Introduction

In the European Union, about 3.6 million animals per year (30% of all the animals used) are used for drug development. Animal studies are the global standard used to evaluate the safety, efficacy and quality of drugs before these drugs are tested in humans. However, the value of animal studies to predict risks for humans has never been extensively established. In fact, many studies indicate that the value of animal studies is often limited. Pharmaceutical companies and regulatory authorities, as well as the public and governments, aspire to reduce the number of animal studies carried out, because of the limited value of these studies and the ethical issues they involve. The development of innovative methods to replace animal studies received a boost at the end of the 1970s, as a result of campaigns by animal welfare organisations that resulted in increased public awareness and the implementation of Directive 86/609/EEC in the European Union. This Directive requires that innovative methods are used whenever possible, and stimulates the development of innovative methods. Many innovative methods have been developed since the implementation of the Directive. Nevertheless, these innovative methods only incidentally replace animal studies. In my recent doctoral thesis, I tried to elucidate why animal studies are still being used in drug development. To answer the research question, “Which mechanisms explain the lock-in of animal studies in drug development?”, six studies were conducted.

Theoretical framework

The persistent use of animal studies in drug development is an innovation problem, as innovative methods have not yet substituted animal studies on a large scale. This lack of success of the implementation of new methods in drug development can therefore be studied from an innovation perspective — i.e. innovation is the successful implementation of an invention into practice. The main lesson from early innovation studies is that science and technology are only two of the numerous ingredients required for innovation. For turning an idea into an innovation, a network of players is essential, that serves to unite the right knowledge, capabilities, skills and resources at the right time. Innovation processes are complex, and are characterised by complicated feedback mechanisms and mutual interactions involving science, technology, production, policy and demand. Thus, innovation is not an isolated process, but comes about as a result of the interplay of players in a specific context. This context is labelled the ‘innovation system’. The Technological Innovation System (TIS) approach is used as an analytical tool to study the innovation process of emerging technologies that can replace animal studies from a system perspective.

The TIS approach is criticised, because it does not take into account processes and influences from outside the TIS itself, such as established conventions (i.e. institutions). Although the success of emerging technologies depends as much on the generation, maturation and use of emerging technologies as it does on escaping practices embedded in the established institutional context, successful innovation is regarded as a consequence of the functioning of the TIS itself. Due to this inward orientation, the TIS approach does not explicitly analyse the persistency of the established institutions, and the effect of this persistency on the innovation process of emerging technologies. To fully understand why animal studies are still being used in drug development, the persistency or ‘lock-in’ of the use of animal studies in drug development, and how that influences the innovation process, is analysed by using institutional theory.

Following institutional theory, established practices such as animal studies are locked-in, because they are embedded in a well-aligned set of institutions (i.e. reg-
ulations, norms and values) that are taken for granted, normatively endorsed, and backed up by regulatory authorities. The sets of institutions that guide the behaviour of players in a particular scenario are referred to as institutional logics. Different sets of institutions guide daily behaviour in different contexts. When driving to work, people stick to the traffic rules and the norms and values of driving. At work, the behaviour of the staff is guided by the norms, values and rules prevailing in the company by which they are employed. To describe the set of institutions guiding behaviour, Alford and Friedland introduced the concept of institutional logic, which involves a set of institutions that independently contribute to a powerful structure that guides daily behaviour of players in specific contexts.

A framework combining the TIS approach with an analysis of the institutional logic governing the use of animals in drug development was used, in order to improve our understanding of why animal studies are still being used in drug development. This combined framework enabled us to elucidate a more complete overview of the different mechanisms that hamper the innovation process toward the implementation of new alternative methods in drug development.

Research design

Animal studies will continue to be used in drug development as long as innovative methods are unavailable or are incapable of overcoming the animal studies lock-in. Innovative methods can escape the lock-in of animal studies via two routes. Firstly, they can substitute animal studies in established drug development processes. Examples of innovative methods that have substituted animal studies are the Isolated Chicken Eye (ICE) test and the Bovine Corneal Opacity and Permeability (BCOP) test, both of which have replaced the Draize eye irritation test in rabbits. The bacterial Ames test substituted, to a large extent, animal tests for the assessment of mutagenicity, and the Limulus amoebocyte lysate (LAL) test, which uses aqueous extract of blood cells from the horseshoe crab, replaced animal studies to detect and quantify bacterial endotoxins. Secondly, innovative methods can escape the animal studies lock-in, by being adopted in novel drug development processes for new drug classes. New drug classes provide opportunities for innovative methods, because the drug development processes for these new drug classes have to be established. These novel drug development processes can be considered to be ‘green fields’, wherein innovative methods can be adopted, without the need for substituting existing animal studies. Analysis of the success, or otherwise, of innovative methods to escape the lock-in of animal studies in drug development via these two routes, provides a comprehensive overview of mechanisms that influence the lock-in of animal studies during the process of drug development.

Explaining the ‘lock-in’ of animal studies

Two case studies were conducted to identify the barriers that hamper the replacement of animal studies in the current regulations. Based on these studies, it can be concluded that, although regulatory authorities and pharmaceutical companies have an ambition to reduce the use of animal studies, replacing animal studies by innovative methods is challenging. On the one hand, there is no urgency to replace animal studies. This lack of urgency slows down the innovation process, because it can make it more difficult to obtain resources. On the other hand, replacing animal studies by innovative methods is challenging, because innovative methods do not sit well with the institutional logic of animal testing. The institutional logic of animal studies is the selection environment, because innovative methods have to be adopted in the regulations (established institutions) as replacements for animal studies. To validate innovative methods, it is generally required to show that these methods deliver similar results as animal studies. However, innovative methods are often based on human data and human mechanisms of action, making them a better predictive model. This makes the validation of innovative methods challenging.

Four studies were conducted to identify why animals are implemented in the guidelines for the development of new classes of drug. Based on these studies, it can be concluded that animal studies often have only limited value in the development of, for example, monoclonal antibodies. These animal studies are implemented in the guidelines, because the design of the development process of new drug classes is experience-driven, rather than being science-driven.

Escaping the animal studies lock-in

Based on the six studies in my thesis, I formulated five recommendations to reduce animal testing in drug development:

a) Governments should create incentives for the pharmaceutical industry to develop and use methods that can substitute animal studies; incentives could be created by rewarding the use of innovative methods and discouraging the use of animal studies.

b) The acceptance of patented innovative methods in regulation will accelerate the innovation process; the patenting of new methods will enable the costs of the development and validation to be recovered.

c) The revision of the validation process will contribute to the implementation of innovative methods; humane endpoints should be used as the reference for validation.
d) ‘Smart’ regulation, enabling science-driven drug development will contribute to the reduction of animal studies; smart regulation provides the opportunity to deviate from the drug development requirements, and thereby enables the use of innovative methods that are not validated.

e) Research on the predictive value of animal studies will increase the innovation process; if more research shows that the predictive value of animal studies is limited, then the legitimacy to use animals as models for humans will decrease, and this will provide opportunities for the implementation of innovative methods.

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