

# First the Trial, Then the Moralizing

When is it legitimate for laws to cite ethical standards? This issue is the focus of an Independent Research Group headed by **Silja Vöneky** at the **Max Planck Institute for Comparative Public Law and International Law** in Heidelberg. Doctoral student **Mira Chang** is investigating the circumstances under which international drug trials may be unlawful.

TEXT **HUBERT BEYERLE**

In the movies, it's very simple: there are the good guys and there are the bad guys. In the recent film version of John le Carré's novel *The Constant Gardener*, the bad guys were the guys from the unscrupulous drug companies who tested their new products in Africa and were willing to accept a few deaths along the way. In an afterword, the author fulminates that "by comparison with the reality, my story [is] as tame as a holiday postcard."

In novels as in films, the world is allowed to be black and white. The reality, however, is somewhat more complex. Just how complex is revealed only through systematic research. But how do you research good and bad or right and wrong in the context of verifiable science?

The scandalous aspect of medical progress is not new: it lies in the divergence between those who provide innovation and those who benefit from it, since advances in medicine – as in every

other branch of science – are made by trial and error. The only difference is that, in medicine, errors can be fatal. Theory goes a long way, but not quite far enough. And sooner or later, in the development of new drugs, there comes a time when the animal experiments have all been conducted and the substance must be tested for the first time on a human subject. He or she becomes part of the experiment: the means and not the end.

## **PHARMA INDUSTRY FOCUSES ON POOR COUNTRIES**

The globalization of pharmaceutical research has further intensified this moral conflict: more and more drugs are being tested in poor countries. In the past 15 years, the focus of drug research has gradually shifted to Latin America, Asia, Eastern Europe and Africa. China and India in particular are the new hotspots in what has since become a multi-billion euro market.

There are two main reasons for this: supply and demand. On the one hand, trials are expensive. It can take ten years or more before a new drug is approved for use. The cost of bringing a product to market can run into the hundreds of millions, even to a billion euros. The figures are disputed, but this much is certain: trials are expensive. That is why it is worth conducting them in poor countries.

But it isn't just money that motivates drug companies to internationalize their research: fewer and fewer people in the rich countries of Europe and North America are willing to act as guinea pigs. Some studies indicate that more than half of the trials conducted worldwide are now taking place outside of the established US, EU and Japanese markets. This globalization of drug research brings with it a plethora of moral issues. The pharmaceutical companies and their service providers, the contract research organizations, have

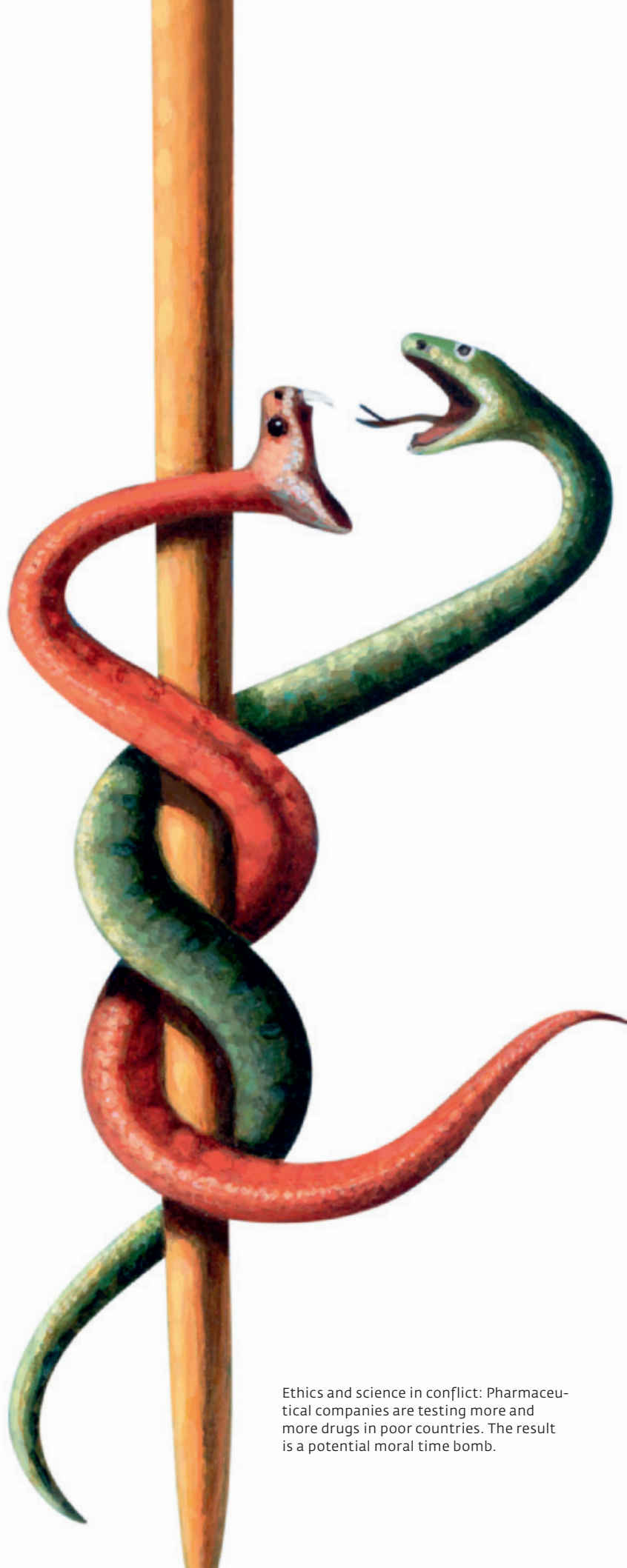


Illustration: corbis

Ethics and science in conflict: Pharmaceutical companies are testing more and more drugs in poor countries. The result is a potential moral time bomb.

recognized this fact and consistently emphasize their observance of “ethical standards.”

Indeed, there has long been an abundance of international codes, conventions and standards of good practice. Regulatory authorities, the drug companies themselves and physicians have laid down international rules that at least sound good. They have even established ethical committees to oversee compliance with the rules. Basically, it is always about expressing commitment to “ethical principles.” Does that mean the problems are solved?

“No,” says Mira Chang. As a doctoral student at the Max Planck Institute for Comparative Public Law and International Law in Heidelberg, she is highly critical of these frequent references to ethical standards. “Ethical standards are all well and good, but it’s more than just a matter of ethics. There are some central legal issues to be considered, as drug trials can in-



Can drug trials infringe on international human rights? Mira Chang is researching this issue at the Max Planck Institute for Comparative Public Law and International Law.

fringe on human rights,” she says. “There are international declarations and guidelines that define ethical standards, but when these emanate from private institutions, their legitimacy may be questioned.”

### **NO CLAIM TO REPRESENT ALL DOCTORS**

The most important declaration, the *Ethical Principles for Medical Research Involving Human Subjects*, was adopted by the World Medical Association (WMA) in Helsinki in June 1964 and most recently amended in 2008. This document specifically states that the welfare of the patient must take precedence over the interests of science and society. In addition, particular consideration should be given to the special needs of economically and medically disadvantaged persons.

That sounds good. Isn't that all there is to it? “No, most certainly not,” says Mira Chang. In fact, for the legal experts, this is where the work starts. “This declaration is not a legal docu-

ment,” Mira Chang continues. “It was adopted by a body of experts whose legitimacy is open to question. This body is dominated by European and North American medical associations. It cannot claim to represent all physicians. And third parties, such as the test subjects, have no say at all.” What's more, membership and voting rights are dependent on payment of a membership fee. Mira Chang is critical: “This is a rather unconvincing basis for a body whose ethical principles are supposed to apply worldwide.”

In its purest form, the whole moral dilemma surrounding medical research is reflected in the placebo problem. Scientists and regulatory authorities largely agree that placebo tests are necessary in order to be reasonably certain, firstly, that a drug is safe, and secondly, that it works. Ideally, such tests are conducted as a double blind study with neither patient nor doctor knowing which pill is which. However, doctors are under a professional obligation to administer the best medicine available. So how can they intentionally withhold a supposedly effective medication from some of their patients?

The dilemma lies in the fact that, on the one hand, those who receive the medication are being used as guinea pigs with no real certainty as to the effect, while those who receive the placebo are denied the medication that might well benefit them. Both aspects are ethically problematic. In Mira Chang's view, there is only one solution: “If another proven

drug already exists, in the case of life-threatening conditions, placebo tests cannot be justified.”

### **RESEARCH AT THE FRONTIER BETWEEN ETHICS AND LAW**

Science cannot ultimately determine what is morally right or wrong. “Morality as an empirical phenomenon may be the subject of scientific study, but there are many moral problems to which ethics cannot provide a single, unquestionably correct answer,” says Silja Vöneky, a professor at the Albert Ludwig University of Freiburg and head of the Independent Research Group at the Max Planck Institute in Heidelberg. There is, however, one key difference between morality and ethics. “Ethics, as a reflective discipline, is a normative branch of science. It addresses the questions: How may we act? What are we allowed to do? Ethics considers whether an answer to these questions is inherently consistent or contradictory,” she explains.

Silja Vöneky works at the frontier between ethics and law, the so-called ethicalization of law. She and her research group are investigating where and how extra-legal ethical rules have found and find their way into legal systems worldwide, and how references to ethical standards can be legitimized. It seems self-evident that the provisions of the law should not contradict ethical principles or moral intuition.

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“Nevertheless, there is a problem, as there is an increasing tendency for laws to include explicit references to ethical principles, and to grant decision-making authority to so-called ethics committees. Who can say that these committees are genuinely competent? In any case, there is justified room for doubt as to whether physicians alone are the right experts to rule on ethical issues with regard to questions of research on human beings,” says Silja Vöneky.

Ethics codes and ethics committees are a relatively new phenomenon. Until a few decades ago, the field of medical research – in practice, at least – seems to have been virtually untouched by ethics or by law. The general belief in progress held sway into the 1960s.

When physician and scientist Jonas Salk wanted to test his polio vaccine against an inert placebo in the US in 1954, the local health authorities refused to take part.

The bone of contention was not, however, the new vaccine, but the inert placebo. So great was their faith in research that the authorities did not consider it acceptable to deny children the new and untested vaccination. When the results of the trials were published, the event attracted national attention. Even the church bells were rung.

This optimism was shattered rather abruptly by the thalidomide tragedy. Between 1957 and 1961, thousands of pregnant women worldwide were prescribed an antinauseant containing the

active ingredient thalidomide. The drug had barely been tested, since there were few if any regulations that required it. In Germany alone, some 5,000 children were born with severe birth defects.

#### DRUG TRIALS ULTIMATELY REQUIRE HUMAN SUBJECTS

One of the consequences was a clear change in the attitude of experts and the public at large toward medical research. Worldwide, development of reg-

Reflecting on fundamental values: The attitude of both experts and the public toward medical advances has changed in recent years. (Banner: human dignity is unviolable)



» The legal studies undertaken by Mira Chang are aimed not just at forming an ethical appraisal of the issue of global drug trials, but at getting a firm legal grip on it.

ulations followed. Since then, drugs have been subject to strict procedures before receiving approval.

The intention is to protect patients. The ethical downside, however, is that drug trials ultimately require human subjects.

To justify the procedure in ethical terms, a central principle applies: it is of the absolute essence that patients give their free, informed consent. This was already one of the ten points contained in the Nuremberg Code issued in 1947 by a US military tribunal in the wake of the Nuremberg Trials of Nazi war criminals. The Tribunal had found 13 German doctors and three other high-ranking accused guilty of medical experimentation on human beings, and sentenced seven of them to death.

### THE TUSKEGEE STUDY WAS TERMINATED AFTER 40 YEARS

For years, these principles were known, but barely heeded. Prior to the 1970s, few if any regulations gave legal force to these ethical principles. It took the thalidomide tragedy and the equally infamous Tuskegee experiment in the US to finally engender an increasing awareness in the 1960s and 1970s that the pharmaceutical market had to be regulated.

In the Tuskegee study from 1932 onward, hundreds of black Americans suffering from syphilis were denied the antibiotics that were already available at the time in order to observe the natural course of the disease. It was not

until the 1970s that reports of the study appeared in the newspapers, prompting a nationwide outcry. The experiment was terminated after about 40 years. Presidents Bill Clinton and Barack Obama both apologized for the human experimentation that was carried out over decades.

The legal studies undertaken by Mira Chang are aimed not just at forming an ethical appraisal of the issue of global drug trials, but at getting a firm legal grip on it. This is no easy task, given that legal systems are still essentially national by nature, as sovereignty ultimately lies with the nations themselves. But who has jurisdiction when a US company tests its drugs in Africa?

This is a matter of international law – a legal discipline that still attracts suspicions of idealism, particularly since, in recent years, individual human rights have consistently gained in significance at the expense of collective national sovereignty, as evidenced by the debate about the legitimacy of military deployments in the Balkans, Afghanistan and Iraq.

“There are currently some interesting developments in the field of international law. Human rights are gaining in importance and companies are, to some extent, acquiring legal personality. This could be very significant for the debate about drug trials,” says Mira Chang. But there is still a long way to go – and so far, the patients concerned have seen little benefit. “Because this still doesn’t result in many obligations

for companies.” But that could change. Sooner or later, citizens of an African country may be able to bring legal action against Europe or the US for breach of their human rights if the conditions of a trial clearly do not meet certain minimum standards.

### THOSE WHO DO NOT HELP ARE JUST AS GUILTY

In fact, this is not such a utopian vision: it is already happening, thanks to an unusual law in the US that permits such claims. The company Pfizer recently felt the effects. During an epidemic of meningitis in Nigeria in 1996, Pfizer tested a new antibiotic against an established drug. Eleven children died, five of whom had received the new drug Trovan, while six had been treated with the proven Ceftriaxon – but, according to the written judgment, in a dosage that was known to be too low.

The case is a prime example of the moral failings of pharmaceutical companies. Nevertheless, Trovan subsequently received partial approval in the US. Last year, the competent US court admitted the claim against Pfizer. But that is not really a solution to the problem. This much is certain: those who do not render assistance despite being able and obliged to do so are guilty of immoral conduct and liable to punishment. But who does that apply to? In the case of a road accident, it clearly applies to those who were at the scene but failed to help. But who is “at the scene” of the AIDS epidemic in Africa?



Scandals such as those provoked by thalidomide (also branded as Contergan, above) and the Trovan trials on child patients in Nigeria (top photo shows a demonstration against the Pfizer group) serve as examples of the moral failings of pharmaceutical companies.

Mira Chang proposes that, in the case of drug trials, the buck should stop with the pharmaceutical company conducting the trial. Conducting a trial conveys an obligation. What's more, the party conducting the trial should be responsible for other things as well, such as proper follow-up care for the patient. That, too, is not a matter of course.

The drug companies' arguments would then collapse. They regularly emphasize in their defense that "We didn't

have to conduct the trial. If we hadn't, those concerned would be worse off, with no treatment at all." It is indeed true that the health systems in many countries of the world are so poor that taking part in a trial is the only treatment option available. But does this "what if we hadn't?" have any role to play? "It cannot be a corollary of the differences between healthcare systems that these people should be treated differently under the law," says Mira Chang.

What does the future hold? Actually, even today's imperfect legal system offers some scope for improvement. "I think we can make a start with the approval procedures," believes the Max Planck doctoral student. EU law requires that overseas studies be accompanied by a statement that they meet the ethical requirements of the EU Directive on Good Clinical Practice. This Directive, in turn, refers to the Helsinki declaration mentioned above. "The terms are very vague," says Mira Chang. "They need to be better structured with legally binding effect."

#### MEDICAL RESEARCH IS THE MAIN BENEFICIARY OF STANDARDS

One concrete legal consequence might be that trials will be approved only if it is intended to subsequently make the drug available in the country where the trial is conducted. Breach of this undertaking could at least attract retrospective sanctions. "To me, it seems that there should be an ethical obligation to allow the population in the country where the trial is conducted to share in the potential benefits, primarily by distributing the drug there once it is approved. This could also be legally framed," says Mira Chang.

There have already been some improvements in recent years. Many countries, China among them, have established ethical and legal standards of protection that, at first sight, appear to be as good as those in Europe or the US. "But only prima facie," Mira Chang



"There is justified room for doubt as to whether physicians alone are the right experts to rule on ethical issues." Silja Vöneky heads an Independent Research Group at the Max Planck Institute for Comparative Public Law and International Law and is a professor at the University of Freiburg.

continues. On closer examination, it is evident that medical research is the main beneficiary of these standards. They are aimed at raising data quality and the subsequent likelihood of approval. They are only partly intended to protect patients. Also, there is little evidence of whether the standards are adhered to in practice.

As a result, legal research needs to take an approach that is as visionary as it is down to earth and pragmatic. There is much to be wished for, but

what is realistic? And what does realistic mean? For law experts, realistic means the ability to develop and derive a compelling position from generally recognized material, such as the Declaration of Human Rights.

In this situation, a unique feature of the law is revealed that makes the work so difficult, but at the same time so interesting. The law is man-made, but it also has a life of its own and is not entirely controllable. It continues to develop in the context of its cultural en-

vironment. What was normal 50 years ago is impossible today, and vice versa. Above all, legal norms today are far more explicitly dependent on ethical norms than was once the case.

### THE DIFFERENCES ARE GROUNDED IN CULTURE

Today, it is held as self-evident that a legally satisfactory solution must also ultimately be morally convincing. Nevertheless, moral intuition may be important, but it is not everything. "Counter-intuitive solutions are permissible, but they require far more justification," says Silja Vöneky.

In recent times, ethical conventions, codes and ethics committees have acquired increasing importance everywhere, not just in medicine. While there is common ground as far as general principles in essential issues are concerned, when it comes to details, there are substantial culturally grounded differences. For instance, between a utilitarian viewpoint, which attaches a relatively high value to sci-

The World Medical Association adopted its "Ethical Principles for Medical Research Involving Human Subjects" 47 years ago. The declaration was last revised in 2008. It states that the welfare of the patient must take precedence over the interests of science and society.



entific progress, and a deontological perspective, which attaches significance to ethical standards per se and tends to favor the protection of the individual – such as expressed by the categorical imperative that no person shall be exclusively the instrument of another.

Asian value systems have yet other emphases. The drug trial issue cuts right across this: on the one hand, there is the benefit to mankind; and on the other, the right of the individual to physical inviolability. Which ethical principle is correct? There is no definitive answer. “That is why ethics committees cannot have the last word,” says Mira Chang. ◀

## GLOSSARY

### Deontology

Deontology refers to a class of ethical theories that define certain actions as intrinsically good or bad. There are various shades of deontological ethics. While moderate deontologists also admit the moral relevance of the consequences of an action, moral absolutism proscribes certain actions under any circumstances, regardless of their consequences.

### Ethics

A major branch of philosophy, dealing with morals and, in particular, their justification. Ethics is the study of human actions and is the starting point for various disciplines such as legal, political and social philosophy.

### Utilitarianism

Utilitarianism bases the ethical evaluation of an action on the principle of utility, applying the maxim: “Act in a manner that promotes the greatest good.”

### World Medical Association

The WMA is a confederation of national medical associations. It was founded in 1947 and represents almost 100 national professional bodies. The WMA endeavors to promote high ethical standards of healthcare and provide physicians with ethical guidance in the form of declarations and position papers.

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