Flow Measurement

Special Interest Group

Life Sciences: A Flow Metrology Horizon

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30th August 2019

EXECUTIVE SUMMARY

Life Sciences is evolving apace in the UK, with significant research and development investment from the Government and industry helping ensure that it remains one of the leading global players in this highly competitive sector. From the application of genomics in the diagnosis of disease and discovery of novel therapies, to the use of medical devices such as skin sensors to detect blood glucose levels, innovation in life sciences is forging a path towards personalised medicine and the ambition to live longer, healthier lives.

In April, horizon scanning activity commenced, with an initial remit to investigate, across a broad scope, potential flow measurement requirements within life sciences for consideration as part of the UK National Measurement System's Research and Development programme as well as supporting wider academic research. Insights were gathered from clinical, academic and industrial sources and revealed that metrology permeates the life sciences, with an integral role for flow in several areas. In response to early positive stakeholder feedback and interest, focus was placed on two key tangible themes:

[1] Industrial – pharmaceutical production, particularly adoption of continuous manufacturing processes;
[2] Clinical – non-invasive assessment of cardiovascular blood flow and haemodynamics.

There is a clear need to develop expertise and capability in the flow measurement and characterisation of pharmaceutical powder and coating solutions within a continuous manufacturing environment to realise quality, yield and cost benefits. Within the clinical setting, non-invasive cardiovascular flow and haemodynamic assessment is currently underdeveloped. One approach to tackling this is through improvement in the quantification, traceability and reproducibility of 4D flow MRI imaging, vital to accelerating its clinical utility.

A number of additional potential future project themes are also outlined within the report and it is anticipated that scanning activity will continue in order to investigate these, and others, in further detail.

Delivering advances in flow measurement capability within these crucial areas will impact positively upon the vision of the UK Government's Industrial Strategy to transform the prevention, early diagnosis and treatment of chronic diseases and ensure the healthy aging of individuals.

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1 INTRODUCTION

1.1 Life Sciences

Life Sciences comprise the branches of science associated with the study of living organisms and life processes and refers to the application of biology and technology to improve health, which includes biopharmaceuticals, medical technology, genomics, diagnostics and digital health.

The UK Life Sciences industry comprises four sectors: Biopharma (Biopharmaceutical) and Med Tech (Medical Technology) with each subdivided into a Core and Service & Supply sector. Almost a quarter of a million people are employed across nearly 6000 businesses within the industry, delivering an annual turnover in excess of £70bn. Over 80% of the leading global pharmaceutical companies have sites in the UK. The Med Tech Core sector houses the highest employment levels and number of businesses, whilst the largest proportion of revenue is generated from the Biopharma Core. Small molecules are the predominant industry segment **[1]**.

Amongst the most competitive sectors globally, many countries recognise the vast potential opportunities that investment in the life sciences can bring. At present, life sciences businesses make the largest contribution to the UK's total research and development spend. Scotland boasts one of the largest life sciences clusters in Europe, employing over 37,000 people and contributing around £2bn in annual Gross Value Added (GVA) to the Scottish Economy **[2].** Whilst the UK currently lags many of its international competitors such as France, USA, Australia and Japan in the proportion of its GDP spend on R&D, the Government has committed to raising UK public and private R&D investment to 2.4% (£80bn) of GDP by 2027 and 3% over the longer term. Continued investment from public, private and third sector sources is needed to ensure the UK does not stand still **[3]**.

Life sciences is a dominant sector in the UK, which continues to grow and evolve rapidly. Historical breakthroughs in diagnostics and treatments span the transformation of HIV from deadly virus to chronic, manageable disease to cures for some breast cancers and the advent of statins to treat cardiovascular disease, each enabling patients to live longer, healthier lives.

While biology underpins the life sciences, technological advances in molecular biology (the study of the composition, structure and interactions of molecules such as nucleic acids and proteins that carry out the biological processes essential for cell functions and maintenance) and biotechnology (the exploitation of biological processes, organisms, cells or cellular components to develop new technologies for use in research, agriculture, industry and clinically) have led to an ever-expanding number of specialisms and interdisciplinary fields, which are fundamentally improving our ability to interrogate biological systems.

1.2 The Bioeconomy

The term 'Bioeconomy' describes the economic activity derived from bioscience and biotechnology to deliver innovative products, processes and services through renewable biological resources – or more simply, the parts of the economy that depend on bioscience. It works across all industrial sectors, including the life sciences, for example through better medicines and improved capability and efficiency within their manufacture **[4]**.

1.3 Precision Medicine

Precision medicine tailors medical treatment to the individual characteristics of each patient. It classifies individuals into their differing susceptibility to a particular disease or response to a specific treatment, which allows preventative or therapeutic interventions to be concentrated on those who will benefit, whilst reducing costs and side effects for those who do not stand to benefit. An aging population, increasing healthcare costs and emerging promising new technologies are the key drivers of change providing opportunity for a patient-centric approach against a backdrop of growing demand for non-invasive and personalised treatments. The UK economy has much to gain from developing and growing existing precision medicine capabilities and this is being recognised through investment in the Medicines Manufacturing Innovation Centre (MMIC); a state-of-the-art facility, due for completion in Spring 2021, facilitating innovation in small, complex molecule medicine manufacture within accelerated timelines and at minimised volumes.

1.4 Life Sciences Innovation

Numerous physiological systems (cardiovascular, respiratory, lymphatic, renal), substances (blood, air, lymph, hormones) and applications (diagnostics, drug manufacture and delivery) present significant potential requirement for flow metrology. A recent data-driven review of R&D trends within the sector identified 3D printing and nanosensors amongst the top 'emerging' and 'developing' tools respectively **[5]**, with probable flow metrology requirements given their potential application as drug delivery technologies.

The UK BioIndustry Association's vision for the UK biotechnology industry in 2025 includes placing strategic focus on health innovation that delivers benefits to patients ahead of both economic benefit and wealth. Notably, it highlights the need to bolster middle tier biotech companies to improve translation from lab to clinic; focus on our assets and capabilities that are better than others and show more willingness to both try and fail in the context of translation of research from lab to clinic and concept testing (the "killer experiment") **[6]**.

Organ-on-a-chip (OOAC) technologies are an example of life sciences innovation that are also helping tackle the ethical issues inherent in the use of animals in research by implementing the 3Rs (replacement, reduction and refinement of animals in research) championed by the NC3Rs (National Centre for the Replacement, Refining, and Reducing the use of animals in research and testing).

The rapid growth of electronic devices (smartphones, tablets, robots, wearables, etc.) and the Internet has brought with it an exponential increase in the volume of information being produced and accessed by researchers, clinicians and wider society. To optimise use of this data from the millions of devices and systems, there is a need to focus research and development (R&D) on the interface between information technologies and human factors to enhance our knowledge and understanding of intelligent systems that combine computational and physical capabilities for human benefit/use.

1.5 Life Sciences Strategy in the UK

The Government has identified the life sciences as a key strategic industrial sector. Sir John Bell's Life Sciences Industrial Strategy emphasises the health technology trends for the next 20 years and sets a clear

direction for the sector's growth. In response, the Government launched two Life Sciences Sector Deals into which it has invested almost £700m for new research programmes, services and infrastructure, including support for healthy aging and a paradigm shift in approach to healthcare through the use of existing health data, artificial intelligence and innovation to improve early diagnosis and precision treatment of disease. These actions similarly address its Industrial Strategy Grand Challenges **[7]**.

The Government's Industrial Strategy sets out 4 Grand Challenges designed to put the UK at the forefront of the industries of the future. The Aging Society Grand Challenge aims to harness the power of innovation to help meet the needs of an aging society with a mission to ensure that people can enjoy at least 5 extra healthy, independent years of life by 2035. The changing demography presents one of the biggest challenges facing our modern society. As we move towards a population where almost 25% will be aged over 65, and 1 in 8 of us above 75, this will lead inevitably to an increase in age-related diseases (e.g. cardiovascular diseases, cancer and neurodegenerative diseases), posing new challenges and opportunities for technological innovation in diagnosis, prophylaxis and therapeutics over the next twenty years. Keeping people healthier for longer will not only benefit patients and bring cost savings within healthcare, it will create jobs and help the UK economy to prosper.

The AI and Data Grand Challenge has the mission to use data, AI and innovation to transform the prevention, early diagnosis and treatment of chronic diseases by 2030 to help save lives and increase NHS efficiency by enabling earlier diagnosis and reducing the need for costly late stage treatment **[8]**. A step towards achieving this will be through the recently-announced joint investment of almost £240m from businesses, charities and the government for the Accelerating Detection of Disease programme, which will use the genomic data of 5 million healthy volunteers to support research into new ways to detect and prevent the development of diseases such as cancer, dementia and heart disease.

The Government is focused on building international research and innovation collaborations to find solutions to its healthcare-related Grand Challenges **[9],** which are also posing similar challenges within the wider European setting **[10]**.

At present, the UK Life Sciences industry is weathering the Brexit uncertainty storm, exemplified by £1.3bn of investment in the second Life Sciences Sector Deal by multinational biopharmaceutical companies over the next 5 years **[11]**. Moreover, the UK's exit from the EU could serve as leverage to grow the sector through expanding its global markets and positioning itself as an attractive choice for inward investment due to its world class innovative research and infrastructure.

1.6 Metrology within the Life Sciences

'Classical' metrology continually faces the task of extending measurement ranges and reducing measurement uncertainties. National Measurement Institutes (NMIs) establish and maintain measurement standards at the highest level of accuracy. These internationally recognised measurement capabilities help UK companies in a broad range of industry sectors meet international trade requirements and gain access to markets worldwide. The enhanced accuracy of measurements and standards they provide promotes fair trade, a safe environment, productivity and products of high quality and reliability. A key role of NMIs is to undertake R&D to develop measurement technology and solutions for the emerging needs of industry. Disciplines such as biotechnology and medicine have been knocking on the door of metrology for some time, which,

ultimately, has a responsibility to contribute to finding solutions for some of the major challenges we face, not least in relation to health.

Government consultation with measurement users, stakeholders and partners upon which its UK Measurement Strategy was developed, revealed the life sciences amongst the top three measurement priority areas **[12]**. Furthermore, the BIA's 'Shaping the Future' workstream, tasked with identifying the areas of science most critical to the continued success of the life sciences industry, has concluded the need for improved support for metrology within the life sciences to underpin progress from concept through development to production and on to patients or customers/users **[13]**.

LGC is leading the way as part of the UK's National Measurement System with biometrology capability spanning proteins, nucleic acids, white blood cells and antimicrobials. Metrology for medical radiation physics is an area in which NPL is active.

2 OBJECTIVE AND SCOPE

The work undertaken sought to identify scientific themes that will drive UK Government investment towards real flow-related metrology challenges within the life sciences industry sector that are aligned with the relevant Industrial Strategy Grand Challenges aiming to place the UK at the forefront of improving lives and the productivity of UK plc.

Horizon scanning activities commenced in April 2019, with the timeline under consideration spanning the next 10 years. The intention of the recommendations made within this report is to provide a blueprint to attract investment in flow measurement R&D to strengthen and enhance flow metrology capability within the life sciences to derive economic growth and allow us to live longer, healthier lives. It is envisaged this will help facilitate the formulation of a technology roadmap for flow measurement in life sciences in 2020.

3 METHODOLOGY

In defining the recommendations made, multiple key stakeholders from academia, industry, healthcare providers, National Measurement Institutes and life sciences and related networks were consulted to provide a wide range of perspectives. This was performed through meetings, written correspondence and a literature review to understand previous, ongoing and future research activity, the current life sciences sector (medical technology and biopharmaceutical) landscape in the UK, and the Government's priorities with respect to the future of the sector in the UK. A desk-based review of international NMI activities by region (Europe, US, Asia) was undertaken to complement this work. Stakeholder perception and assumption has formed an important element of the evidence upon which the report's recommendations are based.

4 DISCUSSION OF KEY THEMES

4.1 International Flow Metrology

The following summarises a review of flow measurement capability and research within NMIs in Europe, USA and Asia.

Table 1: Summary of flow measurement capability within NMIs in Europe, USA and Asia

EUROPE
In addition to country-specific life sciences metrology activities, e.g. a working group performing microflow cytometry studies in Germany, of particular note within Europe is the collaborative research and innovation programme, EMPIR, managed by EURAMET (European Association of National Metrology Institutes). For example, currently 8 European metrology institutes are delivering an EMPIR project aimed at improving dosing accuracy and enabling traceable measurement of volume, flow rate and pressure of existing drug delivery and other medical flow devices operating at very low flow rates.
USA
Numerous programmes within the areas of Health and Bioscience are undertaken by the National Institute of Standards and Technology (NIST). Examples include: nanotube metrology (drug/gene delivery, biosensor diagnostics), a biomanufacturing initiative (protein drugs) and therapeutic protein stability through fluid rheology analysis using capillary viscometry. NIST is also part of a public-private partnership formed between industry, academia, and regulatory agencies tasked with accelerating innovation in biopharmaceutical (vaccines, therapeutic proteins) manufacturing and supporting the development of standards that enable more efficient and rapid manufacturing capabilities.
ASIA
The NMIs across Asia are actively involved in metrology within the life sciences. Specifically, within the National Institute of Metrology in China, there are various labs, e.g. Lab of Bio-diagnostics and Protein Measurement within its Division of Medical and Biological Measurement undertaking studies such as the Non-Newtonian Metrological Standards of Blood Viscosity. As in the UK, Japan is aiming to realise a healthy, active, aged and sustainable society. Accordingly, its strategic priorities include new technologies for drug discovery; stem cell technologies for regenerative medicine and medical diagnostic device technologies.

4.2 Flow Metrology Themes within the Life Sciences in the UK and Ireland

4.2.1 Theme 1: Flow Metrology in Continuous Pharmaceutical Manufacturing

4.2.1.1 Background

Traditional batch pharmaceutical manufacturing is associated with excessive costs, high waste, rejections and delays. Moreover, an inherent lack of thorough understanding of the products and processes and proactive characterisation of the failures, means quality is neither robust nor consistent. Despite this, there has been little change over the past 50 years.

Continuous Manufacturing (CM) has the potential to transform medicines manufacturing. In CM, drug ingredients or finished products are made continuously without having to wait for each batch to finish before starting a new one, essentially, representing an intensification of the production process. CM, therefore, brings compelling advantages to patients, industry and regulators alike in the form of reduced production costs, faster production times, smaller physical and environmental footprints, together with improved quality, scalability and flexibility.

Unlike batch manufacturing, the Quality by Design (QbD) approach of CM sees quality control embedded at each stage of the process rather than at the end where entire batches may need to be rejected. CM uses Process Analytical Technology (PAT), inline analytics such as sensors and near-infrared spectroscopy, to measure the critical physical and chemical properties and processing conditions in real-time to drive the manufacturing process automatically within Good Manufacturing Practice (GMP) - the minimum standard for the quality and control of pharmaceutical production. This allows for an uninterrupted flow across multiple production steps from raw materials to synthesis to final dosage form. The data generated through PAT tools develops risk-based quality control through their use to optimise and maintain processing conditions, identifying and immediately responding to issues, without affecting downstream processes **[14]**. Together, PAT and QbD increase process throughput and yield, reduce rejects, lower the cost of quality and decrease energy costs. Enhanced process knowledge drives higher quality and patient safety and brings improvements in process validation expenditure and time to market.

Average biopharmaceutical R&D costs have increased (almost doubled) over the last 8 years, whilst returns have moved in the opposite direction over the same period to less than half the value **[15]**. A re-think of R&D productivity is, therefore, essential to reverse this trend. Despite pharma's position as laggard rather than leader in embracing innovation, nascent technologies such as machine learning, automation and continuous flow need to be embedded in its culture and processes to realise benefits in efficacy and efficiency. A history of high profitability and regulation and the initial investment needed in new manufacturing assets has seen the pharmaceutical industry be slow to adapt to the continuous manufacturing already being employed by most other industries (e.g. car, steel, petrochemical). However, the trend towards more complex small molecule pharmaceuticals targeting niche illnesses and precision medicine is driving demand for increased flexibility and efficiency through the continuous manufacturing of smaller product volumes. Typical flow rates of tonnes per hour are reducing to kilograms, grams or millilitres. In the US, the Food and Drug Administration (FDA) has recently started approving drug manufacturers' switch from batch to continuous and the European Medicines Agency (EMA) is similarly supportive of the CM approach. All major pharmaceutical companies are either testing or beginning to use such manufacturing processes for finished-

dose drugs, with some even setting production targets using such, showing their clear intent to convert. At present, the synthesis of Active Pharmaceutical Ingredients (APIs) has yet to be performed using continuous processing **[16]**.

The development of CM has the potential to transform traditional batch manufacturing bringing one of the most significant changes for the industry over the next 10 years. In addition to knowledge of production technology, process engineering and the regulatory landscape, sound flow measurement science and standards development will play an important part in bringing CM to life.

Whilst biologics (aka advanced medicines or therapies), i.e. drugs derived from, or containing, living components such as vaccines, blood and gene therapies, are the emerging players in pharmaceuticals, small molecules still dominate the sales portfolios of all major global pharmaceutical companies. The global oral solid dosage (OSD) product (i.e. tablets, capsules) formulation market is predicted to grow until at least 2027, with Western Europe the third largest market behind North America and Asia Pacific (excluding Japan). Contributing to this growth are drug delivery technologies such as targeted delivery and controlled-release, which enhance bioavailability and, thus, reduce dose frequency and improve uniform drug delivery to ensure safety, efficacy and assist patient compliance **[17]**.

4.2.1.2 Scientific and Technological Flow Measurement Challenges

The adoption of continuous flow manufacturing within the pharmaceutical industry brings with it technical flow measurement challenges which manifest from bench/lab, pilot and scale-up, to clinical trial and commercial supply chains. Typical issues experienced when dealing with powders include their failure to discharge reliably from hoppers, silos, etc and their unpredictable flow inside feeders, dosing and packing machines. Powder flow behaviour can affect manufacturing efficiency and product quality through interruption to the manufacturing process whilst flow restrictions and stoppages are corrected leading to unwanted variations in pack weight, product performance, etc.

Granulation (or agglomeration or pelletisation) is the process of enlarging small particles into coherent and stable masses (granules) in which the original particles are still identifiable. Its purpose is to improve the properties and form of the final product. For example, giving better flow properties rendering safer, cheaper transport and storage; lowering of caking and lump formation; improving heat transfer properties; achieving more uniform distribution of the active molecule and lowering powder dispersion into the environment.

Both dry and wet granulation methods exist; however, the latter is used most widely. Wet granulation utilises a liquid ‘binder’ to agglomerate powder particles into a wet mass by adhesion, which is then dried to make the relevant bonds permanent.

Wet granulation comprises three fundamental processes: (i) wetting and nucleation, (ii) consolidation and growth and (iii) breakage and attrition upon whose predictability granule characterisation relies **[18]**.

The production of granular structures with tailored features such as size, flowability and release properties to improve granulation performance yields and costs requires comprehensive quantitative analysis of the granulation process (including equipment, formulation and operating parameters).

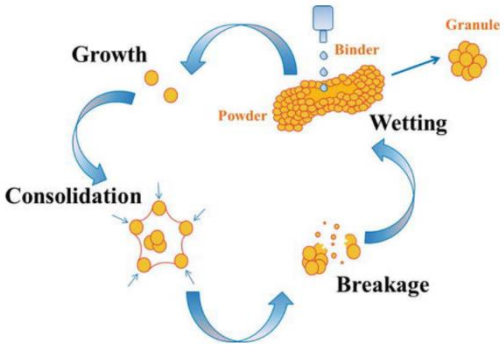

Figure 1: The wet granulation process

Continuous wet granulation is being used more commonly in tablet manufacturing to improve the flow properties of complex powder mixes to ensure reproducible flow and, in turn, consistent tablet weight. Continuous direct compression is another, evolving, technique used in the preparation of OSD with potential benefits due to its simplicity. Direct compression is ideal for powders that can be mixed well, with good flowability. It is a popular choice as it provides the shortest, most effective and least complex way to produce tablets; the API is blended with the excipient and a lubricant before being compressed.

Investigation of powder flow properties and their relationship to particle morphology (shape and size) will improve our understanding of how particle properties impact bulk powder behaviour under various processing conditions and allow their manipulation to achieve optimum performance in OSD production. Moreover, once compressed, attaining homogenous enteric coating suspensions flowing through tubes to spray guns in tablet coating machines or fluid-bed coaters is also important in order to prevent issues arising from coating segregation and gun blockage. Flow metrology is essential across the stages of OSD production, but it must be the right metrology, capable of identifying what constitutes good and bad flow. There is, therefore, a need to develop fundamental flow metrology infrastructure and standards to support adoption of advances in pharmaceutical production.

4.2.1.3 Recommendation

Categorisation

Industrial ☒ **Clinical** ☐

R&D ☒ **New Test Facility Capability** ☒ **Standards Development** ☒

Investment is required to develop solutions for the inline flow measurement of drug powders and coating solutions to improve quality and yield in pharmaceutical production. An initial flow metrology requirement identified by the CPI, an intermediary assisting industry in the development and commercialisation of new products and processes, is the determination of appropriate PAT at R&D level and development of this capability for scale-up to commercial pharmaceutical volumes. Their flow rates in the region of 5-50 kg/hr are at the smaller end of the pharmaceutical production scale and pipe diameters vary according to the equipment in use. Further, and detailed research requirements will be elucidated through continuing engagement with Chemlink Specialities, CPI, MMIC, CMAC and GCU with the aim of delineating specific projects by the end of Q1 2020.

4.2.2 Theme 2: Non-Invasive Vascular Flow and Haemodynamic Assessment

4.2.2.1 Background

What if healthcare professionals were able to replace the use of invasive methods for proactive decision making concerning the prevention, diagnosis and treatment of serious conditions affecting the heart and vasculature? Tools capable of removing the need for catheter insertion into unwell patients with potentially life-limiting cardiovascular conditions? Whose precision and accuracy compared with conventional invasive techniques would transform existing practice enabling interventions personalised to individual patient needs? What if flow measurement could be extended to the microvasculature, considered to play a contributory role in heart failure and other cardiovascular disease? What if there existed solutions with utility outside the clinical or perioperative setting, in the convenience and comfort of an individual's home? What if such devices were implantable and self-powered, offering continuous monitoring? What if software modelling tools could revolutionise risk stratification? Such scenarios of user-friendly, accurate and time-saving non-invasive haemodynamic monitoring illustrate the aspiration and ambition of modern cardiovascular metrology. This pivotal area of clinical research and practice demands innovative technologies in order to reduce complications and improve morbidity, mortality and the profound socio-economic burden associated with heart failure and other cardiovascular disease.

For example, there is current lack of understanding of the pathophysiology of Heart Failure with Preserved Ejection Fraction (HFPEF) and the precision and accuracy of existing tools for non-invasive measurement of systemic vascular flow and haemodynamics. Heart failure is a complex clinical syndrome resulting from the impaired ability of the heart to cope with the metabolic needs of the body and results in breathlessness, fatigue and fluid retention. HFPEF is a form of heart failure where patients have the clinical signs of heart failure, but with normal or near-normal left ventricular pumping function.

Heart failure affects up to 2% of the adult population in developed countries, increasing to above 10% in those aged over 70. Compounded by frequent hospitalisations and mortality rates after one year of almost a third, rising to nearly two thirds after five years, this condition poses a significant burden on healthcare systems and a genuine threat to the quality and longevity of life. With around half of total heart failure cases due to HFPEF, a statistic which is rising, better understanding of the pathophysiology of this less-well recognised form is vital.

4.2.2.2 Scientific and Technological Flow Measurement Challenges

Cardiovascular disease is the leading cause of mortality globally **[19]**. With blood flow and tissue perfusion serving as important biomarkers, their measurement is critical to diagnosis, risk stratification, monitoring and treatment of disease. More specifically, there is clinical impetus for identifying reliable, accurate and precise non/minimally invasive methods for assessing haemodynamics (stroke volume, cardiac output and resistance) and the systemic blood flow of the large vessels (arteries, veins) down to the microvasculature (arterioles, capillaries and venules), the latter being important in regulating local tissue perfusion and blood-tissue exchange.

Presently, angiography is the gold standard for blood flow quantification; however, it is an invasive procedure involving catheterisation, bringing with it risks for the patient. Current non-invasive options are limited by their exposure to ionizing radiation, temporal and spatial resolution and, ultimately, accuracy, with some methods deviating by up to 20% from the results of catheterisation.

According to UKRI, imaging is now the dominant form of analysis of molecules, cells and tissues across the life sciences **[20]**. Developments in bioimaging tools and techniques may provide insight into the pathophysiology of poorly understood conditions such as HFPEF and lead to better detection, prognosis and therapeutic intervention. Furthermore, improved early detection and treatment of disease through improved non-invasive medical imaging methods falls within one of six major societal challenges identified by the AIMBE (American Institute for Medical and Biological Engineering) in the next 10 - 20 years where medical and biological engineers can contribute to solutions **[21]**.

There is an evident role for inclusion of flow metrology in the research and development of new and evolving diagnostic and therapeutic innovations to improve quality, reproducibility and comparability through the provision of reference procedures, materials and data and delivering traceability to primary or secondary standards. Currently clinicians rely predominantly upon qualitative assessment of imaging scans as the basis for making diagnosis and complex decisions regarding treatment regimens. Only through building capability to make quantitative measurements with non-invasive imaging modalities, reproducible and traceable to relevant new standards, will confidence be instilled, and the necessary assurance provided for doctors and patients alike in the accuracy of diagnoses and more personalised therapeutic decisions. Evaluation and reduction of measurement uncertainty will also be essential to reducing the costs of repeat testing and has the potential to enable detection of the signs of disease at an earlier stage in its development. Improving and validating emerging imaging techniques through the routine use of data will enable their translation from a research tool to clinical use.

Presently, the metrological traceability of quantitative diagnostics is underdeveloped, which is limiting the translation of novel technologies to the clinic. Therefore, research focused on developing traceable and reliable procedures for improved imaging resolution, sensitivity, quantification and discriminating power is needed. The increasing complexity, and thus cost, of health metrology demands, emphasises the need for a collaborative R&D approach to developing capability involving end-users, NMIs, academia and industry.

4.2.2.3 4D Flow MRI

4D flow MRI (magnetic resonance imaging) is a non-invasive, non-ionising medical imaging technique providing comprehensive *in vivo* analysis of complex time-resolved 3D blood flow characteristics. Initially applied to the central nervous system in the late 1980s, it found utility in the cardiovascular system in the late 1990s. Based on the fundamental principle that the phase shift experienced by moving nuclei when subjected to a magnetic gradient is proportional to the (blood) flow velocity of the nuclei, 4D flow MRI encodes velocity along all three spatial dimensions (x, y, z-axes) to obtain a time-resolved (the fourth dimension) 3D velocity field.

Continued developments in this method are leading towards 4D flow as a one-stop-shop for simultaneous dynamic blood flow and anatomical assessment (negating the need for additional 2D imaging). The more detailed assessment (measurement and visualisation) provided of heart and blood vessel haemodynamics is delivered through quicker scan times and without the need for patients to hold their breath.

4D flow MRI has the potential to increase understanding of the role that blood flow dynamics play in health and disease. In turn, this could lead to improvements in cardiovascular disease research, identification of potential biomarkers, diagnosis, risk stratification metrics for prognosis and surgical and pharmaceutical

treatments and therapies, thus, presenting a promising approach to precision medicine. Given its potential, flow metrology research into this emerging technology is, therefore, essential.

4.2.2.4 Recommendation

Categorisation

Industrial ☐ **Clinical** ☒

R&D ☒ **New Test Facility Capability** ☐ **Standards Development** ☒

An overarching project, delivered through a number of sub-projects (i.e. 4D flow) with a total estimated time span of up to 10 years, is proposed.

A 4D flow MRI workshop is scheduled for 22 October 2019 at the ICE in Glasgow which will bring together experts from industry, NHS and academia with an interest in flow-related imaging research. Its purpose is to understand the potential range of application of this emerging imaging technology and provide a platform for interaction to identify a portfolio of collaborative 4D flow MRI R&D projects with the fundamental aim of expediting clinical uptake. From a metrology perspective, the anticipated contribution will be to leverage flow measurement expertise to deliver a measurement infrastructure for improving the quantification, traceability and reproducibility of 4D flow MRI imaging.

As 4D flow MRI is unlikely to address all the flow challenges identified, further stakeholder engagement may be required to address fully the area of non-invasive vascular flow and haemodynamic assessment, particularly in the context of HFPEF.

4.3 Other Potential Future Project Themes

- The rise of non-traditional dosage forms (i.e. drug delivery method): several factors in the market are reshaping the approach to dosage forms which is resulting in a rise in non-traditional dosage forms such as nasal sprays. About 40 percent of marketed drugs and as many as 90 percent of drugs in the development pipeline are poorly water-soluble Active Pharmaceutical Ingredients (APIs) making this an increasingly common issue in pharmaceutical development. When these drugs are introduced through traditional dosage forms such as oral solid dose, they fail to dissolve, have severely limited bioavailability and therefore have limited therapeutic effect. There are multiple techniques available to increase the solubility of drugs and improve their delivery, particularly the use of amorphous solid dispersions (these are achieved by dissolving a poorly water-soluble API in a polymer matrix to improve the bioavailability by orders of magnitude) and nanoparticle formulations. Similarly, 3D printing in conjunction with hot melt extrusion is being used in the continuous manufacture of oral solid APIs with poor solubility to improve bioavailability.

- Coating of medical devices provides everything from biocompatibility or lubricity to antimicrobial, anticoagulant and anticorrosion or drug-eluting properties for surgical devices such as stents, catheters or occlusion balloons. Typical coating technology involves the spraying of liquid onto the device under low flow conditions or vapour deposition. The rate of fluid or vapour delivery / flow control technology is critical to ensuring consistency (uniformity and repeatability) in coating application.

- Supercritical fluids for particle engineering in medicines manufacturing to generate tailored to defined physical, chemical, structural and surface characteristics for potential improvements in stability, storage, efficacy and route of administration.
- Application of biocatalysis in API continuous flow manufacturing to accelerate production and reduce the costs and higher manufacturing footprint associated with transition metal catalysts.
- Organ-On-A-Chip (OOAC): Use of CCMs (Complex Cell Models), which include OOAC are being driven by diminishing trust in the translational value of animal models and the increasing availability of data to support human CCMs. Use of fluid flow will be important to a variety of organ types and necessary to ensure the continuing maturity and impact of these technologies.
- Microrobots for drug delivery: tiny elastic microrobots have been developed that can change shape depending upon their surroundings to get to hard to reach areas of the body. Containing magnetic nanoparticles and controlled via an electromagnetic field, they swim through the complex body fluids (blood, lymph) and are small enough to pass through narrow blood vessels, adapting their shape to any changes in the characteristics of the fluid environment they encounter, e.g. viscosity, osmotic concentration, to maintain their movement and speed.

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Annex 1. **Stakeholder Consultation**

Organisation	Contact	Position	Input
Centre for Process Innovation (CPI)	• Dr Dave Berry	• Complex Particles Manager at CPI & MMIC Project Manager, Grand Challenge No.2	Theme 1
Continuous Manufacturing and Advanced Crystallisation (CMAC)	• Dr Thomas McGlone • Dr Claire MacDonald	• Technical Operations Manager • Business Development Manager	Theme 1
Medicines Manufacturing Innovation Centre (MMIC) & CMAC	• Dr Stewart Mitchell	• Project Manager at CMAC & MMIC Project Manager, Grand Challenge No.1	Theme 1
Glasgow Caledonian University	• Professor Don McGlinchey	• Head of Design, Process and Manufacturing Research Group and Head of the Centre for Industrial Bulk Solids Handling	Theme 1
Chemlink Specialities Ltd	• Shilpa Mistry	• Head of Pharma, UK and Ireland	Theme 1
University Hospitals Coventry and Warwickshire	• Professor Prithwish Banerjee • Dr Jamal Khan • Professor Christopher Imray	• Consultant Cardiologist (& Lead of Heart Failure Services) • Consultant Cardiologist (with Specialist Interest in Cardiac Imaging) • Consultant Vascular and Renal Transplant Surgeon	Theme 2
Coventry University	• Professor Michael Fitzpatrick • Professor Helen Maddock	• Pro-Vice-Chancellor (Faculty of Engineering Environment and Computing) • Professor of Cardiovascular Pharmacology & Physiology	Theme 2
Imaging Centre of Excellence (ICE)	• Dr Giles Roditi • Dr Pauline Hall Barrientos	• Consultant Cardiac Radiologist • Clinical Scientist	Theme 2