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Exporting moral problems in animal research. An interdisciplinary study of assessing existing measures to prevent outlawed practices and these measures' translatability to animal research

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ABSTRACT

Animal testing has been centrepiece of medical research for a long time. In the past few decades growing attention was awarded to the development of alternative experimental methods, with the goal to eventually phase out the use of animals. The transition is supported through regulation such as the Directive 2010/63/EU and the FDA Modernization Act 2.0, introduced respectively in the EU and the USA.

A real-life case study with the EU ban on animal testing for cosmetics products proves that such a transition can succeed without jeopardising product safety and commercial profits.

The current paper studies the existing mechanisms in other industries to prevent exports of moral problems from jurisdictions where certain practices are outlawed to places where these might still be permitted. The goal is to consider ways to avoid the export of the moral problem linked to animal testing. Translatable solutions should ensure compliance by delivering a wide spectrum of supporting effects. It is important to both hold transgressors responsible, but at the same time to reward players who follow the rules.

Among the existing measures, Supply chain management is gaining on importance in the raw materials space, and it holds significant promise for the prevention of moral problem export when it comes to animal testing. Key factors to achieve the goal are traceability and transparency.

ZUSAMMENFASSUNG

Tierversuche stehen seit langem im Mittelpunkt der medizinischen Forschung. In den letzten Jahrzehnten wurde die Entwicklung alternativer experimenteller Methoden immer mehr gefordert, mit dem Ziel, den Einsatz von Tieren schließlich einzustellen. Der Übergang wird durch Vorschriften wie die Richtlinie 2010/63/EU und den FDA Modernization Act 2.0 unterstützt, die jeweils in der EU und den USA eingeführt wurden.

Eine real-life Fallstudie zum EU-Verbot von Tierversuchen für Kosmetikprodukte zeigt, dass ein solcher Übergang gelingen kann, ohne die Produktsicherheit und die kommerziellen Gewinne zu gefährden.

Das Papier untersucht die bestehenden Mechanismen in anderen Branchen, um den Export moralischer Probleme aus Ländern, in denen bestimmte Praktiken verboten sind, in Orte zu verhindern, in denen diese möglicherweise noch zulässig sind. Das Ziel ist, Möglichkeiten zu finden, den Export des mit Tierversuchen verbundenen moralischen Problems zu verhindern. Übertragbare Lösungen sollten die Einhaltung gewährleisten, indem sie ein breites Spektrum unterstützender Wirkungen ausüben. Es ist wichtig, sowohl die Übeltäter zur Verantwortung zu ziehen als auch die Teilnehmer zu belohnen, die sich an die Regeln halten.
Unter den bestehenden Maßnahmen gewinnt das Supply-Chain-Management immer mehr an Bedeutung im Rohstoffbereich und ist vielversprechend für die Verhinderung moralischer Problem-Exporte im Zusammenhang mit Tierversuchen. Schlüsselfaktoren zur Zielerreichung sind Rückverfolgbarkeit und Transparenz.

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1. Introduction

The field of medical research is characterised by constant change where new ideas are being developed and existing ones are being adapted to meet evolving needs and requirements. Part of this evolution focuses on the involvement of animals as test subjects during the development of new treatments and medications. The current regulatory direction and objective is for animal testing to be replaced at some point in the future by alternative methods:

"While it is desirable to replace the use of live animals in procedures by other methods not entailing the use of live animals, the use of live animals continues to be necessary to protect human and animal health and the environment. However, this Directive represents an important step towards achieving the final goal of full replacement of procedures on live animals for scientific and educational purposes as soon as it is scientifically possible to do so. To that end, it seeks to facilitate and promote the advancement of alternative approaches. It also seeks to ensure a high level of protection for animals that still need to be used in procedures. This Directive should be reviewed regularly in light of evolving science and animal-protection measures." (1). The Directive 2010/63/EU of the European Parliament and of the Council, 2010 is referred later in the text as "Directive 2010/63". The aim is to both improve the quality of medical research and to reduce or eliminate the perceived negative effects on laboratory animals, while providing the human population with the best possible medical care.

The already introduced European Union ("EU") ban on testing of animals for cosmetics products provides an opportunity to evaluate the results with the benefit of hindsight. It took over 20 years for the change in cosmetics to take place and the success was driven by functional legislation, public opinion, improving availability, predictability and economics of alternative testing methods (2).

The goal of this paper is to contribute to the discussion related to one of the anticipated challenges with the phasing out of animal testing in medical research: such practices being transferred to jurisdictions where relevant legislation will be lacking or enacted at a slower pace.

The question to answer is: Are there already existing functional measures in various other industries, which measures would be suitable as checks and balances to prevent the exporting and outsourcing of outlawed animal testing? To answer this question, a review of some of these existing practices will be performed.
The working hypothesis is that indeed there are available controls, which can contribute to this purpose, with special focus given to supply chain monitoring.

Supply chain monitoring often contains rigorous controls in the raw materials sourcing as counterweights to existing governance gaps and related challenges (3).
Additional measures can be combined with supply chain management to provide a more holistic approach, such as import tariffs valued for their flexibility (4) or Artificial Intelligence ("AI") providing a new and quickly developing dimension for approaching the task (5).
Alongside AI it is worth discussing Blockchain technology, which is very well suited to supply chain controls (6).

Not all of the established control measures in other industries are fit for the purpose of monitoring animal testing, but the ones that could work together might provide a sufficiently strong backbone.
This paper is built in a way to start by sketching the historical and current context on animal testing plus the direction taken by regulators with focus on the European Union.
Thereafter the phase-out of animal testing in cosmetics is presented and social perceptions on animal testing in cosmetics and medical research are compared and contrasted.
The place of animal testing in medical research is then described.
In a following section, cases from other industries are discussed, where moral problems are exported cross-border with a review of the already available and implemented mechanisms to address such situations.
In the last part of the paper consideration is given to which of the reviewed solutions can be applied in the medical research field, to ensure that animal testing is not outsourced under pressure from new regulations.
Potential limitations and risks are considered.

2. Where we stand today

2.1 Animal testing in historical context, moral views and their evolution

Breeding and working with animals in an experimental setting has been a standard practice dating back to the first traces of medicine in human history. Already physicians in ancient Greece in 6th-5th century BC dissected animals and did other experiments. At that time, the use of animals did not raise morally relevant questions (7).

Some centuries later, Immanuel Kant (1724 – 1804) acknowledged that while in his view they hold no moral status, "violent and cruel treatment of animals" should be forbidden. Animals should be slaughtered without causing them pain as humans have the right to work with them from a position of power, but not to go beyond their capacities (8). The Kantianism, as a moral philosophy, fits within an anthropocentric view where humans are the only living organisms entitled to carrying a moral status.

Through time, there has been a gradual shift toward non-anthropocentrism (9), with a pathocentric philosophical view, widening the moral status to apply to all animals that can feel and suffer, and then a biocentric view, covering all living organisms. The argument presented by Hupkes and Hedman is that taking care of ourselves (we, as human beings) means taking care of other species and taking care of an overall larger system, of which all are parts and members.

This view is a step away from Kant, and closer to Utilitarianism as a moral philosophy, where pleasure is intrinsically good, and pain is intrinsically bad. The pathocentric and biocentric views bring animals together with humans into that equation since today we are aware that animals are sentient, capable of experiencing pain and pleasure. Utilitarianism assigns moral status to animals in a major difference to Kantianism (10).

The question on permissibility of animal testing remains open with Utilitarianism since on one hand stands the interest of animals to avoid suffering, but on the other in a Harm-Benefit-Analysis is the overall net benefit (11) – in this case calculated as benefit to humans less animal suffering – which can outweigh the harm done to animals in related experiments. Similar concept is found in Art. 38 (2), Directive 2010/63: "…a harm-benefit analysis of the project, to assess whether the harm to the animals in terms of suffering, pain and distress is

justified by the expected outcome taking into account ethical considerations, and may ultimately benefit human beings, animals or the environment;".

This historical discourse shift energises the discussion on the treatment of laboratory animals, what alternatives to experiments with live animals there can be and even what do humans "owe" the animals involved in experiments – as presented in the January 2023 New York Times article *"What Do We Owe Lab Animals?"*(12) .

Without any doubt, animal testing has been and continues to be an invaluable tool in the development of medications, leading to an improved quality of life and often saving human lives. Here are just a few, non-exhaustive examples (13):

- Hundreds of thousands of cases of Poliomyelitis occur annually around the world with the best chance to fight the virus being a vaccine, which was developed using animals,
- AIDS has been studied on animal models,
- Knowledge on the transplantation of various organs was acquired through animal experiments,
- In the context of the cardio-vascular system animals have been used to study hypertension and the blood vessels or to develop open-heart surgery,
- Testing the nervous system on animals played a role in studies on bodily movement and function, emotional behaviour, visual cortex development, memory, pain.

With the advance of research and development ("R&D"), new techniques and approaches are starting to reduce the number of animals needed for testing, to refine the testing procedures and more and more often to replace live animals as testing subjects. This development is known and established in the experimental field as the 3R Principle (Replace, Reduce, Refine) and was first introduced by William Russell and Rex Burch in their 1959 book "The Principle of Humane Experimental Technique" (14).

In the context of the time of publishing, Russell and Burch did not discuss whether humans are entitled to use animals for R&D, rather their aim was to promote a new methodology where the quality of life for lab animals would be improved, and they would be treated in a more humane way.

2.2 Current regulatory framework and direction in the EU

More than six decades after Russel and Burch, their 3R Principle is proving to be increasingly relevant as a groundwork concept for current legislation and is forming the backbone of the methodological approach taken by the EU in the Directive 2010/63 on the protection of animals used in scientific procedures with some of the requirements described in the following two paragraphs:

The legislation's ultimate goal is the "full replacement of procedures on live animals … as soon as it is scientifically possible to do so" (1). The Directive 2010/63 does not go as far as to set a fixed deadline to achieve the phase-out, but already requires that the use of animals only be considered in cases where appropriate non-animal replacement methods are not available.

Transparency is a main consideration under the Directive 2010/63 and a severity classification of the conducted procedures attempts to estimate the levels of pain, suffering, distress and lasting harm inflicted on the animals, with such levels subject to a maximum allowed.

The severity of the experimental procedures falls into the following categories (Art. 15 (1), Directive 2010/63):

- mild
- moderate
- severe, or
- non-recovery

and is defined for each experiment based on its own specifics. This categorisation must be substantiated by the applicants for the experiment by populating a criteria catalogue and must be agreed to by the approval bodies.

Art. 1 (1), Directive 2010/63 introduces rules on:

- the replacement and reduction of the use of animals in procedures and the refinement of the breeding, accommodation, care and use of animals in procedures,
- the origin, breeding, marking, care and accommodation and killing of animals,
- the operations of breeders, suppliers and users,
- the evaluation and authorisation of projects involving the use of animals in procedures, including approvals of the key persons serving as project leads.

In a later resolution 2784 of 16 September 2021 (15) the European Parliament lays out its strategy to accelerate the transition to medical innovation without the use of animals in the fields of research, regulatory testing and education (addressed later in the paper).

Existing EU and US regulatory certification programmes are at present targeted at individuals, rather than at companies or laboratories:

- The American Association for Laboratory Animals Science ("AALAS") has trainings for laboratory technicians focused on the level of knowledge in laboratory animal technology as well as training for laboratory and resource managers (16). AALAS offers an authoritative standard where the certification guarantees a certain level of professional achievement.
- In Europe, the Federation of European Laboratory Animal Science Associations ("FELASA") offers four types of functional trainings to fulfil the requirements of Directive 2010/63 (17).

The goal of such certifications is for the individuals involved in animal experiments to be qualified for the tasks they are faced with and to perform at a certain standardised comparable level, which is critically important for comparability and reproducibility and to ensure that the animals are treated in accordance with current recommendations and regulations protecting their wellbeing.

What is presently missing in terms of certification is an effort to establish widely recognised, global certifications for both individuals and establishments/organisations – such as laboratories, educational institutions, or corporates. Such a system would exert peer pressure on participants in the field to strive to qualify for a certification.

2.3 Animal testing in cosmetics

The cosmetics industry provides a real-life case study for the phasing out of animal testing. The global cosmetics market was estimated at USD 341.1 billion in 2020 and is expected to reach USD 560.5 billion by 2030, for a strong CAGR of 5.1% (CAGR = compound annual growth rate) (18). Other sources quote even higher amounts, with MarketWatch referring to a projection valuing the global cosmetics market at USD 523.5bn already in 2028 (19).

There is substantial amount of money to be made, leading to capital requiring return on investment – several Financial Times headlines from April 2023 provide financial context:

– "L'Oréal buys Australian luxury cosmetics group Aesop in $2.5bn deal",
– "Johnson & Johnson reports loss after taking $6.9bn charge over talc claims",
– "LVMH becomes first European company to hit $500bn market value".

Continuous R&D and innovation aims at the introduction of products ahead of the peer group, increasing sales and shareholder return. The process requires proprietary testing by businesses.

European data shows that such rapid development and frequent adaptive changes make the enforcement of all related regulations a mammoth task: on average the product portfolio of large industry companies contains around 10,000 different products, of which some 25-30% are reformulated annually (20). Some 10% of such reformulations introduce ingredients that are new to the market or to the cosmetics industry with total annual R&D expenditure in Europe is estimated at EUR 1.3bn (20).

EU Regulation No 1223/2009 (21) outlawed animal testing in the EU with implementation date in 2013 in connection to the placing on the market (selling or promoting) of cosmetic products where the final formulation or any of the ingredients or the finished product itself is subject to animal testing.

Validated alternative methods were made mandatory to replace in vivo experiments. Some examples of such alternative methods (22) include:

– Computer models and simulations, which find application in the design of new drugs. For example, a receptor binding site can be predicted and testing on animals can be then reduced to a confirmatory procedure, which can also be shortened.
– Cells from humans and animals and 3D tissue cultures can be used to text drug toxicity and efficacy. Various organs or cell cultures can be supported outside the body for as long as months or in some cases even years.
– Alternative organisms, such as lower vertebrates (e.g. Danio rerio – zebra fish), invertebrates (e.g. Drosophila melanogaster – fruit fly), microorganisms (e.g. Saccharomyces cerevisiae – brewing yeast).

Different rules on animal testing in cosmetics across countries create significant trade barriers even in the case of individual companies who operate internationally.
Ferreira (18) compares and describes widely diverging standards, where:

- the EU leads the way in terms of applying a total ban in the Union,
- eight US states have also banned animal testing for cosmetics, whereas in the rest of the country it is up to the manufacturer to decide on the necessity to test to ensure safety for the consumers,
- Canada is an example of how long it can take to enact change – a bill to end testing on animals for cosmetics was introduced in 2015, but has still not been passed into law,
- Japan is in the process of phasing out, but without a set timeline, and
- China has long even had a mandatory animal testing requirement for cosmetics but is starting to adapt its legislation in order to align to the prevailing standards in the global market – since May 2021 the testing is not mandatory and can be replaced by certain certifications.
- In a similar fashion to the US, some states in Brazil have also banned cosmetic tests on animals, though ANVISA (the state health regulatory agency) still recognises tests on animals to assess the dangers of cosmetic products and their ingredients.

All in all, according to the Humane Society of the United States (23), as of June 2023, 42 countries all over the world have passed laws to limit or ban testing cosmetics on animals.

Had the EU regulator taken a position that animal testing for cosmetics should be banned in the Union, but free trade allowed (allowing imports to the benefit of the end consumer), this would have very likely resulted in regulatory arbitrage with an export of the moral problem to other jurisdictions while still selling related products in the EU.

Where the legal framework is not in place, efforts to speed up the end of animal testing in cosmetics are being made by not-for-profit organisations. People for Ethical Treatment of Animals (“PETA”) has initiated a certification programme, where businesses in the cosmetics industry can receive a badge on their products, confirming that they and their suppliers “do not conduct, commission, pay for, or allow any tests on animals for their ingredients,

formulations, or finished products anywhere in the world and that they will never do so in the future" (24). While this is not a regulatory binding measure, it increases transparency for self-conscious shoppers who are actively seeking to spend their money on products fitting within their personal beliefs. It is also targeting the whole supply chain, thus spreading the effect beyond the brand on the packaging.

The steps already taken in the direction of phasing out of animal testing for cosmetics around the world are posing challenges in the process by negatively impacting free trade, leading to higher production and marketing costs (25):

- Selling the same identical product in every market is virtually impossible both due to regulations and tastes,
- Classification of cosmetics varies between countries (a problem that would directly apply to drugs too, for example food additive vs medication),
- Regulatory stance on animal testing ranging from a complete ban (EU) to a mandatory requirement (until recently in China),
- Varying restrictions on ingredients.

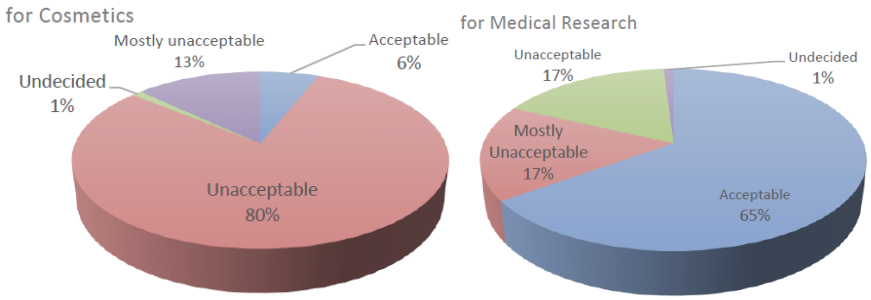
These findings come with the benefit of hindsight and allow us to foresee similar challenges that will face the medical industry in terms of new drugs development once animal testing is outlawed in some of its bigger markets, which are also spending the most on R&D (26). In 2020 total global pharmaceutical R&D was £154bn, of which the US's share was £48bn, Japan came in second with £6.6bn, the UK third with £3.9bn, Germany invested £3.8bn, France £2.9bn, etc. (26).

2.4 Social perception of animal testing

A UK government survey conducted in 2016 (27), referred to in a paper on Bioethics (28), clearly indicates that the general public sees the need for animal testing differently when it comes to cosmetics and medical research:

Figure 1:

Social Acceptance of Animal Testing for Cosmetics and Medical Research in the UK 2016



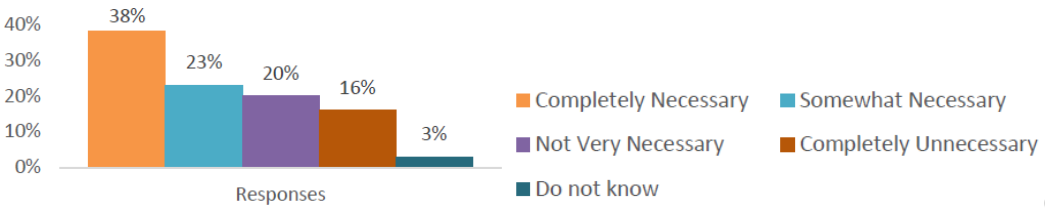
(28)

Where a massive 93% of respondents see animal testing for cosmetics in a negative light, this sharply drops to 34% when respondents are asked about animal testing in medical research. Two-thirds of respondents accept that animals should be tested for drug development.

According to Kabene und Baadel, 38% of the respondents saw animal testing for medical research as "completely necessary", 23% saw it as "somewhat necessary" with 16% opting for "completely unnecessary" and only 3% undecided, indicating a readiness to take a side:

Figure 2:

Social Perception on the Necessity of Animal Testing for Medical Research in the UK 2016



(28)

Given that the ban on cosmetics-related experiments receives significantly more social support, one can expect that moving toward a complete phasing out of animal testing for medical research will meet greater headwinds due to the lack of social engagement and the perceived greater benefit to the human population from such testing.

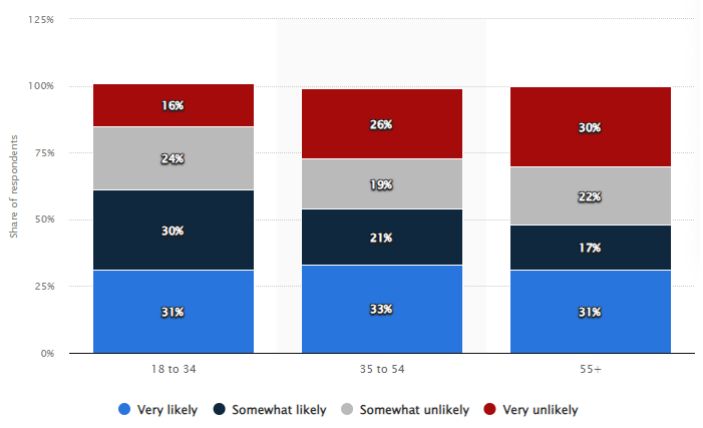
A similar public perceptions' Ipsos MORI survey (29) saw almost identical 7% of respondents agreeing that animal testing for cosmetics should be allowed, but also demonstrated a great lack of awareness for the actual situation, with 38% believing that animal testing for

cosmetics is allowed – 9 years after the decision to have it banned across the EU and 5 years after its coming into force. This lack of awareness demonstrates that animal testing is not high on the social agenda and the public discourse and informed opinions are rather the exception than the rule.

According to Statista (30), attitudes in the US are also shifting when it comes to animal testing for cosmetics – the below chart represents the share of US consumers who would stop purchasing from cosmetics companies that test on animals as of April 2017, by age group:

Figure 3:

US attitudes to Animal Testing for Cosmetics Research per Respondent Age Group 2017



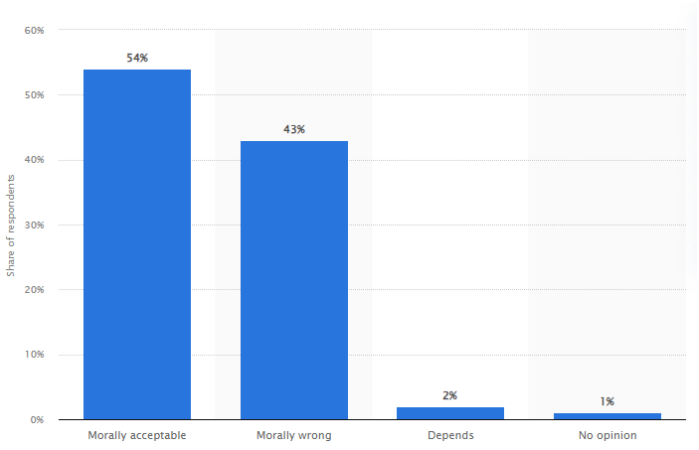
(30)

The data demonstrates that the younger generations are more aware and feel more strongly on the topic with already a rather small minority of 16% in the 18 to 34 age group very unlikely to stop using products tested on animals. Almost twice as many respondents (at 30%) over 55 years of age give the same reply.

The attitudes in the US to animal testing for scientific purposes is somewhat similar to what we see in the EU. In 2018 on the formulation “Do you consider medical testing on animals morally acceptable or morally wrong?”, 54% or respondents found it morally acceptable, with 43% opting for morally wrong (31):

Figure 4:

Attitudes in the US to Animal Testing for Medical Research 2018



(31)

To put it all together, social awareness of animal testing is low, though the trend points to higher engagement among the younger generations. There is a much stronger perceived need for animal testing in medical research than in cosmetics.

2.5 Phasing out of animal testing for medical research in the EU and the US

The European Parliament states in its resolution from 16 September 2021 that the ban on animal testing for cosmetics "has successfully shown that phasing out the use of animal testing is feasible without jeopardising the development of the sector" (15).

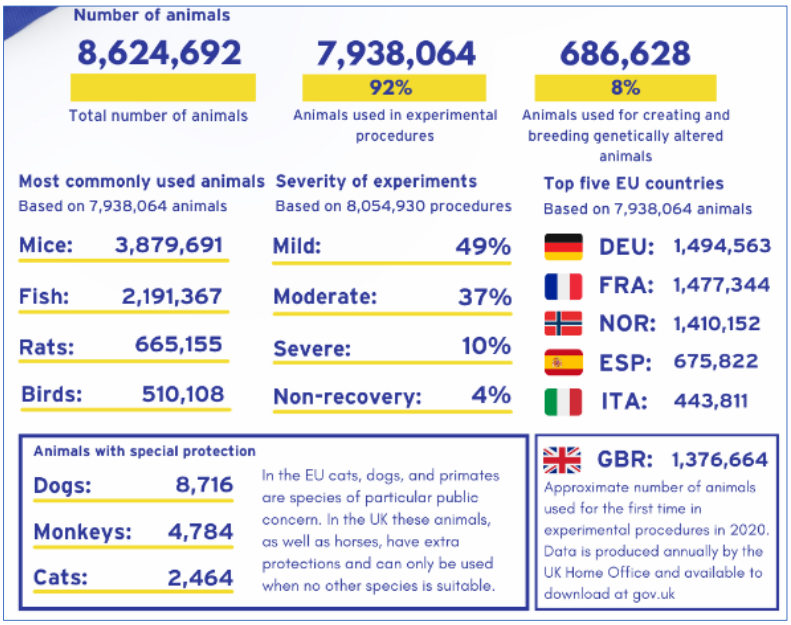
Nevertheless, looking at the already described challenges posed to free trade by diverging regulatory requirements (25), it is sensible that the EU opted for a different approach when it comes to testing for medical purposes in order not to create the same trade difficulties in a market space that is more global than ever.

A firm deadline for phasing out of animal testing has so far not been set, which should allow all involved parties to gradually address the complexity of the issue.

A quick exit would in addition have the potential to create a threat to the wellbeing of the human population in the EU as animal testing is still widely relied on for the development of new treatments as per the following figures in 2020 (32):

Figure 5:

Number of Animals used in Medical Research in the EU and the UK 2020



(32)

In a semblance to a chicken and egg situation, at present non-animal methods are not yet available to replace all animal procedures, while too heavy of a reliance on animal testing reduces the potential for breakthroughs for animal-free approaches. (20)

The language of the EU Resolution 2021/2784(RSP) is balanced and recognises both the need to develop alternative methods (not solely on humane grounds, but also in order to improve the efficacy of drug development) as well as the important role that animal testing is still playing and will be playing for the foreseeable future, referring to "…advances in developing treatments for human health conditions, as well as medical devices, anaesthetics and safe vaccines, including COVID-19 vaccines, and has also played a role in animal health".
The resolution also clearly states that priority is already to be given to validated non-animal alternatives.

Why can one believe that if the EU is the first mover in introducing stricter regulation, this might eventually lead to subsequent adopters, moving over time toward harmonisation in the

phasing out of animal testing? Reference is made to the so-called *Brussels Effect* through regulation (33):

In many diverse ways the EU has already impacted regulation worldwide in areas ranging from data protection to trade or antitrust because of the sheer size of the EU market and the costs associated with not participating in it. The EU is the largest single market by number of potential clients in the world with 440m consumers, with transparent rules and regulations and is seen as a secure destination for investment. The EU also ranks first both in inbound and outbound international investments and is a top trading partner for over 80 countries outside of the block. For context, the US is the top trading partner for just over 20 countries, according to official EU data (34).

Regulations, therefore, spread through market forces, i.e., companies adopt the rules that the EU established as a cost of operating in the Union and then tend to apply these standards to the rest of their business globally to homogenize their running of the business, minimizing costs of compliance with the regulation (33).

Looking to the US, the Environmental Protection Agency ("EPA") is the first in the world to come out with a stated deadline for phasing out of funding for animal testing when it specifically comes to mammals. The EPA is aiming to reduce mammal study requests by 30% by 2025 and to completely eliminate them by 2035 (35). At the same time the EPA expanded funding for the development of alternative testing, awarding total R&D grants of USD 4.25m to the following universities: John Hopkins, Vanderbilt, Oregon State and University of California Riverside (36).

Based on quoted broad spectrum of reactions in the EPA release, from members of Congress to physicians to professional organisations to animal protection non-profit structures, the decision resonated in the public space with supportive opinions covering anything from the positive financial implications (taxpayer animal testing money saved) to references to the low reliability of results coming from the corner opposing the practice.

Simultaneously, some scientists were bemoaning the decision claiming it "is going to allow potentially dangerous chemicals to get out there into the environment and into consumer products", in the words of Jennifer Sass, a senior scientist at the Natural Resources Defense Council (35). Her concern is that a lot of the non-animal testing is proprietary, done by private

companies who develop the testing protocols – therefore with the reduction in public funding and related disclosure, transparency would decrease.
On 27 December 2022, the President of the United States, Joe Biden, signed the FDA Modernization Act 2.0 (37) as a bipartisan bill, which allows the FDA to use and rely solely on alternative testing methods, meaning that a drug can go into clinical trials involving humans without previous animal testing. That is a major step since previously all drugs had to undergo testing on animals in pre-clinical stages.

It is not practically possible to establish a direct cause-and-effect relationship between a ban on animal testing and an increase elsewhere, but less red tape in one place can be realistically expected to lead to draw scientific work there.
Kabene und Baadel mention in their work that since the EU ban on animal testing for cosmetics came into force, the number of experiments in Britain had declined, but it had been increasing in other countries, outside of the regulator's jurisdiction (during this period, the UK was still a member of the Union): "In the meantime, the number of experiments conducted on animals has declined in Britain but is increasing in other countries." (28)
Taking into account the proprietary nature of some of the testing, exact and reliable data on the numbers and types of planned and conducted tests is nearly impossible to obtain.

Summarising the discussion so far:

- There is an expectation that animal testing will be outlawed at some point in the future, likely starting through regulation in developed markets and spreading globally,
- A real-life case-study in phasing out of animal testing for cosmetics in the EU proves that markets can and do cope with such changes in regulation,
- Consumer awareness is slowly shifting in favour of replacing animal testing,
- A concentrated regulatory effort over the last few decades aims to ensure the wellbeing of laboratory animals for as long as they are necessary,
- A need exists to develop and validate testing alternatives to protect human health,
- Numerous challenges must be overcome – both of scientific nature and from purely market perspective (differing regulations, capacity to invest, know-how sharing etc.),
- Some of the effects are difficult to impossible to predict, much less to quantify.

Next, the place of animal testing in medical research as well as existing practices in other industries will be discussed, together with contextual examples of exporting moral problems. The existing control measures will then be considered for their suitability in the field of medical research.

3. Medical research and animal testing

Before jumping into a discussion on what can be borrowed from other industries it is worth taking some time to consider the argument that we find ourselves in times of a major shift in the way medical research is conducted. New successful drugs are needed to generate return for pharma companies, while regulations change the R&D rules.

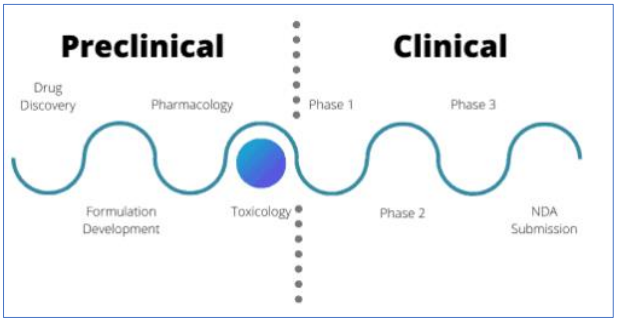
Normally, drug development is split in two main phases: pre-clinical and clinical. The clinical phase is the one that makes the most noise in mass media and refers to testing new drug candidates on human volunteers in three stages, before going through a final approval. Animal testing (among other procedures) belongs to the pre-clinical phase as described by fios genomics in the bullets below (38):

- Potential drug discovery is where combinational chemistry is helping to generate extensive compound libraries, which can be screened for promising substances.
- Formulation development provides clues as to how best to prepare a given drug for its clinical use, taking into consideration administration (frequency and solubility), formula stability, palatability, among others.
- Pharmacology provides a theoretical assessment of the safety of a proposed drug, as well as its absorption, distribution, metabolism and excretion. Important are the bioavailability (how much of the administered substance reaches its target in the organism) and how much of it is distributed elsewhere, the metabolites produced during breakdown, the location of breakdown and the effect of the metabolites, and finally – how the drugs and its metabolites leave the organism. The safety assessment monitors also the pharmacodynamic (the quantitative study of the relationship between drug exposure in terms of concentrations or dose and pharmacologic or toxicologic responses) as well as pharmacokinetic (the study of the dynamic movements of foreign chemicals during their passage through an organism through absorption and elimination).
- Toxicology examines effects that stem from longer-term drug exposure as well as effects from repeated exposure. Animals are involved and often the exposure is longer than what would be anticipated for humans. A variety of parameters can be assessed,

such as food and water consumption, weight gain/loss, blood analysis and urine analysis. Also monitored are immune system responses, tumour development and histological changes. The goal of this stage is to detect and evaluate any adverse effects resulting from taking a given drug. A considerable number of drug candidates (60% or more) never make it out of the pre-clinical phase.

Figure 6:

Preclinical and clinical stages of medical research with their phases

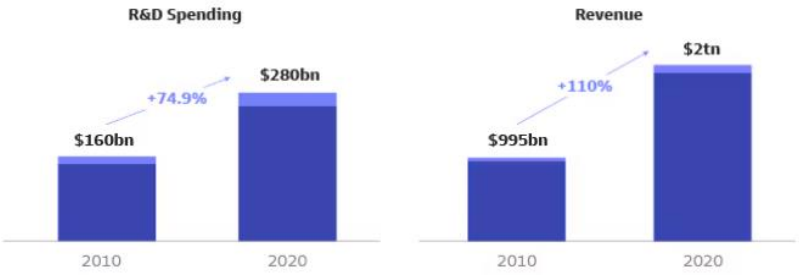


(38)

The market-leading US investment firm Goldman Sachs (39) makes an argument that medical research is at crossroads, experiencing a shift in the way R&D happens, after a decade of massive investment and increase in revenues:

Figure 7:

Medical research R&D spending and revenue



(39)

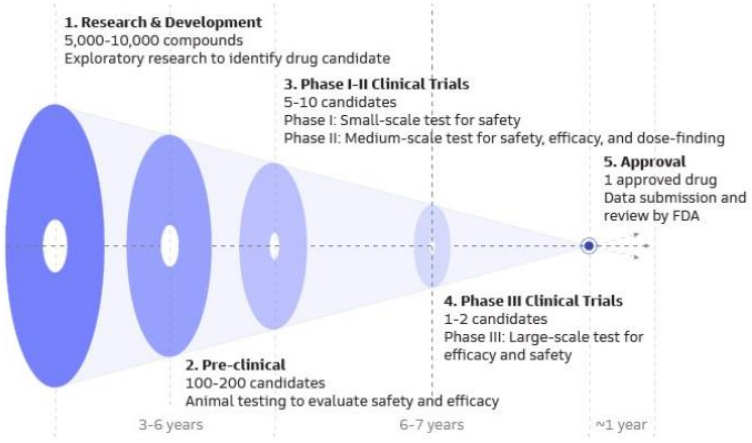
Their analysis refers to both breakthroughs in various fields (genetics, immunology, cell biology) as well as the use of artificial intelligence, leading to faster drug development and personalised treatments.

15 of the top-selling drugs in 2020 will lose patent exclusivity in the next decade, wiping out USD 100bn+ of current sales (39). This is pushing research from in-house to outsourced at various smaller biotech companies in an effort to replenish pipelines with new drugs. Smaller companies have more difficulties accessing capital, which opens up the door for innovative new companies and technologies – linking up to the major change in pre-clinical development while stepping away from animal testing:

Goldman Sachs predicts that the switch to newer technologies for drug development will also shorten the time necessary for the development of a new drug – historically estimated at around 9 years in the US:

Figure 8:

Illustrative drug development process



(39)

From the above diagram one sees that animal testing is at the core of R&D and takes place in the most time-intensive stage of drug development, which lasts up to 3 years, or half of the time necessary before the first clinical trials involving humans take place.

Because with the advancement of the regulatory framework and public awareness more and more stakeholders are involved in the process, pharmaceutical companies actively engage with academic and research organisations in early development and testing, regulatory bodies and financing partners and insurers. It will become more and more critical for pharmaceutical companies to ensure compliance with regulations such as the phasing out of animal testing going forward.

A deeper look at the published annual report of two stock-exchange listed major international pharma companies implies that EU regulations might be playing a role in concentrating R&D in other jurisdictions. While long-term trends are harder to predict, in the short to medium term it might be easier and more economical to conduct R&D in more favourable regulatory regimes:
GlaxoSmithKline ("GSK") states (40) that last year they opened a new major testing and manufacturing facility at Jurong in Singapore.
GSK's competitor Merck currently has its principal research facilities in the US, UK, Switzerland and China – all of them outside of the EU (41). While Merck does not mention EU regulations as a decision factor, it chooses to run manufacturing and other facilities in Europe, but no R&D.
Although the data from the audited reports is not hard proof linking EU regulations to R&D moving away from the Union, such data serves as an indication that such a trend exists.

Regulations co-exist that on one side require animal testing in the pre-clinical stage and on the other, aim to phase out such testing. Despite the very low rate of drugs successfully making it through pre-clinical and clinical testing into a final product, the in vivo models remain the principle screening tool for new drug discovery (42). Similarly, in other industries products are needed in jurisdictions, where their production is not allowed.

Having clarified the role of animal testing in medical research as well as the regulatory direction taken with regard to such testing, it is time to check whether there are already existing functional measures in various other industries, which measures would be suitable as checks and balances to prevent the exporting and outsourcing of outlawed animal testing.

4. Practices in other industries

By applying various checks and balances, many industries with global reach have already made steps toward solving the issue of exporting various moral problems.
For context, some infamous examples from the raw materials field (Oil & Gas) will be presented. Established approaches to counter such practices will be reviewed and in a final step their transferability to animal testing will be considered.

4.1 Real-life examples

Unfortunately, still to this day, international companies sometimes bend the rules trying to arbitrage varying regulatory standards or their enforcement. British Petroleum ("BP") in England and Trafigura in Singapore are both well-known truly global businesses, held accountable to the highest standards in their respective home countries:

- After the Iraq war (2003 – 2011), BP was awarded oil contracts in the Rumalia region in Iraq and extracted close to $15bn worth of oil (43). A widely employed practice during oil extraction is Gas Flaring – the burning of natural gas during oil extraction (43). It reduces the pressure in the oil wells and is sometimes essential for safety. Often oil firms would flare solely to reduce costs as flaring is more economical than capturing, storing and transporting limited quantities of natural gas as a side product. Cancerogenic substances such as "benzene" and "naphthalene" (among others) are released in the air during gas flaring (43). A BBC investigation revealed (44) a high incidence of cancer near the BP oilfield in Rumalia and the company had to publicly address the matter (45).
- On 19 August 2006 the vessel Probo Koala, chartered by the oil and metals trading giant Trafigura, dumped more than 500 cubic metres of toxic waste generated during the processing of a cheap petroleum product with a high sulphur content. Trafigura had tried to get rid of the waste in Malta, Italy, Gibraltar, the Netherlands and Nigeria (the attempt in Nigeria was similar to what eventually took place in the Ivory Coast) but balked at the associated costs – USD 620k was quoted in the Netherlands. Instead, the company paid to a local Abidjan community USD 17k to dispose of the waste in several locations in the city's outskirts. In this case "disposing" meant simply spilling the material in the open. More than 100,000 people required medical assistance for

headaches, skin irritations and breathing problems, with at least 15 related deaths reported in the case report by Amnesty International, 2016 (46). To put things into perspective, Trafigura's 2006 profits were whopping USD 511m (the related "high" disposal costs in the Netherlands would have been approximately 0.1% of the annual profit). Trafigura ended up settling for USD 198m out of court with the Ivory Coast government in 2007 (47).

A clear demarcation line exists in terms of the level of economic and social development between home markets and the countries to where the described practices were "outsourced": England and Singapore vs. Iraq and the Ivory Coast.

As we will see below, current measures in the raw materials space are not always intended to work in a synchronised manner and represent a mix of stick (e.g. regulatory fines, taxes and tariff-linked financials effects) and carrot (better social image and client appeal or access to cheaper financing). Such measures are developed in various jurisdictions and by numerous legislative bodies, often focused on a specific issue, sometimes on a temporary basis.

4.2 Tariffs and taxation

Tariffs are very successfully used for countering dumping (4): a situation where a country can produce something of value much cheaper and through imports under cost of production can flood another market.

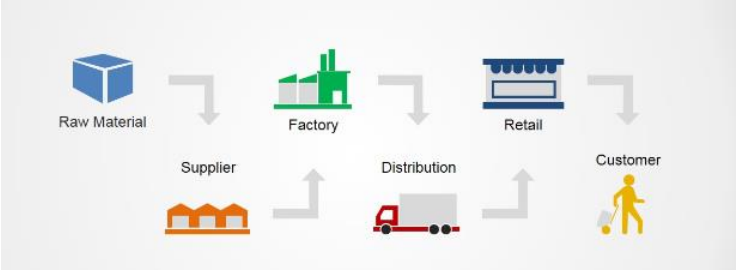
Taxation can also be applied differentially to stimulate or dissuade consumer choices for and against spending on specific products. A good example are taxes applied on alcohol (effectively raising the price to end consumers) with the aim to reduce alcohol-related health harm. Because heavy drinkers and moderate/light drinkers have different purchasing patterns, taxation based on alcohol strength and minimum unit will generally have a stronger impact on harmful drinking and lower impact on moderate drinkers (48).

4.3 The supply chain and its controls

The global consulting firm McKinsey and Co. offers a simple definition of a supply chain: “The supply chain is the interconnected journey that raw materials, components, and goods take before their assembly and sale to customers.” (49)

Figure 9:

Supply Chain Diagram



(50)

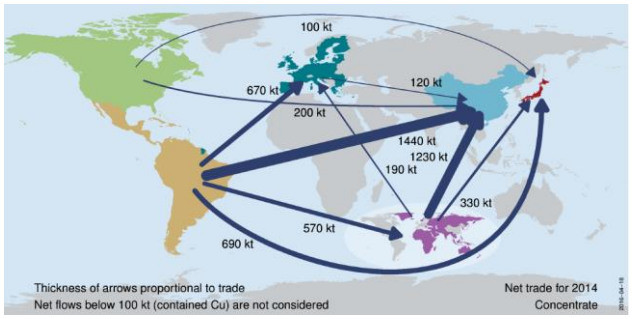
Because service providers at these different steps are mostly independent of each other, they require specific monitoring and control mechanisms. Simultaneously, truly independent stages can serve as a barrier to collusion and concerted mishandling.

In a complex and intertwined world economy often sourcing, processing and selling take place on different continents. The main reasons for such massive logistical efforts are cheap labour and the availability of processing capacities, which often is a moral problem export – it is the dirty part of the supply chain and is generally located in less developed economies.

- Copper illustrates this well: it is being mined in South America as concentrate, raw material is transported by sea to Asia for processing with the refined product re-exported and sold for further processing around the world:

Figure 10:

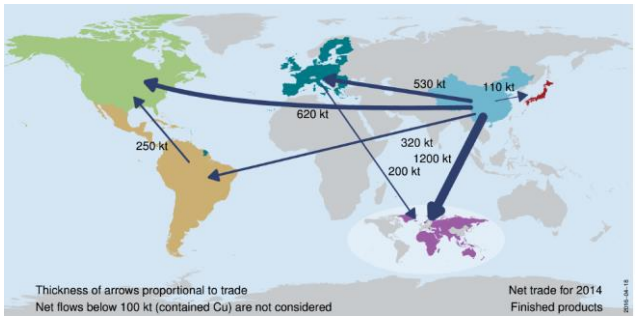
Copper Concentrates (Raw Material) Global Flows 2014



(51)

Figure 11:

Processed Copper (from Raw Material) Global Flows 2014



(51)

- Valuable raw materials mined in Africa attract demand from all over the globe as in cobalt mining (52),
- Technological developers in countries with higher living standards outsource where production bears lower cost, with end consumers spread as described for smartphones by Ohio State University (53).

Insufficient traceability and transparency make cleaning up supply chains a difficult task. This is evident in a famous civil action lawsuit in the US: Civil Action 1:19-cv-03737 (54) against Apple, Google, Tesla, Dell and Microsoft for alleged violations of the Trafficking Victims Protection Reauthorization Act (55). It was an attempt to hold the firms accountable for enjoying profits resulting from human rights violations during the sourcing of cobalt as raw material, more specifically forced labour (also child labour), enforced servitude and slavery. The lawsuit was brought not against the companies immediately controlling the sourcing (buying from mines) and the processing – Glencore, Umicore, Huayou Cobalt – but against the producers of the end devices that are placed on the consumer market.
While the court assumed the truth of all material factual allegations, the case was dismissed:

“While Plaintiffs' Amended Complaint describes tragic events, it suffers from several flaws. Plaintiffs must have standing to bring their claims, but here they do not: the harm they allege is not traceable to any Defendant.”
In this motivation, we see that the flow is not traceable from source to end product, making the supply chain also non-transparent. It is therefore impossible to enforce regulations existing in end markets for alleged events at the source.

The EU specifically targets the supply chains for certain metals, which are seen as coming from high-risk areas. The Union’s Regulation (EU) 2017/821 (56), later in the text referred to as “EU Regulation 2017/821”, is focused on the sourcing of tin, tantalum, tungsten and their ores, as well as gold.
The traceability system defined in the EU Regulation 2017/821 requires information on:

- description of the mineral, including its trade name and type,
- name and address of the supplier to the Union importer,
- country of origin of the minerals,
- quantities and dates of extraction, if available, expressed in volume or weight,
- if available, records of the third-party audit reports of the smelters and refiners, or evidence of conformity with a due diligence scheme recognised by the Commission,
- where minerals originate from conflict-affected and high-risk areas or, where other supply chain risks as listed in the OECD Due Diligence Guidance (“DDG”) have been ascertained by the Union importer, additional information in accordance with the specific recommendations for upstream economic operators, as set out in the OECD DDG – this last step expanding the scope to borrow from OECD measures.

The European Commission allows for a remedy period in case of breaches and also develops a global list of responsible smelters and refiners, thus also providing a kind of a certification. The actual checks are to be carried out by the Member States’ competent authorities with records kept for five years, ensuring a long-term audit trail.

Key take-aways are that EU Regulation 2017/821 on traceability addresses critical points such types and quantities of goods, supplier, origin and works together with similar regulations. An audit trail, a quasi-certification and a functionality verification are additional core provisions.

4.4 Transparency in supply chains and why it is key

Specialisation and the resulting outsourcing and global production dispersion are already firmly rooted in the way business is done. This leads to a different kind of exposure to social problems and human rights violations, moving out of the organisational structure and into the companies' supply chains (57), presenting a complex challenge for SCM. Naturally, companies are becoming more and more aware that even indirect suppliers can cause a variety of financial, operational, and sustainability problems (58).

Because globalization brings along governance gaps where companies are not sanctioned for human rights abuses from the actions of independent third parties they work with, regulators in developed countries have been trying to reform the rules to address such gaps and allocate also indirect responsibility (59).

The Dodd-Frank Wall Street Reform and Consumer Protection Act (60) demands of supply chain managers to check that purchased goods come from conflict-free areas and to implement measures to manage the issue and not allow funds to flow to conflict areas. As a consequence of the introduction of the Dodd-Frank Act, the topic of conflict minerals automatically becomes one of SCM rather than being restricted to the compliance procedures within individual companies. In most cases the SCM critical points lay anyway outside of the major multinational companies – for example these are smelters and refineries in the metals and mining industry (61).

A 2018 article on conflict minerals and supply chain due diligence ("SCDD") (62) summarises SCM existing practices leading to higher transparency:

- Certification of processes and single firms,
- Chain of custody – assessment of processes along the entire supply chain for every entity with financial ownership of the respective product,
- Traceability – focus on materials and following through extraction, production, processing and distribution,
- Due diligence / SCDD – focus on single firm and gathering of internal and external information as well as its counterparties.

The monitoring and enforcement of regulatory standards on supply chains has only become possible to a certain extent in the last few decades – sometimes a period referred to as the "Information Age". In his "Environmental Protection in the Information Age" work Daniel C. Esty, a Yale University Professor of Environmental Law and Policy, argues that one problem with establishing workable laws are "information gaps" that present opportunities for regulation evasion (63). Reliable mechanisms for data collection, analysis and dissemination are prerequisites for any functioning supply chain controls. The aim is to achieve a level of transparency allowing for proper checks and balances.

Transparency refers to the extent to which information is accessible to both internal counterparties to an exchange and to external third parties (64). In supply chain management ("SCM") context, transparency is linked to traceability from raw material origins to final product or service.

Traceability is the ability to identify and verify inputs, modifications and transfers at all steps of the supply chain (65). Higher traceability does not necessarily lead to higher transparency as it addresses the junctures between the different steps in the chain, but not the parties themselves. On the other hand, higher transparency almost always brings about higher traceability. A key take-away is that the aim is to achieve transparency and not only traceability – while both concepts are related, traceability does not guarantee and is not a substitute for transparency (66).

Through sharing information on complex supply networks, transparency can make it easier and less costly for participants to identify non-compliance with regulation and to improve their own practices and the practices of their partners. The end effect is reducing information asymmetries that exist along supply chains. Such reduction in asymmetrical information is commonly achieved through simplification of local context when it comes to cross-border supply chains. While this can lead to the obscuring of certain elements, the key ones will be brought at the forefront achieving a level of standardisation (67).

With the rapid expansion in the ways data and information are produced and shared, the phenomenon "radical transparency" has become increasingly prominent (68). It refers to information appearing in the public space through third parties and not wilfully disseminated

by the target actors. It is associated with new digital technologies and media changes and brings with it a transformational capacity with a positive effect on the level of total transparency (69).

Transparency is not a static situation, or an isolated action and must be shaped and re-shaped by companies and governments, clients, competitors and partners in the supply chain.
As a starting point, it is key that all parties involved at least have the option to benefit from an overall higher level of transparency.

4.5 Sanctions

As a specific and currently ongoing (as of early 2024) real-life case study on supply chain controls serve the sanctions introduced after Ukraine was attacked in a full-blown invasion in 2022. Rounds of sanctions were imposed by (among others) the EU, the US and the UK, with checks along the supply chain against direct or indirect funding of the war for the invaders. In world trade there are specific HS codes (Harmonised System codes), developed and maintained by the World Customs Organisation (70) and linked to all goods that are being bought and sold and imported into foreign lands. In its current application it mainly serves the function of uniform global goods classification in order to identify precisely the product and determine the applicable tariffs and rules. All in all, 5,000 commodity groups are covered. The HS codes turned out to be a great tool to monitor adherence to the sanctions as they are listed on customs forms when borders are crossed. Regulatory bodies, compliance teams in banks, traders, processors and producers can check if the goods that they deal with are listed by any of the sanctioning bodies. The traded products already come with detailed specifications in commercial contracts and invoices as well as information on the source. Each risky transaction is reviewed by compliance teams on paper and border agents cross-check this information providing the link between documents and the actual goods. All steps along the chain must be controlled – for example if material was processed in a third country. In late Spring of 2023, through HS codes checks, it became clear that sanctions circumvention attempts take place in some of the former Soviet Union member-states (71). Goods were being processed and then remarketed with the goal to obscure their origin – reduced traceability and transparency. The increase of trade in sanctioned goods via the Caucasus

countries was detected through an analysis of the HS codes. The reaction of European banks was to stop processing payments into the region and avoid financing material with questionable origin (71).

4.6 Artificial intelligence

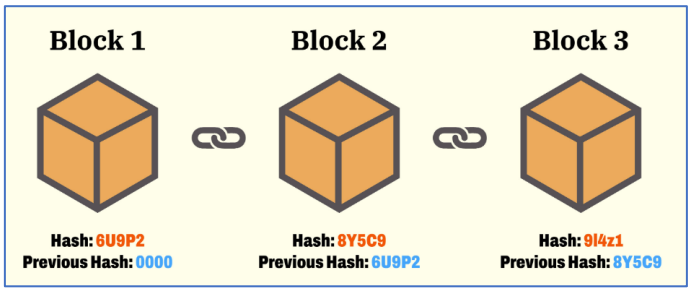
A novel idea is the engagement of Artificial Intelligence ("AI") to monitor supply chains as it can process large quantities of information with high speed and accuracy. Its capacity to learn and function autonomously and without interruption offers an improved remote monitoring and control. AI promises to not only execute, but also optimise processes with SCM recognised as one of the fields to benefit the most due to its high level of complexity (5).
Artificial Neural Networks ("ANN") is a technique, which is especially well suited to marketing as it excels in solving problems where rules and algorithms are unknown or difficult to express and a large amount of data is used (72). It is widely used for predicting and targeting sales and for customer segmentation.
Another intriguing technique is Federated Learning/modelling – because it sits on the border between AI and non-AI techniques, it might be the most intuitive to implement (73). This AI tool learns from data spread out in various locations instead of bringing data together to a single server and aggregating it. In this way, Qualitative information is addressed in a similar way humans make inferences (74).
Agent-Based and Multi-Agent Systems ("ABS", "MAS") simulate actions and interactions of and among autonomous agents/parties both as a group and as individual actions, at the end assessing their overall influence on the system (75).

4.7 Blockchain

Blockchain has already entered the world of finance, but is also making waves in logistics and SCM. A key characteristic is the open-source database with distributed and decentralised information storing (6). In a step away from depending on a centralised command centre, here all participants in the system communicate and transact with each other directly through duplicate linked ledgers, known as blockchains.

Figure 12:

Blockchain Diagram



(76)

The key benefit is transparency through the traceability of all individual transactions based on the individual identifiable blockchains. The steps in the supply chain are trackable in both directions and the participating parties in each transaction are identified.

A very important identification characteristic of blockchain records is that they are time-stamped, accessible to the network community, permanent and cannot be altered at a later point (77).

This is achieved by a process called “hashing” where an item existing in the real world is marked with a digital token, which remains connected to it. This token can be registered, traded and tracked with a private key on a given blockchain. Such ability to uniquely identify physical items opens the door to segregating certified from non-certified such items. It means that the end user of a product can follow it (and its input materials) throughout an integrated network all the way back to point of origin.

The concept works in practice and traceability was already demonstrated through a project enabled by an application from the crypto-currency firm Ethereum (78). From January to June 2016, end consumers had the opportunity to track their tuna fish through the entire supply chain, from fishermen catching it to distributors. Via a smartphone, one could follow the past of his or her fish sandwich with information about producers, suppliers, and procedures undergone in order to arrive at the end product. Through individual digital tokens, end consumers enjoyed a viable model for product certification on demand.

Blockchain raises the level of transparency, simultaneously exerting significant peer pressure on competition to match best practices. This is especially valid for brands that are highly visible and care about their social image, which is the case of players in the medical field. In addition to the presented measures ratings and financing through supranational institutions were considered, but not discussed in depth as these were deemed inappropriate and adding little value to future controls of animal testing.

Next, an opinion on the transferability and applicability of the discussed measures to the field of animal testing will be presented and the potential limitations will be discussed.

5. Borrowing from other industries to apply to medical research

Topics covered centred around regulation, social perceptions, tariffs and taxes, certifications, supply chain controls and transparency, AI and blockchain technologies.

The reviewed measures can be classified into the following three groups:

1. Regulation as a mandatory framework will be at the core in all possible scenarios,
2. Social pressure, ratings, financing will not be easily translated with limited impact,
3. Tariffs and taxes, certification, AI, blockchain and especially supply chain controls and transparency hold a substantial promise for translatability to animal testing.

5.1 Regulations

That change without regulations will not be possible is clear, but it is also critical to strive for maximum impact. Directive 2010/63 lays the groundwork for phasing out of animal testing for medical research, while maintaining flexibility.

EU Regulation 2017/821 on conflict minerals is a good example of how rules can be designed in such a way, as to work in sync with other existing measures – in its case the regulation being aligned to the OECD's Due Diligence for conflict minerals. By combining main concepts of more than one regulatory body, the area of coverage can be expanded.

Regulations are also flexible and subject to change and adaptation – the current position of the EU on a gradual phase out of animal testing for medical research and its replacement with alternative methods demonstrates that the regulator retains the ability to determine the speed and degree of change.

In the case with the ban on animal testing for cosmetics in the EU, we have practical proof that regulations can work without hurting businesses.

5.2 Social perceptions, ratings and financing

Unlike in many other fields, social pressure cannot be counted on to keep corporates in check when it comes to animal testing for drug development – there is relatively little visibility and low level of social engagement to support a ban as already described in the Kabene und Baadel article above. The data quoted implies that there is an intrinsic conflict of interest, where any R&D related to drugs potentially benefits humans with a majority believing that

animal testing for medical purposes should continue. In contrast, the support for phasing out is very strong when it comes to cosmetics.
Ratings work well in the world of finance but would be less suitable when it comes to lab animals and controls related to experiments. In accounting there are very strict sets of rules on data presentation, which create a solid basis for comparability among accounts of various companies, even when active in different industries. When it comes to animal testing, the drugs being developed, the testing procedures, the jurisdictions and their regulations, the results are much more unique and thus difficult to put under a common denominator and to compare to each other. There are many types of study design depending on stage (pre-clinical, clinical, epidemiological, etc.) and whether the research is primary or secondary (79). Such a variety is prohibitive to a reliable ratings system.
Financing is important above all in industries that are very capital-intensive and where debt and equity are raised short to medium term in the financial markets with break-even and positive returns coming in often already after a couple of years. In contrast, medical R&D has a much longer time horizon with uncertainty of return for each individual drug much higher.

The third group of measures shows the most promise when it comes to translatability to animal testing. Supply chain controls and transparency are the critical elements to ensuring that the moral problem in animal testing does not get exported to locations with a weak or not strictly enforced regulatory environment. AI and blockchain technologies can improve the workability of supply chain monitoring and control.
Tariffs, taxes and certifications can round up a more holistic approach to controlling who is involved in the development processes for drugs and how these processes are structured.

5.3 Supply chain controls as a core measure

To simply argue that supply chain controls can be translated to the field of animal testing would be an understatement of their importance. In the context of the Information Age with its available channels to share data, controlling the supply chain is an expectation and a must – by regulators, investors, society at large. The goal is to ensure that drugs and treatments are developed without the involvement of animals, being able to transparently trace all processes

and ingredients from the initial idea to the actual pill or treatment procedure offered to the end consumer.
It is of critical importance to always consider that the supply chain must be addressed with the understanding that diverging regulations could mean that one and the same part of the supply chain can conduct procedures that are legal in certain locations, but not in others. It should be therefore avoided that R&D findings from animal testing meant for a market where it is allowed end up being used for marketing and in production for markets where animal testing will have been outlawed. This is especially relevant for global pharmaceutical players.
Supply chain controls must address transparency and bring benefit for participants who readily adhere to the required procedures. Among others, such benefits can take the form of distinction by certification (making the certified a desired partner in the medical field), lower fiscal burden (differential taxes or tariffs based on presence or lack of animal testing in specific projects) or preferred status for consumers that would be consciously interested in using products free of animal testing.

Applied in practice to medical research, a system similar to the HS codes specific to the medical field could provide a very robust tracking tool within a supply chain, especially when combined with blockchain technology. Such codes will be individually assigned to all ingredients and products of research – inputs and outputs. Ideally these will be standardised – any input substance would have the same unique identifier anywhere in the world.
In addition to input materials and end products, codes can be expanded to a subcategory with identifiers assigned uniquely to persons, facilities and even sub-units within larger facilities. The identifiers will be permanent and will constitute part of the CV of anyone involved in medical research and will provide industry-related designation of facilities. Such personal identification will crucially be also to the benefit of the individuals, allowing for the tracking of accumulated experience and involvement in projects. Facilities' identifiers will deliver focused data on participation in specific research projects, institutional know-how and track-record on keeping up with regulations.
The information will be continuously updated on qualification and specialisation (for individuals), certifications, services offered and purpose (for facilities), as well as potential

areas of application and working mechanisms when it comes to substances. Such a system will not be only a control mechanism, but also a marketing tool for all certified participants.

5.4 AI and blockchain, taxes and tariffs, certifications

Through blockchain technology all supply chain elements will be individually connected and the desired traceability will be achieved.

As a next step to address transparency, one will have the opportunity to connect the individual identifiers to the blockchain transactions and follow both downstream and upstream.

Since traceability and transparency would allow patients to take a trip back in upstream direction to study the development process for their pills (similar to the Ethereum fish demonstration previously described), involvement and awareness will be raised, resulting in increased social engagement as a welcome side effect.

While such a level of transparency might also be difficult for pharmaceutical producers to accept, end consumer desire for expanded information on the medications they are taking might create an advantage for the producers willing to share.

Artificial intelligence can play a significant role in simplifying interactions and in optimising processes and controls.

ANNs (Artificial Neural Networks) can add value in selection based on evaluation of partners based on predefined criteria. Established track record, audited procedures and personnel qualifications for the necessary research can all be desired matching tools. The strength of ANNs is that they can work as predictive mechanisms and be employed in designing the supply chain – instead of identifying the problem at a future point when a drug will have been developed. This will have a strong positive financial impact by avoiding situations with high write offs where drugs are not marketable due to a breach of animal testing regulations.

Federated Learning can step in to perform checks in networks with decentralised locations, addressing the outsourcing in R&D to various locations as well as diverse suppliers. By providing results more intuitive to the way humans think, Federated Learning can successfully link ANNs to ABS and MAS (Agent-Based and Multi-Agent Based Systems).

ABS and MAS bring in a game theory approach and could be useful to determine individual players' propensity to break the rules. While in this approach there would be no proof-based

findings (as these tools are based on simulations), supply chain parts with higher probability for breaches will be identified and resources to monitor such parts better allocated with higher hit-rate, disincentivising future wrongdoings.
The combination of these three AI capabilities and blockchain enables the processing and analysis of large data quantities, bridging the gap between AI algorithms and human thinking, introducing a game theory aspect to make simulations, all the while with identification attached to every transaction for traceability and transparency.

Tariffs and taxes should be used to encourage change before definitive regulations are in place – as is the case with the phasing out of animal testing in medical research in the EU – where development and implementation of alternative methods is encouraged, but there is only conditional ban on animal testing. This fiscal instrument can be linked to still accepted identifiable practices that are targets for elimination. It offers flexibility in providing a measurable direct financial impact on medical companies by affecting their margins.
A regulatory two-step approach with a transition period making animal testing expensive will stimulate R&D via alternative testing methods and wider adoption of such available methods. Such an approach not only concentrates on identifying actual rule-breakers, but rather uses tariffs and taxes as a tool and a stimulus to encourage the transition to animal-free R&D.

Certification must be extended from individuals to organisations such as research facilities, transport companies, marketing entities and retailers. It is another way to offer competitive advantage to participants of the supply chain. With ANNs' marketing and matching capacity, it could empower medical companies to easily design research projects to include mostly or only certified partners already during a transition phase. Certification has the potential to financially benefit the certified players and will gradually put peer pressure on the rest.
To be effective, certification will need to be performed and monitored by a credible independent organisation with clear methodology and ideally global cover.

6. Limitations and risks

6.1 Potential health risks to the human population and popular support

The ultimate goal is for the human population to be well covered by medical care and to have adequate available and accessible treatments. Popular opinion is split on whether animal testing is still necessary or not (28).

Without a doubt, the use of animals has historically been instrumental in the development of treatments – a benefit that will have to be given up at some future point. It is also very difficult to quantify the potential risk from relying on new approaches.

Related to concerns about adverse health effects for the human population is the speed of adoption of new regulations. Pushing for a change too quick can swing the pendulum too far, leading to companies employing unproven alternative testing methods under regulatory pressure or pressure to remain competitive and to keep or gain more market share, thus tolerating excessive risks during drug development.

6.2 Diverging regulations and their functionality

The legislative landscape across the world and even among the developed economies is very diverse. Given the complexity and importance of medical research to the human population, this can contribute many unpredictable conundrums when phasing out of animal experiments gets effectively underway – as introduction and implementation of regulation will likely take place with various speed in various jurisdictions.

Diverging regulations along the supply chain will complicate the flow and monitoring of goods and activities.

Legislation must be drafted in a way that enables it to achieve its goals with competent drafting, control and enforcement are requirements to achieve the desired effect. A good example is the discussed Civil Action lawsuit in California (54), which was unsuccessful, despite existing related regulatory framework.

6.3 Transparency pitfalls

Seen as inherently positive, transparency can also have unintended consequences and make the powerful even more powerful (80).

It has the potential to inflict harm on weaker parties, thus exacerbating inequality – for example by financially disadvantaging willing, but vulnerable parties. Stronger, more powerful players employ typically more sophisticated information processing systems and are better able to use available knowledge to their advantage, thus increasing the gap between themselves and the "laggards" (81). There are market players who cannot afford to meet the regulatory reporting standards and to spend effort and funds on related external services making it difficult to set up "fair" trade rules (82). Parties sharing information should be motivated to do so and should benefit from it. The information itself needs to be useful for external parties and its sharing must not harm its providers – such as losing competitiveness in a race to a new drug between medical companies.

Transparency can also be abused as a smokescreen for companies looking to greenwash their image. Social pressure and the need for a clean image can push companies to spread out false claims on their operations (83). Under financial pressure, a company may choose to shy away from incurring real costs and instead settle for empty words – as described to mean "greenwashing" (84).

6.4 Financial motivation for foul play and asymmetrical information

Medical research has gone into the financial realm and for the most part it is run and controlled by investors whose goal is to make return on their invested funds as is very well described in Timothy Snyder's excellent book Our Malady (85). The propensity for wrongdoing where money can be made will remain.

The real limitation here is not only that some players will try to cheat the system, but that often such players will have advantage in terms of asymmetrical information against regulators and consumers.

6.5 Negative effects from free trade perspective

The introduction of unilateral regulatory measures brings along benefits (as described earlier in the context of the *Brussels Effect*), but also generates its own challenges:

- Tensions between countries appear as such measures could be construed as non-tariff barriers to trade, leading to various countermeasures by non-EU member countries and generating unintended detrimental financial and social effects,
- The stricter EU regulatory environment could open the door for regulatory arbitrage – "taxonomy shopping" (33) – for businesses without EU nexus in the quest for higher margins.

6.6 Willingness and capability to make the switch and associated costs

When things are done in a certain way for long periods of time and they seem to work, it is often difficult to change mindsets. This refers not only to current activities, but also to the availability of learning opportunities and infrastructure to prepare for the wider introduction of alternative methods in practice.

Even when the willingness is there in less developed jurisdictions, it could well be that the resources to make the switch are not available.

For the millions of animals that are used in test environments annually there is an existing infrastructure, put together at a significant cost and consuming effort to maintain. During a transitional period, the existing practices will need to be maintained in parallel to introducing alternative methods resulting in additional high costs.

6.7 [Re-]qualification in alternative testing methods

Many highly qualified specialists will need to either newly qualify or find niches where their current skills will be valued with fulfilling new assignments. If this is not the case, there is a danger of an immense loss of precious existing know-how.

Newly qualified scientists will also be needed and this is an expense of resources before the returns will be yet available or even sure to come.

6.8 Adaptability of alternative testing methods

At present the laboratory animal models are to a large extent standardised, which allows their wide and flexible use. When it comes to alternative methods, they need to still prove reproducibility and adaptability to fulfil various R&D needs since experiments are of a widely

varying nature. As reflected in a recent article "…there is still a great need to discover and develop new, accurate, and reliable methods to replace experimental animals." (86).

6.9 Ability to control compliance

In a global world for experimental drug development, coupled with a global market, ensuring compliance becomes a mammoth effort, which does not directly result in an increased top line. Monitoring, documentation and verification need to fit various local regulatory frameworks but must simultaneously work at a multinational level as many of the drugs in circulation are researched, developed and produced by companies operating globally. Applying checks and balances in itself brings up additional costs, which will either affect business margins or be passed on to patients.

7. Conclusion

Are there already existing functional measures in various other industries, which measures would be suitable as checks and balances to prevent the exporting and outsourcing of outlawed animal testing? The simple answer is: Yes.

Significant changes are taking place in the field of medical research and in the way laboratory animals are being used in the process. The pace of change around the world varies without consistent regulations. One of the upcoming challenges is to ensure that banned animal testing practices in one place do not move to other jurisdictions, thus exporting a moral problem.
The goal is known – to completely phase out R&D involving animals. There is still no clarity on timeline and how this can be monitored and enforced.

Since this issue is a relatively new and developing one, certain other global industries have already faced and addressed similar situations. Some of the measures employed in these industries can be helpful in preventing the export of the moral problem during and after the phasing out of animal testing.
The findings of this paper indicate that generally there does not seem to be a coordinated approach across these measures to make cross-border controls work in sync. There are possibilities for evasion and a recent example with sanctions circumvention demonstrates that. Nevertheless, each individual practice has its own positive impact in the context in which it is applied.
Some of these practices hold promise for being effective in addressing the monitoring and controls of animal testing. Leading in terms of importance here is supply chain management, supported by new AI and blockchain technologies, certification and selective tariffs and taxes during a transitional period to a complete phase-out of animal testing.

There is an existing precedent, which serves as a proof that a well-directed and executed phase-out can work and will not result in negative consequences for animals or the human population – the regulated elimination already eleven years ago of animal testing related to cosmetics products marketed and placed in the EU was a success.

Targeted and enforceable legal framework is a pre-requisite to allow the applied measures to address the moral problem of exporting animal testing – through sufficient traceability and transparency. A coordinated approach would result in increasing peer pressure and external pull through higher social awareness.
The EU and US markets already have specific phase-out supporting measures and the discussion is at an advanced stage. There is evidence that regulations tend to spread out when introduced in a critical centre of global trade, driven be the desire of external market players to align to it, in order to be allowed to continue to do business with and in such centre of global trade. *The Brussels effect* is a good example.

To phase out animal testing, the establishment of reliable alternative methods is a prerequisite. Switching to alternative testing methods must be structured in a way to bring about financial benefits to the adopters and overall competitiveness in the marketplace must be maintained. Information sharing should not hurt any segment of the market players but serve as a benefit to all participants.

For centuries medical research has been heavily dependent on pre-clinical trials with animals and the benefit to the human population has been tremendous in historical context. The phase out mandates a high level of care and needs to address a number of limitations and challenges, ensuring that regulations, financial motivation, existing know-how and new knowledge can be all put to work together to arrive at the best outcome for both animals and the human population, without hindering free trade, market competitiveness and R&D progress. The process can be a success, there are existing solutions that can be adapted and adopted, but prudence is paramount and proper structuring and execution should take precedence over speed.

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