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

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Health and Safety Executive

A Regulatory Perspective of "New Approach Methodologies (NAMs)"

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Pharmaceuticals differ from Chemicals and Agrochemicals because human exposure is deliberate because it's generally a requirement and the product is expected to have an effect!

The development of a pharmaceutical is a stepwise process involving an evaluation of both animal and human efficacy and safety information.

Nonclinical studies are a necessary part of drug development for both rare and common diseases.

Nonclinical studies can contribute to a better understanding of the drug's mechanism of action.

With most people, unbelief in one thing springs from blind belief in another –Georg Christoph Lichtenberg

The data generated from nonclinical studies **are important,** particularly to the design of the early stage clinical trials with respect to selecting the starting clinical dose level, dose escalation plan, dosing regimen, and route of administration.

The nonclinical data may help guide patient eligibility criteria and will often determine some important safety monitoring procedures.

BUT Nonclinical Does Not Necessarily mean Animal and many Advanced Therapy Medicinal products (ATMPs) can not be adequately tested this way.

The use of New Approach Methodologies (NAMs) in drug development are not only possible, but are recommended in many cases.

In 2017, Achilles Therapeutics approached the MHRA to discuss quality, non-clinical, clinical and regulatory aspects of ATL001 , an advanced therapy medicinal product consisting of autologous clonal neoantigen reactive T cells advanced derived from patients' tumour-infiltrating lymphocytes. The initial indication was for the treatment of non-small cell lung cancer.

The MHRA advised that this type of therapy needed new thinking, especially regarding the non-clinical support. The view was that, unlike more 'conventional' products, *in vivo* animal studies were unlikely to provide any additional understanding of the safety profile of ATL001 and were not required and, indeed, were discouraged.

Through close collaboration with the MHRA, Achilles Therapeutics managed to take their investigational therapy from a concept into the clinic in less than three years, saving the company at least two and a half years.

The UK Government's position on the use of animal testing in drug development is clear.

The Government encourages the development of *in vitro* methods in place of animal testing and the development, and use, of new tests and alternative methods to the use of animal tests

In accordance with Directive 2010/63/EU, transposed into UK legislation by the Animals (Scientific Procedures) Act 1986, the principle of the 3Rs (Replacement, Reduction and Refinement) needs to be considered when selecting testing approaches to be used for regulatory testing of human and veterinary medicinal products.

This guideline aims to encourage stakeholders and authorities to initiate, support and accept development and use of 3Rs testing approaches.

The MHRA have, in the past, written to a number of pharmaceutical companies openly criticising their un-warranted use of animal studies that do not add any appreciable value to the determination of the potential safety of an Investigational Medicinal Product.

Animal studies should only be conducted to evaluate safety concerns that **cannot be adequately addressed** in other nonclinical studies.

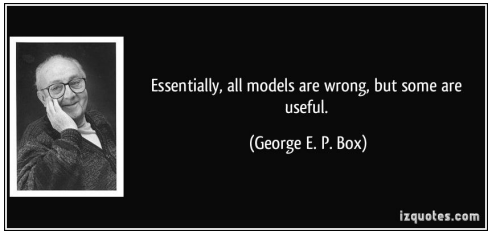
Conducting animal studies to provide “a comfort factor” before exposing humans is totally unacceptable.

There is a clear need for better, more predictive and better validated non-clinical models of disease and efficacy.

NMAs and other alternatives must be integral part of drug Discovery and Development.

But, the 3Rs HAS TO BE SCIENCE and technology driven.

Legislation cannot make it happen. Political deadlines do not make sense if the SCIENCE solutions are lacking. We must avoid actions which might simply drive work abroad to countries where lower standards or less stringent testing guidelines apply.



The challenge to academia, industry and regulatory scientists is to remain focused on designing nonclinical studies in relevant models, including NAMs, to answer specific questions in time to support clinical decision making and communication of potential risks.

Maintaining effective dialogue among scientists in academia, industry and Regulatory Agencies during model development, qualification and validation will be essential to address this challenge.

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This is where the NC3Rs come in ☺

The NC3Rs collaborates extensively with the pharmaceutical sector to identify opportunities for the 3Rs. This includes **acting as an honest broker for data sharing across companies and sectors to support research projects**.

The MHRA and other Regulatory Authorities are willing to participate in these SCIENCE driven projects that have defined aims.

Regulators, do not want these projects to take years. They want changes as soon as possible!!

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The benefits of working with the NC3Rs are obvious.

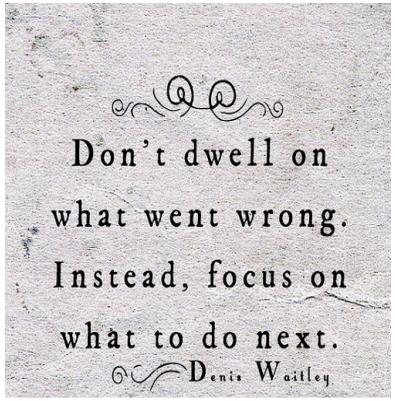
The challenges are persuading companies and sectors to share data (usually the lawyers!).

Another challenge is persuading companies (and some other Regulatory Authorities) not to do something or ask for something just because that's the way they've always done it.

Educating companies not do something just because they think they're expected to is also challenging at times!

Rigorously following Regulatory Guidelines is the last refuge of those who don't know how to develop medicines!!

Problem Areas and How to Resolve Them



Scientific Advice!!

Risk comes from not knowing what you're doing!

Warren Buffett

The MHRA, and many other Regulatory Authorities, have provided scientific and regulatory advice to sponsors.

Scientific advice from MHRA can be requested during **any** stage of the initial development of the medicinal product, even before animal safety studies have been conducted.

Currently, a meeting with the MHRA to discuss Safety, *i.e.* nonclinical, studies costs £2201.

That's not what I expected
when I asked for advice !

The MHRA also has an Innovation Office (https://www.gov.uk/government/groups/mhra-innovation-office). This is open to ideas for innovative medicines, medical devices and manufacturing processes.

It provides **FREE** and confidential expert regulatory information, advice and guidance to organisations of all backgrounds and sizes based nationally or internationally

Any Questions ?