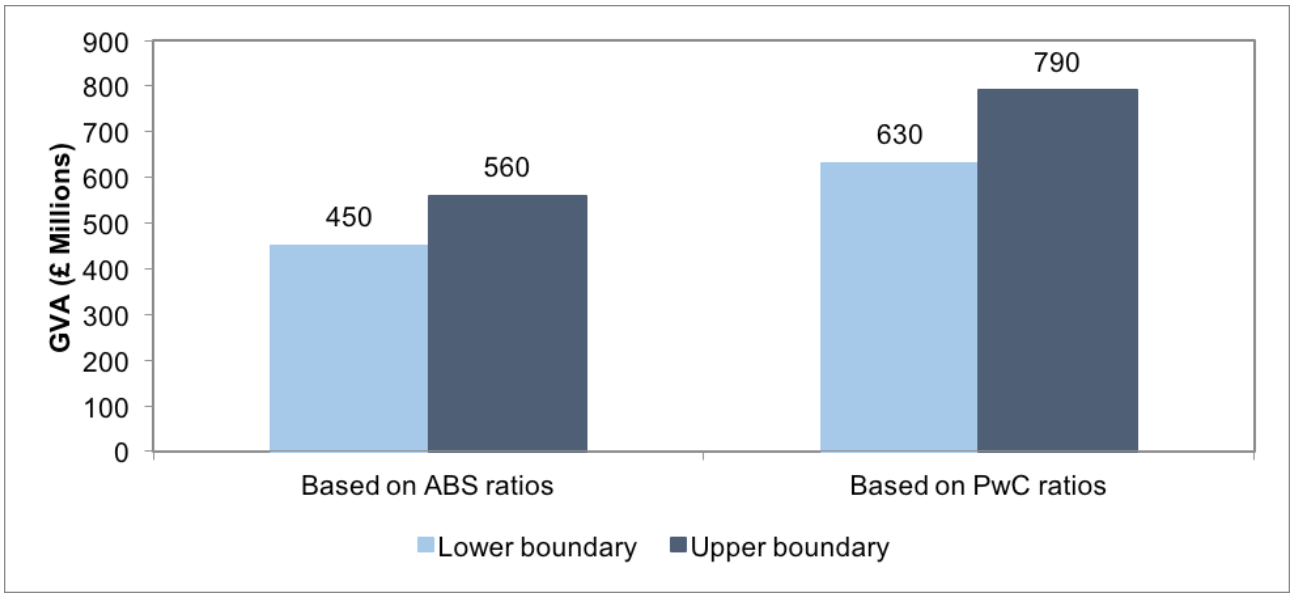

Figure 8: Estimates of North East pharmaceutical manufacturing GVA (£ millions)
Source: Research team, based on employment data and PwC and ONS GVA per employee ratios.

The North East's GVA of £450 to £790 million[12] is equivalent to:

- Between 0.9% and 1.6% of North East GVA and between 6.5% and 11.3% of North East manufacturing GVA.
- Between 3.5% and 6.2% of UK pharmaceutical manufacturing GVA. Again, the proportion of manufacturing process will be higher as the GVA figure includes all activities undertaken by pharmaceutical manufacturers.

[12] Details of the ratios are given in Appendix 2.
[13] The ONS estimate of the North East's pharmaceutical manufacturing industry's GVA is £711 million, within the range of £450 to £790 million. This would seem to suggest that current official statistics provide an accurate estimate of the GVA of the sector in the North East.

The North East pharmaceutical manufacturing sector contributes between £0.73 and £1.28 billion to the UK economy once direct, indirect (£170 to £300 million) and induced (£110 to £200 million) contributions are taken into account[13,14,15,16].

Exports

All 9 of the interviewed pharmaceutical manufacturers were exporters. 8 were able to estimate the proportion of their production that was exported.

- The proportion ranged from 55% to 100%.
- It is not possible to calculate the combined value of the exports from these companies as not all were able to provide turnover data.

Looking at the 8 pharmaceutical manufacturers for which financial data is available through Fame/MintUK, export data is available from Fame/MintUK for 7 of these.

- The proportion of turnover coming from exports ranged from less than 1% to 95%.
- Exports from these companies totaled £200 million.

As data is not available for all pharmaceutical manufacturers on the value of their exports, it is not possible to estimate the total value of exports from the region's sector and (by extension) the proportion of North East and UK pharmaceutical manufacturing exports or the extent to which the sector is accurately reflected in the official statistics[17].

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[13] No specific multipliers for the pharmaceutical manufacturing sector in the North East are available.
[14] The PwC pharmaceutical development and manufacturing GVA multipliers are: Type I – 1.38; Type II – 1.63.
[15] The PwC report used a broad definition of pharmaceutical development and manufacturing. It is not possible to assess whether the inclusion of 'manufacture of other inorganic basic chemicals', 'manufacture of other organic basic chemicals', 'manufacture of other chemical products not elsewhere classified' and 'wholesale of pharmaceutical products' will have led to a higher or lower multiplier than if a narrower definition was used.
[16] Rounding means total GVA may not equal the sum of direct, indirect and induced GVA.
[17] A number of stakeholders have suggested that official HMRC data may underestimate the scale of the exports by the pharmaceutical manufacturing sector in the North East. This is likely to reflect the method of calculation used by HMRC with each business' trade allocated to a region based on the proportion of its employees employed in that region and that exports from CMOs will be attributed to their client organisations (which may be based in other regions). Based on the feedback from the pharmaceutical manufacturers, it would appear that the assertion that the sector's exports are underreported is correct – but without fuller data it is not possible to quantify the scale of this underreporting. To do so would require all pharmaceutical manufacturers being able and willing to share both turnover data and the proportion of turnover arising from exports for their North East sites.

The high proportion of production that is exported combined with the relatively low cost of raw materials and consumables purchased by the interviewed companies relative to their turnover will mean the sector is likely to be an important contributor to the North East's balance of trade.

Other companies

Three non-pharmaceutical manufacturing companies (referred to as 'supply chain company or SME' in glossary of terms) were also interviewed during the research. These companies play a range of roles within the pharmaceutical manufacturing supply chain.

- These companies were all small – with each having fewer than 20 employees in the North East. Total employment in the North East across the 3 companies was 34.
- The employment and GVA of these companies will be included in the 'multiplier effects' discussed above.
- 2 of the companies were able to provide details on their exports. Exports accounted for 5% of turnover in one company and 40% in the other.

Key Messages

1. Pharmaceutical manufacturers in North East employ between 4,300 and 5,300 – equivalent to:

    - Between 0.4% and 0.5% of North East employment and between 3.8% and 4.7% of North East manufacturing employment.
    - Between 12.0% and 15.0% of Great Britain's pharmaceutical manufacturing employment. The proportion of manufacturing process employment will be higher as the employment figure includes all activities undertaken by pharmaceutical manufacturers.

2. Using multipliers, North East's pharmaceutical manufacturing sector is estimated to support:

    - 9,100 to 11,400 jobs across the UK in their supply chain (indirect effects).
    - 5,400 to 6,700 jobs across the UK through spending by their employees and their supply chain's employees (induced effects).

3. Gross Value Added (GVA) measures the contribution to the economy of each individual producer, industry or sector in the United Kingdom. The GVA contribution of the North East pharmaceutical manufacturers is estimated at £450 to £790 million – equivalent to:

    - Between 0.9% and 1.6% of North East GVA and between 6.5% and 11.3% of Nort East manufacturing GVA.
    - Between 3.5% and 6.2% of UK pharmaceutical manufacturing GVA. Again, the proportion of manufacturing process will be higher as the GVA figure includes all activities undertaken by pharmaceutical manufacturers.

4. The North East pharmaceutical manufacturing sector contributes between £0.73 and £1.28 billion to the UK economy, once direct, indirect and induced contributions are taken into account.

5. All pharmaceutical manufacturing companies for which data is available exported.

    - Amongst interviewed pharmaceutical manufacturers, between 55% and 100% of production was exported.
    - Amongst pharmaceutical manufacturers for which there is Fame/MintUK financial data, this showed that exports accounted for between <1% to 95%.

6. Future Needs

Looking forward a series of reports at UK and sub-national level have identified the significant opportunity that pharmaceutical manufacturing, and life sciences more generally, represents for the UK as it seeks to ensure long term competitiveness by driving growth and productivity in strong, innovation and employment rich parts of the economy.

The UK Life Sciences Industrial Strategy published in August 2017 identifies a vision of growth and a group of key opportunities and issues to demonstrate the breadth and vibrancy of the life sciences ecosystem in the UK and to promote collaboration across the sector, the critical role of the NHS in delivering the development and use of new medical technologies, and the contribution of the sector to the UK economy. It sets out a series of areas including skills, science and technology, data, infrastructure and access to the NHS as central components for a future sector deal.

The North East Strategic Economic Plan identifies 5 opportunities for its Life Sciences strategy within which support for and engagement with pharmaceutical manufacturing would be central:

- Provision of a comprehensive support system for key high growth businesses and sub-sectors.
- Development of support for the sector opportunity around world-leading companies selecting the North East for production plants by supplementing the pharmaceuticals supply chain.
- Unlocking the commercial potential of North East university world class research.
- Supporting links between business and NHS infrastructure to translate discovery through development to adoption.
- Being a leading region for NHS adoption of innovation.

In this context, the findings of the research offers the following insights into the needs of the North East pharmaceutical manufacturing sector as follows:

Technology Innovation

The ability to reinvest is aligned with the future technology innovation needs for the sector's companies, and the survey answers identified a number of insights into future industry manufacturing technology demands to address changing drug manufacturing business models and customer needs.

In particular, three future capabilities were of particular interest to the sector:

1. Ultra High Potency Manufacturing

- Medicines are becoming increasingly targeted towards smaller patient cohorts and concurrently the potency of medicines is increasing. Consequently, the demand for large scale batch drug production sizes begins to decrease.
- Highly potent molecules have greater toxicity than typical drug APIs and so require a higher facility specification in order to process. One such application for higher potency molecules

can be through the conjugation of a high potency cytotoxic compound to an antibody drug to form an antibody drug conjugate.

2. Continuous Pharmaceutical Manufacturing

- The concept for continuously manufacturing pharmaceutical drugs is well-known, but as of yet it has not been utilised as the preferred option for manufacturing pharmaceutical drugs.
- A multinational drug developer has invested £20 million in the region to build a unique continuous manufacturing pilot plant as a means to compare directly the continuous manufacturing process against the batch production methods historically used by the site and the wider industry.
- Several reasons exist as to why continuous manufacturing will be a preferred option for drug production in the near future. These range from the well-known financial savings of a continuous process versus a batch process to process specific safety-related issues. For safety-related issues, complex chemical pathways during the manufacturing process can form hazardous and potentially unacceptable safety risks in the reaction chamber. Utilising a continuous process will enable a reduced reaction chamber size making the safety risks acceptable. This approach can also be used as part of batch process allowing a semi-continuous process to be applied for safety reasons.

3. Smart Pharmaceutical Packaging

- Some sites recognised the benefits of smart pharmaceutical packaging and were interested in opportunities to explore the opportunities in the area and benefits to the company. There are a number of ways in which smart pharmaceutical packaging could be applied to the pharmaceutical and healthcare industry:

    - Intelligent and smart packaging for medicines and medical devices - (e.g. for distribution quality monitoring, clinical supply monitoring, traceability, authentication, anti-counterfeiting and patient compliance).

    - Physical, chemical and biological sensing capabilities - Enabled by emerging technologies (such as flexible electronics, photonics and digital) for use in monitoring the quality and processes used in the manufacture, distribution of medicines and to monitor patient compliance.

    - Novel formulations and delivery of medicines - This activity could include a unique combination of product formulation and data on delivery, simultaneously to improve the targeting of treatments. The controlled/timed drug delivery could utilise nanotechnologies to incorporate new and novel methods to deliver transdermal medication over time controlling dosage. In combination with smart packaging, patient compliance with the medication can also be monitored.

Innovation and Process Developments

Innovation is often thought of as a highly disruptive process in which newly commercialised technologies transform a well-established industry or create new industries, often dramatically changing or replacing more aged practices and industries in the process. Whilst this form of innovation is powerful and highly noticeable in the business to consumer markets, this form of disruptive innovation is not common in highly regulated business to business markets such as pharmaceutical manufacturing. Innovation in the pharmaceutical manufacturing space is often aligned with incremental innovation that change the industry to a much lesser degree against disruptive innovation, but it is the accumulative effect of multiple incremental innovation cycles that will aggregate together to transform an industry over a period of years.

In this context, business also identified that process innovation offering constant and continual improvements to reduce lead times and improve efficiency in the manufacturing, quality and supply processes are the chosen innovation pathways of choice for the pharmaceutical manufacturing industry. This is the case as the highly regulated nature of pharmaceutical manufacturing, with patient safety at its core, means it is hard to radically disrupt manufacturing processes without significant experimental data at varying production scales to ensure any process changes do not adversely affect the drug quality and manufacturing output.

The interviewees were therefore keen to engage with initiatives which continued to advance, demonstrate or create new manufacturing processes within the parameters of current regulation aligned to the needs of customers, global compliance bodies and investors is key for the sector and there are numerous planes of innovation that will enable this; these include lean manufacturing, incremental cost reductions, new chemistry, investment in new equipment, technologies, skills and culture.

Investing in future support in the North East

The sector's future is of high importance to the North East and of significant importance to the UK's pharmaceutical manufacturing productivity. The sector is acutely aware of future industrial challenges and competition, but the ability to meet these must be maintained into the future. The three main future technology areas identified by the sector are key to providing technology capability to the future industrial business models.

A small selection of sector companies have incurred significant internal cost and risk by investing in continuous manufacturing pilot plants and have high potency molecule production capability. The combination of sound market foresight and the ability to invest has made this possible, but to enhance the uptake of new manufacturing technologies, innovation test beds are a strong option to reduce industry investment risk and expenditure. This benefits industry by reducing the barrier to entry and provides manufacturing data to compare with internally produced manufacturing data that will heavily inform future business manufacturing plans and potentially overall business strategy.

Potential routes and facilities to support the uptake of the three sector identified future technology areas are:

1. **Medicines Manufacturing Innovation Centre:** The centre will support the deployment of novel manufacturing technologies into manufacturing sites. The benefits these new technologies will deliver have been well documented. Product quality, manufacturing cost, capital spend at risk will all be positively affected and the benefit to patients will come from the move to agile supply chains delivering more stratified medicines. The facility will be able to run proprietary projects, but it will also enable the sector to work together when beneficial, in the development of regulatory standards, development of standardised technology platforms and the training of people with the right skills.

2. **SmartMed Project Phase 1:** This Phase 1 project will define the scope for the proposed Medicines Smart Packaging and drug-delivery activity, and prepare a User Requirement Brief (URB), which would inform the needs and if required, design and build. This will be achieved by combining domain knowledge in smart/intelligent packaging, sensing and formulations and draw upon input from an industry led advisory group as well as other leading industry experts and stakeholders. The outcome from the Phase 1 will be a URB document and a business case for Phase 2 of the project, which will form the foundation of a proposed forward delivery plan.

Learning from Global regions

The study also asked interviewees to identify areas of world which could offer opportunities for enhanced trade, export or investment or for learning in terms of regional and sector development activities in pharmaceuticals manufacturing. Eight main areas were highlighted by the sector's companies which each have areas of comparability or complementarity to companies within the North East sector, or which offer insights in terms of the sector moving to a higher level of development.

The features of the region which are complementary to the North East in these terms would consist of:

- A high proportion of drug discovery companies who are progressing towards either toxicology stages within preclinical development or are progressing through clinical trials and require GMP material supply and/or process development and scalability.
- Systems to align these activities with a commercial strategy in use by the sector's CDMOs/CMOs to win drug manufacturing contracts at an early stage in the drug development process. This would significantly increase the likelihood of holding the drug manufacturing contract throughout the drug's clinical development due to the bespoke accumulation of research data and quality assurance documentation attributed to the site.
- Over the longer terms this should aim to be converted to a clinically approved and commercialised product and a long-term clinical supply agreement.

Another commercial strategy used by the sector is to win late-stage clinical stage contracts from drug development companies who may need to change pharmaceutical manufacturers due to an increased need for larger scale production or commercial supply if their current pharmaceutical manufacturer cannot meet supply demand.

A brief summary of these regions is offered in appendix 4. It is recommended that more work be done to benchmark the North East eco-system against some of these places.

Key Messages

Skills, reinvestment capability and future technology innovation are three key areas in which will be vital to ensure the sector's competitive position is maintained and strengthened. The sector raised some pertinent points on these matters:

1. The sector must increase the visibility nationally of its capabilities, competence, economic impact and capacity to grow high productivity employment.

2. Attracting high-level talent to the North East sector can be challenging, especially in the areas of senior management, scientific analysts and formulation scientists.

3. Access to finance for reinvestment varies significantly depending on the specific site's business model, operating conditions and holding company.

4. Many sector companies have used debt financing previously to fund reinvestment as access to other forms of capital are limited.

5. Incremental innovation cycles are the preferred method of the pharmaceutical manufacturing industry.

6. Three key areas of interest were highlighted by the sector, these were high potency manufacturing, continuous manufacturing and smart packaging.

7. Conclusions & Recommendations

This report has described the growth and development of the North East pharmaceutical manufacturing sector over a number of decades. It demonstrates that leaders of the North East manufacturing community have been able to act as innovators in business, investment and manufacturing processes to sustain the sector through substantial global changes and challenges. It highlights a number of key environmental factors which have contributed to this performance, including the stable regulatory environment and the availability of skills.

In the current environment, the following recommendations aim to ensure that this performance can be sustained by providing a stable environment and support to current and future leaders to enable them to sustain and grow North East pharmaceutical manufacturing into future decades.

Promotion of the sector and its needs

The report has developed a clearer picture of the scale, diversity, needs and opportunities of North East pharmaceutical manufacturing. It is important that this report is used to promote awareness of shared issues within the North East sector to identify opportunities for collaboration, to highlight needs and opportunities which could be fulfilled through strengthened relationships with other parts of the regional Life Sciences manufacturing communities and within the sector national and regional.

Development of a supply chain and logistics strategy

The ability to procure raw materials and processing equipment from foreign suppliers is key to the success of businesses in the sector, with lower value supplies currently accessed from Asia and higher value equipment and materials from North America, the UK & Ireland, and mainland Europe.

Import and export and logistics strategies are varied across the businesses and there is potential to collaborate to strengthen intelligence and co-ordination to secure a strengthened and more cost-effective supply chain,

It is recommended that work is more detailed work is undertaken between the regions businesses to understand opportunities to strengthen the supply chain in the region and identify opportunities for improving the logistics support, including taking advantage of the North East growing digital capabilities.

Innovation

As the global sector looks towards need forms of medicines delivery including new treatments, more personalised delivery and more productivity in manufacturing a number of innovation opportunities have been identified which could be fostered in the North East, or within the UK to support the performance of manufacturers based in the region, taking advantage of existing

regional capability. These include:

- The following future capabilities; Ultra High Potency Manufacturing; the application of Continuous Pharmaceutical Manufacturing for drug manufacturers; Smart Pharmaceutical delivery including packaging, sensing and new formulations including monitoring capabilities.
- Incremental process developments including application of digital, robotic and low carbon technologies.

It is recommended that the partners continue to identify strategies within the North East to foster or access initiatives which can support these areas of opportunity. This may include public and private capital investment including investment in existing sites and inward investment strategies for new sites.

Skills

The ongoing supply of skills into the sector is a feature of its success with senior level and technical recruitment often delivered from national and international markets and other skills secured locally through Universities and movement within the sector.

The current demographic and policy environment, including changes to freedom of movement in the labour market, implies potential challenges to existing sources of labour supply, and businesses are actively considering how the apprenticeship levy can be used to continue to develop the future supply of skills. Some specific roles, such as formulation scientists, have been identified as problematic.

There are initiatives underway in the region which have the potential to support these needs including the new Northern Futures UTC, specific initiatives in North East Universities and the Government proposal to create new Institutes for Technology, including a proposed North East distributed model being encouraged by the North East LEP

It is recommended that the sector work with the North East LEP develop a clearer analysis of current skills gaps and potential future needs and to inform the content of these initiatives

Regulatory Environment

The importance of the regulatory environment has been a key observation within this research which is regarded as central to the sector's success, providing a competitive advantage to the sector given its application of high quality manufacturing practice (GMP) standards, and a potential risk should regulatory standards be diminished in the search for lower cost supply of ingredients or final products.

Interviewees were particularly concerned that, whilst the devaluation of Sterling prompted by the vote to leave the European Union has eased exchange rate pressure on export heavy industries and had delivered a short term positive effect, this would be outweighed if the impact were to disrupt the regulatory environment, particularly with the strengths that the UK's regulatory

framework provided through the Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Agency (EMA) guidelines.

Interviewees emphasised the importance of the UK's regulatory strengths being maintained during and beyond the transition to leaving the European Union and discussion has indicated that should the UK not join the EEA a minimum viable model would be to replicate the EU-Swiss agreement ensuring that regulatory standards were maintained and labour market and research relationships were retained.

It is recommended that these issues should be communicated during the current period of consultation on the negotiations.

Co-ordination

These proposals have the potential to imply further co-ordination between North East pharmaceutical leaders and other partners to take these recommendations forward.

It is recommended that this be the focus of future discussion within First for Pharma.

8. Appendices

Appendix 1: Glossary of Terms

Active Pharmaceutical Ingredient (API): Any substance or mixture of substances intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient in the drug product.

Contract Manufacturing Organisation or Contract Development Manufacturing Organisation (CMO or CDMO): is a company that serves other companies in the pharmaceutical industry on a contract basis to provide comprehensive services from drug development through to drug manufacturing. This allows small or virtual drug discovery companies and large multinational drug developers to outsource those aspects of the business, which can help with manufacturing scalability or can allow the major company to free internal manufacturing capacity and/or focus on other aspects of drug development. This definition includes companies with the ability to manufacture active pharmaceutical ingredients through to finalised packaging for commercial distribution.

Good Manufacturing Practice (GMP): A manufacturing and quality system for ensuring that products are consistently produced and controlled according to regulated quality standards. It is designed to minimize the risks of noncompliance involved in any pharmaceutical production. Compliance with GMP is a legal necessity, sites are routinely inspected and licenced. Product processes are approved and licenced and product that does not comply with GMP protocols is rejected by internal quality controls, independent of any inspection. GMP regulations are set by the Federal Drug Administration (FDA) in the US, the Medicines and Health products Regulatory Agency (MHRA) in the UK and the European Medicines Agency in the European Union. Similar agencies regulate drugs for release in other countries. Specific requirements vary by agency, and deep knowledge of these requirements and capability to meet them is required by sites supplying product to global markets. All regulatory agencies exist to set standards and maintain compliance, ultimately to protect the patient from risk of harm and ensure efficacy of the products they receive

Large Multinational Drug Developer: discovers, develops, produces, and markets drugs or pharmaceutical drugs. Pharmaceutical companies may deal in branded medications or off-patent generic drugs. These companies have internal manufacturing networks and logistical capability to serve global markets.

Pharmaceutical Manufacturer: Within this report, this term relates to those company types defined by CMO, CDMO or large multinational drug developer. A key point of consideration in this definition is the ability to manufacture to a Good Manufacturing Practise (GMP) standard, however there is one company within this definition that has no GMP manufacturing capability.

Stock Keeping Units (SKUs): A product and service identification code for a store or product, often portrayed as a machine-readable bar code that helps track the item for inventory. A stock keeping unit (SKU) does not need to be assigned to physical products in inventory, but in this study the term is used for identification of specific product family type and variations within that

product family, such as size.

Supply chain company or small to medium enterprises (SMEs): These are companies based in the North East who are either progressing drug candidates or medical diagnostics through preclinical or clinical trials. They are dependent on venture capital funding raising at their current stage in the company's development.

Appendix 2: Technical Note – Economic Impact

Definitions

The Office for National Statistics (ONS) publishes employment and Gross Value Added (GVA) data by industry. ONS use the 2007 Standard Industrial Classifications (SIC) to define sectors. In this report we have defined pharmaceutical manufacturing as:

- 21 - Manufacture of basic pharmaceutical products and pharmaceutical preparations which includes:
  - 21.1 – Manufacture of basic pharmaceutical products.
  - 21.2 – Manufacture of pharmaceutical preparations.

HMRC Regional Trade Statistics use the UN Standard International Trade Classifications (SITC) to define goods (commodities) that are exported from the UK. In this report we have used SITC codes:

- 54 – Medicinal and pharmaceutical products which includes:
  - 541 – Medicinal and pharmaceutical products, other than medicaments of group 542 which includes:
    - 541.1 – Provitamins and vitamins, natural or reproduced by synthesis (including natural concentrates), derivatives thereof used primarily as vitamins, and intermixtures of the foregoing, whether or not in any solvent, not put up as medicaments of group 542.
      - 541.3 – Antibiotics, not put up as medicaments of group 542.
      - 541.4 – Vegetable alkaloids, natural or reproduced by synthesis, and their salts, ethers, esters and other derivatives, not put up as medicaments of group 542.
      - 541.5 – Hormones, natural or reproduced by synthesis; derivatives thereof, used primarily as hormones; other steroids used primarily as hormones, not put up as medicaments of group 542.
      - 541.6 – Glycosides; glands or other organs and their extracts; antisera, vaccines and similar products.
      - 541.9 – Pharmaceutical goods, other than medicaments.
    - 542 – Medicaments (including veterinary medicaments) which includes:
      - 542.1 – Medicaments containing antibiotics or derivatives thereof.
      - 542.2 – Medicaments containing hormones or other products of subgroup 541.5 but not containing antibiotics.
      - 542.3 – Medicaments containing alkaloids or derivatives thereof but not containing hormones, other products of subgroup 541.5, or antibiotics.
      - 542.9 – Medicaments, n.e.s.

The report cites two reports that use alternative definitions.

- The Office for Life Sciences and Department for International Trade *Bioscience and Health Technology Database* uses 'biopharma', which is defined as:
  - *"Core Biopharma includes all companies whose business involves developing and/or producing their own pharmaceutical products – from small, R&D-focused biotechs to multinational Big Pharma.*
  - *Biopharma Service & Supply comprises companies that offer goods and services to Core Biopharma companies. These include contract research and manufacturing organisations, suppliers of consumables and reagents for R&D facilities, providers of specialist analytical, IT, recruitment and logistics services as well as legal and regulatory expertise and finance companies specialising in biopharma investments."*

  This is broader than pharmaceutical manufacturing as it includes the supply chain but is included in this report as it is the source of data for the advanced medicines manufacturing 'area of opportunity' in the North East Strategic Economic Plan (SEP).
- The PwC *The economic contribution of the UK Life Sciences industry* report uses 'pharmaceutical development and manufacturing'. This is defined using SIC codes. As well as 'manufacture of basic pharmaceutical products and pharmaceutical preparations' (included in our definition), they include 'manufacture of other inorganic basic chemicals', 'manufacture of other organic basic chemicals', 'manufacture of other chemical products not elsewhere classified' and 'wholesale of pharmaceutical products'.

Gross Value Added

Gross Value Added (GVA) measures the contribution to the economy of each individual producer, industry or sector in the United Kingdom. Figure A1.1 shows ONS's estimates of GVA by industry for the North East and the UK. In 2015, the manufacture of 'basic pharmaceutical products and preparations' in the North East generated £711 million in GVA. This is equivalent to 5.6% of UK GVA in this industry. For comparison, the North East accounts for just 3% of UK GVA across all industries.

An alternative way of looking at this is by using location quotients. Location quotients measure the geographic concentration of industries.

- A value of 1 means that the area has the same share of GVA in the industry as its share of national GVA.
- A value greater than 1 means the region has a higher share of GVA in the industry than its share of national GVA.

The manufacture of 'basic pharmaceutical products and preparations' in the North East had a location quotient of 1.88 – meaning the sector is overrepresented within the North East economy. There are only 2 sectors in the North East with higher location quotients – 'chemicals and chemical products' and 'machinery and equipment not elsewhere classified'.

Figure A1.1: Gross Value Added (GVA) (Income Approach) by industry at current basic prices, North East and UK, 2015

Industry	North East GVA (£ millions)	UK GVA (£ millions)	North East as % of UK	North East Location Quotient (LQ)
Agriculture, forestry and fishing	348	10,833	3.2	1.08
Mining and quarrying	326	16,947	1.9	0.65
Manufacturing	6,934	162,829	4.3	1.43
• Food products, beverages and tobacco	579	26,109	2.2	0.74
• Textiles, wearing apparel and leather products	190	5,875	3.2	1.08
• Wood and paper products and printing	473	11,401	4.1	1.39
• Coke and refined petroleum products	32	1,569	2.0	0.68
• Chemicals and chemical products	976	10,004	9.8	3.27
• Basic pharmaceutical products and preparations	711	12,716	5.6	1.88
• Rubber and plastic products	600	11,995	5.0	1.68
• Basic metals and metal products	997	19,729	5.1	1.70
• Computer, electronic and optical products	107	8,569	1.2	0.42
• Electrical equipment	147	4,643	3.2	1.06
• Machinery and equipment not elsewhere classified	779	10,882	7.2	2.40
• Transport equipment	934	23,546	4.0	1.33
• Other manufacturing and repair	408	15,791	2.6	0.87
Electricity, gas, steam and air-conditioning supply	957	24,824	3.9	1.29
Water supply; sewerage and waste management	656	16,708	3.9	1.32
Construction	3,071	101,937	3.0	1.01
Wholesale and retail trade; repair of motor vehicles	5,172	182,510	2.8	0.95
Transportation and storage	2,075	77,103	2.7	0.90
Accommodation and food service activities	1,470	49,674	3.0	0.99

Industry	North East GVA (£ millions)	UK GVA (£ millions)	North East as % of UK	North East Location Quotient (LQ)
Information and communication	2,433	108,474	2.2	0.75
Financial and insurance activities	1,912	120,351	1.6	0.53
Real estate activities	5,574	216,115	2.6	0.87
Professional, scientific and technical activities	2,392	124,730	1.9	0.64
Administrative and support service activities	1,960	80,398	2.4	0.82
Public administration and defence; compulsory social security	3,461	78,548	4.4	1.48
Education	3,950	98,025	4.0	1.35
Human health and social work activities	5,476	130,723	4.2	1.41
Arts, entertainment and recreation	551	22,983	2.4	0.80
Other service activities	878	35,585	2.5	0.83
Activities of households	81	7,045	1.1	0.39
All industries	49,677	1,666,342	3.0	-

Source: Regional Gross Value Added (Income Approach) (ONS)

Calculating GVA

There are three broad methods for measuring the Gross Value Added (GVA) of a company. GVA can be calculated by:

- Using data on company performance, gathered through specific research. Specifically, GVA is calculated as turnover (or sales) minus cost of bought in materials, components and services.
- Using company accounts, for example, from Companies House filings. In this case, GVA is calculated as operating profit plus employee costs, depreciation and amortisation.
- Using a ratio to convert data available for another measure (typically employment or turnover) into GVA. This requires analysis to have previously been carried out to establish the ratio between GVA and these other measures for the specific sector.

In relation to this research:

- Company performance data are not available.
- Company accounts are available for 8 pharmaceutical manufactures through Fame/MintUK (5 that have been interviewed and 3 that have not). All of these are either solely based in the

North East or have the majority of their operations in the North East.
- The recently published *Life Sciences Industrial Strategy* cites the Annual Business Survey (ABS) rate of GVA per employee of £105,000.
- *The economic contribution of the UK Life Sciences industry* report provides 2 ratios for the relationship between GVA and employment for the pharmaceutical development and manufacturing sector:
  - GVA per employee of £154,000 for the pharmaceutical development and manufacturing sector.
  - GVA per employee of £81,000 for small companies within the pharmaceutical development and manufacturing sector.

As the most comprehensive data available in relation to the North East's pharmaceutical manufacturers is employment, the employment ratio approach has been used in the main report.

As outlined above, company financial data are available for 8 of the North East's pharmaceutical manufacturers. Using this method to calculate GVA:

- The combined GVA for these companies is £150 million.
- In all except one of the 8 companies, the GVA calculated using financial data is lower than the figure generated using the ABS and PwC GVA per employee ratios.
- The combined GVA calculated using the company financial data for these companies was 45% of that calculated using the PwC GVA per employee ratio and 72% of that calculated using the ABS ratio.

Reasons for underreporting of North East pharmaceutical manufacturing exports

There are a number of potential reasons the North East pharmaceutical manufacturing exports may be underreported in the HMRC Regional Trade Statistics (RTS). These include:

- RTS data is compiled by merging trade data collected by HMRC with employment data from the Inter-Departmental Business Register (IDBR). A business' trade is allocated to a region based on the proportion of its employees employed in that region. Some of the companies interviewed as part of this research have multiple employment sites across the UK. The proportion of their employment which is in the North East will not necessarily be an accurate proxy for the proportion of their exports from the region.
- A number of the companies in the North East pharmaceutical manufacturing are CDMO/CMOs. RTS data is based on company declarations made to HMRC. It is the company concluding the contract giving rise to the movement that makes the declaration as they are the principal who is exporting/dispatching the goods via an arrangement with the purchaser. This means that goods exported from CDMO/CMOs will be attributed to their client organisations and the region they are based in.

Appendix 3: Switzerland-EU Trade in Pharmaceuticals

1. Custom duties

- The general framework is set by a multilateral agreement within the WTO: the trade in pharmaceutical products of 1994 (also known as the "Pharmaceutical Zero-for-Zero Initiative).[18]
- The current signatories are the EU, United States, Japan, Canada, Switzerland, Norway and Macao. Other WTO members are encouraged to join.
- The agreement provides duty-free treatment to pharmaceutical products from its members. The product scope includes all finished products as well as a closed list of inputs.
- The agreement foresees periodical reviews to incorporate new active pharmaceutical ingredients, called International Non-Proprietary Names (INNs) which are published every year by the World Health Organisation.
- Beyond custom duties, the agreement has virtually no provision on rules expect for a broad commitment not to replace tariffs by TBTs or NTBs.

2. Rules

- Mutual recognition rules on products inspection, batch certification and certification of manufacturers are laid down in Chapter 15 of the EU-Switzerland Mutual Recognition Agreement (MRA) of 2002[19].
- The agreement covers all medicinal products manufactured in Switzerland or the EU and to which Good Manufacturing Practice requirements apply.
- The three EEA EFTA States (Iceland, Liechtenstein and Norway) are not parties to the EU-Switzerland MRA but are de facto covered by it:
  - Article 4-2 of the EU-CH MRA on origin states that *"In the event that such products are also covered by agreements on mutual recognition in relation to conformity assessment between Switzerland and Member States of both EFTA and the EEA, the present Agreement shall also cover products of those EFTA Member States."*
  - Annex 1, Appendix 1 , Chapter 15 of the EFTA convention covers pharmaceuticals (Article 1: *"Switzerland and the EEA EFTA States hereby grant mutual acceptance of reports, certificates, authorisations and conformity marks issued by the recognised conformity assessment bodies"*)[20].
- In addition the EMA, (DG SANTE), the Swiss Agency for Therapeutic Products and the Swiss Federal Department of Home Affairs have concluded a confidentiality agreement in 2015. It is valid for 5 years (renewable) and covers non-public information on the safety, quality and efficacy of medicines, already authorised or under review.

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[18] https://www.wto.org/gatt_docs/English/SULPDF/91770009.pdf

[19] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500018270.pdf

[20] http://www.efta.int/sites/default/files/documents/legal-texts/efta-convention/council-decisions-amending-the-convention/8978VaduzConventionAnnexIMutualrecognitioninrelationtoconformityassessment.pdf

3. Implications for the UK

- Should the UK join the EEA it would automatically be subject to the provisions of the EU-CH MRA. But should it stay out of the EEA there is nothing preventing the conclusion of a separate EU-UK MRA.
- Such an agreement would indirectly cover EEA EFTA states in accordance with Protocol 12 of the EFTA Convention:
  - *"Mutual Recognition Agreements with third countries concerning conformity assessment for products where the use of a mark is provided for in EU legislation will be negotiated on the initiative of the EU. The EU will negotiate on the basis that the third countries concerned will conclude with the EEA EFTA States parallel MRAs equivalent to those to be concluded with the EU[...]"*
- But it would not cover Switzerland, for which a separate arrangement would have to be made.
- As for custom duties, the UK would have to retain the EU's schedule at the WTO to continue benefiting from duty free treatment and/or join the Zero-for-Zero initiative.

4. Governance issues

The EU-Swiss agreement(s) is as close to Internal Market membership as is possible and is managed through a series of bilateral agreements, and essentially includes all 4 freedoms. It is complex and not popular with the EU as all the agreements are conditional on each other (for example the free movement agreement was called into question by a referendum and the EU retaliated by halting the Erasmus+ agreement).

Each agreement has its own dispute settlement. Pharmaceutical disputes on rules are settled in a joint committee under the MRA – any trade dispute could ultimately go to the WTO.

This set of arrangements was a consequence of the rejection of EEA membership in 1992 by the Swiss people, Switzerland and the EU agreed on a package of seven sectoral agreements signed in 1999 (known in Switzerland as "Bilaterals I"). These include: free movement of persons, technical trade barriers, public procurement, agriculture and air and land transport (road and rail). In addition, a scientific research agreement fully associated Switzerland into the EU's framework research programmes. A further set of sectoral agreements was signed in 2004 (known as "Bilaterals II") covering, inter alia, Switzerland's participation in Schengen and Dublin, and agreements on taxation of savings, processed agricultural products, statistics, combating fraud, participation in the EU Media Programme, the Environment Agency, and Swiss financial contributions to economic and social cohesion in the new EU Member States. In 2010 an agreement was signed on Swiss participation in EU education, professional training and youth programme.

Subsequently, the EU has made it clear that it would prefer a general agreement rather than this type of patchwork model.

Appendix 4: Global regions of interest in terms of comparison & complementarity

San Francisco Bay Area, California – A world-renowned area of pharmaceutical and biopharmaceutical drug discovery and development expertise. The Bay Area employs approximately 25% of all California's life science industry and the State attracted 50% more VC investment than Massachusetts between 2013-2015 showcasing the abundant capital available for non-revenue generating companies in the State.[21]

Boston, Massachusetts – Has an excellent integration of high quality academic research with innovation capability, world-renowned industry presence and large private-sector capital availability for spin-outs and SMEs. A North East-based SME noted during the interview that within 0.5 miles of the Department for International Trade's Boston premises there is more VC under management than the within the whole European Union.

Research Triangle Park, North Carolina – Founded in 1959, RTP is one the largest research parks in the world and has three major research universities (Duke University, NC State University and University of North Carolina at Chapel Hill) and three cities (Durham, Raleigh and Chapel Hill) within its sphere. The combination of universities, industrial location and major population centres in relatively close proximity have all contributed to RTP's success. There are a combination of drug discovery and drug manufacturing companies within the research triangle, but due to the heavy academic integration into the industry, overall there are substantial levels of complementarity with the North East sector.

'Golden Triangle', United Kingdom – The UK's golden triangle comprising Cambridge, Oxford and London has a highly entrepreneurial spirit and is the location of choice within the UK for drug discovery focused pharmaceutical and biopharmaceutical start-ups and SMEs for many reasons, but particularly the proximity to London's financial sector. However, there are some issues which were raised during our interviews with companies who considered locating in Cambridge, but instead elected to locate in the North East. Cost was a key issue and a North East-based SME stated that it would have doubled their development costs to locate in the golden triangle, hence increasing their investment needs from the venture capital industry.

North West, United Kingdom – The former AstraZeneca site at Alderley Edge has undergone a transformation into a life science incubation park, however AstraZeneca still have a presence in the region through their Macclesfield site. There are numerous drug discovery companies who have located here which may form a potential customer base for some North East companies.

Regions of Comparability

The population of companies within these regions generally focus on manufacturing and process development. This is likely to be either as part of an internal manufacturing network for a large multinational drug developer or CDMOs/CMOs, therefore will be similar to those companies

[21] http://sfced.org/why-san-francisco/sectors/life-sciences-biotech/sector-data/ - Accessed July 2017

present in the North East sector. Even though many of the companies in these regions are comparable to the North East sector, there are varying means which have led to the creation of these regional sectors ranging including academic and industrial integration, tax incentives and inward investment incentives.

Texas, United States – This is a relatively new and growing biomanufacturing sector, but the direct involvement with the State Government has incentivised globally-renowned companies to locate within the region with particular focus on next generation medicine manufacturing such as cell therapies and viral vectors.

Dublin, Ireland – Ireland has aggressively targeted the pharmaceutical and biopharmaceutical manufacturing industry to which the results have been very beneficial for the country. A combination of education, academic integration, early stage funding and low taxation incentives for industry have facilitated a concentration of companies to locate and stay within the country.

Certain regions of Germany & Switzerland – Germany was cited as a secondary competitor when compared to the United States and Ireland, but manufacturing and innovation hubs around Berlin, Frankfurt and Munich are of note. The Basel region in Switzerland was also mentioned due to its sector of drug manufacturers and developers and the fact that it cooperates well with the European Union as discussed in the 'Regulatory & Competition Overview' section and appendix 3.

Profile and Importance of the North East Pharmaceutical Manufacturing Sector:

Growing Its Contribution

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