A non-animal technologies roadmap for the UK

Advancing predictive biology

NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

MRC Medical Research Council

BBSRC bioscience for the future

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Innovate UK

[dstl]

A non-animal technologies roadmap for the UK

This roadmap, vision and strategy for non-animal technologies in the UK has been drawn up by Innovate UK, the National Centre for the Replacement Refinement and Reduction of Animals in Research, the Biotechnology and Biological Sciences Research Council, the Defence, Science and Technology Laboratory, the Engineering and Physical Sciences Research Council and the Medical Research Council, and has been published on their behalf by Innovate UK. It is intended to guide the efforts of all those working in this area. The issues outlined and the recommendations have come out of extensive discussions between the six organisations that are endorsing the roadmap and with many other key stakeholders. The participation and endorsement by the six organisations reflects their continuing interest in non-animal technologies, but should not be construed as a commitment to ensuring its delivery.

Contents

Executive summary

Human life has become increasingly dependent on the use of chemical and biological substances to promote health, prosperity and wellbeing. The companies that develop and manufacture these products, including pharmaceuticals, veterinary medicines, agrichemicals, chemicals and consumer products, provide significant economic benefit. They are, however, faced with major challenges in meeting the sometimes conflicting demands for innovative and effective products, improved consumer safety and greater environmental protection. It means the safety and efficacy of their products must be tested, and this has traditionally been based on animal studies. In the longer term non-animal technologies (NATs) could potentially replace the use of animals for these purposes. Until then the regulated use of animals for research will continue to be necessary in order to understand how the body works and develop medical and veterinary applications.

Innovate UK has identified non-animal technologies as one of a series of emerging technologies with the potential to drive future UK economic growth. The UK has world-leading research in this area and companies, large and small, with the ability to take advantage of new commercial opportunities. The market potential is huge. The global market for cell based assays in drug discovery, safety, and toxicology will reach $21.6 billion by 2018. The estimated global market for induced pluripotent stem cells is expected to reach $2.9 billion in 2018, and the 3D cell culture market is expected to grow to about $2.2 billion in 2019.

Innovate UK, the National Centre for the Replacement Refinement and Reduction of Animals in Research, the Biotechnology and Biological Sciences Research Council, the Defence, Science and Technology Laboratory, the Engineering and Physical Sciences Research Council and the Medical Research Council have been working together to develop a strategy and vision for non-animal technologies for efficacy and safety in the UK and to draw up a roadmap to guide the efforts of all those working in this area.

The vision, strategy and roadmap were developed during a series of consultations and workshops involving academia, public bodies, government and industry. This publication is relevant to a wide range of industries and sectors including pharmaceutical, veterinary, consumer goods and personal care, and chemicals and agrichemicals. Relevant non-animal technologies include complex 3D tissue models, organ-on-chips, stem cell platforms, *in silico* tools and cell imaging approaches.

The vision

The vision is of a thriving UK NATs sector that:

Operates at the forefront of science, technology and innovation, driving the development and commercialisation of NATs through multidisciplinary science and cross-sector collaboration

Supports a strong instrumentation, hardware and supply industry to deliver the commercial success of NATs, and attract inward investment

Delivers improved decision-making tools that result in more rapid discovery and development of medicines, agrichemicals, chemicals and consumer products

The roadmap

The workshops considered a roadmap for non-animal technologies across a range of timeframes stretching towards a 2030 vision. The individual elements captured in the roadmap diagram are not intended to represent a comprehensive set of activities with a precise timescale but should be seen as an illustration of the broad landscape.

Strategic themes

Six key strategic themes emerged from the workshops.

Skills. A broad range of skills is required to support innovation in NATs, and funding to support capacity building is critical.

Collaboration and networks. Fostering collaborations across sectors and disciplines nationally and internationally is pivotal to maintaining momentum and establishing a community to support delivery of the NATs vision.

Technology development. There is a need to maintain investment in the underpinning research and to direct this towards industry use across a number of sectors. It will be important to overcome scepticism in some parts of the scientific community about the effectiveness of using non-animal technologies.

Commercialisation and uptake. The UK has significant industries that could benefit from the uptake of non-animal technologies, but they must be ready and equipped to take advantage of developments in this area.

Regulatory engagement. There is a need for early engagement with regulators to ensure that non-animal technologies can be used in regulatory risk assessments.

International factors and landscape. There is a significant global opportunity for UK industry in developing products and services based on non-animal technologies. Significant investment in non-animal technologies is also taking place in the United States and elsewhere in Europe.

RECOMMENDATIONS FOR THE UK

- Support capacity building in multidisciplinary science and technology development to ensure that the UK has the right skills base to drive NATs for company decision-making and risk assessments.
- Foster collaborations between industry, the SME sector and academia to improve understanding of cross-sector requirements and bottlenecks in the development and deployment of NATs.
- Support collaborative working to ensure that the most promising technologies are identified, developed, validated and integrated into the product pipeline with minimum risk for those involved.
- Maintain investment in underpinning basic research and business-led technology development in NATs.
- Widen engagement in the development of NATs to include disciplines, expertise and individuals not previously involved in toxicology and efficacy testing.
- Build capacity and confidence in NATs and accelerate the path to market by supporting the development of NATs with powerful predictive ability and bridging the gap between development, proof of concept and scale-up.
- Ensure early engagement of regulators in the development and use of NATs to expedite a path to regulatory acceptance.
- Analyse emerging international trends and activities to identify collaborators, avoid duplication and ensure that the UK is well positioned to influence global developments.
- Promote the UK NATs industry globally to maximise economic growth.
- Establish a strategic advisory board, with academic and industrial members, to provide advice and to help drive forward the roadmap in the UK.

1. Introduction

Many industrial sectors, from pharmaceuticals to consumer products, are required to provide toxicity data on their products to demonstrate that they are safe for patients, consumers and the environment. This typically includes data on whether the product affects the normal function of critical organ systems such as the heart, liver, lungs, skin, kidneys and central nervous system. Animal studies are often used. However in many cases the tests do not reflect what is subsequently observed in humans due to differences in exposure and species sensitivity. In the pharmaceutical industry there are additional concerns about whether some animal models effectively predict the efficacy of drugs.

The lack of translation of data from animals to man has far-reaching implications, from wasted resources spent on the early development of compounds destined to fail in humans, to large financial losses due to late-stage attrition. Consequently, many organisations are increasingly interested in alternative non-animal technologies (referred to here as NATs) for providing information on the safety and efficacy of their products.

There are an exciting range of NATs emerging from the science base that include advanced *in vitro* tools using stem cells and complex *in silico* modelling. Many of these technologies are based on human cells, tissues and data and therefore they provide the opportunity to potentially replace animal studies with systems that better predict the effects of new drugs and chemicals.

More broadly, they also provide other benefits that go beyond replacing the use of animals, such as increasing throughput, cutting development time and costs, and providing mechanistic insights that are not possible with *in vivo* research. For these benefits to be realised there is a need for NATs to be scaled up for industrial use, scientifically validated and fully integrated into the pharmaceutical and chemical development pipelines.

Innovate UK has identified NATs as one of a series of emerging technologies and industries that have the potential to drive future economic growth[1]. The UK has world-leading strength in the science that supports NATs. It is home to two of the world's biggest pharmaceutical companies, more than 380 smaller pharmaceutical companies, a number of leading consumer goods and personal care companies, large agrichemical businesses, and an active laboratory supply, instrumentation and automation sector. We are well placed to take advantage of an emerging NATs sector.

The market potential for NATs is large. The top 25 pharmaceutical companies (based on recorded global sales for 2014) spent a combined total of more than $100 billion on R&D in 2014, and a recent survey of the members of Pharmaceutical Research and Manufacturers of America estimated that more than 20% of total R&D spend was on preclinical research[2].

It has been estimated that the global market just for cell based assays in drug discovery, safety, and toxicology will reach $21.6 billion by 2018[3]. The estimated global market for induced pluripotent stem cells is expected to reach $2.9 billion in 2018[4], and the 3D cell culture market is expected to grow to about $2.2 billion in 2019[5].

The National Centre for the Replacement Refinement and Reduction of Animals in Research (NC3Rs), the Biotechnology and Biological Sciences Research Council (BBSRC), the Engineering and Physical Sciences Research Council (EPSRC), and the Medical Research Council (MRC) have been active in this area over the last ten years and have been instrumental in developing the relevant technologies. They have funded and engaged relevant communities through programmes, projects and workshops to a level where a case for long-term strategic investment can be made.

Innovate UK has worked with NC3Rs, BBSRC, the Defence Science and Technology Laboratory (DSTL), EPSRC, MRC and other partners to draw up a national vision, strategy and roadmap to support the work of everyone involved in this field. The authors are extremely grateful for the input of a wide number of stakeholders and senior figures in the sector.

This publication sets out the vision for NATs in the UK and describes a roadmap for supporting a world-leading industry where NATs developed in academia and the SME sector are exploited and commercialised to improve the safety and efficacy testing of chemicals and pharmaceuticals.

Delivery of the recommendations in the roadmap will drive innovation in NATs and underpin economic growth and improved productivity by tackling major

2. A shared vision

The vision for the roadmap was developed through a process of consultation and workshops convened by Innovate UK and the NC3Rs in May 2014. More than 60 experts from industry, academia, public bodies and other organisations, and representing a range of technologies and sectors, were involved in the work.

business challenges facing the pharmaceutical, veterinary, chemical, agrichemical and consumer product industries, and creating a vibrant NATs sector to provide products and services.

The overall goal of the roadmap is to promote the development of non-animal technologies to better predict human, animal and environmental responses to a wide range of chemicals and pharmaceuticals. In the short term the roadmap focuses on supporting company decisions made early in product development but in the longer term it is intended to provide a suite of technologies that can be used for regulatory purposes which have historically relied on the use of animals.

The roadmap articulates a vision for NATs, outlining the drivers, opportunities, capabilities and enabling organisations that are essential for success. It recommends increased support for NATs R&D, and the greater coordination and integration of activities from a number of organisations and sectors.

Key objectives

Non-animal technologies span a number of distinct disciplines and technology platforms/approaches that will need to be combined with the development of the next generation of methods and instruments to enable improved prediction of safety and efficacy. These include biology disciplines (for example genetics, biochemistry, pharmacology, toxicology, pathology, clinical science and medicine), medicinal chemistry, material sciences, informatics (bioinformatics and cheminformatics), engineering, instrument development and manufacturing, software development, database management.

These disciplines will need to work together to ensure cross fertilisation of ideas and to deliver solutions that enable improved decision-making and allow industry to develop products with an increased likelihood of success.

The vision is of a thriving UK NATs sector that:

Operates at the forefront of science, technology and innovation, driving the development and commercialisation of NATs through multidisciplinary science and cross-sector collaboration

Supports a strong instrumentation, hardware and supply industry to deliver the commercial success of NATs, and attract inward investment

Delivers improved decision-making tools that result in more rapid discovery and development of medicines, agrichemicals, chemicals and consumer products

3. Global industry trends

The NATs roadmap is relevant to a range of industries. This section considers the problems facing these individual sectors in providing safety or efficacy data and the opportunities that NATs provide.

Pharmaceutical sector

The global pharmaceuticals market is worth US$980 billion a year[6]. It can take 10 to 15 years to develop a new medicine at an estimated cost of $1.8 billion[7]. Drug attrition rates remain high despite rising R&D expenditure. An analysis in 2014 showed that the likelihood of approval by the US Food and Drug Administration (FDA) was 10.4% of compounds that entered phase 1 clinical development, about half the rate of the 2010 analysis[8].

The majority of drugs fail in development as a result of efficacy or safety issues[9], with oncology, infectious disease and neuroscience having the highest attrition rates. There is increasing recognition among companies and regulators of the limitations of preclinical models, including animal models, and the need for more predictive approaches, which would allow those drugs that fail in the clinic because of safety or efficacy issues to have been identified earlier in development prior to costly clinical trials (so-called "fail early, fail cheap").

In the longer term there is the potential to use NATs to support the development of personalised medicines through the use of human-based approaches to understand the potential for adverse effects or variation of efficacy in the population. Selection of patients on the basis of their predicted response may allow a drug to continue through development into clinical use in circumstances where it would otherwise be dropped from the pipeline. This would bring significant benefits to both patients and companies.

Veterinary sector

The worldwide market for animal health (excluding food additives) stands at around $22 billion a year[10], with sales split almost evenly between the companion and farm animal sectors.

The development of new veterinary products is on the whole faster and much cheaper than for pharmaceuticals, with a development time of around 5 to 11 years and an average cost of $150 million per product. Many veterinary products are based on those developed for human use, meaning that a large part of the R&D cost has already been met by the pharmaceutical sector. However, the assessment of the safety of veterinary products and drug residues in food animals and the need for alternatives to antimicrobials to ensure sustained yield and animal health provide new opportunities for NATs to be used.

Consumer goods and personal care products sector

The consumer goods industry in the UK spans a number of different product types, including foods, drinks, homecare and personal care/cosmetic products. The total value of the worldwide personal care/cosmetics market is expected to reach $265 billion in 2017[11]. In the cosmetics industry, it is estimated that the annual rate of inclusion of new ingredients is 4% of the total portfolio, with many (25 to 90%) products reformulated annually.

Since 2013, legislation in the European Union has banned the marketing of cosmetics and personal care products that contain ingredients that have been tested on animals. Similar bans on cosmetic testing have been adopted (for example, in India) or are being considered in other countries (for example, in Brazil and Australia).

For some toxicity endpoints, Organisation of Economic Cooperation and Development (OECD) test guidelines exist to allow data generation without using animals. However, for other important toxicity endpoints, such as skin sensitisation – the core test for cosmetics – no guidelines currently exist. The ban has the potential to stifle innovation in the sector and as a result there has been extensive investment in the development of NATs by the cosmetics industry, although significant work remains to be done.

Chemicals and agrichemicals sector

The chemicals industry global turnover in 2013 was €3,156 billion and represented £9.4 billion of added value to the UK economy[12]. Half of all manufacturing in the UK is accounted for by the process (chemical and chemical using) industries. Agrichemicals remain an important part of ensuring global food security, at a time when there is additional pressure on agricultural systems. There is however an increase in plant resistance to pesticides (including fungicides, insecticides and herbicides) and with regulations reducing the number of existing crop protection chemicals that can be used, the discovery of new and safe active ingredients is high on the agenda.

4. Non-animal technologies

The NATs relevant to the pharmaceutical, veterinary, chemical, agrichemical and consumer products sectors span a wide range of scientific disciplines, technology platforms and approaches which often sit at the interfaces between biology, engineering, chemistry and mathematics. They include (but are not limited to) complex 3D tissue models, organ-on-chips, stem cell platforms, *in silico* tools and cell imaging approaches. For these technologies to be effectively exploited for industrial and regulatory uses they need to be combined with automation and manufacturing technologies, and amenable to multi-format data analysis and visualisation.

The chemicals and agrichemicals sectors rely heavily on animal data to provide information on toxicity for risk assessments related to consumer use, employees working with chemicals and environmental impacts (for example, on fish and bird species). The implementation of the EU REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulations[13] and the requirement for toxicity and ecotoxicity data on all manufactured and imported general chemicals by certain deadlines depending on their volume, will have a significant impact on animal use and cost for companies.

There are an estimated 30,000 chemicals to be tested and some predictions suggest up to 50 million animals will be used. The need to identify substances of very high concern, particularly endocrine disruptors, means that the test requirements under REACH and also the plant protection product regulations may increase.

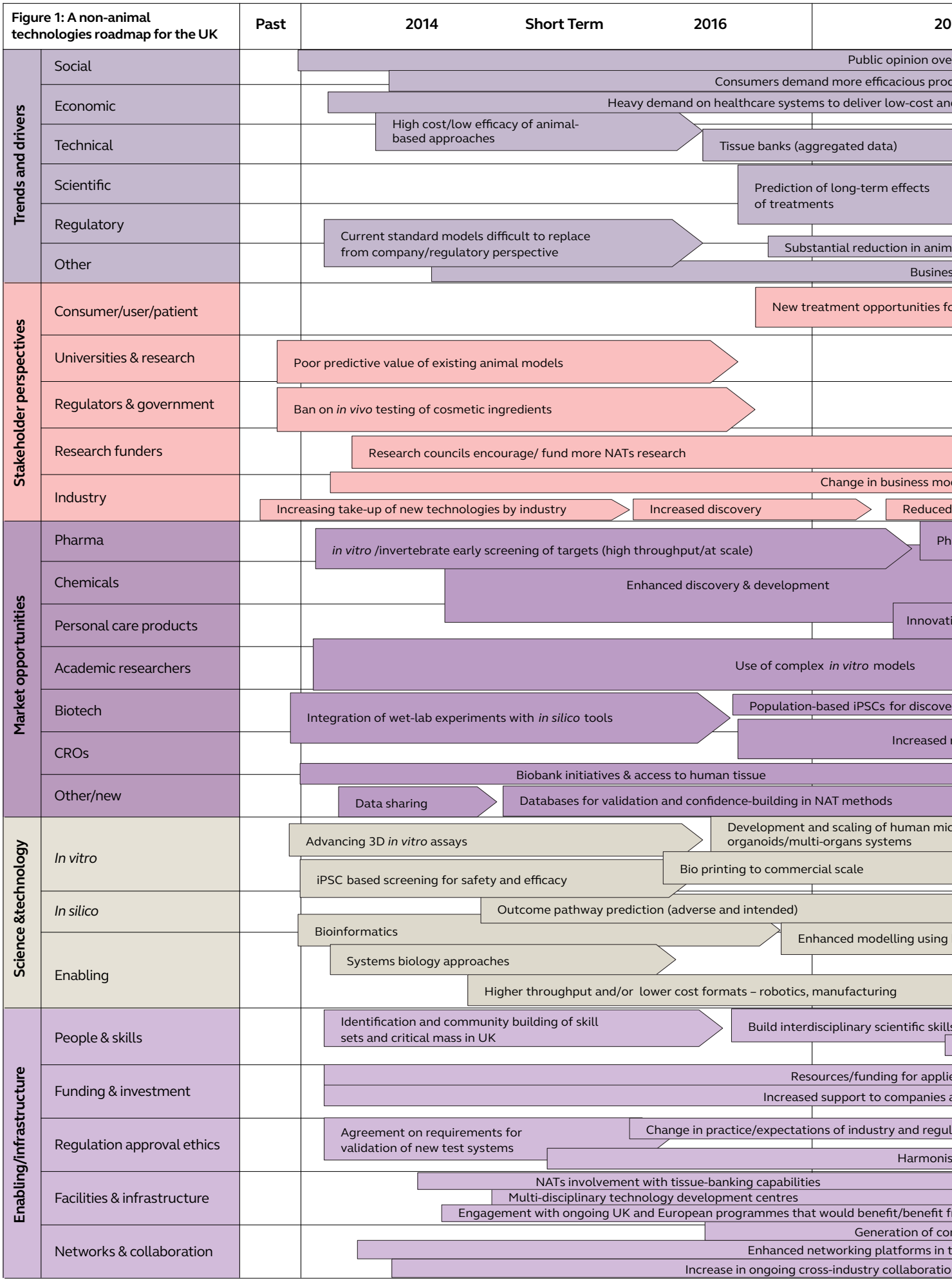
Often the dose levels in toxicity studies required by the regulations do not relate to human exposure (up to a million fold higher than likely human exposure) and this often generates findings such as carcinogenicity or reproductive toxicity that then trigger additional mode of action studies in animals to understand the human relevance.

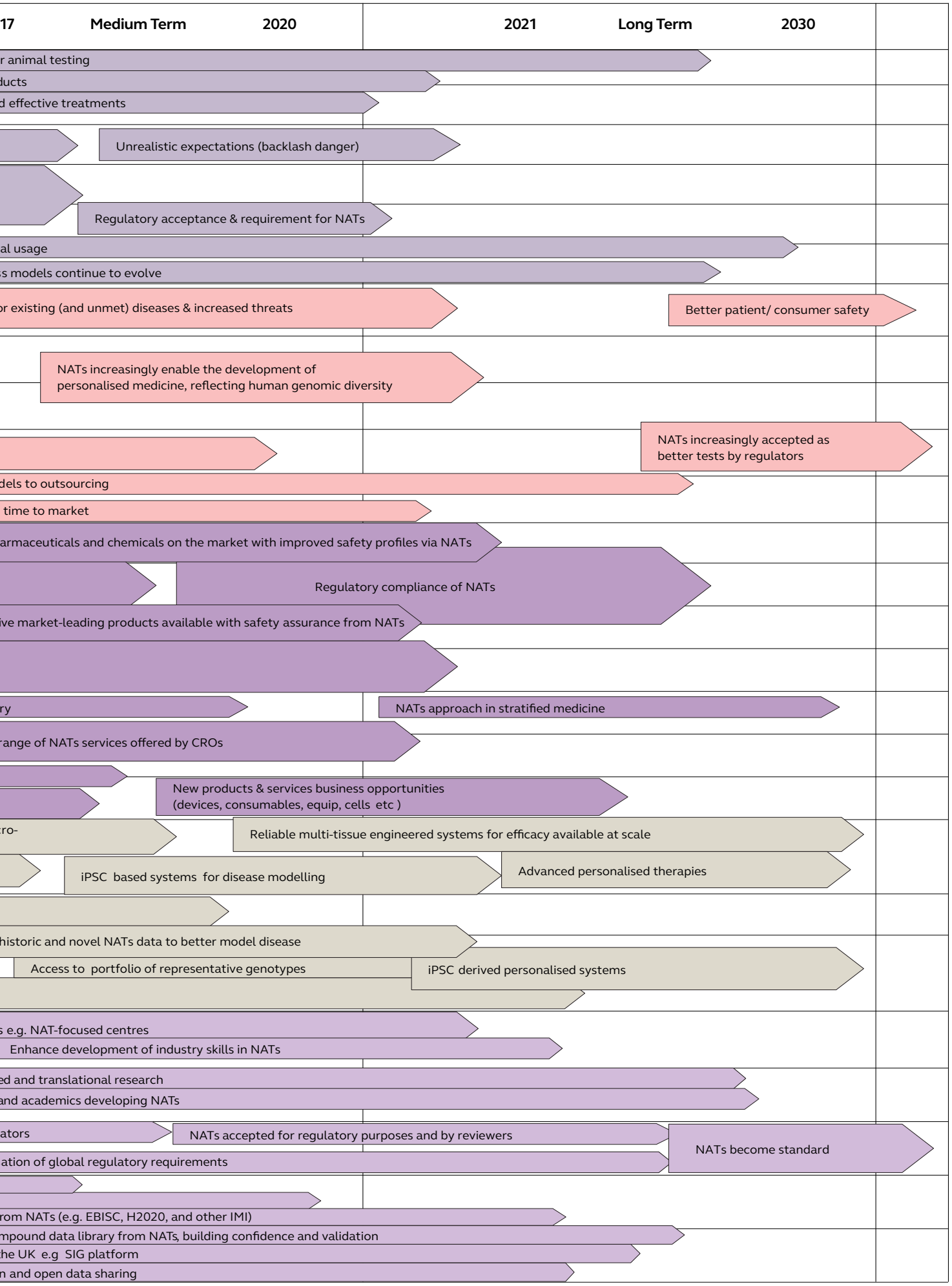
The development of NATs in this area could have considerable advantages, providing the opportunity for high throughput screening of chemicals to improve chemical selection prior to regulatory studies as well as reducing time to market. In the longer term NATs could also reduce the use of animals in regulatory testing.

It is essential that NATs are reproducible, reliable, scalable and validated. These criteria apply to the fabrication of NATs and their quality control (for example, for organ-on-chip devices), and the data generated from them. Scalability will depend on the needs of the sector, for example, the 3D printing of scaffolds for human cardiac tissue used for testing the efficacy of new pharmaceuticals will be different in scale and throughput to a system used in initial toxicological screening of chemicals.

Similarly, validation will depend on whether the technology is to be applied to company processes and decision-making or regulatory submissions and it will be necessary to agree the data sets against which to benchmark NATs. In many instances, the technologies require further basic development and characterisation to reach appropriate technology readiness levels for uptake. A collaborative cross-sector and cross-disciplinary approach is needed to ensure that those developing the technologies understand the needs of potential industrial end users, and conversely end users recognise the capability of the technologies emerging from the science base.

Figure 1: A non-animal technologies roadmap for the UK




17
Medium Term
2020
2021
Long Term
2030
r animal testing
ducts
d effective treatments
Unrealistic expectations (backlash danger)
Regulatory acceptance & requirement for NATs
al usage
s models continue to evolve
or existing (and unmet) diseases & increased threats
Better patient/ consumer safety
NATs increasingly enable the development of
personalised medicine, reflecting human genomic diversity
NATs increasingly accepted as
better tests by regulators
dels to outsourcing
time to market
armaceuticals and chemicals on the market with improved safety profiles via NATs
Regulatory compliance of NATs
ive market-leading products available with safety assurance from NATs
ry
NATs approach in stratified medicine
range of NATs services offered by CROs
New products & services business opportunities
(devices, consumables, equip, cells etc)
ro-
Reliable multi-tissue engineered systems for efficacy available at scale
iPSC based systems for disease modelling
Advanced personalised therapies
historic and novel NATs data to better model disease
Access to portfolio of representative genotypes
iPSC derived personalised systems
s e.g. NAT-focused centres
Enhance development of industry skills in NATs
ed and translational research
and academics developing NATs
ators
NATs accepted for regulatory purposes and by reviewers
NATs become standard
ation of global regulatory requirements
rom NATs (e.g. EBISC, H2020, and other IMI)
mpound data library from NATs, building confidence and validation
he UK e.g SIG platform
n and open data sharing

5. UK strengths

The UK has the necessary academic and industrial strengths to develop, exploit and deploy new non-animal technologies, positioning it as a global powerhouse in this area.

In 2012, there were over 380 companies working in the pharmaceutical sector in the UK, employing nearly 70,000 people, and with an annual turnover of £30 billion[14]. While the UK is home to two of the world's largest pharmaceutical companies, AstraZeneca and GlaxoSmithKline, recently there has been an increasing shift in the pharmaceutical ecosystem from internally sourced R&D to more early stage, preclinical work being done externally in partnership with SMEs, resulting in SMEs and contract research organisations becoming key drivers of growth.

Also present in the UK are large consumer goods and personal care companies (for example, Unilever and P&G) and a number of agrichemical companies (for example, Dow, Interfarm, Nufarm, and Syngenta).

These industries are supported by a thriving contract research organisation sector that includes major players (for example, Covance, Charles River Laboratories, Envigo and Quintiles) along with a large number of specialist SMEs. It also has an active laboratory supply, instrumentation and automation sector (for example, GE Healthcare, Life Technologies and Sartorius).

The UK has a world-renowned research base, with 2 out of the top 3 ranked universities in the world[15]. There are a growing number of university spin-outs, science parks and start-up companies offering services and technologies which exploit the knowledge base.

Many of the academic research funders, including the research councils and the NC3Rs, support activities across a broad range of areas which are relevant to the NATs agenda. There are also significant commitments from the public funders to support early career training and development, including doctoral training centres, with increased focus on multidisciplinary approaches.

Linking the academic and industry (large and SME) sectors will be critical to the delivery of the NATs roadmap. The UK has extensive experience in supporting such cross-sector collaborations effectively, for example, through the NC3Rs CRACK IT programme and Innovate UK's Catapults, collaborative research and development competitions and Knowledge Transfer Network.

Multidisciplinary collaboration will also be essential, and again the UK is well positioned to deliver this as exemplified by initiatives such as the UK Regenerative Medicine Platform, which is funded by the BBSRC, EPSRC and MRC.

6 A roadmap for non-animal technologies

The primary purpose of this roadmap is to establish a vision for NATs in the UK, and to identify the processes that must be applied to realise it. It provides a framework within which to consider future options and coordinate actions. Because non-animal technologies is a very broad, emerging and rapidly developing sector, the purpose of the roadmap is not to provide a detailed project plan but to identify key elements that need to be put in place as a basis for innovative developments now and in the future.

The process of generating the roadmap is itself an integral part of opening up stakeholder discussion, seeking consensus and starting the process of building an informed, energised and effectively supported UK-wide community. This roadmap incorporates material generated during two UK roadmap workshops attended by 60 participants representing a broad range of stakeholders from industry, public bodies, academia and other organisations.

The workshops followed a process established through extensive experience by the Institute for Manufacturing in Cambridge, ensuring substantial engagement of all participants and generating a wealth of valuable material and insight that have been captured, combined and summarised in the landscape figure (Figure 1). The workshops considered the activity as a whole, developing an integrated overview of all the key influences upon and stages within the process, whilst informing the discussion with essential details and knowledge from experts representing a broad cross-section of stakeholders.

Throughout the process there was a focus on early identification of the steps that must be taken along the journey, to avoid delay in anticipating and responding to the opportunities and challenges that lie ahead. We recognise that there are many other stakeholders who will need to engage in further shaping the future as the non-animal technologies community develops.

The workshops considered the roadmap landscape as a whole, across a range of timeframes, stretching out towards a 2030 vision. This was populated in detail from both a 'top-down' perspective, considering trends, drivers and stakeholder perspectives, and a 'bottom-up' perspective, considering enabling/infrastructure, science and technology and market opportunities. Key outcomes are summarised in the roadmap.

The individual elements captured in Figure 1 are not intended to represent a comprehensive set of activities with precise timings, but rather to illustrate the landscape, options available and timescale that must be considered. It is clear that non-animal technologies should not be approached in a sequential, piecemeal fashion, but as an integrated whole, addressing issues across sectors in the short term, whilst maintaining a long-term perspective.

7. Strategic themes in non-animal technologies

Six interconnected strategic themes have emerged. The themes are:

- Skills
- Collaboration and networks
- Technology development
- Commercialisation and uptake
- Regulatory engagement
- International factors and landscape.

How the strategic themes interconnect is shown in Figure 1. In this section, the background to each theme is outlined with recommendations for actions that the UK should take to support a NATs industry that is able to meet the demands of multiple sectors.

1) Skills

A broad range of skills is required to support innovation in NATs, and funding to support capacity building is critical. Both "wet" and "dry" lab expertise and skills are required as well as the ability to integrate approaches from different disciplines. An aptitude to work with multiple stakeholders including industry is essential. The skills base extends beyond the technological development required for NATs. Focus will need to be given to generating a workforce that can interpret, interrogate and organise information from different types of data sets including transcriptomic, proteomic and metabonomic ones. This includes regulators who will also need to be equipped with the tools and knowledge necessary to assess novel data sets, moving away from the traditional animal pathology and dose responses included in regulatory submissions.

RECOMMENDATION

- Support capacity building in multidisciplinary science and technology development to ensure that the UK has the right skills base to drive NATs for company decision-making and risk assessments.

2) Collaboration and networks

Fostering collaborations across sectors and disciplines nationally and internationally is pivotal to maintaining momentum and establishing a community to support delivery of the NATs vision. Opportunities to share ideas and knowledge, horizon scan and showcase technologies, collaborate on the development and testing of NATs, and seek input from end users and regulators will need to be provided.

A range of tools and infrastructure are required for community building. These include network and translational funding to bridge the gaps between disciplines, easy access to information and collaborators through online platforms and dedicated events, and hubs for technology developers to work with end users. The latter is essential to explore the feasibility of the technology, how it might integrate into product development pipelines and potential challenges for scale-up and manufacturing.

RECOMMENDATIONS

- Foster collaborations between industry, the SME sector and academia to improve understanding of cross-sector requirements and bottlenecks in the development and deployment of NATs.
- Support collaborative working to ensure that the most promising technologies are identified, developed, validated and integrated into the product pipeline with minimum risk for those involved.

3) Technology development

Multiple organ systems are studied in order to accurately assess the toxicity and efficacy of products and this complexity will need to be reflected in the development of NATs. Investment in underpinning basic research is essential. There is much relevant research funded by the research councils and other agencies that is already ongoing across the fields of biology, chemistry, engineering and mathematics. The majority of this research is conducted for purposes not related to the assessment of the toxicity or efficacy of chemicals and pharmaceuticals and it will be necessary to harness this to drive the development and application of novel NATs towards industry use across multiple sectors.

There are a number of challenges. These include facilitating collaborations between the academic and industry sectors to improve understanding of the needs of the end user and the capabilities of the technology developers. Multidisciplinary approaches will need to be fostered and emphasis will need to be placed on encouraging scientists to think beyond their immediate research areas to how their skills, technology and "know-how" can be leveraged and exploited to accelerate the development and adoption of NATs. A major barrier will be the degree of scepticism in some sectors of the scientific community about the ability to model complex biological processes using NATs, which can discourage wider engagement in the development, validation and translation of alternative approaches. Changing perceptions and building confidence will be as important as building capacity.

RECOMMENDATIONS

- Maintain investment in underpinning basic research and business-led technology-development in NATs.
- Widen engagement in the development of NATs to include disciplines, expertise and individuals not previously involved in toxicology and efficacy testing.

4) Commercialisation and uptake

The UK has significant resident industries that will benefit and generate wealth from NATs. The successful development of NATs will only have economic impact if the businesses they serve in the pharmaceutical, veterinary, chemical, agrichemical and consumer products sectors are ready and equipped to adapt and implement them into their product development pipelines.

The changing business model, particularly in the pharmaceutical sector, to outsourcing studies to contract research organisations, SMEs and academics provides the ideal landscape for inserting disruptive technologies into the product development pipeline, and some UK companies have already started to increase their investment in *in vitro* technologies.

While it is difficult to predict which technology advances will be successfully developed, scaled and go on to achieve successful adoption and commercialisation there are a number of recognised deficiencies in current methods for determining safety and efficacy. Some examples of what is needed to facilitate uptake over the next 5 to 10 years include:

- methods and instrumentation to improve the efficiency of and increase the scale of *ex vivo* tissue analysis using automated multiplexed digital image analysis
- the use of routinely collected human tissue for innovative approaches to understanding function and outcomes
- compound screening using genetically defined panels of induced pluripotent stem cell (iPS) derived cells with associated patient history and genome sequence data. This will enable the discovery and development of precision medicines
- improved *in vitro* disease models using gene editing methods to enable more predictive compound screening
- the development of complex 3D cell culture models that better mimic tissue structure, function and processes
- model systems that incorporate nutrient flow and flux and multiplexed organ-like models that can interact and mimic multiorgan systems and physiology
- topologically predefined multicellular 3D printed model systems
- access to, and sharing of, historical commercial compound datasets for improved predictive cheminformatics
- the development of preclinical models that more faithfully reflect human biology for use in the development of new types of therapies such as cell and gene therapy

Some companies have sufficient capability, scale, and budget to develop their own NATs, tailored to their individual requirements. However, for many companies deploying NATs in their product development pipelines will be dependent on being able to buy "off-the shelf" products or to outsource to specialist SMEs and contract research organisations that provide tools, products or services.

This is where there is the greatest opportunity for economic impact from NATs, but realising this potential will require bridging the gap between NATs development and innovation in the provision of marketable products or services. Early stage funding is often needed to generate sufficient data or experience to show that NATs are fit for purpose, with the emphasis on minimising risk to encourage collaboration and longer-term investment.

There are a number of potential funding sources, including charities, H2020, university technology transfer funds, crowd sourcing, business angels and schemes such as CRACK IT Solutions. Innovate UK in partnership with the NC3Rs, BBSRC, EPSRC and MRC has already committed to invest up to £10 million in 24 business-led feasibility studies and collaborative R&D projects, through two Innovate UK NATs themed competitions run in 2014 and 2015.

Sustained funding will be required for the NATs to be truly transformative in improving business processes and generating economic growth. This will need to be complemented with infrastructure (for example, dedicated centres) to provide technical and manufacturing advice; access to collaborators, investors and business expertise; and guidance on validation and regulatory acceptance.

RECOMMENDATION

- Build capacity and confidence in NATs and accelerate the path to market by supporting the development of NATs with powerful predictive ability and bridging the gap between development, proof of concept and scale-up.

5) Regulatory engagement

It is likely that the earliest development and use of NATs will be to guide non-regulatory product development decisions made within companies. In the longer term there is the potential for NATs to inform regulatory submissions for chemicals and pharmaceuticals and ultimately to replace some of the traditional tests. There are a small number of NATs that have been approved for regulatory use by the OECD, which mainly focus on skin

Figure 2: OECD test guidelines for NATs

OECD Test guideline	Description
OECD TG430	*In vitro* Skin Corrosion: Transcutaneous Electrical Resistance Test Method (TER)
OECD TG431	*In vitro* Skin Corrosion: Human Skin Model Test
OECD TG439	*In vitro* Skin Irritation: Reconstructed Human Epidermis Test Method
OECD TG432	*In vitro* 3T3 NRU phototoxicity test
OECD TG471	Bacterial Reverse Mutation Test
OECD TG476	*In vitro* Mammalian Cell Gene Mutation Test
OECD TG428	Skin Absorption: *In vitro* Method

models (see Figure 2). Regulatory acceptance has, however, historically been a considerable challenge for those developing alternative approaches, and the route for validation can be complex and lengthy.

The situation is further complicated by the considerable disparity in global regulatory data requirements faced by the sectors, which has a significant impact on their ability to market products and animal use. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, broadly speaking, provide a consensual and consistent framework for the assessment of pharmaceutical safety across Northern America, Europe and Japan.

For chemicals and agrichemicals there are major regional differences in requirements. For example, often there is a regional preference for a test species, with no biological basis for its use, which can result in testing in two species when one would have been sufficient. Without harmonisation of test requirements, the uptake of NATs for regulatory testing may be severely compromised.

It is important to actively engage all users and evaluators of disruptive technologies early on in their development and commercialisation to ensure that the right steps are taken to adequately validate NATs for their intended use before being taken up to scale in the market. Early engagement with regulators is key to ultimately ensuring that NATs can be used in regulatory risk assessments. In the USA the Food and Drug Administration, through its *Critical Path Initiative*, has signalled the importance of *in vitro* and *in silico* technologies to address the bottlenecks of predictivity and translation in the drug development pipeline[16].

Some regulators are providing innovative routes to facilitate the use of new technologies and types of data sets. For example, the European Medicines Agency has developed the "safe harbour" concept to allow companies to submit data obtained using a novel approach in parallel with data generated using existing methods. The former is not used as part of the regulatory decision-making process but instead for consideration of its possible future regulatory acceptance, in effect helping to build regulatory confidence in new approaches whilst minimising risk to the companies[17].

RECOMMENDATION

- Ensure early engagement of regulators in the development and use of NATs to expedite a path to regulatory acceptance.

6) International factors and landscape

Health, personal care, and agriculture are global industries and companies offering better products or services based on NATs will have a worldwide market. There is significant potential for economic growth and the UK is not alone in recognising the importance of NATs. There are also international programmes funding research relevant to NATs including in Europe the Innovative Medicines Initiative and Horizon 2020.

In the USA, there has been a recent step-change in the focus on human stem cells, advanced *in vitro* techniques and *in silico* methods for safety testing, supported by significant investments such as the establishment of the $125 million Wyss Institute at Harvard and the $140 million programme developed by the Defense Advanced Research Projects Agency and the National Institutes of Health[18].

Although the UK has significant strength in the science and expertise in many of the constituent technologies necessary to accelerate the development of NATs, and a strong base of end users, it has not so far drawn them together at the scale required to revolutionise toxicity and efficacy testing. Coordination with international activities is an essential part of the development of NATs in an increasingly connected and globalised world.

RECOMMENDATIONS

- Analyse emerging international trends and activities to identify collaborators, avoid duplication and ensure that the UK is well positioned to influence global developments.
- Promote the UK NATs industry globally to maximise economic growth.

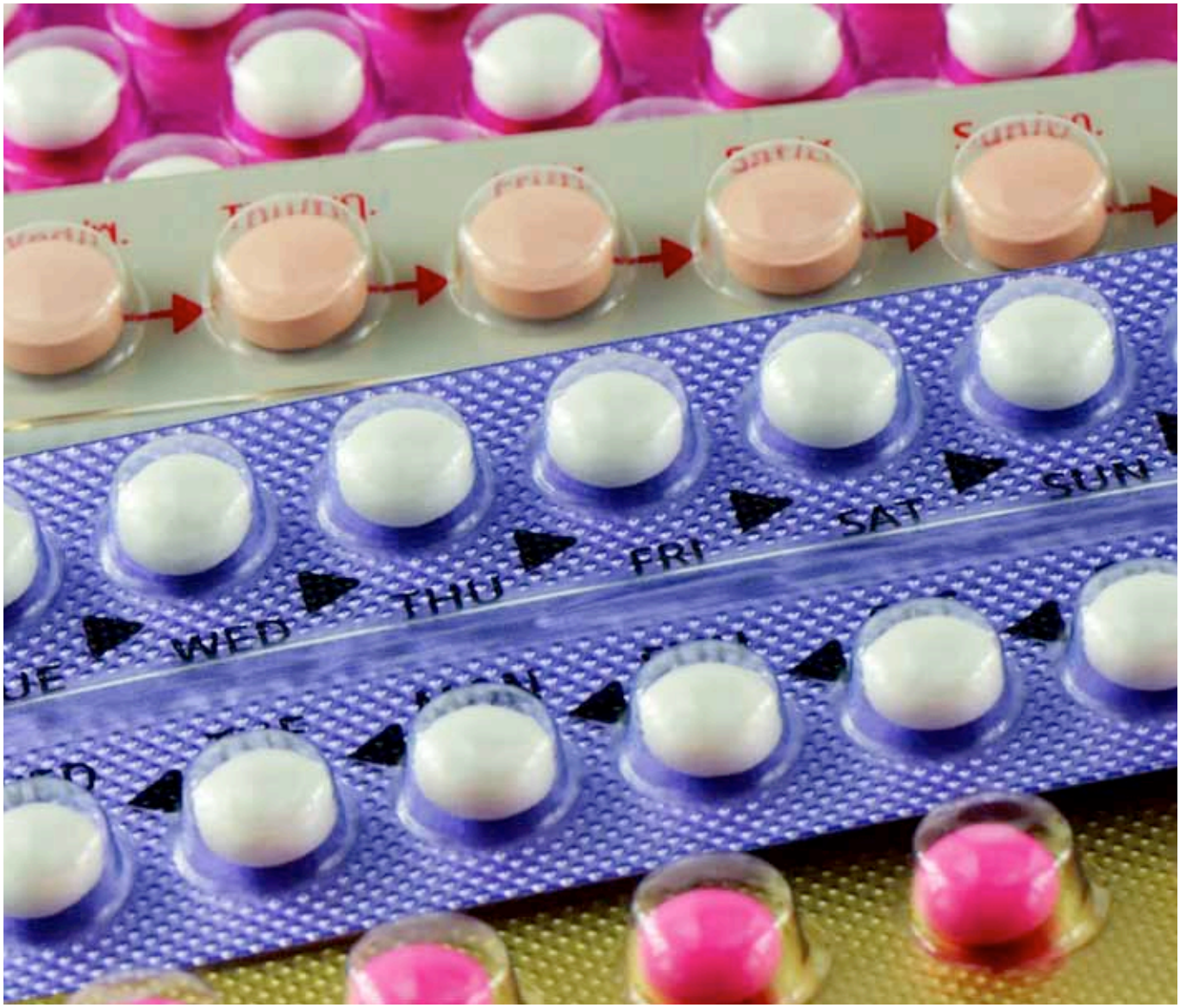
8 Strategic perspective

The momentum built up through the generation of this roadmap must be maintained. A focal body could be formed to further develop and help drive the UK NATs vision described in this roadmap, engaging key sectors in a collective approach.

It will be important to engage the key sectors in a collective approach to push forward the ambitions described in this roadmap and to enable its refreshment at periodic intervals.

RECOMMENDATION

- Establish a strategic advisory board, with academic and industrial members, to provide advice and to help drive forward the roadmap in the UK.



9 Summary of recommendations and impacts

RECOMMENDATIONS FOR THE UK

- Support capacity building in multidisciplinary science and technology development to ensure that the UK has the right skills base to drive NATs for company decision-making and risk assessments.
- Foster collaborations between industry, the SME sector and academia to improve understanding of cross-sector requirements and bottlenecks in the development and deployment of NATs.
- Support collaborative working to ensure that the most promising technologies are identified, developed, validated and integrated into the product pipeline with minimum risk for those involved.
- Maintain investment in underpinning basic research and business-led technology development in NATs.
- Widen engagement in the development of NATs to include disciplines, expertise and individuals not previously involved in toxicology and efficacy testing.
- Build capacity and confidence in NATs and accelerate the path to market by supporting the development of NATs with powerful predictive ability and bridging the gap between development, proof of concept and scale-up.
- Ensure early engagement of regulators in the development and use of NATs to expedite a path to regulatory acceptance.
- Analyse emerging international trends and activities to identify collaborators, avoid duplication and ensure that the UK is well positioned to influence global developments.
- Promote the UK NATs industry globally to maximise economic growth.
- Establish a strategic advisory board, with academic and industrial members, to provide advice and to help drive forward the roadmap in the UK.

Implementation of these recommendations will have a transformative impact on the way in which safety and efficacy are assessed by a wide range of sectors, ensuring that the UK remains at the forefront of NATs and derives long-term economic and societal benefits. By implementing the recommendations the UK will:

- Leverage the strengths of its commercial, academic and public sectors and trade and professional bodies to develop the critical mass of core skills and expertise needed to deliver the NATs vision.
- Advance the science and accelerate the development of novel and robust non-animal technologies which can be validated by end users.
- Facilitate access to commercial and business expertise to support companies in embedding NATs technologies early on in development to enable rapid adoption and accelerated uptake by industry.
- Support better decision-making and regulatory acceptance in all relevant sectors:
  - Reducing attrition across the pharmaceutical pipeline at all stages to provide more effective and safer medicines.
  - Enabling more effective and safer crop protection chemicals.
  - Facilitating the introduction of novel consumer product ingredients.
- Develop a unique NATs sector that can deliver economic and scientific benefit to the UK and provide a global focus for the development of effective treatments and products.
- Reduce the use of animals in toxicity and efficacy testing.

References

1. Emerging technologies strategy 2014 to 2018: https://www.gov.uk/government/publications/emerging-technologies-and-industries-strategy-2014-to-2018
2. Pharmaceutical Research and Manufacturers of America, 2013 Biopharmaceutical Research Industry Profile. Available as a pdf at: http://www.phrma.org/sites/default/files/pdf/PhRMA%20Profile%202013.pdf
3. Cell-based Assays: Technologies and Global Markets, BCC Research, April 2014.
4. Induced Pluripotent Stem Cells: Global Markets, BCC Research, June 2014.
5. 3D Cell Cultures: Technologies and Global Markets, BCC Research, Jan 2015.
6. http://www.statista.com/statistics/263102/pharmaceutical-market-worldwide-revenue-since-2001/
7. J.A. DiMasi and H.G. Grabowski. The Cost of Biopharmaceutical R&D: Is Biotech Different? Managerial and Decision Economics 2007; 28(4–5): 469–479. J. Mestre-Ferrandiz, J. Sussex, and A.Towse. The R&D Cost of a New Medicine. London: Office of Health Economics, 2012. S.M. Paul, et al. How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge. Nature Reviews Drug Discovery 2010; 9: 203–214
8. M. Hay et al., Clinical Development Success Rates for Investigational Drugs. Nature Biotechnology 2014; 32(1): 40-51. J.A. DiMasi, et al. Trends in Risks Associated with New Drug Development: Success Rates for Investigational Drugs. Clinical Pharmacology and Therapeutics 2010; 87(3): 272–277.
9. J. Arrowsmith & P. Miller. 2013. Trial watch: phase II and phase III attrition rates 2011-2012. Nature Reviews Drug Discovery. 12(8):569.
10. http://www.fierceanimalhealth.com/special-reports/top-10-animal-health-companies-2013
11. Global Beauty Care Products Industry 2012-2017: Trend, Profit, and Forecast Analysis. Research And Markets, 2012.
12. CEFIC Chemdata International 2014 http://www.cefic.org/Facts-and-Figures/. UK Chemical and Pharmaceutical Industry Facts and Figures 2014. Chemical Industries Association. http://www.cia.org.uk/Portals/0/Documents/CIA%20facts%20and%20figures%202014_MR.PDF
13. Registration, Evaluation, Authorisation & restriction of CHemicals (REACH). http://www.hse.gov.uk/reach/
14. Strategy for Life Sciences One Year On: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/36684/12-1346-strategy-for-uk-life-sciences-one-year-on.pdf
15. http://www.topuniversities.com/university-rankings-articles/world-university-rankings/top-universities-world-201415
16. U.S. Food and Drug Administration. Innovation or stagnation: challenge and opportunity on the critical path to new medical products http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM113411.pdf
17. Guideline on Regulatory Acceptance of 3R (Replacement, Reduction, Refinement) Testing approaches EMA/CHMP/CVMP/JEG-3Rs/450091/2012
18. http://www.nih.gov/news/health/sep2011/od-16.htm

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