HUMAN GUINEA-PIGS
ON THE CHEAP

An exclusive investigation carried out by the Berne Declaration into the offshoring of clinical trials and ethical violations during the testing of drugs on vulnerable populations.
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OUR DEMANDS
Imagine what would happen if you arrive at the test centre for your next compulsory road test without your car but with an impressive pile of documents, explaining to the inspectors that they can base their assessment of the condition of your car on the results of the tests you performed on your car yourself, which can be found in the report you’ve produced. They would think you were mad. This example from an eminent Danish medical researcher illustrates how the marketing authorisation procedure of drugs works.

Clinical drug trials are at the heart of this system. Decided upon, financed, conducted and analysed by the multinational pharmaceutical companies themselves, they form the subject of voluminous reports that are examined by Swissmedic, our “drugs policeman”, in order to give a ruling on the efficacy and safety of the treatment being tested. However, given that the properties of the product are either skilfully embellished or cleverly concealed, that the data is obtained under ethical conditions scarcely questioned by Swissmedic, and that Swissmedic depends on the pharmaceutical industry for its financial survival, the least that can be said is that the whole system faces a crisis of credibility.

When drug testing in poor countries is mentioned, images from John Le Carré’s novel *The Constant Gardener* and the film of the same name immediately spring to mind. However, throughout the scandals linked to the increase in offshoring of clinical trials in southern and eastern countries, the pharmaceutical companies have been perfecting their strategy: they do most of their testing in emerging countries where the infrastructure and health personnel are purportedly good in all respects, but always behind closed doors and with a plan to move on fast when necessary. And international ethical standards get trampled underfoot in the process.

The dynamics of the global pharmaceutical market are such that the Swiss authorities have considerable leverage to prevent medicines tested under unethical conditions being marketed in our country. This needs to happen now. Switzerland’s health minister, Alain Berset, has the power to make this happen if he dares to face up to the omnipotence of the pharmaceutical companies. If allowed to carry on acting as described above, they will determinedly continue to develop ever more expensive drugs at the cost of vulnerable populations, purely for reasons of profit. If nothing is done, further scandals are likely to arise very soon.

Patrick Durisch,
Health Programme Coordinator
THE ETHICAL COST OF OFFSHORING

The testing of drugs on humans is a crucial stage in the process of research and development (R&D) and often takes the form of trials conducted in parallel in a number of different countries. For strategic reasons, but also to maximize profit, pharmaceutical companies are increasingly conducting such trials offshore in developing countries, particularly emerging countries. All the big companies are involved, including the Swiss firms Roche, Novartis and Actelion. However, this “globalisation of clinical trials” entails frequent ethical violations.

Although the majority of clinical trials are conducted in the United States and Europe, there is a movement towards offshoring to developing and emerging countries. The proportion of testing in emerging markets increased from 10% in 1991 to 40% in 2005; then between 2006 and 2010 it continued to increase, while the proportion of clinical trials conducted in Western Europe and the United States fell from 55% to 38%. Although figures for clinical trials worldwide differ due to the absence of any comprehensive binding international register, all estimates point to the same trend: offshoring is increasing, particularly for the most costly ones, the phase III trials. The countries primarily in question represent a huge potential market for the multinational pharmaceutical companies (see bar charts, page 5).

Offshoring leads to a major reduction in costs (see map, page 13). The reality is that there are more potential subjects who are more inclined to take part in a trial because, in many cases, it represents their only treatment option. Labour, recruitment and monitoring are also cheaper. The overall cost for a patient in China is a third of that in the United States. Where regulations are more lax, procedures are often faster and the measures in place for the protection of subjects are less strict. Recruiting in a developing country can reduce the length of a trial by up to six months on average. Shortening the clinical research phase makes it possible to prolong the very lucrative period during which a drug is marketed. Each additional day of marketing a drug in a monopoly situation (where it is protected by a patent) can be worth in excess of a million dollars.

This “globalisation of clinical trials” is extremely problematic. It does not benefit, in real terms, the availability of or access to treatments in the countries where trials are held. And as our investigations in various countries have shown, it entails major ethical violations.

Offshoring: but at what price? Most of the populations in developing or emerging countries do not have access to basic healthcare because there is no social security or health insurance system. Patients must pay for drugs out of their own pocket, and many drugs cost much more than they can afford. Seen as highly risky in industrialised countries, taking part in a clinical trial represents for many the only hope of (better) care. When a company tests its drugs offshore with the sole aim of speeding up its research, without due regard to the relevance of trials for the participating population or to the level of protection given to them, it can be considered to be exploiting the vulnerability of local populations.

On the other hand, regulation is less strict in developing countries and...
Almost half of all drugs marketed in Switzerland were tested in developing or emerging countries.

**GEOGRAPHICAL DISTRIBUTION OF CLINICAL TRIALS**

**THE GLOBALISATION OF CLINICAL TRIALS**

A critical stage
Clinical trials represent a crucial stage in the R&D process. Between 60% and 70% of the R&D budget is allocated to them, or 80 to 90 billion dollars out of the 130 billion spent annually by the pharmaceutical industry worldwide. The fact is that once an active substance has been discovered, synthesised and studied in the laboratory, its efficacy and safety have to be tested on humans. Companies do this in three waves of trials, which serve as the basis for the marketing authorisation of a drug (i.e. licensing). A fourth phase is sometimes undertaken for the purposes of complementary research following licensing. Regularly demanded by the regulatory authorities, this last stage is often criticised for being subject to inadequate supervision, and is thought to serve economic (marketing) ends rather than scientific ones. Pharmaceutical companies are increasingly entrusting the conduct of clinical trials to specialised companies known as contract research organisations (CROs), which organise this type of “turnkey” testing in almost half of all drugs tested worldwide. This sub-contracting multiplies the number of players and makes the traceability more difficult. It also raises the issue of dilution of responsibility: who from the promoter, the CRO, or the research team, is responsible in the event of an ethical violation? According to the international texts in force, it is the promoter or sponsor of the study who carries ultimate responsibility for the proper conduct of clinical trials, even though sponsors sometimes attempt to shift this responsibility onto other players.

**SEVERAL TYPES OF CLINICAL TRIALS**
The BD’s research concentrated on clinical drug trials sponsored by the multinational, mainly Swiss, pharmaceutical companies. But there are many other types of clinical trials. For example, a certain number of clinical trials are conducted by not-for-profit institutions such as academic centres, although an estimated 80% of all trials conducted worldwide are financed by industry. Also, there are trials related to medical equipment, treatment strategies or surgical procedures, not about drugs. Others do not involve any experimental situation (or intervention) and are purely observational (for example, the study of the dynamics of an illness within a given population or the study of behaviours in relation to health). According to the currently most complete international database, out of the approximately 149,000 clinical trials registered globally in July 2013, only 80,000 involved the interventional testing of drugs. (www.clinicaltrials.gov, status on 27.7.2013).
Almost 70% of the R&D budget, i.e. more than 80 billion dollars, is spent on clinical trials.

Researchers involved in clinical trials:
- Promoter (usually a pharmaceutical company): financing, overall responsibility and final analysis of data.
- CRO: company contracted to conduct the trial (sub-contractor).
- Principal Investigator: responsibility for and coordination of the trial.
- Research team: conducting the trial.
- Drug agency of country where the trial is conducted: official authorisation of the trial, inspection and marketing authorisation of the drug in that country, where applicable.
- Ethics committee: ethical examination upon which authorisation and follow-up of the trial are dependent.
- Drug agency of the country in which the application for marketing authorisation of the drug is made: scientific and, theoretically, ethical evaluation of the results of trials; marketing authorisation.

Participants in developing countries:
The disadvantaged and uneducated fringes of the population, with limited or no access to drugs, who have great confidence in the medicine of wealthy countries.
Tableau 1
NUMBER OF ACTIVE INTERVENTIONAL CLINICAL TRIALS BY COUNTRY, APRIL 2013
A clinical trial can include dozens of locations (hospitals, clinics, etc.)

<table>
<thead>
<tr>
<th>Country</th>
<th>Roche</th>
<th>Novartis</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>Russia</td>
<td>83</td>
<td>71</td>
</tr>
<tr>
<td>Thailand</td>
<td>36</td>
<td>62</td>
</tr>
<tr>
<td>India</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>China</td>
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<tr>
<td>Mexico</td>
<td>68</td>
<td>33</td>
</tr>
<tr>
<td>Brazil</td>
<td>84</td>
<td>83</td>
</tr>
<tr>
<td>Argentina</td>
<td>61</td>
<td>66</td>
</tr>
</tbody>
</table>

Source: Compiled by the BD from data at www.clinicaltrials.gov
THE MOST FREQUENT ETHICAL VIOLATIONS

- Exploitation of a population’s socio-economic and health-related vulnerability
- Absence of free and informed consent
- Improper use of placebos
- Insufficient or non-existent financial compensation in cases of problems
- Absence of a guarantee of access to treatment at the end of the trial

THE MAIN ETHICAL STANDARDS

- Declaration of Helsinki (DoH)
- Guidelines on Good Clinical Practice of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-GCP)
- Guidelines of the Council for International Organisations of Medical Sciences (CIOMS)

WHY OFFSHORE?

CHEAPER
Cost per patient is lower in developing and emerging countries.

FASTER
Participants are more numerous, which speeds up the conducting of trials.

SIMPLER
Monitoring by local authorities is often inadequate.
they have less capacity to monitor compliance. The risk of ethical violation is therefore high. A number of investigations over the past few years have reported serious deficiencies concerning the process of obtaining the informed consent of participants, the problematic use of placebos as proof of efficacy, failure to pay compensation in cases of serious adverse events, and access to treatment at the end of trials. While pharmaceutical companies deny the existence of double standards with regards protection, ethical violations have been confirmed by investigations conducted by the BD in Argentina, Russia, India and the Ukraine (see pages 15 onwards). And, as trials often take place simultaneously in several different locations internationally, if the Indian or Argentinian branch of a trial is tainted by ethical violations or lack of scientific reliability, the entire clinical trial is compromised.

This state of affairs is all the more worrying because the ethical controls carried out by the drug regulatory agency, Swissmedic, are clearly inadequate, as confirmed by an investigation conducted by the BD in Switzerland (see page 10). As a result, there is a major risk of drugs being sold in Switzerland that have been tested under ethically questionable conditions – and of no-one being able to find out about it because of the current lack of transparency prevailing.

**THE MOST FREQUENT ETHICAL VIOLATIONS**

**Exploitation of a population’s socio-economic and health-related vulnerability**

The simple act of offshoring clinical trials for no legal or scientific reason to regions where the population wants to participate in order to have access to treatment or to earn a little money (depending on the trial phase) raises an ethical question: can we allow ourselves to exploit the socio-economic and health vulnerability of a population in order to test drugs at the lowest possible cost, drugs which in many cases will not be made available to them? Research carried out within vulnerable populations is only justified if it is useful to them and if the results are of benefit to them.

**Absence of free and informed consent**

The person taking part in a trial must give his / her free and informed consent. This requirement is often not met in contexts of socio-economic or health-related vulnerability, where there is a very high degree of trust in doctors. It is not unusual for a doctor to exert inappropriate influence over the person he or she wants to recruit (especially if they are in charge of the research), and for subjects to be incorrectly informed or to even be unaware that they are going to take part in an experiment.

**Improper use of placebos**

The use of a placebo makes it easier to obtain clear results and allows the efficacy of a drug to be compared to that of no treatment at all. However, if drugs exist that have already been used and are known to be effective for the type of pathology being studied, and if the absence or interruption of treatment represents a risk, using a placebo constitutes an ethical violation.

**Insufficient or non-existent financial compensation in cases of serious adverse events**

When injury or death occurs in the context of clinical trials and it is linked to the drug being tested, financial compensation must be provided for the person concerned or his/her family. It goes without saying that the majority of participants in clinical trials are ill, and the risk of their health deteriorating during the trial is not negligible. But others suffer from serious adverse events or die as a result of the drug tested, and they must be compensated. Frequently, any link between the injury caused and the drug being tested is not evaluated independently but by those responsible for the trial. What is more, the participant is seldom given the benefit of the doubt with regard to the causes of death or of debilitating side effects, because they have no means of defending themselves.

**No access to treatment at the end of the trial**

A person who agrees to participate in a study should be guaranteed access to the treatment when the trial ends if the drug was found to be beneficial during the trial, or to any other treatment or appropriate benefit. In reality, treatment is often stopped at the end of the trial, a problem which is all the more acute in countries where access to drugs is limited.
COMPLIANCE WITH ETHICAL NORMS

SWISSMEDIC, A TOOTHLESS TIGER

Through the marketing authorisation procedures, the drug regulatory agency, Swissmedic, plays a central role in the monitoring of respect for ethical standards in relation to clinical trials conducted abroad. Our investigation has shown that Swissmedic focuses on the soundness of the medical data gathered, so that it can rule on the efficacy and safety of drugs. By contrast, virtually no ethical control takes place. There is a strong risk of drugs being marketed in Switzerland that were tested unethically.

The main function of the Swiss Institute for Therapeutic Products, Swissmedic, is to guarantee the quality, safety and efficacy of therapeutic products, including medicines. Swissmedic is an autonomous institution under public law and managed by the Swiss Confederation with the assistance of the cantons. Its activities are governed by a multi-year service mandate from the Swiss Federal Council. It is attached to the federal department of the interior (the DFI), with which it enters into a service contract every year.

Swissmedic plays a central role in controlling the ethics of drug trials conducted in third countries. In fact, when a company decides to conduct a multi-centre international clinical trial, all the data generated – and not only that originating in the Swiss branches of the trial – is consolidated in reports submitted as part of the application for permission to market the product on Swiss territory. Trials to be conducted in Switzerland must be authorised by the drug regulatory agency before they can begin. However, Swissmedic is not empowered to authorise those that are conducted on the same drug in third countries. That must be done by the national authorities concerned. And Swissmedic is not aware of the trials until the marketing authorisation procedure in Switzerland commences.

This being the case, is this institution sufficiently vigilant in checking whether the trials were conducted in accordance with international ethical standards? Unfortunately, the reply to
Incomplete control mechanisms
At the time of application for permission to market a drug, Swissmedic does not adequately meet the requirement of checking whether that drug was tested both under scientific conditions and under irreproachably ethical conditions. As far as the former is concerned, international efforts have allowed the strict regulation of the manner in which data is gathered and recorded. However, nothing of the sort exists with regards the ethical dimension. With trials conducted in Switzerland and in countries where the mechanisms in force to ensure respect for standards run generally well, Swissmedic is able to rely on the work performed by the ethics committees. However, when trials are conducted in countries with more lax regulations, the Institute cannot take the conclusions of local ethics committees at face value. Relying on the promoter, as Swissmedic itself says it does, is also an inadequate practice because the promoter has absolutely no interest in investigating possible ethical deficiencies that may have come up during its own clinical trials. Swissmedic cannot ignore ethical violations occurring during trials conducted in other countries and used in marketing authorisation applications filed in Switzerland. The law is clear on this subject (see box, page 12).

Start by establishing contact...
The internationalisation of research means that excellent coordination is needed between the drug regulatory agencies. While Swissmedic maintains close contact with its European and US counterparts (the EMA and the FDA respectively), it does not maintain regular contact with its counterparts in developing and emerging countries such as India or China. There are no mutual assistance agreements that would allow on-site inspections. A first step would be to contact those local agencies in cases of doubt. The EMA, for example, has taken the initiative of reflecting on ways to strengthen international cooperation. It has also been giving thought to stronger mechanisms for controlling ethics in relation to clinical trials conducted in third countries. This is an approach that Swissmedic would do well to emulate. But when questioned on the matter by the BD, the Institute said that it was not contemplating anything along those lines.

A lack of transparency that makes public scrutiny impossible
Swissmedic publishes only a minimal amount of information on granted marketing authorisations. It is not even possible to find out which trials formed the basis of a particular authorisation. On top of this, there is the absence of a Swiss register of clinical trials (see box, page 12). Switzerland is again behind the European Union on this issue. The EMA started moving towards greater transparency in 2010, with the announced publication of all reports of clinical studies that served for marketing authorisations (see page 14). Will Switzerland follow suit, and will it finally place the interests of those taking part in clinical trials above the much-emphasised commercial confidentiality? For that to happen, Swissmedic would have to stop thinking of the pharmaceutical industry as a “client” that feeds its budget, and start thinking of it as a player to be regulated.

MENINGITIS EPIDEMIC USED AS A TESTING GROUND
Kano, Nigeria, 1996: Humanitarian organisations were deployed to help the 110,000-odd people affected at the height of a serious meningitis epidemic. They fought the disease with drugs approved and recommended by the World Health Organisation. This was the moment that the US pharmaceutical company Pfizer chose to test Trovan, an antibiotic, on 200 children. Eleven of those children eventually died, and numerous others were left disabled. Serious departures from clinical trial protocols were recorded, as well as faults in the procedure for obtaining consent and falsification of official authorisation documents. Moreover, the clinical trial took place in a public hospital, mobilising important human resources to the benefit of private interests – and this during a health crisis when the burden on the staff was enormous. The case was the subject of complaints in both Nigeria and the United States. An out-of-court settlement of 75 million dollars finally put an end to the matter in 2009, and the first damage payments to victims were granted in 2011. Trovan has never been authorised for children. It has been authorised for adults but sales are severely restricted in the United States and suspended altogether in Europe because of the large number of serious side effects that have come to light.
In 2014, a new federal law relating to research on human subjects (the LRH) will come into force in Switzerland, which will aim to protect the dignity, personality and health of research subjects. It complements current legislation, namely the law on therapeutic products (the LPTh) of 2001. The LPTh will continue to govern both procedures for the marketing authorisation of drugs and the formal authorisation of clinical trials, whereas the new law will make reference to the ethical principles associated with research projects. It will set out provisions relating to their supervision and their transparency, as well as to the coordination between the various bodies concerned.

Thanks to the LRH, therefore, there will be a strengthening of standards relating to the protection of participants in clinical trials, some of which are directly inspired by the Declaration of Helsinki, although no explicit reference is made to it. A reason to rejoice, perhaps. But all this relates only to research carried out in Switzerland. The LRH has missed an opportunity to address the globalisation of clinical trials. It does not provide a clear legal basis for coordinating the ethical control of research activities outside Switzerland with the authorities of the countries concerned. It is thus necessary to turn to the LPTh to find a legal basis concerning respect for ethical standards in the context of clinical trials conducted offshore. The implementation order of the LPTh does in fact stipulate that the documentation on clinical trials submitted as part of marketing authorisation applications must demonstrate that trials involving humans were conducted in accordance with the generally accepted rules of good practice. This means that studies conducted offshore must observe the same principles as those set out in the LRH, and it is up to Swissmedic to verify that this is fulfilled.

Finally, the LRH provides for the establishment of a public register, but it will limit itself to clinical trials conducted in Switzerland and will only include a minimum of information. No offshore trials or tests will be included, so they will continue to be shielded from scrutiny. It will still not be possible to know which clinical trials are based on which authorisation decisions. Swiss legislation still demands only minimum transparency.

**A NEW LAW WITH MAJOR GAPS**

A SERIOUS LACK OF TRANSPARENCY

It is impossible to know, solely on the basis of information in the public domain, upon which clinical trials the marketing authorisation of individual drugs is based, nor the details of such decisions. Worse still, half of all clinical trials conducted in the world are never published, particularly those presenting unfavourable results. This lack of traceability prevents independent scientific assessments and the public scrutiny of decisions.

When drugs are tested on voluntary subjects, the results should logically be made available to society. In making their bodies available in the interests of science, participants in clinical trials are in fact taking a risk. However, the pharmaceutical companies are not concerned about this and consider that the data gathered belongs to them. Under various pretexts, they do everything possible to keep the data confidential.

As a result, half of all clinical trials conducted in the world are never published. This is truly a scandal. In the case of those that are made public, unfavourable data is concealed or minimised in order to present the drug being tested in a better light.

There is much documented evidence of this phenomenon. It leads to drugs that could prove to be more dangerous than useful being marketed or remaining on the market (see box, page 13). It illustrates the total hold that pharmaceutical companies have over the testing of drugs they intend to market, i.e. 80% of all clinical trials. The regulatory authorities are both complicit and powerless in this because they are financially dependent on the pharmaceutical industry.

The intention of the European Medicines Agency (EMA) to publish from 2014 all the reports on clinical trials in its possession is a step in the right direction, even if the obstacles to its fulfilment are far from being removed (see box, page 14).

Commercial confidentiality or public good?

Reports on clinical trials must make it possible to judge the efficacy and safety
of the product being tested. No information is divulged on either the composition of the drug or on any secret of its production. When questioned about this as far back as 2010 the European Ombudsman confirmed that these reports contain nothing pertaining to commercial confidentiality (see case 2560/2007/BEH). They should therefore be considered public property and made available in their entirety.

Confidentiality: a false pretext
Researchers must ensure that the privacy of participants is protected. Under the directives currently in force, their identity is protected through the use of codes. Except in very rare cases when it is possible to put exception mechanisms in place, the dissemination of anonymous reports makes it impossible to identify participants. Nevertheless, the pharmaceutical industry continues to hide behind the shield of patients’ associations to prevent the publication of data.

TAMIFLU AND VIOXX – SELECTIVE PUBLICATION WITH MAJOR CONSEQUENCES

The decision taken by governments worldwide, including Switzerland, to stockpile the antiviral drug Tamiflu, made by Roche, as a precaution against flu pandemics, was based on a number of individual studies, eight of which have never been published. The pharma giant has also kept the lid on the results of other clinical trials. Independent scientists have been asking Roche since 2009 for access to all the data from the 74 clinical trials carried out on the drug. Having promised to do so on numerous occasions, it was only last April that Roche finally announced that it intended to offer that access, although not without certain conditions. The fact is that since 2002 Roche has sold more than 12 billion Swiss francs worth of Tamiflu, a product whose efficacy is questionable. They have made no mention of potential undesirable side effects (see Solidaire 224).

In September 2004, Merck Sharp & Dohme (MSD) announced the immediate withdrawal from the market of its anti-osteoarthritis drug Vioxx due to risk of cardiovascular complications. As long ago as 2001, the US drugs agency, the FDA, had found that Vioxx caused five times more infarcts than a rival anti-inflammatory product, although it did not suspend its marketing authorisation. Several clinical trial reports, some of which were not published immediately, confirmed this risk. In response, Merck stepped up its lobbying of doctors to counter the impact of these findings. The result was more than 100,000 cardiac arrests, leading to some 10,000 deaths in the United States alone. These could have been avoided if the results had been made public at the right time.
Plenty of registers but little information

There is a whole host of databases of clinical trials, fifteen of which meet the criteria for primary registers defined by the WHO. The most complete are those of the US government (ClinicalTrials.gov) and of the European Union (ClinicalTrialsRegister.eu). However, none are exhaustive because there is no international obligation to register clinical trials. The decision taken in 2004 by the most prestigious medical journals to require studies to be registered before articles can be published about them led to a drastic rise in the number of entries in registers. But it is possible to get around that rule. Switzerland still does not have a register, but is planning to establish a “minimalist” one for trials conducted in Switzerland only (see box, page 12).

Another problem is that these registers only contain a summary of the clinical trials. The research protocol, which would allow in-depth analysis of the scientific and ethical aspects of a study, is not accessible to the public.

Ethical standards trampled

According to the WHO, the registration of all clinical trials is a scientific, ethical and moral responsibility. The Declaration of Helsinki requires all clinical trials to be recorded in a public register, prior to the recruitment of volunteers and before companies publish the results of their research, whether positive or negative. These companies habitually pay scant attention to ethical standards. What is needed to achieve greater transparency is a single global register, with binding registration measures, and a more direct link to the granting of marketing authorisations.

THE MAIN INTERNATIONAL ETHICAL STANDARDS

A number of ethical standards have been drawn up over the years. What they have in common is to place people’s interests and protection above those of science and society.

• The Declaration of Helsinki (DoH), adopted by the World Medical Association in 1964 and subsequently amended several times, is the text of reference in the field. It covers all the ethical violations mentioned in this report.

• In 1996, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, which brings together the authorities and the pharmaceutical industries of Europe, Japan and the United States, published guidelines on good clinical practice (the ICH-GCP) intended to facilitate acceptance of clinical trials data by the authorities of those three jurisdictions. The ICH-GCP is less strict than the DoH on the subject of ethics.

• In 2002, the Council for International Organisations of Medical Sciences (CIOMS), in collaboration with the WHO, published the third version of its guidelines, with the aim of showing how to implement universal ethical principles such as those defined in the DoH, particularly in developing countries.

None of these texts are binding in nature as long as they are not transposed nor explicitly referred to in the laws of the respective nations. In Switzerland, this only concerns the ICH-GCP standards, not the Declaration of Helsinki.
INVESTIGATIONS BY THE BD

SWISS PHARMACEUTICAL COMPANIES AT THE SOURCE OF ETHICAL VIOLATIONS

The investigations carried out by the BD in four of the most popular destination countries for clinical trials confirm that the systems of ethical control are extremely deficient. The multinational pharmaceutical companies — including Swiss corporations — take advantage of this fact to conduct faster, and therefore more profitable, drug trials. Even if this means trampling on the standards they claim to respect.

Investigations entrusted to investigative journalists and an NGO specialised in the field took place between July 2012 and June 2013 and have been the subject of detailed reports. The countries were chosen from among the main destinations for clinical trials by Swiss firms in particular. It is important to stress the extreme difficulty in accessing the stakeholders involved in clinical trials and in corroborating information. Research teams bound by confidentiality clauses are not very communicative because of the threat of legal action if they do talk. Identifying and approaching the people taking part in the trials was extremely challenging, often compounded by their fear to speak. However, we were able to reconstitute facts confirming the existence of ethical violations in these countries on the basis of statements from key players, from confidential documents and through cross-checking of official data.

Investigations by the BD in the Ukraine and Russia

WEAK SURVEILLANCE BODIES

The countries of the former Soviet Bloc, in particular Russia and the Ukraine, are host to an increasing number of clinical trials. With recruitment of subjects up to twenty times faster than in Western Europe, the multinationals have no hesitation in offshoring a large proportion of their drug trials there. These countries are attempting to bring their legislation into line with European regulations, but changes are still a long way from being implemented.

THE EXPERIMENTAL LAB OF THE FORMER EAST GERMANY

Attracted by lower costs and encouraged by a state in search of strong currency, numerous firms including Roche, Ciba-Geigy and Sandoz (ancestors of Novartis) conducted hundreds of trials in the former German Democratic Republic during the seventies. Constrained by a centralised and hierarchical system and sometimes influenced by sweeteners from promoters, the medical profession enrolled several thousand people as part of this “trade in human guinea-pigs”. It was tainted by numerous irregularities, particularly concerning informed consent and the dangerous use of placebos. Called “export of immaterial assets”, this shoddy form of offshoring continued right up to the fall of the Berlin wall, after which promoters started turning to countries further to the East and South.

As far as the environment in the region is concerned, both Russia and the Ukraine can be characterised as having moved from a strong central state to a decentralised system, having an all-powerful medical profession which the population is not accustomed to challenging, a state health system in decline, corruption and highly compromised press freedom.

The Ukraine; eager to attract Western pharmaceutical companies

International clinical trials have been conducted in the Ukraine since 1996,
but the business is currently expanding rapidly. The country has a number of advantages: it is situated at the gateway to the European Union, and the greater part of its population (65%) is urban and genetically close to that of western countries. Because their state health system is in a very bad state, and the economic situation difficult, patients are both easy to recruit and reluctant to ask questions, an historical legacy. According to official figures, there was an explosion in the number of facilities authorised to conduct drug trials, from 175 in 2001 to more than 1300 in 2009, although many of the municipal hospitals involved do not have the necessary infrastructure. Conducting a drug trial costs as little as half as what it costs in Western Europe.

Unfortunately, this resurgence brings with it an increased risk of ethical violations for a number of reasons. Firstly, the legislation has been changed to reflect international standards but reforms have yet to be assimilated by all, in particular doctors and ethics committees. Whereas everything used to be centralised, since mid-2012 the authorisation of a trial has to be endorsed by the local ethics committee. However, not all of these structures are operational yet, due to a lack of both resources and a clear framework. Moreover, they are linked with the institutions that host such trials, with the doctors in charge of the trials sitting on the committees. They are therefore anything but independent. What is worse, the central committee of the ministry of health has ceased to be operational since mid-2012, thus leaving a worrying vacuum in the system of ethical control. Then there is the absence of public debate on the subject. Patients see an opportunity in clinical trials to access care of a quality that they would never be able to afford. But this puts them at the mercy of a medical profession which intends to benefit financially from the activity. Doctors have been known to speak of a “humanitarian programme handing out treatment free of charge”, while failing to mention that they are talking about clinical trials. Others even say openly that “it isn’t particularly important that a patient can’t sign a consent form, a family member can do it for them”. And as the law permits signature by a “witness”, hospital employees have allegedly signed instead of the patient or their family.

Exacerbated by both the lure of profit and the lack of transparency surrounding this taboo subject, and supported by a decaying infrastructure, this situation creates an omnipresent risk of ethical violations, as recent controversy has shown (see box, page 17).

Russia: the mirage of Swiss trials
A recent report on clinical trials cooperation between the European Union and Russia underlines the compatibility of the two systems. But it also highlights a notorious feature of the Russian system: direct contact between patients and ethics committees is prohibited. In 2010, Russia legislated on the establishment of decentralised ethics committees, but the central committee at the ministry of health has been retained, unlike in the Ukraine. The result is an “official” committee with the power to prohibit a trial but overwhelmed with work, and “local” committees, occasionally including, where they exist, independent representatives such as journalists or priests, who can study cases in greater depth but have no power to prohibit anything. Another problem with certain local committees, such as that of a Moscow hospital, is that the doctor in charge of the trial is also president of the ethics committee. When asked about this, he professed to see no conflict of interest.

In attracting and recruiting patients via the internet, doctors sometimes refer to an “observation programme”, not to drug trials carrying risks. They tend to do this because they benefit financially from the clinical trials, potentially to the tune of up to several times their basic salary. And when participants experience serious adverse events, they pretend to keep taking the drug while instead stockpiling them at home, for fear of being excluded from the trial. The results are thus skewed.

Some people who took part in a study by Novartis of Gilenya (used to treat multiple sclerosis) have confirmed a number of ethical violations: the signature of consent obtained after the start of treatment, the absence of compensation for side effects and interruption of treatment at the end of the trial. A consent form for this trial included an insurance policy in the event of problems. In fact, there do not seem to have been any cases of compensation in Russia: between 2007 and 2009, not one of the more than 70,000 patients insured received compensation.

The inspectors at Russia’s medicines agency are powerless, partly due a lack of resources but mostly because the law does not permit serious sanctions to be imposed on doctors involved in research or on clinical trial facilities that do not respect the law. In addition, these inspectors

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**NUMBER OF ACTIVE CLINICAL TRIAL SITES IN THE FOUR COUNTRIES INVESTIGATED (FIGURES: 2012)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Novartis</th>
<th>Roche</th>
<th>Actelion</th>
<th>Merck Serono</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ukraine</td>
<td>31</td>
<td>132</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>Russia</td>
<td>314</td>
<td>659</td>
<td>57</td>
<td>72</td>
</tr>
<tr>
<td>Argentina</td>
<td>326</td>
<td>659</td>
<td>57</td>
<td>72</td>
</tr>
<tr>
<td>India</td>
<td>490</td>
<td>219</td>
<td>17</td>
<td>58</td>
</tr>
</tbody>
</table>

Source: Compiled by the BD from data at www.clinicaltrials.gov and from accessible national registers (India and Argentina)
are not allowed to meet the patients. Further, an inspector and a manager of a CRO mentioned the existence of “phantom research”, without patients or a doctor in charge.

Timid patients believing their participation in a Swiss trial to be a real opportunity, doctors with a personal financial interest chasing positions, powerless or corrupt authorities, pharmaceutical companies delegating the follow-up of clinical trials, and a law that has changed so much that it is becoming impossible to interpret: such is the dangerous cocktail leading to repeated ethical violations in a country where Swiss firms are very active.

THE UKRAINE: ORPHANS AS GUINEA-PIGS?

In March 2013, members of the Ukrainian parliament claimed that three clinical trials conducted by international companies between 2011 and 2012 on children, in particular orphans, violated provisions of the law, including consent procedures. These trials included one conducted by the Swiss firm Actelion on Tracleer (bosentan), a treatment for pulmonary arterial hypertension. Involvement of children is subject to the consent of both parents or, in the case of orphans, of a representative of the state. The members of parliament claimed that this did not happen in the cases of several of the children. In addition to this, the trials were said to have taken place at facilities not in possession of the necessary accreditations. The Ukrainian authorities flatly denied the accusations, while the companies concerned remained silent. An official enquiry was launched but, in spite of promises, its results were not published. Whatever the case may be, conducting tests on vulnerable people such as orphans, in a context in which ethical surveillance is weak, is irresponsible.

Investigation by the BD in Argentina

DECEPTIVE APPEARANCES

Abusive use of placebos, unauthorised standard treatments, interruption of treatments, mishandling of consent procedures, and incompetent ethics committees: although Argentina is often cited as a reference for best practice, our investigation recorded serious faults in the conduct of clinical trials, including trials conducted by Swiss firms.

Argentina is listed third among countries hosting the largest number of drug trials in South America, behind Brazil and Mexico. Although the country has many advantages due to the quality of its infrastructure and the typology of its population, it also has some major flaws: no national law on drugs trials, national ethics committees which are independent only in name, and an overly permissive medicines agency, Anmat.

Unscrupulous private ethics committees

In the face of the legal vacuum, and given that Anmat does not guarantee respect for the ethical standards of protocols, the only two national bodies that should be able to secure the protection of participants in trials are private institutions that set themselves up as “independent ethics committees”. These bodies are mere rubber-stamp organs that accept everything put before them, thereby lending a semblance of legality to trials that may include serious ethical deficiencies. And they are accountable to no-one. These two committees alone approve 80% of the trials carried out in Argentina. One of them, the FEFyM, audits the protocols of 85% of the clinical trials conducted by Roche and Novartis in Argentina.

The quality of the FEFyM’s work was called into question by an analysis of 36 clinical trial protocols from 2005 and 2006. Carried out by a doctor from a hospital in Mar del Plata¹, the analysis identified nearly a 100 points in 85% of the protocols examined that did not comply with the standards in

¹ Gonorazky S. E., Comites de ética independientes para la investigación clínica en la Argentina: Evaluación y sistema para garantizar su independencia, Medicina (Buenos Aires) 2008;68:113-119.
In 2008, Roche tested the use of an immuno-suppressant, ocrelizumab, in the treatment of lupus nephritis, an autoimmune disease causing kidney problems. Conducted in several countries, including Argentina, the trial was finally suspended due to serious side effects. But that is not where the problem lies. According to the consent form, obtained by the BD, in addition to ocrelizumab or the placebo, patients also received a so-called “standard” treatment comprising CellCept (mycophenolate mofetil), an immunosuppressant used to prevent rejection of transplants. CellCept is not authorised for the treatment of this disease in Argentina, although doctors prescribe it unofficially (“off-label”) for lupus. To present it as a “standard” treatment is a lie, and constitutes an ethical violation. Further, it means that patients would not have access to it at the end of the trial, even if CellCept was demonstrated as being effective against this pathology, as happened to one patient interviewed by the BD.

SCHIZOPHRENIC ADOLESCENTS DEPRIVED OF THEIR TREATMENT

Testing a drug against a placebo is standard practice if you want to obtain clear results. But administering a “sugar pill” to patients who need treatment, when doing so is not indispensable from a methodological point of view, is dangerous and ethically unacceptable. But the US company Merck did just this in a clinical trial begun in 2010 in a large number of countries in the southern and eastern hemispheres, including Argentina. The study tested the use of an anti-psychotic drug, Saphris (asenapine), on adolescents suffering from schizophrenia. Although approved by Anmat, the trial placed those participants in grave danger by withdrawing all their treatments (antipsychotic, antidepressant, etc.), and replacing them with either asenapine or a placebo. Anmat finally suspended the trial after this was reported by an anonymous whistle-blower. However, no legal proceedings were opened and total secrecy was maintained around the case: the BD is the first to bring it to light.

GSK guilty of ethical violations

There was a lot of media attention in Argentina about GlaxoSmithKline’s (GSK) trial of Synflorix, a vaccine against pneumonia, otitis and meningitis, conducted between 2007 and 2011 on 14,000 newborns. Fourteen babies died, causing outrage and an official enquiry. Even though it was not possible to prove a link between the vaccine and the deaths, the Argentinian authorities imposed fines on the multinational, the first time they had done so for ethical violations. The decision was upheld by the Argentinian justice system.

The irregularities included faults in the system for enrolling subjects (inclusion criteria) and in recruitment practices (exploitation of the vulnerability of the population). Parental consent was often obtained by alarming parents about the health of their baby and ignoring their refusal to have their baby vaccinated. Moreover, GSK paid 350 dollars to researchers for each baby recruited, an enormous sum for doctors whose monthly salary was about 1200 to 1400 dollars. This practice put them in an obvious conflict of interest. We should point out that the main coordinator and a provincial manager of the trial, both convicted in court of violation of ethical rules, were engaged in similar trials by Novartis. When questioned on the subject, Novartis was unable to see a problem.

UNLICENSED TREATMENT USED BY ROCHE

In 2008, Roche tested the use of an immuno-suppressant, ocrelizumab, in the treatment of lupus nephritis, an autoimmune disease causing kidney problems. Conducted in several countries, including Argentina, the trial was finally suspended due to serious side effects. But that is not where the problem lies. According to the consent form, obtained by the BD, in addition to ocrelizumab or the placebo, patients also received a so-called “standard” treatment comprising CellCept (mycophenolate mofetil), an immunosuppressant used to prevent rejection of transplants. CellCept is not authorised for the treatment of this disease in Argentina, although doctors prescribe it unofficially (“off-label”) for lupus. To present it as a “standard” treatment is a lie, and constitutes an ethical violation. Further, it means that patients would not have access to it at the end of the trial, even if CellCept was demonstrated as being effective against this pathology, as happened to one patient interviewed by the BD.
As Novartis learned to its cost in the Glivec case, India has a strong generic industry and government when it comes to defending the right to health and access to medicines. One is therefore surprised by the weak regulations governing drugs testing in India, as highlighted in several official reports, at a time when the clinical trials industry in India is booming. In the wake of various scandals, the subject is now in the public arena, including at the level of the Supreme Court. But numerous conflicts of interest stand in the way of finding solutions.

Our enquiries show that the issues of recruitment, consent, compensation (see box) and treatment at the end of a trial are far from being resolved. India is very attractive to the multinationals because trials are two or three times less expensive than in Europe and there is a gigantic recruitment pool. By gaining the loyalty of the doctors involved, clinical trials are also a way to penetrate this emerging market.

But there is an obvious conflict of interest when the doctor is at the same time the principal investigator of the trial and when he or she receives payment, in cash or kind, for every patient recruited. It is an illusion to think that informed consent can be obtained in a disinterested fashion under such circumstances, particularly from vulnerable patients who are easily influenced. Nevertheless, this mixing of roles is common in India, and the ethics committees do little to combat such conflicts of interest.

Another example of conflicting interests is the large number of “institutional” ethics committees in India linked to health infrastructures that are receptive to and benefit financially from clinical trials. Whether they are independent or not, it is rare for these bodies to verify consent procedures: they barely check if the correct form exists. Nonetheless, Indian law is clear: any deficiency in procedure is equivalent to a refusal of consent, including when the person responsible does not read the form, when it is not
BHOPAL, OR THE HEIGHT OF EXPLOITATION OF VULNERABLE PATIENTS

One of the most serious industrial disasters in history caused thousands of deaths in Bhopal, India, in 1984, and left many more thousands with major health complications. In 2004, around ten firms, including Pfizer, GlaxoSmithKline and Astra Zeneca, conducted clinical trials in the hospital in Bhopal reserved for victims of the chemical disaster. The clinical trials were not actually intended to treat the consequences of the disaster, such as post-operative complications, nosocomial infections or cardiovascular diseases. They were called off in 2008 on the orders of the hospital’s management. The fact was that numerous irregularities had been recorded in the recruitment and consent procedures, compensation for injury and the work of the ethics committee of the hospital. To conduct trials on victims of a disaster, in a hospital where the patients come to be treated free of charge, with drugs that are unlikely to be made accessible to them and are perhaps not even useful, constitutes a major violation of ethics, and smacks of cynicism of the purest kind.

understood by the participant, or when any undue influence is exerted on the patient to sign. In such cases, the clinical trial is illegal.

No treatment at the end of the trial

Despite high expectations of participants, our investigation shows that access to treatment at the end of “Swiss” clinical trials is far from guaranteed. When asked about this, doctors are often incapable of answering and simply repeat the policy of the sponsors. However, it is a provision of the Declaration of Helsinki which the multinationals – Swiss included – make explicit reference to in their policy on drugs testing.

For further information:

The complete reports of the BD’s investigations in Argentina, India, Russia and the Ukraine, conducted between July 2012 and May 2013, are available at www.ladb.ch/clinicaltrials or upon request by e-mailing info@ladb.ch
MANY DEATHS, LITTLE COMPENSATION

Although duly regulated, the announcement of adverse events during drug trials leaves a lot to be desired in India. The temptation to keep quiet about them, for fear of jeopardising the trial and losing participants, is often too great. Official sources reveal that between 2005 and 2012 there were 2600 deaths from the 40,000 participants in clinical trials in India. More than half of those (1317) were registered between 2010 and mid-2012, which suggests there has been a recent surge. Novartis is among the companies involved, with 7 and 57 deaths registered for 2010 and 2011 respectively. When questioned on the subject, Novartis declared that none of those deaths were linked to the trials it was conducting in India. However, no second assessment was carried out to determine whether this was in fact the case. Further, according to our intelligence, Novartis has not paid compensation for any of the deceased.

Only 22 deaths in total were attributed to the drugs tested in 2010, and only 16 in 2011. The families that were compensated in 2010 received around 3000 to 4000 Swiss francs – a tiny amount relative both to the millions earned from drug sales once on the market and to the loss suffered. This disparity has stirred up emotions and led to a review by the Indian parliament on how compensation payments are calculated, which is currently on-going.

The situation is no better for those who suffered serious side effects: injured parties have to go through a tedious process in order to prove the link to the product tested. Most do not have the necessary resources to tackle such an obstacle course.
MORE ETHICAL SURVEILLANCE
AND TRANSPARENCY

Both the literature on the subject and our own research show major gaps in the regulation of clinical trials in developing and emerging countries. Data from potentially unethical trials is used to obtain marketing authorisation of drugs in Switzerland, where there are virtually no serious ethical checks. The Swiss authorities must act urgently to enforce ethical standards and establish more transparency. They cannot continue to take the opinions of local ethics committees and reassuring statements from the pharmaceutical industry at face value. If Switzerland wants to avoid future scandals, this should be seen not just as a moral imperative but also as a matter of public health.

Like its European and US counterparts, Swissmedic cannot continue to ignore ethical violations during clinical trials carried out in the southern and eastern countries that are then used in applications for marketing authorisations in Switzerland. According to our calculations, half of all drugs marketed in Switzerland were at least partially tested in one of those countries in which the test conditions are unknown. Switzerland is thus running a serious risk of marketing products tested in an unethical manner.

Strengthen ethical controls
A first step should be to establish official channels of communication with the drug regulatory agencies of the main countries affected by offshoring. Swissmedic freely admits it is not doing this. Next, additional checks of the ethical aspects of trials conducted offshore should be strengthened. Concerted efforts to harmonise examination procedures of scientific data prior to marketing authorisations have yielded results. There is absolutely no reason why the same should not be done with ethical aspects. The new law relating to human research (the LRH), which comes into force in 2014, will certainly improve the legislation relating to clinical trials conducted in Switzerland. However, it will not resolve the issue of ethical surveillance for trials conducted offshore. The instrument which could lead quickly to establishing such monitoring is the service mandate granted to Swissmedic every four years by the Federal Council. In effect, the law currently in force allows the government to assign it additional tasks by means of this instrument. For its part, the European Medicines Agency (EMA) has announced that it wants to strengthen its internal procedures to ensure that ethical standards are being respected in trials identified as being “at risk”. Switzerland should follow its lead, for example, by subjecting the reports of such trials to additional checks in Switzerland with regard to ethics prior to granting marketing authorisation. This would encourage the pharmaceutical industry to be more vigilant in ensuring that ethical standards are respected in clinical trials in order to avoid delays in placing products on the market.

More transparency
While the subject is rarely debated in Switzerland, from 2014 the EMA is planning to publicise all reports it holds on clinical trials of products for which marketing authorisations have been granted. By comparison, Swissmedic’s inertia and lack of transparency are flagrant, and contradict its service mandate. It is impossible to know from the information available in Switzerland which trials are linked to which authorisations and under what conditions the trials took place. Before any examination, Swissmedic should require promoters to list all clinical trials in the public register provided for by the LRH. Finally, it should make all the reports in its possession public, as its European counterpart is planning to do. The data generated in connection with clinical trials does not pertain to commercial confidentiality; it should be considered public good and published in its entirety.
Ethical violations committed in the context of clinical drug trials must stop. They violate human rights linked to the protection of research subjects and enshrined in universally recognised ethical standards.

Priority must be given to tackling the ubiquitous problem of lack of transparency and to drug trials which pose the greatest risk of ethical violations, those sponsored by the pharmaceutical industry and conducted offshore in contexts where regulation is inadequate.

The Federal Council must require Swissmedic to establish enhanced additional ethical controls for clinical trials conducted in developing and emerging countries as part of the procedure for the marketing authorisation of drugs in Switzerland.

Swissmedic must demand of promoters that all clinical trials – including offshore trials – used in applications for marketing authorisations in Switzerland be listed in the upcoming supplementary Swiss register.

Swissmedic must publicise all reports on clinical trials in its possession that provide the basis of marketing authorisation decisions.

The pharmaceutical industry must stop using countries in the southern and eastern hemispheres as giant experimental laboratories. Vulnerable people in these countries must not be used as human guinea-pigs purely for reasons of profit. Clinical trials should not be conducted offshore unless those populations benefit directly and in real terms from the results; the trial must be of a treatment related to a specific disease that affects them in particular, and the sponsor must make sure that the treatment will be available and accessible to that same population if it proves more effective than existing treatments.

For further information, visit: [www.ladb.ch/clinicaltrials](http://www.ladb.ch/clinicaltrials)
To request a list of bibliographical references, e-mail: info@ladb.ch
A drug must undergo clinical trials conducted on human subjects before being authorised for marketing in Switzerland. However, such trials are expensive and so pharmaceutical companies are increasingly opting for offshoring in developing or emerging countries. Roche and Novartis each invest about 6 billion dollars annually in clinical trials, a proportion of which are in countries such as India, Russia and Argentina: in other words, in countries where a sufficient number of poor people live who are prepared to take part in risky drug trials because they represent their only chance of treatment. This can lead to abuses in countries where controls are more lax. Investigations carried out on the ground by the BD confirm that “globalisation of clinical trials” entails frequent ethical violations. National regulatory authorities such as Swissmedic do too little to redress the situation. The BD demands that the Swiss authorities and pharmaceutical companies do what is necessary to guarantee that offshore clinical trials respect ethical standards.

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Founded in 1968, the Berne Declaration (BD) is an independent Swiss non-governmental organisation formed to combat the root causes of poverty by promoting more equitable and sustainable relations between Switzerland and the developing world. As a not-for-profit organisation with 23 500 members, the BD is committed to global justice and addresses issues of trade policy, commodity production and trade, the politics of food, finance, fair trade and health. As part of a worldwide network of human rights groups, environmental and development organisations, the BD promotes a more equitable and humane route to global development. To this end, the BD carries out investigative research, runs public campaigns to raise awareness and undertakes successful advocacy work in Switzerland and on the international stage.