Written Evidence Submitted by Safer Medicines Trust (C190079)

Executive summary

- Significant advances in science and technology have provided a variety of new approach methodologies (NAMs) based on the use of human cells and tissues,[1] which have the potential to transform biomedical science and enable the UK to respond quickly and more effectively to disease outbreaks and biological threats

- Rapid implementation and approval of these technologies in regulatory settings would transform the development of treatments and vaccines to global biological threats and prevent resources being wasted on legacy technologies which continue to fail at great cost and after protracted efforts

- NAMs have been developed worldwide and their use accepted for various safety and disease modelling approaches in other countries. The UK has a chance to become a global leader in NAMs research and innovation with government backed action and support for the technologies already available in UK institutes and industries. It stands poised to respond swiftly and effectively to a global crisis such as COVID-19 only by fully embracing and adopting human relevant new approach methodologies into mainstream biomedical discovery

Safer Medicines Trust[2] is a UK patient safety charity whose mission is to make medicines safer by facilitating the transition to *human*-focused drug development and testing. Our scientists have extensive expertise in drug discovery and development. We have hosted international conferences at the Royal Society and the House of Lords to discuss the benefits offered by a focus on *human*, rather than animal biology. We are a founder member of the Alliance for Human Relevant Science.[3] We welcome the opportunity to submit evidence to the Science and Technology Committee on the contribution that scientifically valid, human-relevant methods and technologies can make to the development of treatments and vaccines for COVID-19 and other disease outbreaks.

1. The contribution of research and development in understanding, modelling and predicting the nature and spread of the virus.

COVID-19 is an ongoing but rapidly changing crisis. At the time of writing, over 150 vaccines are in development for the virus and progressing at an unprecedented speed. While this sounds promising, there is a high failure rate for vaccines (estimated at 90%)[4] and it is imperative that UK R&D learns lessons from previous attempts to develop vaccines and contain disease outbreaks. Most of the COVID-19 vaccines in development are currently in the preclinical (animal studies) phase, prior to progressing to human trials. Unfortunately, while animal studies may show positive results, these rarely translate to success in humans for a variety of reasons, ranging from fundamental species differences to specific individual responses to disease pathogens.[5]

COVID-19 has a unique response in humans that is not seen in animals. Biological and social factors such as age, sex and ethnicity appear to influence susceptibility, as do lifestyle factors such as smoking and pre-existing diseases. We can only understand the human differences in susceptibility to infection by studying humans. Furthermore, immune activation is a key part of COVID-19 disease progression but human immune systems cannot be modelled in animals. Large scale breeding of genetically modified 'COVID-19' mice is underway because they are not naturally susceptible to the virus.[6] Whether these mice develop human-like COVID-19 disease after infection with SARS-CoV2 remains to be seen, further delaying the discovery of potential treatments. It is therefore vital that research into SARS-CoV-2 is performed using new approach methodologies (NAMs). Our response to Q2 provides further details on these human relevant NAMs.

2. The capacity and capability of the UK research base in providing a response to the outbreak, in terms of:

- advice to government, public bodies and others on managing the outbreak;
- **the development of testing, diagnostic methods and technologies;**

The COVID-19 pandemic provides UK R&D with an unprecedented opportunity to exploit and develop its use of new approach methodologies (NAMs) and sets a precedent for future global outbreaks.

NAMs are already providing human relevant data in the context of testing drug safety and efficacy within the pharmaceutical industry. Moreover, they are attracting the interest of regulators; for example, the US Food and Drug Administration is currently testing Multi Organ Chip systems for potential use in drug development and regulatory evaluation,[7] while the European Medicines Agency (EMA) guideline for the assessment of investigational advanced therapy medicinal products in clinical trials[8] acknowledges that animal models may not be available. For example, where a functional immune system is required, testing in animals may not provide meaningful information and could be replaced with in vitro and ex vivo cell and tissue based models, in silico analyses, literature-based evidence and clinical experience with related products. The guidance further states that the development and use of cell- and tissue-based models, including 2D and 3D tissue-models, organoids and microfluidics are encouraged, especially for evaluating mode of action.

With specific reference to the current coronavirus pandemic, the EMA has confirmed it is using all available tools and platforms to accelerate the research and development of medicines for COVID-19[9] and there is opportunity now to build on this knowledge for future outbreaks. It is expected that the UK Medicines and Healthcare products Regulatory Agency (MHRA) will mirror many EMA initiatives and processes following Brexit at the end of 2020, but there is also a unique opportunity for the UK research base and MHRA post-Brexit, to lead the science on the development and regulation of NAMs. Already, the remit of the Medicines Discovery Catapult to identify, industrialise and drive adoption of technologies and methods that will improve productivity and predictability of medicines discovery, is being addressed, with key strengths in the UK's science and talent base, as well as challenges in translation and commercialisation of humanised preclinical models, advanced bioanalytical tools, Artificial Intelligence (AI) and machine learning systems being identified for further focus.[10] Jonathan Mogford, Policy Director at MHRA, recently acknowledged that the rapid development of technologies in the pharmaceutical sector requires the MHRA "to step up" its activity in this area.[11]

- **the development and testing of vaccines;**

NAMs already developed and used for research into other viral vaccines offer great potential for research into a vaccine for COVID-19. Human tissue constructs have been successfully used to develop an accurate model of the human immune system and have been implemented in flu vaccine research.[12] Other examples include organoid technology, which has already been used successfully in other types of research and is now being used for the COVID-19 pandemic.[13] Microphysiological systems (MPS) developed for preclinical vaccine testing also offer more human relevant potential for COVID-19 research.[14] The funding, development and acceptance of NAMs will not only improve the UK's chances in the race for a COVID-19 vaccine but will increase the ability of the UK to manage and respond to any future disease outbreaks.

- **and the development and testing of therapeutics;**

There is a great deal of interest in investigating how existing drugs might be repurposed to treat COVID-19[15] and NAMs can be used to test both new and existing therapeutics quickly and efficiently.[16]

The use of high throughput drug screening programmes[17] has the potential to improve predictivity and save time and costs involved in using animal models, thereby accelerating the approval of treatments for specific COVID-19 patient populations. In March 2020, UKRI awarded Professor Ultan Power and Professor Ken Mills of Queens University Belfast £0.3 million from an initial pot of £10.5m to test a library of ~1,000 drugs already approved for use in humans on human airway epithelial cells to determine if any could reduce the toxic effects of novel coronavirus infection. This work could identify promising drugs for further testing and clinical trials in 12 months and is an example of ongoing UK based science driving rapid therapeutic repurposing.[18] In addition, scientists from PrecisionLife have used the company's AI precision medicine platform to identify 59 repurposed drug candidates which could be used to develop new therapeutic options for patients who develop sepsis while suffering from severe COVID-19. The analysis of patient datasets compiled by the UK Biobank allowed the identification of mutations in 70 sepsis risk genes, 61 percent of which were also present specifically in severe COVID-19 patients. This type of research, using real world data from established UK databanks and computational analysis, could form the basis for future drug trials

and repurposing projects and also offer potential to identify high-risk disease biomarkers.[19]

NAMs also have excellent potential for research into the development of new therapeutics and vaccines, including personalised medicines. New computational design methods are being developed to construct high target therapeutic vaccines for COVID-19[20] and in the UK, the role of NHS England in preparing the NHS to harness the power of genomic technology and bioinformatics, should facilitate personalised treatments and interventions where patient cohorts differ in susceptibility to disease.

3. The flexibility and agility of institutions, Government departments and public bodies, and processes to respond appropriately during the crisis including:

- the availability and responsiveness of funding; and
- **the optimal functioning of regulatory and ethical processes;**

Two institutions, the University of Oxford and Kaiser Permanente research facility in Seattle, on behalf of Moderna Inc, trialled COVID-19 vaccines in humans without the usual preceding animal safety trials since in this case both vaccines used pre-existing technologies and contained components known to be safe to use in people. COVID-19 has forced an appraisal of what is truly necessary to deliver safe medicines as quickly as possible and a recognition by regulatory agencies that traditional animal-based tests are too slow and unreliable to meet the ambitious goal of a vaccine or treatment within a year. Human relevant approaches, on the other hand, offer the crucial advantages of relevance, robustness and speed, all of which are necessary to formulate a quick response to pandemics such as COVID-19.

We have also witnessed extraordinary flexibility from MHRA in approving treatments for COVID-19. Within one week of reaching out to the MHRA at the end of January, Gilead Sciences had a manufacturing license for Remdesivir granted,[11] highlighting what can be possible in a crisis situation. We can now learn from this experience to develop agile processes for future crises and even adopt certain aspects in everyday regulation to drive innovation in regulatory sciences and match the pace of innovation and technologies such as NAMs with regulatory process updates.

- the availability and influence of scientific advice in all Government departments and public bodies—including by departmental Chief Scientific Advisers; and
- the extent to which decisions taken drew on that advice;

4. The capacity to manufacture and distribute testing, diagnostics, therapeutics and vaccines:

- both standing capacity and capacity able to be mobilised;

5. The capturing during the crisis of data of the quantity and quality needed to inform:

- decisions made during the crisis; and
- to maximise the learnings afterwards;

6. The mechanisms for communication of scientific evidence internationally, within national governments and with the public:

- including the handling of conflicting scientific opinions; and

7. The UK's readiness for future outbreaks, including a consideration of:

- the National Risk Register;
- the UK Pandemic Influenza Strategy; and
- PHE's Global Health and Infectious Diseases Strategy.

References

1. http://ddn-news.com/index.php?newsarticle=14430
2. https://safermedicines.org
3. https://www.humanrelevantscience.org/

4. https://journals.plos.org/plosone/article?id=10.1371/journal.pne.0057755
5. https://www.futuremedicine.com/doi/pdf/10.2217/17460913.2.6.667
6. http://www.informatics.jax.org/mgihome/other/coronavirus.shtml
7. https://cn-bio.com/fda-signs-collaborative-agreement-cn-bio-innovations-use-organs-chips-improve-drug-development-evaluation/
8. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-non-clinical-clinical-requirements-investigational-advanced-therapy_en.pdf
9. https://link.springer.com/article/10.1007/s00204-020-02787-2
10. https://md.catapult.org.uk/resources/state-of-the-discovery-nation-2019/
11. https://www.westminsterforumprojects.co.uk/publication/Medicine-regulation-20
12. https://www.liebertpub.com/doi/pdfplus/10.1089/dst.2012.0006
13. https://organovir.com/covid-19-and-organovir/
14. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6256288/pdf/fimmu-09-02634.pdf
15. https://science.sciencemag.org/content/sci/368/6493/829.full.pdf
16. https://caat.jhsph.edu/programs/grants/covid19_awardees.html?
17. https://www.nature.com/articles/s41586-020-2577-1_reference.pdf
18. https://www.ukri.org/news/covid-19-vaccine-therapy-research-boosted-by-six-new-projects-in-rapid-response/
19. https://lifesciencenewswire.com/covid-19/ai-based-precision-medicine-mining-of-uk-biobank-finds-13-human-covid-risk-genes-and-identifies-59-drugs-with-potential-to-improve-survival-in-severe-covid-19-patients-and-sepsis/
20. https://bioengineer.org/designing-anew-radical-covid-19-drug-development-approach-shows-promise/

(31 July 2020)