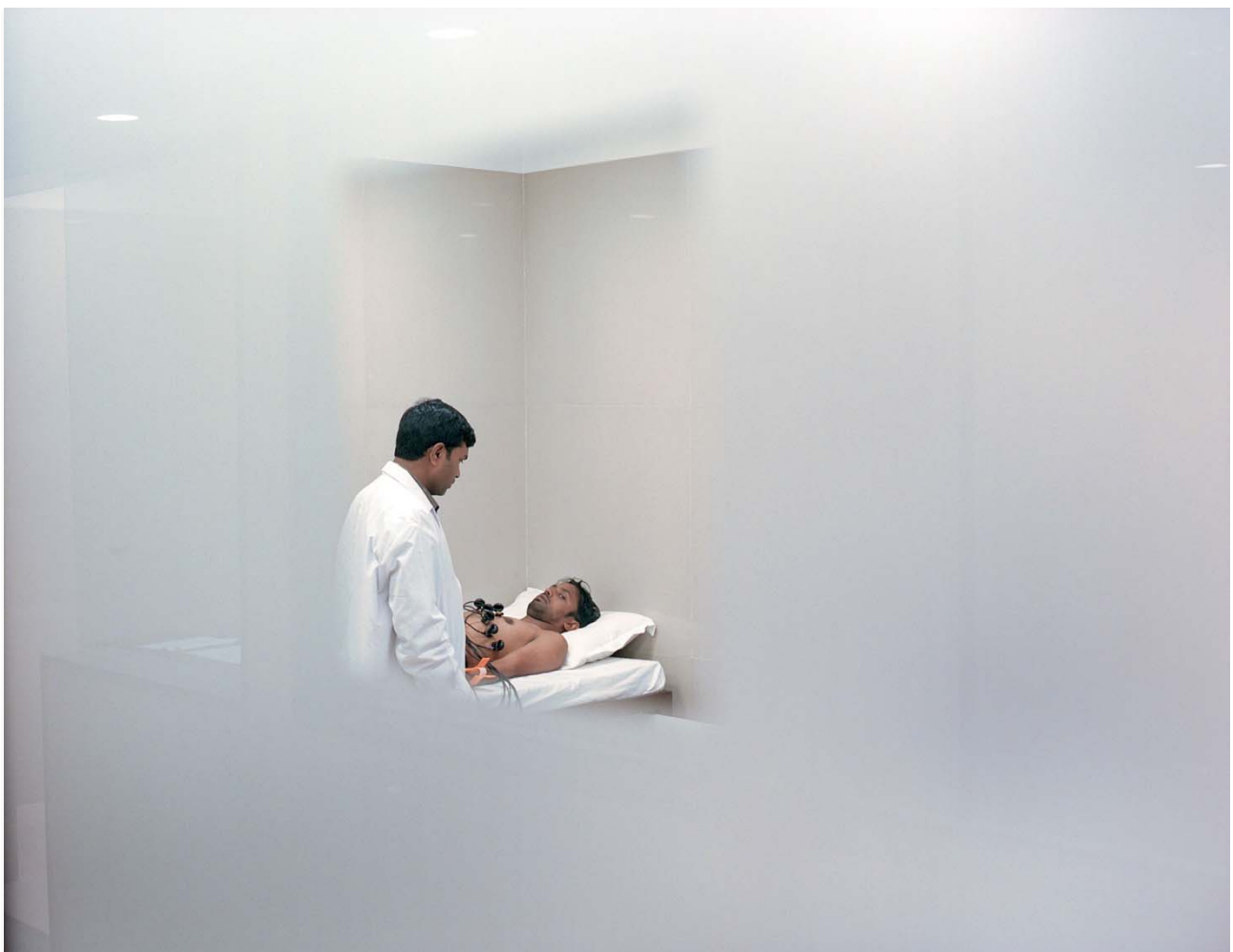


Clinical trials in developing countries and Swissmedic's role in protecting vulnerable participants



The Berne Declaration

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.

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Photo on first page: Indian patient participating to a drug testing © KEYSTONE/LAIF – Stephan Elleringmann

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Introduction	6
1. Bringing a new drug to market	9
1.1. Developing a drug	9
1.2. Scientific and ethical standards	11
1.3. Medical devices	11
2. Swissmedic's <i>modus operandi</i>	12
2.1. Swissmedic's mandate	12
2.2. Organisational structure	12
2.3. Marketing authorisation	13
2.4. Funding	14
2.5. The expert committee	15
3. Ethics in clinical trials	17
3.1. Introduction	17
3.2. Ethical Principles	17
3.3. Swissmedic and Swiss Law	18
3.4. Ethical standards: differences between the DoH, ICH-GCP and Swiss law	21
3.5. The different players involved in clinical trials	24
3.6. Limits of regulation	26
4. Ethical control of clinical trials	27
4.1. Possible checks and monitoring	27
4.2. Monitoring by foreign ethics committees	29
4.3. Monitoring by foreign drug regulatory agencies for clinical trial requests	31
4.4. Checks and monitoring carried out by Swissmedic for MA assessment	31
4.5. Swissmedic actions during the MA process	33
4.6. Improving ethical controls	34
5. Conflicts of interest and transparency	38
5.1. Introduction	38
5.2. A regulated industry or client?	38
5.3. The problem of the "revolving door"	39
5.4. The independence of the expert committee	40

Swissmedic & Clinical Trials in Developing Countries	4
5.5. Transparency	42
5.6. Recommendations	43
Conclusions	44
Appendix I: Cases of ethics violations in Switzerland	45
Appendix II: ICH-GCP Ethical standards	46
Appendix III: Original correspondence between Swissmedic and the Berne Declaration	47
Appendix IV: Some sources	60

For strategic reasons and to maximise profits, industry-sponsored clinical drug trials on human subjects are increasingly offshored in developing and emerging countries. In those countries, pharmaceutical companies can find a large pool of vulnerable people willing to take part in drug trials as it represents often their only treatment option. In addition, weak regulatory environments enable the pharmaceutical multinationals to shorten clinical trials duration. This increases significantly the risk of ethical violations. Concerned about this situation, the Berne Declaration launched several investigations in 2012 and 2013. Four field studies took place in Argentina, India, Russia and Ukraine to better understand these contexts in which numerous clinical trials take place. How is the regulatory system performing? Are the ethical standards respected? How do Swiss firms conducting clinical trials behave in these countries? A research was also carried out in Switzerland to understand how Swissmedic – the Swiss medicines agency – functions and carries out the ethical control of clinical trials that were conducted in third countries. The field studies were done by investigative journalists and by an NGO specialised in the field. The five investigation reports are available on www.ladb.ch or upon request at info@ladb.ch.

This report is based on the research conducted regarding **Swissmedic** by **Daniel Saraga**, a scientific journalist.

Abbreviations

MA	Marketing authorisation
EC	Ethics Committee
FDC	Swiss Federal Drug Commission
CRO	Contract Research Organisation
DoH	Declaration of Helsinki
FDHA	Swiss Federal Department of Home Affairs
ICH-GCP	Good Clinical Practice Guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
EMA	European Medicines Agency
FDA	Food and Drug Administration
LAMal	Swiss Federal Law on Health Care
LRH	Swiss Federal Law on Research on Human Beings
LPTh	Swiss Federal Law on Therapeutic Products
Oclin	Ordinance concerning clinical trials with drugs
OEPT	Ordinance concerning fees on therapeutic products
FOPH	Swiss Federal Office of Public Health
Omal	Ordinance concerning health care
SM	Swissmedic
SMEC	Swissmedic Medicines Expert Committees

Introduction

The globalisation of clinical trials and the problems associated with it

Medical research is essential for developing new treatments. A vital aspect of this work involves clinical trials on human beings to ensure that a treatment is safe, effective and rationally used.

Western pharmaceutical companies are increasingly turning to developing countries or emerging economies to conduct their clinical trials, particularly Eastern Europe and the former Soviet Union, South America, India and even South Africa.¹ They find these destinations attractive due to reduced costs, more flexible regulatory frameworks and the availability of large numbers of participants who are easily motivated and recruited. They are also aware that conducting trials in poor countries strongly reduces the risk of expensive litigation in the event of problems.²

However, participants from poor communities may have limited access to the health care system and often participate in the hope of receiving free healthcare. They are poorly informed about proper trial procedures and their rights, such as the right to abandon the study at any time without giving a reason, or the opportunity to continue receiving the treatment free of charge if it proves to be effective.

International conventions such as the Declaration of Helsinki – and to a lesser extent the Good Clinical Practice Guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-GCP) – provide clear ethical rules for medical research. The World Health Organization, the UN and some national governments have expressed intention to improve protection for participants in clinical trials, with an equal or even special focus on those conducted abroad.³

But these ethical rules are not observed. Violations of basic ethical rules have occurred even in industrialised countries⁴, and while they seem to have diminished, the globalisation of clinical trials increases the potential for abuse in developing countries.⁵ The scientific community has begun to discuss openly the problems associated with the globalisation of clinical trials.^{6,7} Cases of ethical violations denounced by NGOs⁸ and the media, or brought before the courts, have attracted the attention of the general public and the political world.

Ethical violations in clinical trials

Trials without the consent of participants

None of the 137 participants in a trial of the drug Cariporide, conducted in Argentina in 1997, had given their consent. The signatures of eighty of them had been forged.⁹

In January 2012, an Argentinian court found GlaxoSmithKline guilty of failing to inform the parents of babies recruited for their clinical trials of the Synflorix vaccine. Some 24,000 babies had participated in Argentina, Colombia and Panama.¹⁰

Poorly informed “guinea pig” participants

One of the most infamous cases is that of Trovan (Trovafoxacin), an antibiotic developed by Pfizer and tested in Nigeria during a meningitis epidemic and compared with a low dose of another antibiotic. Patients were apparently not informed that they were participating in a clinical trial on an experimental drug and that an effective treatment already existed. Eleven children died.¹¹

In 2003, the American company Viral Genetics conducted trials for an AIDS treatment without informing the participants of the risks associated with the study. The participants subsequently stated that they had not understood the consent forms, had not been reimbursed for the costs of their participation in the trial and had not been informed of the results.¹²

Patients prevented from leaving a trial

During a trial on iron supplements conducted in Bangladesh, around 80% of the participants stated that they had no idea that they were free to leave the trial at any time.¹³

One mother who participated in a fertility drug trial in Poland described how the private organisation that organised the research for the pharmaceutical company (a CRO or Contract Research Organisation) tried to discourage her from leaving a second clinical trial and pressured her to sign a confidentiality clause.¹⁴

Dangerous and unjustified use of a placebo

In 2005 and 2006, a new formulation of the antipsychotic drug Seroquel (AstraZeneca) was tested on people in India, Russia, Ukraine, Poland and Bulgaria. The majority of the participants had been diagnosed with paranoid schizophrenia. Half of them were given a placebo and were required, for the purposes of the trial, to stop their treatment. Among the 87 participants in the placebo group, 36 relapses (41%) and one suicide were reported, as opposed to 9 relapses for the 84 participants in the other group who received Seroquel (10.7%).¹⁵ The use of a placebo was completely unjustified, especially since the clinical trial was not testing a new molecule, but a new slow-release formulation of the drug.

Insufficient ethical monitoring

According to a study in 2004, a quarter of the clinical trials conducted in India had not been approved by an ethics committee.¹⁶ According to research from 2005, only a quarter of Indian ethics committees followed the prescribed guidelines, and conflicts of interest could not be excluded for half of them.¹⁷ Only 16% of the 73 clinical trials conducted in sub-Saharan Africa complied with international ethical principles.¹⁸ Finally, a more recent study conducted in India, Brazil, Argentina and Peru confirmed shortcomings in clinical trial monitoring, both on the part of regulatory authorities and the ethics committees in the relevant countries.¹⁹

Hidden trial results

The results of clinical trials are regularly hidden, either deliberately or unintentionally, especially when the results are negative (referred to as publication bias)²⁰. This is despite promises of increased transparency made by scientific journals²¹ and regulatory agencies²². Pharmaceutical companies themselves have stated that they would like more transparency and have committed²³ to systematic notification of their clinical trials in advance via public registers like Clinicaltrials.gov, which, in theory, serve as databases for all clinical trials.

However, many clinical trials are simply never announced. Participants' involvement – making their bodies available, and devoting their time to the tests, without considering the risks involved – ends up being wasted and sacrificed for commercial and marketing reasons.

The role played (or not) by the regulatory authorities

By monitoring the therapeutic products market, drug agencies like the Food and Drug Administration (FDA) in the United States, the European Medicines Agency (EMA) in the European Union or Swissmedic in Switzerland play a crucial role in monitoring the way in which pharmaceutical research and clinical trials are conducted. These trials are a key aspect of the applications submitted by pharmaceutical companies for authorisation to bring products to market. The legislation of these different countries clearly stipulates that these agencies must only authorise a drug if trials presented in the application have been ethically conducted, and, in particular, comply with international conventions. These agencies, therefore, not only have the power, but also the duty, to require additional information in order to ensure that both scientific and ethical rules have been observed. They also have the power to refuse a request for authorisation if they have doubts.

The pressure exerted by the FDA, for example, with regard to the quality of scientific information, has brought results. Today, promoters know that it is in their interests to do their best to ensure that their data is “clean” (scrupulous

recording of data, up-to-date documentation for equipment used, etc.). This prevents subsequent problems or delays when the authorities examine their marketing authorisation application.

This level of effort is still clearly lacking with regard to ethical questions. Drug agencies carry out little, if any, monitoring that could provide them with information on the way in which the clinical trials in the application have been conducted on the ground. While putting checks in place would be challenging because many of the trials were concluded years ago in far-off countries, control mechanisms remain absolutely essential to ensure compliance with the law. Sometimes applications presented to drug regulatory agencies fail to even mention ethical considerations.²⁴

With no pressure from the authorities, and in particular drug agencies, it is hard to believe that the ethical principles set out in international conventions, and sometimes restated by the pharmaceutical companies themselves,²⁵ are being effectively observed.²⁶ The most effective means of enforcing ethical principles is through the drug regulatory agencies in industrialised countries. By delaying or preventing products developed in unethical ways from reaching the market, they could force pharmaceutical companies to do everything in their power to ensure that their clinical trials comply with international ethical principles.²⁷

In order to successfully carry out their regulatory role, drug agencies need absolute independence and reputations that are beyond reproach. Their close relationships with the industry that directly contributes to their funding, however, threaten this independence. The question of conflicts of interest and transparency therefore needs to be addressed to ensure that ethical standards are followed during clinical trials.

The scope of this report

This report details the role played by the Swiss Agency for Therapeutic Products, Swissmedic, in the monitoring of the ethical aspects of clinical trials for new therapeutic substances. It focuses in particular on trials conducted in developing countries and used in marketing authorisation applications for the Swiss market. It analyses the issues of conflicts of interest and transparency in the agency's activities and suggests certain measures that could be taken to improve monitoring and ensure the implementation of international ethical rules on the ground.

This document looks only briefly at the situation in other countries – it is worth highlighting that Europe, in particular, is making progress in becoming keenly aware of the need to take ethical problems into account. This report also provides only a brief overview of the significant problem posed by the lack of transparency in clinical trial

data, which allows pharmaceutical companies to hide the negative results found during their studies and to mislead regulatory agencies, and the research and the medical professions.²⁸ As mentioned above, this lack of transparency also raises ethical questions for participants, whose commitment to advancing medical knowledge ends up being buried at the bottom of a drawer.

The first section explains the procedure for placing a drug on the market and Swissmedic's role. The structure of the Agency and its *modus operandi* are detailed in Section 2.

Section 3 details the ethical questions set out in the international conventions which must be taken into account

during a clinical trial, and the way in which Swiss legislation (and, briefly, European legislation) does, or does not, include them.

Section 4 analyses the role that Swissmedic plays, could play and should play, in the monitoring of compliance with international ethical standards during clinical trials conducted abroad for the purpose of gaining access to the Swiss market. Finally, issues of transparency and conflicts of interest are examined in section 5.

1. Bringing a new drug to market

1.1. Developing a drug

Before being placed on the market, a drug needs to undergo numerous clinical trials to demonstrate its efficacy and safety. On average, developing a new drug requires 65 clinical trials and the participation of 4000 patients.²⁹

A new drug must undergo the following steps:³⁰

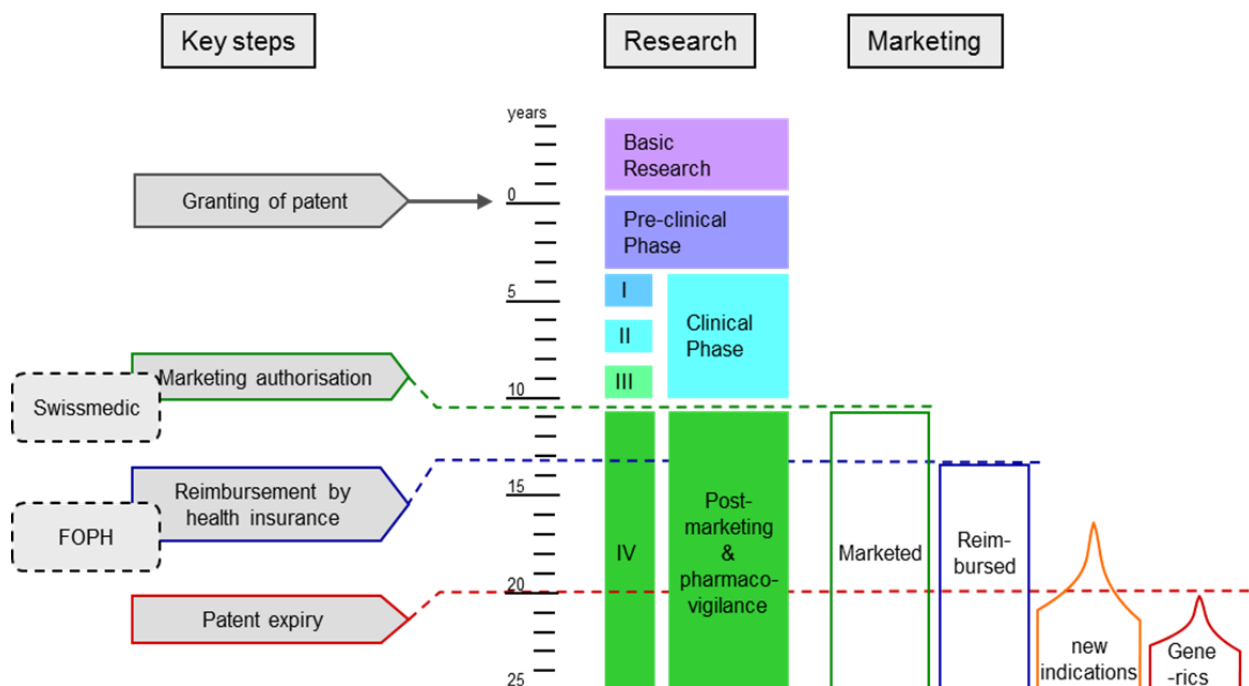
1. Basic research and preclinical phase: studies on cell cultures and animals.
2. Phase I clinical trials: safety, tolerance, side effects on healthy subjects (10-100 participants).

3. Phase II clinical trials: molecule efficacy, finding the optimum dose for subjects with the relevant disease (100-300 participants).
4. Phase III clinical trials: comparison with the placebo and standard treatments on sick people (>1000 participants).

Once placed on the market, phase IV trials may begin:

5. Phase IV clinical trials: pharmacovigilance (monitoring of side effects, including long-term ones); studies on sub-groups of patients; development of new therapeutic uses and markets.

Figure 1: The development of a new drug.³¹



1.1.1. Clinical trials

In principle, all clinical trials conducted in Switzerland must:³²

1. have been approved by a competent ethics committee;
2. have been notified to the competent monitoring authority (Swissmedic).

Swissmedic has the power to prohibit a clinical trial and to carry out inspections to monitor compliance with the submitted protocol at any time.³³

The issue of Swiss legislation, its scope of application (jurisdiction) and its influence on the practices of Swissmedic will be discussed further in sections 3 and 4.

A new law

The clinical testing of therapeutic products is currently governed by the Swiss Federal law on Therapeutic Products (LPTh) of October 2001 and by its enforcement provisions (ordinances). Following the approval of a new article to the Swiss constitution by popular vote in March 2010, the Swiss Parliament adopted the new Swiss Federal Law on Research on Human Beings (LRH) in September 2011, with a view in particular to “*protecting the dignity, personality and health of human beings in the context of research*”³⁴. It is expected to enter into force once the ordinances have been finalised, on 1 January 2014.

1.1.2. Authorisations

There are two types of authorisation for drugs, once clinical trials have been completed:³⁵

Marketing

In order to be marketed and used in Switzerland, a drug first needs to receive marketing authorisation (MA) or licensing from Swissmedic. The MA procedure is governed by the LPTh and its enforcement provisions.

Reimbursement by mandatory health insurance

In order to be reimbursed under mandatory health insurance (LaMal), drugs need to be on the Swiss Federal Office of Public Health (FOPH) List of Pharmaceutical Specialities.

1.1.3. Marketing authorisation from Swissmedic

The results of clinical trials (in particular phase III trials) form an essential part of the file submitted to Swissmedic for a marketing authorisation (MA) application. In accordance with the LPTh, Swissmedic either issues or refuses to issue an MA once it has checked that the therapeutic product fulfils the following criteria:³⁶

1. The drug or procedure is of good quality.
2. The drug or procedure is safe.
3. The drug procedure is effective.

In addition, the company that submits the MA application must be authorised for manufacturing, importing or wholesale trading.

Swissmedic makes its decision on the basis of the recommendation of groups of experts, the “Swissmedic Medicines Expert Committees” (SMEC).

Importantly, economic considerations (relationship between the drug’s efficacy and its cost) are not taken into account during the MA assessment³⁷, but are taken into account during the inclusion (or otherwise) on the FOPH List of Pharmaceutical Specialities.

Ethical aspects

The LPTh does not explicitly mention compliance with ethical standards as a criterion for granting MA. However, the Ordinance concerning drug requirements (OEMéd) stipulates that “*the documentation on clinical trials must demonstrate, in particular, that tests on humans have been conducted in accordance with the recognised rules of Good Clinical Practice*”³⁸, which include compliance with ethical rules (see 3.3. *Swissmedic and Swiss law*).

1.1.4. Health insurance reimbursement and price setting by the FOPH

Drugs with an MA may be marketed in Switzerland, but are not necessarily subject to reimbursement under mandatory health insurance (LaMal).

The List of Pharmaceutical Specialities

In order to be reimbursed under the LaMal system, drugs must be on the Federal Office of Public Health (FOPH) List of Pharmaceutical Specialities. The main conditions are as follows:³⁹

1. The drug must be effective, appropriate and economical.
2. It must produce the desired therapeutic effect at as low a cost as possible.
3. Prices are assessed by comparing the effectiveness of the drug with existing treatments and prices abroad, taking into account the costs associated with the development of the new drug.⁴⁰

The FOPH decides whether a drug should be reimbursed under mandatory health insurance and sets the price. It bases these decisions on the recommendation of a group of experts, the Swiss Federal Drug Commission (FDC), which plays a role similar to that of the “Swissmedic Medicines Expert Committees” (SMEC).

Reimbursement apart from the List of Pharmaceutical Specialities

The Ordinance on health insurance allows for the reimbursement of drugs not on the List of Pharmaceutical Specialities (or the use of a drug on the list for a purpose

other than that for which it is authorised) under two sets of circumstances:⁴¹

1. if its use is essential for other services reimbursed under mandatory health insurance;
2. if the drug offers significant benefits against a disease that is potentially lethal or could create serious chronic health problems for which no other authorised and effective therapeutic alternative exists.

1.1.5. Monitoring the market

Swissmedic also has the mandate to monitor the Swiss therapeutic products market by implementing the following measures:⁴²

1. pharmacovigilance and monitoring of medical devices;
2. monitoring of the therapeutic products market;
3. monitoring of advertising.

Pharmacovigilance requires that practitioners communicate all the side effects or contraindications of drugs so that the authorities (Swissmedic) can react quickly if this data shows safety problems.

Monitoring of the market involves, among other things, the problem of counterfeited or substandard therapeutic products and their uncontrolled sale, for example, over the Internet.

Swissmedic also monitors advertising of, and information on, therapeutic products.⁴³

1.2. Scientific and ethical standards

The development, authorisation and use of drugs must comply with scientific and ethical standards (see Table 1: *Ethical principles for drug development*).

General ethical principles for drug development according to Swiss law

Protection of human beings must take priority over the interests of science and society.⁴⁴

Participants in clinical trials must be correctly informed and protected.⁴⁵

Scientific data collected by the manufacturer and researchers must be reliable and must demonstrate the effectiveness (or otherwise) of the therapeutic substance.

Industrial production of the drug must be of a high quality⁴⁶ and marketing must comply with standards.⁴⁷

Information pertaining to the use of the drug (advertising, patient and doctor information) must be correct.

Table 1: Ethical principles for drug development.

1.3. Medical devices

Marketing authorisations for medical devices (implant, stent, measuring instruments, etc.) differ from those for drugs.

In principle, the accreditation procedure is recorded through notified private bodies with a licence to issue accreditations without the direct involvement of the authorities. Transparency is harder to achieve since the private bodies may (or must, according to the law) refuse to supply commercial data (see Appendix I, *The Geneva heart implants*). While this different procedure may be justified for certain simple devices, it should be adjusted for devices that involve more risk.⁴⁸

The Poly Implant Prothèse (PIP) breast implant scandal has contributed to increased awareness of the problems associated with this practice, and particularly of the issues associated with monitoring and transparency.

2. Swissmedic's *modus operandi*

2.1. Swissmedic's mandate

2.1.1. Responsibilities

The central role of the Swiss Agency for Therapeutic Products (Swissmedic) is to ensure the quality, safety and efficacy of therapeutic products for human and veterinary use, including drugs and medical devices.⁴⁹ The Federal Council establishes a multi-year service mandate and the Federal Department of Home Affairs (FDHA) then signs an annual service contract with Swissmedic. Swissmedic is specifically responsible for the following:⁵⁰

1. Granting authorisation for conducting clinical trials in Switzerland;
2. Granting marketing authorisation (MA) for drugs or medical devices so that they can be marketed in Switzerland;
3. Granting authorisation for producing therapeutic products (including inspection of factories);
4. Setting legal and technical standards;
5. Providing information to the general public and industry on therapeutic products; and
6. Organising market monitoring, specifically pharmacovigilance and the prevention of illegal or low-quality therapeutic products.

The Institute must ensure that therapeutic products authorised are safe, effective and above reproach.⁵¹

2.1.2. Divergent interests

This mandate clearly places Swissmedic in the middle of two divergent interests, because it is supposed to

1. on the one hand, protect consumers and patients; and
2. on the other, allow the industry to market its products within a reasonable timeframe and at a reasonable cost.

Swissmedic's mandate clearly identifies conflict of interest as an issue created by this situation⁵², but also highlights the need to avoid burdensome administrative procedures⁵³ by raising the question of the proportionality of means (increased monitoring and slower procedures) and the goal to be achieved (avoid conflicts of interest and monitor them).

The problems raised by this dual allegiance will be discussed in more detail in section 5, *Conflicts of interest and transparency*.

2.2. Organisational structure

2.2.1. Swissmedic's status

Swissmedic is part of the “decentralised” administration – it is an autonomous institution under public law managed by the Swiss Confederation with the assistance of the cantons⁵⁴ and comes under the FDHA. Its activities are not directly subject to the FDHA⁵⁵, but are governed by the service mandate and contracts set with the Federal Council and the FDHA. Its status shows the government's desire to create a drug market regulator that is independent of politics and industry. “*The reliability and independence of Swiss monitoring of therapeutic products [must be] ensured.*”⁵⁶

2.2.2. Organisational structure

Swissmedic is divided into 4 units – marketing, market monitoring, authorisations and the legal sector – together with the headquarters, the personnel and finance department, and the infrastructure department. The Federal Council appoints the Executive Director (currently Jürg Schnetzer).

The Agency Council plays the same role as a board of directors in a public limited company, i.e. overseeing the performance of the service mandate and service contract.⁵⁷

Swissmedic Agency Council	
Christine Beerli (Chair)	Lawyer, Vice-President of the International Committee of the Red Cross, former Head of the Bern University of Applied Sciences technical and IT division, former Swiss National Council member
Dr. iur. Carlo Conti	State Councillor; Head of the Health Department of the Canton of Basel City
Dr. med. vet. Markus Dürr	Former State Councillor of the Canton of Lucerne
Anne-Sylvie Fontannaz	Cantonal Pharmacist, Canton of Vaud, Lausanne
Prof. Dr. med. Reto Obrist	Former Head of the Oncology Department of the Canton of Valais
Prof. Dr. Gerhard Schmid	Lawyer, Basel
Prof. Dr. med. Peter M. Suter	Vice-President of the Swiss Academy of Medical Sciences

Table 2: Composition of the Swissmedic Agency Council

2.3. Marketing authorisation

One of the most important and well-recognized roles of Swissmedic is to grant or refuse authorisation for marketing therapeutic products in Switzerland. This relates both to products manufactured in Switzerland and to those imported from abroad, whether they are manufactured by a Swiss company or not.

2.3.1. Basic criteria

Swissmedic's primary role is to ensure that products are safe and effective:

1. They must not present a danger to human beings and any side effects must be clearly stated.
2. They must operate in compliance with their intended use.

2.3.2. The MA and the List of Pharmaceutical Specialities

It is important to remember that it is not Swissmedic but the FOPH that weighs the benefits of a treatment against the risks/costs that it engenders for society.

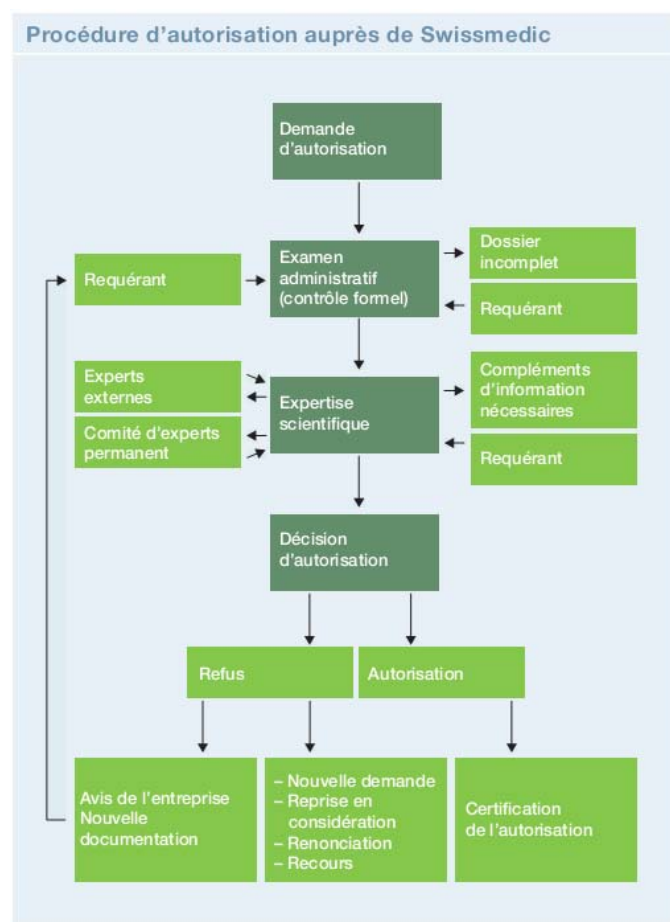
Obtaining an MA is not an absolute guarantee of efficacy. An authorised drug is not necessarily featured on the List of Pharmaceutical Specialities and may not necessarily be recommended by medical associations.

2.3.3. Procedure

Promoters of a new therapeutic substance (pharmaceutical companies) submit a full application to Swissmedic that contains, in particular, the results of clinical trials. It should be noted that they often start procedures with a number of different agencies (EMA, FDA, etc.) at the same time.

Swissmedic studies the application to ensure that it complies with submission requirements and submits it to its expert committee, which issues a positive or negative opinion. More often than not, a negative opinion is accompanied by questions or new requirements for the promoter, who can then respond and improve the application, before resubmitting it. A positive response means that the MA is granted.

Figure 2: Swissmedic authorisation procedure ⁶⁸



2.3.4. Key figures

Swissmedic authorises several new active substances for human use every year. Out of the hundreds of supposedly “new”⁵⁹ drugs authorised by Swissmedic, only some contain genuinely new molecules (“new active substances”).

Number of authorisations (Au) and applications (Ap)	2010	2011	
New drugs and essential changes of indications	315	171	Au
New active substances	37	20	Au
<i>of which for fast-track approvals (high importance)</i>	6	10	Au
Non-innovative drugs (generics, new galenic formulation or dosage)	1,708	609	Au
Drugs previously authorised by foreign drug agencies recognised by Swissmedic (EMA, FDA, etc.)	142	113	Ap

Table 3: Number of main MA assessments carried out by Swissmedic.⁶⁰

Swissmedic’s annual reports differentiate between new active ingredients – for which it states the number of MA issued, but not the number of applications submitted – and known active ingredients, or ones that are already

authorised abroad – for which it only gives the number of applications.

Publishing the number of MA requests submitted, accepted and refused and providing reasons for any refusals would be more transparent. Making associated clinical tests clearly identifiable would also be an improvement (see section 5 *Conflicts of interest and transparency*).

2.4. Funding

Swissmedic is funded 20% by the Swiss Confederation and 80% by the therapeutic products industry (see Table 4).

The Confederation’s funding is intended to cover tasks of general interest including in particular the monitoring of the medical devices and drugs market (partly funded by fees).⁶¹

The industry’s contributions are collected on the sale of therapeutic products authorised in Switzerland⁶² and from payments for procedures carried out by Swissmedic⁶³ – a marketing authorisation generally costs around 70,000 Swiss Francs (see Table 5).

Swissmedic’s heavy dependence on the therapeutic products industry clearly raises questions about its independence from the sector that it is supposed to regulate. These commercial relationships also encourage close links between Swissmedic employees and industry representatives, which creates risks of conflicts of interest and a “revolving door” issue. These points will be discussed in section 5, *Conflicts of interest and transparency*.

Swissmedic funding in 1000 CHF	2009		2010		2011	
Fees	64,128	79.6%	63,979	79.8%	64,135	80.2%
Procedure fees and revenue	23,777	29.5%	24,493	30.5%	24,346	30.4%
Sale fees	40,351	50.1%	39,486	49.2%	39,789	49.7%
Other revenue	89	0.1%	82	0.1%	58	0.1%
Federal contribution	16,164	20.1%	15,943	19.9%	15,624	19.5%
Other operating results	169	0.2%	175	0.2%	180	0.2%
Total	80,550	100%	80,179	100%	79,997	100%

Table 4: Swissmedic funding⁶⁴

Examples of fees collected by Swissmedic, in CHF		
Marketing authorisation for drugs for human use	New active ingredient	70,000
	Known active ingredient with innovation	28,000
	Known active ingredient without innovation	15,000
Marketing authorisation for complementary medicines	New active ingredient	6,000
	Homeopathic or anthroposophic drugs for general use	500
Fees for authorisation of a clinical drug trial		1,000

Table 5: Examples of fees collected by Swissmedic⁶⁵

2.5. The expert committee

The Swissmedic Agency Council appoints the Swissmedic Medicines Expert Committees (SMECs), which play an essential role in the operation of Swissmedic and in marketing authorisations, in particular.⁶⁶ Their initial opinions on MA applications are generally followed.

The SMECs are the Human Medicines Expert Committee for drugs for human use and the Veterinary Medicines Expert Committee for veterinary drugs. The Human Medicines Expert Committee (HMEC) meets twelve times a year and issues around sixty recommendations – more than the number of new active ingredients authorised (between 20 and 40 per year), but less than the number of new drugs (between 100 and 400).

2.5.1. Plurality of voices

Swissmedic's expert committees

SMEC experts are selected by Swissmedic for their skills and their ability to evaluate the information and data presented in an MA. They are all scientists, and the vast majority of them are physicians (most work in university or cantonal hospitals; others are in the private sector). The HMEC includes 7 permanent members and 37 temporary members. Of these 44 members, 43 are scientists specialising in biomedical fields (including 39 physicians) and one statistician. One member (Klaus-Heinrich Zimlich) is self-employed.⁶⁷

The FOPH Federal Drug Commission (FDC)

The uniform composition of the SMECs can be compared with the make-up of the FOPH Federal Drug Commission (FDC) which issues recommendations for the acceptance of new substances in the List of Pharmaceutical Specialities (which means that they can be reimbursed via mandatory health insurance) and for the price of the drug.

The composition of this commission is set by law⁶⁸: it must have 16 members, including:

1. two representatives of insured persons;
2. two representatives of health insurance companies;
3. two representatives of pharmaceutical companies;
4. three physicians, including a representative from complementary medicine;
5. three pharmacists, including a representative from complementary medicine;
6. a representative of the hospitals;
7. a representative of the medical and pharmaceutical faculties (scientific expert);
8. a representative of the cantons;
9. a representative of the Swiss Agency for Therapeutic Products (Swissmedic).

This distribution is intended to ensure a balanced representation of the various stakeholder groups: the insured, insurers, the industry, physicians, pharmacists, hospitals, scientists, cantons and the monitoring authority.

The opposite is true of Swissmedic's SMEC, which is entirely made up of scientists who must, according to the Federal Council, "be free of specific interests" (as for the members of the Swissmedic Agency Council).⁶⁹

Compromise or independence?

Both approaches – representing stakeholder groups and using scientific experts – have relative strengths and weaknesses.

The representation of stakeholder groups has the advantage of facilitating a compromise that can take into account multiple requirements: the drug must be effective (patients) but also economical (insurers) and practical for medical staff (physicians and hospitals), while being viable for the pharmaceutical company (industry). The weakness of this approach is that "the decisions taken are not the result of the strict application of legal or scientific rules, but of a struggle between divergent interests."⁷⁰

A committee composed solely of scientific experts guarantees technical expertise and apparent neutrality and makes decisions that seem more “objective”. But the criteria that the SMEC experts take into account seem weighted towards the effectiveness of the drug from more of a scientific perspective than a practical one. Some products authorised by Swissmedic are refused by the FDC because the benefits do not outweigh the challenges of the realistic and practical context.⁷¹

A uniform expert committee creates a consensual group dynamic in which far fewer divergent views are expressed and critical thinking tends to be diminished.⁷² An SMEC group of experts composed solely of researchers used to conducting clinical trials takes far less account of social and, in particular, ethical factors during an MA assessment. They also often work closely with the pharmaceutical industry on clinical trials, which, setting aside the issue of conflict of interest, could unconsciously bias their judgement. A

greater diversity in Swissmedic’s expert committees would therefore be a good thing.⁷³

Greater transparency (for example, publication of all minutes of meetings) would reduce this problem because the knowledge that their work will be subject to scrutiny generally encourages people to express their opinion – at least for the sake of the minutes.⁷⁴

2.5.2. Conflicts of interest

The risk of conflict of interest is a real one because most SMEC experts have professional relationships with the pharmaceutical industry. Their research often relates to pharmaceutical company products and they are often funded by the industry. Experts sometimes hold shares in listed companies or take on private consulting contracts. These points will be examined in section 5, *Conflicts of interest and transparency*.

3. Ethics in clinical trials

3.1. Introduction

The World Medical Association's Declaration of Helsinki⁷⁵ (DoH) is one of the first texts to have set out universal ethical principles for research on humans. Developed in partnership with the industry, the Good Clinical Practice Guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use⁷⁶, ("Good Clinical Practice" or ICH-GCP), include a set of best practice guidelines that define scientific quality standards including ethical aspects.⁷⁷ These ethical principles concern research conducted on humans in countries all over the world.

Importantly, for pharmaceutical companies, neither the DoH nor the ICH-GCP are binding (even though the ICH-GCP was mainly developed by the industry). Compliance with these conventions is therefore strictly voluntary. The situation is different for drug agencies whose legal frameworks refer explicitly to the DoH or the ICH-GCP and compliance with their standards (see 3.3. *Swissmedic and Swiss Law*).

3.2. Ethical Principles

The main ethical criteria set out in the DoH, ICH-GCP and Swiss legislation are summarised in Table 6, in which Swiss legislation refers both to laws currently in effect

(particularly the LPTh) and those that are set to enter into force in 2014 (particularly the LRH, see 3.3.1. *New Legislation: the LRH*). Swiss Law refers directly to the ICH-GCP – as opposed to European Law, which refers directly to the ICH-GCP as well as the DoH – but in some cases specifies different or more explicit rules.

While the essence of the DoH concerns ethics, the ICH-GCP focuses more on harmonising regulations rather than ethical commitments.⁷⁸ Although the pharmaceutical industry tends to minimise the differences between the DoH and ICH-GCP⁷⁹, it is clear that the ICH-GCP does not go as far as the DoH. Many commentators believe that, in general, the ICH-GCP does not protect participants as well.^{80,81}

The ICH-GCP also implies that it can distance itself from the DoH:⁸²

*Clinical trials should be conducted in accordance with the ethical principles **that have their origin** in the Declaration of Helsinki, and that are **consistent** with GCP and the applicable regulatory requirement(s).*

ICH-GCP 2.1, p. 9

The differences between the DoH, ICH-GCP and Swiss legislation are discussed in more detail in Section 3.4. *Ethical standards: the differences between the DoH, ICH-GCP and Swiss Law.*

	Principle	Description	DoH	ICH-GCP	Swiss Law
1	Ethics Committee	Clinical trials must obtain authorisation from an ethics committee and comply with the established protocol.	83	84	85,86
2	Clinical trial register	All clinical trials must be registered in a database before participants are recruited.	87	N/A	88
3	Risk/benefit	The predicted benefits of research must justify the implicated risks.	89	90	91
4	Safety	Participant safety must take precedence over all other considerations.	92	93	94
5	Compensation	If participation in a clinical trial should negatively affect the health of a participant, compensation must be awarded.	(95)		96,97
6	Informed consent	Participants must be informed of the nature of the clinical trial, its risks, the process and their right to leave the trial. They must understand this information.	98	99	100,101

7	Vulnerable populations	Special attention must be paid to the protection of vulnerable populations that may be forced to participate for social, economic or health reasons.	102	103	(104)
8	Utility of treatment	Clinical trials involving the participation of vulnerable populations are only justified if there is a reasonable likelihood that the research will lead to treatments that will be useful for them. ¹⁰⁵	106	N/A	
9	Access to post-study	Should treatment prove to be effective, arrangements must be made for vulnerable participants to have post-trial access.	107	N/A	
10	Placebo	In principle, placebo-controlled clinical trials to test treatment (in the control group) must not be authorised. The control group must receive the best existing treatment.	108	N/A	109

Table 6: Main ethical criteria associated with clinical trials.

3.3. Swissmedic and Swiss Law

The Swiss Federal Law on Therapeutic Products (LPTh), which currently governs marketing authorisations and clinical trials, requires that all clinical trials for therapeutic products on human subjects be conducted in accordance with recognised “Good Clinical Practice” regulations.¹¹⁰ These are “specified by the Federal Council” while “taking into account recognised international standards and directives”. In the end, only the Ordinance concerning drug requirements (OEMéd) and the Ordinance concerning clinical trials with drugs (OClin) clearly refer to the ICH-GCP:

Documentation on clinical trials must demonstrate in particular [...] that trials on human subjects have been conducted according to the recognised rules of Best Clinical Practice

OEMéd Art. 5 Paragraph 1

International directives. 1. Clinical drug trials must comply with Good Clinical Practice Guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-GCP Directives) of 1 May 1996.

OClin Art. 4.

In summary, via the OClin, the LPTh requires that clinical trials comply with ICH-GCP principles. The Declaration of Helsinki therefore only appears indirectly, via the ICH-GCP (see Figure 3: Current legal basis of ethical principles underpinning Swissmedic activities).

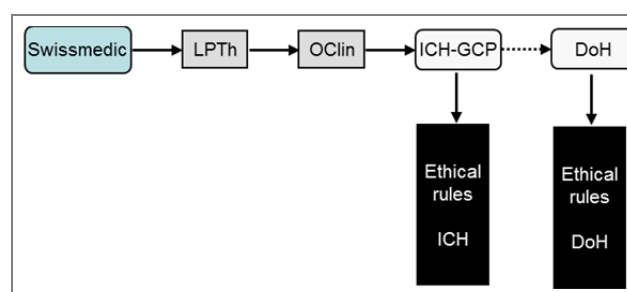


Figure 3: Current legal basis of ethical principles underpinning Swissmedic activities

Trials in Switzerland and abroad

By referring to international conventions, in practice these laws implicitly include clinical trials conducted abroad and submitted as part of an MA application (see 4.4. *Checks and monitoring carried out by Swissmedic for MA assessment*).

3.3.1. New legislation: the LRH

From 1 January 2014, the legal basis will undergo major changes as the new law on research on human beings (LRH) comes into effect. It will replace certain articles of the LPTh, and particularly those dedicated to compliance with ethical standards during clinical trials (Art. 53 to 57 included).

The LPTh will continue to regulate marketing authorisation procedures (MA) as well as formal authorisations for clinical trials, while the new LRH will stipulate the ethical principles for research projects. It will detail their supervision (particularly the work of ethics committees), transparency issues and coordination between different bodies (under the responsibility of the FOPH).

A law that is also relevant for trials abroad

The LRH was designed for clinical trials in Switzerland. It does not set out any clear requirements for authorising, conducting or supervising clinical trials conducted abroad, which may yield results that may be used in Switzerland for an MA.

But nothing stipulates that the provisions of the LRH be limited exclusively to Switzerland. In particular, nothing prevents Swissmedic from contacting foreign authorities in order to take into account the international dimension of clinical trials. The LPTH requires compliance with good clinical practice for clinical trials seeking an MA for drugs in Switzerland, whether trials were conducted in Switzerland or abroad (see 4.4. *Checks and monitoring carried out by Swissmedic for MA evaluation*).

Separation of ethical aspects

A significant outcome of the new LRH and related ordinances is the separation, at least at the legal level, between ethical and scientific aspects.

Ethical aspects will mainly be covered by the LRH. According to the ordinances submitted for public consultation in 2012, a body may be established within the FOPH to coordinate the work of ethics committees, researchers and Swissmedic, and perform communication tasks.¹¹¹

However, scientific issues will continue to be covered by the LPTH and primarily concern Swissmedic. At the time of writing, grasping the extent of this separation and the concrete consequences that will result from it is difficult because the ordinances according to which the LRH will be implemented are still under discussion.

However, the new legislation could end up separating ethical and scientific issues and divert ethical aspects away from Swissmedic's jurisdiction.¹¹² Today, Swissmedic uses the recommendations of ethics committees in its decisions whether to approve clinical trials in Switzerland or not. But with the new law, ethics committees may become more independent. It is therefore possible that cutting back Swissmedic's responsibility for the ethical aspects of clinical trials conducted in Switzerland could influence the willingness and ability of the agency to address the conditions under which research is conducted (in Switzerland and abroad): Is there not a risk that it will place less emphasis on monitoring ethical aspects under the pretext that that responsibility now belongs to the ethics committees?

Other concerns

Dominique Sprumont, law professor at the Institute of Health Law at the University of Neuchâtel, raises several criticisms of the LRH:^{113,114}

1. Conflicts of interest

The law would only consider the issue of conflicts of interest from a scientific angle¹¹⁵ and would therefore only allow those issues to be resolved between scientists, even though the problem of conflicts of interest clearly goes beyond this framework.

2. International Research

According to Dominique Sprumont, the LRH would also fail to properly address the globalisation of research:¹¹⁶ a provision should have been made to give jurisdiction to a federal body (for instance the FOPH) to resolve issues raised by international research, which is becoming a growing practice. Although entities such as the Swiss National Science Foundation (responsible for funding active researchers in Switzerland) or Swiss pharmaceutical companies are able to finance foreign research, the LRH would not provide a clear legal basis to coordinate research monitoring with the relevant authorities in the countries concerned and to cooperate with them in order to ensure the efficient protection of participants, regardless of the country in which research is conducted.

3. Ethics committees

The LRH would not solve the issue of ethics committees either: they have too much power although they need to be completely reorganised.¹¹⁷ They can of course "advise researchers on ethical issues in particular and take a stance, at their request, on projects that are not subject to the current law and particularly foreign projects"¹¹⁸. However this is only a possibility and not an obligation.

4. A missed opportunity

The LPTH clearly requires that Swissmedic ensure that clinical trials conducted abroad for MA approval of drugs in Switzerland comply with international conventions. But the LRH does not set out any provisions to verify the work of Swiss researchers abroad. Although it is supposed to regulate what happens during clinical trials, it only does so partially.¹¹⁹

3.3.2. Ethical and legal basis in the United States and Europe

The situation in the United States (FDA)

In 2008, the American Food and Drug Administration (FDA) decided it would no longer follow the DoH and would refer solely to the ICH-GCP, a change that raised substantial criticism from scientists, bioethicists and NGOs.^{120,121} For some commentators, the decision was probably spurred by a desire to avoid more restrictive rules for placebo-controlled trials.¹²²

The situation in the European Union (EMA)

A 2005 European directive¹²³ explicitly states that clinical trials must comply with principles of the DoH.

Clinical trials shall be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996).

Art. 2.1.3.

But significantly, the directive refers to the 1996 version of the DoH, which differs significantly from the 2000 and 2008 versions. The 1996 version of the DoH notably makes no mention of post-trial access to treatment, which only appears in the 2000 version (see 3.4.2. Access to post-trial treatment)

Notably the European Union is working on a new EU regulation.¹²⁴ The *Proposal for a regulation on clinical trials* only mentions the DoH twice, in ambiguous terms:

This Regulation is in line with the major international guidance documents on clinical trials, such as the most recent (2008) version of the World Medical Association's Declaration of Helsinki and good clinical practice, which has its origins in the Declaration of Helsinki.

Art. 63, p.24

The document also fails to address the usual ethical questions (placebos, post-trial access to treatment) or even mention the issue of vulnerable populations in developing countries.

But the EMA seems to want to address these issues explicitly. In its *Reflection Paper* of April 2012 dedicated to the ethical aspects of clinical trials conducted outside the EU¹²⁵, the EMA included a clear reference to the 2008 version of the DoH, and particularly with regard to vulnerable populations¹²⁶, placebos¹²⁷, and access to post-trial treatment.¹²⁸ This reflection paper, however, has no binding effect.

3.3.3. Declaration of Helsinki or only the ICH-GCP?

Swiss Law (and legislation of other countries referring to the ICH-GCP) is immediately confronted with a difficult question: does it imply compliance with the ICH-GCP only or the Declaration of Helsinki as well (via its implicit reference in the ICH-GCP)? There are differing opinions on the subject.

The ICH-GCP only

According to law professor, Valérie Junod¹²⁹, "mention of the DoH in the ICH E6 (ICH-GCP) does not imply that all the principles of the DoH are incorporated in the ICH directive"¹³⁰. The text of the ICH-GCP remains deliberately vague:

*Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, **consistent** with the principles **that have their origin** in the Declaration of Helsinki, and that the clinical trial data are credible.*

ICH-GCP Introduction, p.1

*Clinical trials should be conducted in accordance with the ethical principles **that have their origin** in the Declaration of Helsinki, and that are **consistent** with GCP and the applicable regulatory requirement(s).*

ICH-GCP 2.1, p. 9

Instead of alluding directly to the *principles of the DoH*, the ICH-GCP text alludes to the principles *that have their origin in the DoH*. It also adds the condition that these principles be *consistent* with the ICH-GCP, which raises significant ambiguity: is compatibility defined by joint presence in both texts or simply by the absence of clear incompatibility?

Two interpretations can be made:

- 1. Joint presence in both texts: according to the ICH-GCP, only principles that originate from the DoH and are explicitly restated in the ICH-GCP are valid. (In which case mentioning the DoH is actually pointless).
- 2. Absence of incompatibility: all principles that have originate from the DoH and do not explicitly contradict the principles of the ICH-GCP are valid, thus including the principles that only exist in the DoH.

Since Swiss legislation only refers to the ICH-GCP, according to this interpretation, Swiss law does not include the DoH. Therefore, for instance, clinical trials conducted in Switzerland should not necessarily avoid the use of placebos. If trials considered in Switzerland for an MA application were carried out on vulnerable populations, Swiss law would not require access to post-trial treatment.

Many governments of industrialised countries have opted only for the ICH-GCP (and not the DoH, or its less restrictive 1996 version) in order to avoid having to comply with some of the principles of the DoH.¹³¹ In reality, the Declaration of Helsinki is either not complied with or hardly complied with, particularly to avoid restricting the use of placebos and encouraging access to post-trial treatment.

1	According to this point of view, the Declaration of Helsinki is not respected in practice.
2	According to Swiss Law, it does not need to be respected, whether for trials conducted in Switzerland or elsewhere.

The ICH-GCP implies the DoH

Law professor Dominique Sprumont defends another point of view. According to him, the reference to the DoH in the ICH-GCP makes the principles of the DoH binding, even for Swiss Law.

This reference to the Declaration of Helsinki is completed in appendix G of the ICH-GCP which reproduces in extenso its 1996 version. This is of particular importance, as the ICH-GCP has been formally incorporated into the drug regulations of the EU, the US FDA and the Ministry of Health, Labour and Welfare in Japan.

(...) Indirectly, this static reference to the ICH-GCP [in OClin art. 4] should be understood as a reference to the 1996 version of the Helsinki Declaration. In that sense, the situation in the Swiss law is similar to the one in the EU and the US [author’s note: in 2007, before the FDA abandoned the DoH,] concerning drug trials.

*(...) a physician should follow the 2000 version [of the DOH] according to his professional rules [FMH], while, on the other hand, he is obliged to comply **with the 1996 version [of the DoH] as required by the drug regulation.***

The Helsinki Declaration and the Law: An International and Comparative Analysis¹³²

According to this article, even though the DoH is not explicitly mentioned in Swiss Law, it is similar to EU and United States Law, which contain (or which did until 2008 in the case of the United States) explicit references to the DoH.

According to this point of view, the Declaration of Helsinki is an integral part of Swiss laws on trials conducted in Switzerland. As will be shown later (see 4.4.2. *MA to monitor ethical aspects*), Swiss Law does not distinguish between clinical trials conducted in Switzerland and those conducted abroad as far as compliance with international ethics conventions is concerned. Consequently, this second interpretation (ICH-GCP implies the DoH) would mean that foreign clinical trials used for MA applications in Switzerland would have to comply with the DoH.

According to this point of view, trials submitted for an MA application in Switzerland must comply with the Declaration of Helsinki, for both clinical trials conducted in Switzerland and trials conducted abroad.

3.4. Ethical standards: differences between the DoH, ICH-GCP and Swiss law

Swiss law refers directly to the ICH-GCP but not the DoH, which raises the question of the importance of the DoH in terms of Swiss Law (see above 3.3.3. *Declaration of Helsinki or only the ICH-GCP?*).

Below are the most significant differences between the DoH, ICH-GCP and the explicit provisions of Swiss law.

3.4.1. Vulnerable populations

DoH

The DoH clearly requires that vulnerable populations participating in this type of research be protected and that there be a likelihood that they stand to benefit from results.¹³³

ICH-GCP

ICH-GCP clearly defines what a vulnerable population is, but does not give any necessary criteria to justify their involvement in a clinical trial.

Swiss law

Chapter 3 of the LRH is dedicated to additional requirements associated with research on “particularly vulnerable persons”.

A research project may only be conducted on particularly vulnerable persons if equivalent results cannot otherwise be obtained.

LRH Art. 11 paragraph 2

This category concerns:

1. persons incapable of discernment (in particular children);
2. adolescents;
3. pregnant women;
4. in vivo embryos and fetuses;
5. persons deprived of liberty;
6. research in emergency situations.

In its definition of vulnerable populations, Swiss legislation focuses mainly on persons incapable of discernment. This limitation contrasts with the usually accepted definition of vulnerable populations. The latter focuses on people in a situation of constraint (economic or health) who hope to benefit from treatment, individuals whose “agreement to volunteer [in a clinical trial] may be unduly influenced, whether justified or not, by the expectation of preferential treatment if they agree or by fear of disapproval or retaliation if they refuse”¹³⁴ and persons “incapable of protecting their own interests”¹³⁵. Pharmaceutical companies also recognise this definition.¹³⁶

Swiss law makes no mention of poor populations in developing countries or emerging economies that would be vulnerable to being in a situation of constraint and to participating in clinical trials with the hope of obtaining treatment that would otherwise be inaccessible.

3.4.2. Post-trial access to treatment**DoH**

The DoH mentions post-trial access to treatment for vulnerable participants:

(...)The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

DoH (2008 version) Art. 14

At the conclusion of the study, patients entered into the study are entitled (...) to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

DoH (version 2008) Art. 15

It can be noted that this clause was introduced in 2000:

At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

DoH (2000 version) Art. 20

and did not appear in the 1996 version. For some commentators, it is this change that led to the 2008 FDA decision to abandon any reference to the DoH.^{137,138}

ICH-GCP

The ICH-GCP does not mention participant access to treatment, whether vulnerable or not.

Swiss law

Swiss law does not mention this issue.

International efforts

Even if the issue of post-trial access to treatment may seem ambiguous¹³⁹, the governments of several emerging economies are working on that very question. In Brazil, several resolutions of the Conselho Nacional de Saúde (National Health Council under the Ministry of Health, the highest ethics authority in the country) have since 1996 highlighted the need for subjects to be able to continue to receive best possible treatment after the trial, without any time limitation.¹⁴⁰ Lawsuits have been brought against pharmaceutical companies that refused to provide post-trial treatment.¹⁴¹

In India, the Indian Council of Medical Research (ICMR) guidelines included a chapter on this question in 2006; a bill is currently being prepared, but the project has yet to be made public.¹⁴² In Argentina, Ministry of Health resolutions since 2007 stipulate that participants continue to receive the best possible treatment after the trial and that the ethics committee concerned is responsible for determining the length of treatment if access cannot be guaranteed via other means.¹⁴³

3.4.3. Compensation in the event of a problem

DoH

The DoH only mentions the possibility of compensation in the event of a problem, without explicitly requiring it:

(...) The protocol should include information regarding (...) provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

DOH Art.14

ICH-GCP

ICH-GCP proceeds in the same way:

Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following: (...) The compensation and/or treatment available to the subject in the event of trial-related injury.

If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

ICH-GCP art. 4.8.10 and 5.8.1

Swiss law

Swiss law goes further by explicitly mentioning the obligation to provide financial compensation in the event of a problem.

Full compensation for harm suffered within the scope of the trial [shall be] awarded to research subjects.

LPT Art. 54 Al. 1b

Anyone who initiates a research project on human subjects shall be responsible for harm suffered in relation to the project. [...] Entitlement to compensation for harm shall expire three years from the date on which the person in question becomes aware of the damage and liable person, and at the latest, ten years from end of the research project.

Liability must be appropriately covered by insurance or another form of coverage.

LRH Art. 19 and 20 (as of 2014)

3.4.4. Placebo

DoH

The DoH clearly limits the use of placebo-controlled trials and highlights that great care must be taken to avoid abuse of this option.

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances: The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

DoH (2008 version) Art. 32.

The 2008 version is deemed less restrictive¹⁴⁴ than previous versions

In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

DoH (2000 version) Art. 29

The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

DoH (1996 version) Art. II. 2 and 3

The 2008 version adds a second possibility for the use of placebo, formulated somewhat vaguely: “Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm”. This change actually appeared in an intermediate version of the DoH in 2002, in a note added to Article 29.¹⁴⁵

ICH-GCP

ICH-GCP does not mention it, but another ICH-GCP directive clearly makes room for the possibility of using placebo-controlled trials:

(...) whether a particular placebo-controlled trial of a new agent will be acceptable to subjects and investigators when there is a known effective therapy is a matter of patients, investigator, and IRB judgment, and acceptability may differ among regions and (...) populations chosen.

ICH-GCP Topic E 10¹⁴⁶

This is an important point for the industry because it is much easier to obtain positive results in a placebo-controlled trial than against the best available treatment.¹⁴⁷ According to a European study, the ICH-GCP offers participants “poor” protection in this context.¹⁴⁸

Swiss law

When the new law concerning research on human beings (LRH) comes into effect in January 2014, Swiss legislation will also include an article dedicated to the question of placebo use.

Use of placebo or the forgoing of a treatment shall not be authorised unless no additional risk of serious or irreversible harm to the person concerned is expected; in addition, one of the following conditions must be met:

- a. absence of existing proven therapy;*
- b. use of placebo is necessary for compelling and scientifically sound methodological reasons in order to determine the efficacy or safety of a therapeutic method.*

LRH Art. 13 (as from 2014).

This article draws heavily on the corresponding DoH (2008 version) provision.¹⁴⁹ A notable difference can be found in Paragraph b, which allows the use of placebo for “compelling and scientifically sound methodological reasons”: this option also appears in the DoH, but it specifies

that “extreme care must be taken to avoid abuse of this option”, a statement that is not made in the LRH. Without this diligence requirement and the lack of a specific definition of “compelling and scientifically sound methodological reasons”, there is a risk of many placebo-controlled clinical trials for drugs, as is already the case.¹⁵⁰

3.4.5. Summary of differences

Between the ICH-GCP and DoH – In contrast to the DoH, the ICH-GCP does not require:	
1	limiting studies on vulnerable populations for treatments that are likely to be useful to them;
2	that vulnerable participants be guaranteed access to the treatment studied or other appropriate care or benefits once the trial is over
3	that placebo-controlled clinical trials be limited.
Between Swiss law and the DoH	
1	Swiss law (as from 2014) does not limit studies conducted on vulnerable populations for treatments likely to be useful to them.
2	It does not guarantee vulnerable participants access to post-trial treatment but requires the implementation of a compensation system in the event of a problem.
3	It also states a desire to limit placebo-controlled clinical trials, but with few restrictions.

3.5. The different players involved in clinical trials

A clinical trial involves many players who can play important roles in compliance with ethical standards.

3.5.1. The promoter of the clinical trial

The promoter (usually a pharmaceutical company) decides on the form of the clinical trial and its application:

1. its length;
2. its location and the patients involved;
3. its use of placebo or the type of drugs that will be administered to the control group;
4. the circumstances under which the trial will be stopped or prolonged;
5. whether the results will be published or not;
6. whether, and to what extent, participants will be informed or compensated.

The promoter will exert pressure to obtain quick, and if possible, positive results (with “clean” data), and in large numbers.

For a commercial pharmaceutical company, the primary motivation for complying with ethics in its clinical trials stems from financial considerations. This type of pressure could be achieved if drug agencies increase monitoring (see 4.4. *Checks and monitoring carried out by Swissmedic for MA assessment*).

3.5.2. Ethics committees

Ethics committees must monitor clinical trials and how they are conducted. Their role will be discussed in Section 4.2. *Foreign ethics committee monitoring*).

3.5.3. Physicians, researchers and research institutions

These people play crucial roles because they are the ones who in fact conduct the study and inform participants (whether well or poorly).

Not all researchers have the same degree of familiarity with ethical rules and may behave in very different ways. For Dominique Sprumont, they must be considered responsible¹⁵¹, regardless of whether they are public or private researchers.

Arguably, examining ethical questions in connection with the submission of an MA application is much too late: trials have already taken place months, or even years earlier, and most often have already ended. This argument pleads the case for much earlier intervention, such as on monitoring during the clinical trial itself. This requires increased interest in researchers and ethics committees.

In Switzerland, the most recent ethical problems in medical research have concerned researchers in the public sector more than pharmaceutical companies (see Appendix I, *Ethical violations cases in Switzerland*), according to Dominique Sprumont, who also deplores a decrease in the amount of attention researchers pay to the ethical issues raised by their research.¹⁵²

Even for studies done by pharmaceutical companies, the researchers who actually conduct the clinical trials usually work for public institutions (in industrialised countries). Consequently, they play an important role in ensuring that ethical rules are complied with. The situation is different in the Global South, where private clinics are often interested in participating in clinical trials.

3.5.4. The participants

Participants are often very poorly informed of their rights and do not fully understand the stakes involved in participating in a clinical trial.

Awareness campaigns would help improve the situation and encourage participants to exercise their rights and

demand the best possible information concerning the subject of the studies in which they are participating.

3.5.5. Drug regulatory agencies

Drug regulatory agencies bear final responsibility. They can play a major role in ensuring compliance with ethical standards by clearly indicating during the MA application process that compliance with ethical standards is a non-negotiable condition for obtaining an MA. If at that point it is too late to monitor the clinical trial via inspections, the drug agency may certainly check the data submitted by ethics committees and consult them to attempt to verify ethical standards.

In being able to control market access, drug regulatory agencies possess a very powerful economic instrument. The sanction, a denial of access to the market, or even just a delay in the MA procedure, could hold great sway, as MA applications are assessed well after patents have been filed and each delay in the decision amounts to tens and even hundreds of millions of dollars in losses for the promoter. Faced with the risk of such a delay, pharmaceutical companies would see that it is in their own interests to comply with international ethics standards and take sufficient measures to ensure that this is done.

The key point therefore is the efficiency of ethical monitoring carried out by authorities, and the consequences of violations.

The role of the Swiss drug agency, Swissmedic, will be discussed in Section 4.2. *Foreign drug agency monitoring of clinical trial applications*, and Section 4.4. *Checks and monitoring carried out by Swissmedic for MA evaluation*.

3.5.6. CROs

Pharmaceutical companies do not necessarily conduct clinical trials themselves. They can use the services of private companies, called Contract Research Organisations (CROs), which take charge of the entire organisation and management of trials. CROs may draft research protocols, find research hospitals to conduct trials, recruit participants, monitor the trials and issue research results to the pharmaceutical company that has commissioned them.

The increasing use of CROs has raised strong concerns¹⁵³ because, in most countries in the South, they function in a poorly regulated legislative framework.¹⁵⁴ They inherently have a major conflict of interest: they are supposed to carry out comprehensive studies but risk losing their clients (pharmaceutical companies) if they are unable to satisfy them with positive results.

Using CROs, however, is not necessarily a negative thing: CROs have contributed to enforcing ICH-GCP technical standards (“clean data”).¹⁵⁵ This is what makes it possible to consider the possibility that they could also help ensuring

that ethical standards are complied with, since they are already in the field.

As long as drug regulatory agencies exert enough pressure, it is possible to imagine a virtuous circle falling into place: convinced that compliance with ethical standards is a key financial advantage, pharmaceutical companies could demand that CROs perform onsite monitoring of clinical trials.

3.6. Limits of regulation

Ethical principles aimed at protecting research subjects already exist and have been incorporated, both explicitly

and indirectly in the laws of various countries. But violations of these principles continue to occur and have been documented (see *Introduction*). In any case, the existence of regulations is not enough to ensure that conventions are complied with.¹⁵⁶ To achieve this, it is essential that promoters not only sense moral pressure from civil society, but above all, enough economic pressure to convince them that compliance with ethical rules is crucial to their business. To exert this pressure, regular monitoring must take place and violations must carry consequences: investigations must be carried out (which would result in delays in granting the MA), market access denied and sanctions imposed.

4. Ethical control of clinical trials

Good intentions and trust are not enough to ensure respect for ethics conventions. Monitoring and sanctions play a crucial role.

4.1. Possible checks and monitoring

4.1.1. Main ethical standards

According to Dominique Sprumont, all clinical trials presented in an application to Swissmedic for a marketing authorisation (MA) must comply with international ethical standards, regardless of the country in which they were conducted (see *ICH-GCP implies the DoH*, p. 21).

The main ethical components are:

1. the participant's informed consent ;
2. consideration of participants' vulnerability;
3. limited use of placebo;
4. insurance for participants and financial compensation in the event of a problem;
5. access to post-trial treatment (for vulnerable participants).

4.1.2. Current situation

Figure 4 depicts the various players involved in clinical trials and the types of checks and monitoring they may perform.

These points will be discussed in detail below.

4.1.3. Options for monitoring

Monitoring can be done primarily at three levels:

1. by the "local" ethics committee in the country where the clinical trial is conducted, before authorisation and for any significant modification of the clinical trial;
2. by the local drug regulatory agency, when a new clinical trial is notified;
3. by the local drug regulatory agency or drug regulatory agency in an industrialised country when evaluating an MA application.

Before commencing, clinical trials must be approved by a local ethics committee (EC) and authorised by the relevant drug regulatory agency. The authorisation procedure must ensure that the clinical trial protocol and characteristics correspond with national requirements and in particular, the ethical standards in effect. These may be based on international ethics conventions (ICH-GCP and DoH) or refer directly to them.

When evaluating an MA application, the drug regulatory agency must ensure that the data presented comes from clinical trials that comply with ethics conventions.

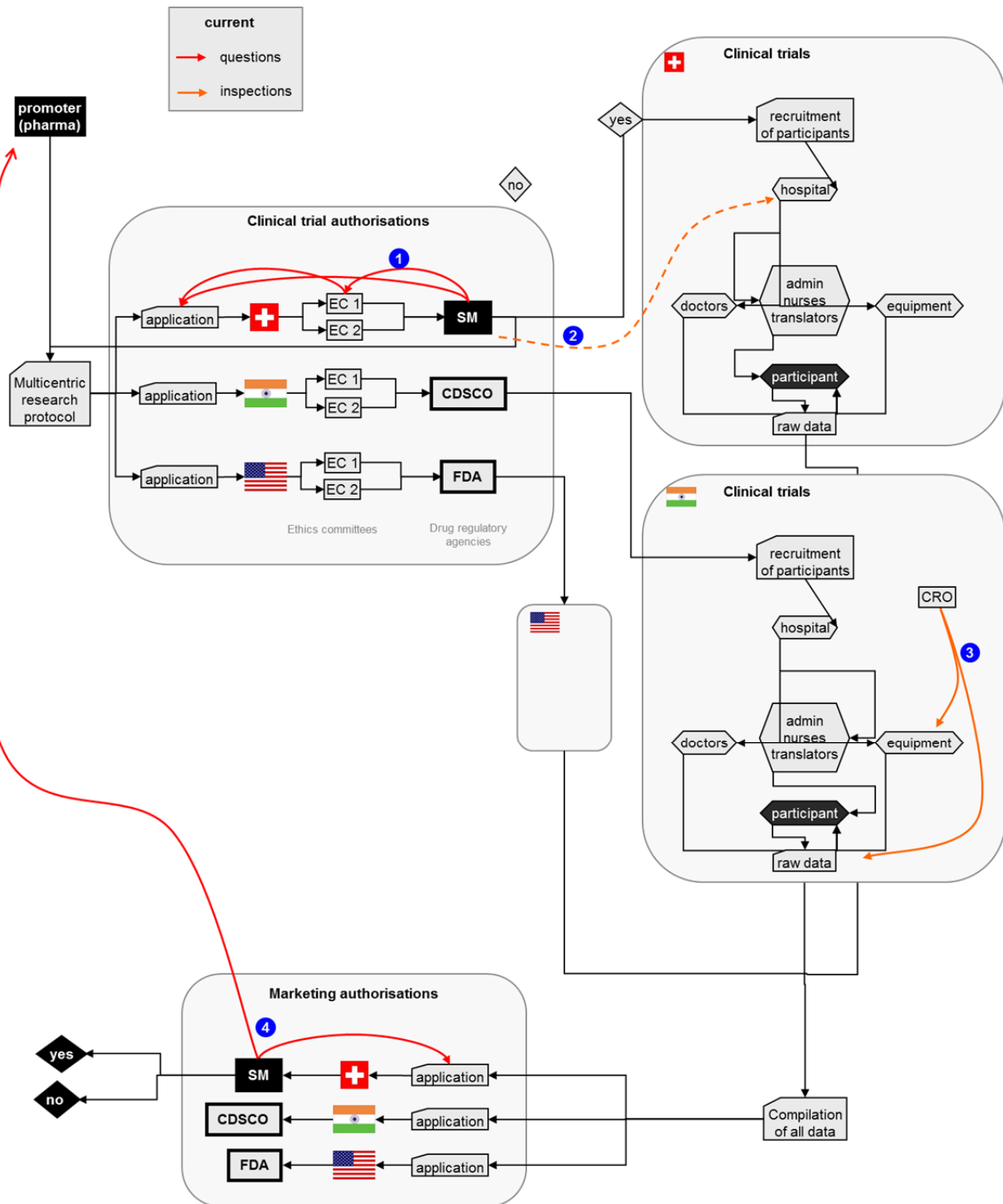


Figure 4: bringing a new drug to market and possible checks and monitoring – current situation

4.2. Monitoring by foreign ethics committees

Ethics committees (EC) – Independent Ethics Committees (IEC) or Institutional Review Boards (IRB) – assess applications for conducting clinical trials in the institutions under their responsibility. Research conducted abroad is therefore managed by a local ethics committee in the country in question. If a pharmaceutical company organises a clinical trial through local researchers (e.g. in developing countries), a local EC will be responsible for evaluating the project.

Ethics committees can exist in various forms: they can be regional or decentralised, state-run or connected to private institutions. For instance, in most countries of the former Soviet Union, decentralised ethics committees have been created recently to complement the traditional centralised ethics committee under the Ministry of Health.

4.2.1. Varying quality of local ethics committees

Western and Swiss ethics committees have questioned the independence and expertise of ethics committees abroad^{157,158} but the case of ECs in developing countries is particularly concerning.^{159,160} In her 2006 book, Sonia Shah exposed the problem of the lack of independent ECs in developing countries¹⁶¹: in 2000 there were no ECs in Morocco, nor in Haiti until 1999 and the concept of a non-biased EC was new in Uganda.

Over the last decade, several emerging economies have changed their legislation on clinical trials and, particularly in countries where everything had previously been centralised, demanded that decentralised ethics committees be established. However, due to a lack of experience and resources, these bodies still remain inoperative or have little independence.

Swiss researchers who want to independently conduct research abroad must submit the project to a Swiss EC, connected to their institution. However this principle does not apply to multi-centre studies conducted in several countries at the same time.¹⁶²

Some researchers may voluntarily decide to submit their research project to an EC in an industrialised country if they are worried that local ECs are unable to evaluate their work properly.¹⁶³

4.2.2. Improving local ECs

Some initiatives have been put in place to train members of foreign ECs, help them build resources and capacity, share knowledge and to standardise the quality of ECs around the world.

For example, WHO has established the SIDCER Project¹⁶⁴ (Strategic Initiative for Developing Capacity in Ethical Review), which brings together four different platforms for discussion and capacity building: FECCIS¹⁶⁵ (Former Soviet States), FERCAP¹⁶⁶ (Asia and Pacific), FLACEIS¹⁶⁷ (Latin America) and PABIN (Africa). Other initiatives from the academic world and NGOs support training on ethical issues.¹⁶⁸

Drug regulatory agencies can play a major role in these initiatives by participating in discussions, supporting the organisation of workshops and sharing their knowledge. The French *Agence Nationale de Sécurité du Médicament* (ANSM, formerly known as AFSSAPS) has participated in projects aimed at building the capacity and expertise of ethics committees in developing countries.¹⁶⁹

However, ethical questions are intrinsically linked to culture. Some experts we interviewed^{170,171} believe that ECs in industrialised countries should not be asked to make decisions about clinical trials conducted in the Global South. This is the role of the local ECs where the trial is being conducted. Setting up partnerships is therefore important.

An example of partnership

Transferring knowledge among ethics committees in countries in the northern and southern hemispheres can be relatively flexible, as shown by the example of the Drugs for Neglected Diseases initiative (DNDi), a non-profit organisation that promotes partnerships among pharmaceutical industries, public institutes and patient representatives in the South in order to develop new drugs for neglected tropical diseases. It can serve as a promoter of drugs, in which role it can apply for clinical trial authorisations with local drug regulatory agencies.

The DNDi wanted to organise clinical trials to test treatment for sleeping sickness (Human African trypanosomiasis) in the Democratic Republic of the Congo.¹⁷² Because local ethics committees were particularly weak, the DNDi organised a one-day informal workshop in February 2012, bringing together French and Congolese ethics committees, as well as more experienced committees from other African countries. The aim was not to make a decision in the place of the Congolese committee, but to share practices. The Congolese EC then assessed the request alone.

The issue of North-South relations

The globalisation of clinical trials creates problems and real risks of abuse. However, the analysis of the situation remains relatively divided: industrialised countries fear that developing countries are not capable of resolving these problems, Dominique Sprumont explains.¹⁷³ But in fact, the situation is more complex: “Some members of African ethics committees are better trained than their western counterparts. There are also problems in Switzerland.” It is therefore important to avoid a simplistic analysis.

4.2.3. Beyond ethics committees

ECs play an important, but not exclusive, role in ensuring compliance with ethical standards. The manner in which clinical trials are conducted depends entirely on research centres (private clinics and hospitals) that recruit the participants, physicians and other people involved (nursing and administrative staff, translators).

In principle, local ECs are responsible for ensuring that these actors behave properly. However, if the local EC lacks expertise or capacity, drug regulatory agencies should consider directly monitoring research centres, even when they are abroad – as they currently do for pharmaceutical production plants.

4.2.4. Current role of Swissmedic

International relations

Swissmedic collaborates with WHO in several international programmes:¹⁷⁴

1. accelerated marketing of priority drugs, particularly in developing countries (Prequalification of Medicines Programme¹⁷⁵);
2. pharmacovigilance;
3. counterfeit drugs;
4. GMP inspections of vaccine manufacturers;
5. regulation of blood products;
6. participation in regulatory agency conferences.

However, it should be highlighted that these programmes do not generally concern ethical issues associated with clinical trials.

Position of Swissmedic

In preparing this report, we were able to meet once with Swissmedic management officials. During the meeting, managers from the Institute gave us a presentation about its international commitments.¹⁷⁶ The only programme mentioned that has anything to do with ethics was:

7. Participation of Swissmedic in the Paediatric Medicines Regulators’ Network, which brings together 26 regulatory authorities. Its objectives include promoting appropriate performance of paediatric clinical trials and working on the scientific and ethical assessments of clinical trials.

Swissmedic did not agree to additional meetings despite our repeated requests. In a written response (see Appendix III), its representatives emphasised that they maintain “close relations with foreign authorities and international organisations” and that, in 2008, they hosted a conference bringing together the various drug regulatory agencies (International Conference for Drug Regulatory Authorities). These efforts seem insufficient considering the major challenges raised by the globalisation of clinical trials.

A greater commitment by Swissmedic?

The problems posed by the varying quality of local ECs are well-known, and raise questions regarding the responsibility of western drug regulatory agencies, which passively ignore the problem.

It would be good to see Swissmedic take active measures to improve the expertise of local ECs, for instance, by participating in international training and capacity-building programmes or by directly establishing knowledge and experience sharing projects.

Questions:

- | | |
|---|---|
| 1 | Should Swissmedic participate more actively in international programmes aimed at building the capacity of local ECs, such as SIDCER? |
| 2 | Could Swissmedic help organise bilateral workshops in order to share knowledge between Swiss and local ECs – similar to the workshop organised by DNDi? |

4.3. Monitoring by foreign drug regulatory agencies for clinical trial requests

Drug regulatory agencies can only authorise or deny a request to conduct a clinical trial in their own country. In principle, clinical trials conducted abroad are not notified to Swissmedic, and it has no jurisdiction to authorise them. They are authorised, or denied, by the local drug regulatory agency.

Do these bodies have enough staff to examine the requests for clinical trials and carry out monitoring? Are they as motivated as their counterparts in industrialised countries?

The globalisation of clinical trials requires considerable coordination between the various drug regulatory agencies. The lack of contact between Swissmedic and its counterparts raises the question of whether the Agency's implicit confidence in its foreign counterparts is well-founded. Increased collaboration would lead to the sharing of information and experience.

The assumption that a foreign agency carries out onsite monitoring is a naïve one because onsite monitoring is rare even in Switzerland. Swissmedic has rarely conducted hospital inspections during a clinical trial. It consulted participants to check that they were well informed only once^{177,178} – in fact, under the law, this is the responsibility of the ethics committee.¹⁷⁹

This lack of monitoring is of concern because the results of scientific studies clearly show that most participants, even in wealthy countries, do not fully understand the nature, risks and potential benefits of the clinical trial in which they become involved.^{180,181}

Questions:	
1	Can Swissmedic continue to rely fully and solely on foreign drug regulatory agencies to ensure that the authorisation procedure for clinical trials conducted in other countries but used for MA authorisation in Switzerland complies with the rules?
2	Swissmedic maintains regular contact with its European and American counterparts but has practically no contact with developing countries or emerging economies. Given the globalised context, should Swissmedic seek more opportunities to share its experience in clinical trial authorisations with foreign drug regulatory agencies?

3	Should authorities organise interviews with participants to ensure compliance with the principle of informed consent and encourage – or even demand – that ethics committees do the same? As an essential aspect of ensuring compliance with the informed consent principle, should authorities encourage research into participants' understanding of the trial, in order to better evaluate the quality of information provided to participants?
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4.4. Checks and monitoring carried out by Swissmedic for MA assessment

Swissmedic could probably play the most effective role at this level: by carefully considering the ethical aspects of clinical trials conducted abroad that appear in an MA application submitted in Switzerland.

4.4.1. The MA and clean data

The clean data requirement

Drug regulatory agencies have successfully exerted pressure for clean data. This concept refers to specific standards that strictly regulate the way in which data is collected and recorded¹⁸². Forms must be filled out properly, the use of pencil is prohibited, changes or crossed out information must be substantiated, maintenance of measuring equipment must be documented, etc. The requirements are extremely detailed.

Drug regulatory agencies check these aspects when assessing an MA application. If any breaches are detected, data can be rendered invalid and contagion is even possible. In other words, the entire clinical trial can be rendered invalid if some of the data is not "clean".¹⁸³

The power of drug regulatory agencies

Earlier on, outsourcing clinical trials abroad was not always beneficial because "dirty" data could invalidate results and lead to significant loss of investment.¹⁸⁴ However, pressure from drug regulatory agencies has proven successful. According to Valérie Junod, promoters will now do everything they can to ensure that data is clean in order to minimise the risk of having problems with regulatory agencies, especially for phase III clinical trials, which are the most expensive.

Promoters often outsource the organisation of clinical trials to Clinical Research Organisations (CROs), private entities that have grown into major organisations. They are hired to deliver clean data and organise audits of research sites that are conducted internally or outsourced.¹⁸⁵

Pressure from authorities has therefore established a virtuous circle: promoters themselves seeking clean data inform CROs, which organise audits, even (or particularly) for clinical trials conducted abroad.

4.4.2. MA for monitoring ethical aspects

In principle, Swissmedic can only authorise or deny clinical trials conducted in Switzerland.

However the situation is more complex for clinical trials that provide data that appears in an MA application. In such cases, the law does not distinguish between research conducted in Switzerland or abroad: both must comply with international ethical standards.

Swissmedic can only monitor clinical trials conducted in Switzerland but trials conducted abroad must of course comply with the same fundamental principles as those in Swiss Law. This stems directly from the fact that to obtain an MA in Switzerland, Swiss Law must be complied with.

Dominique Sprumont¹⁸⁶

Important point:

There is no legal basis for Swissmedic to ignore violations of international conventions. Applying the law requires Swissmedic to ensure that clinical trials submitted in an MA application comply with ethical standards.

The passiveness of drug regulatory agencies

There is every possibility that ethical violations go unnoticed during an MA assessment because drug regulatory agencies do not appear to investigate these aspects systematically. They only react and take measures if they happen to encounter problems.¹⁸⁷

These agencies therefore play a passive, reactive role by intervening only in cases of obvious violations. They automatically rely on civil society (NGOs, journalists, patient or researcher associations) to investigate and reveal violations.

Any major ethical scandal can cause drug regulatory agencies to react and invalidate part or all of the data obtained in violation of international ethical standards. It is in the interests of pharmaceutical companies to avoid such major scandals, but they are not as cautious about minor ethical violations.¹⁸⁸

International agreements

Performing checks and monitoring would require Swissmedic to contact local regulatory agencies in those countries where clinical trials, submitted in an MA application, were conducted. It would therefore have to establish international cooperation agreements to facilitate the coordination of regulatory agencies and their work.

Such agreements already exist. For instance, they enable an authority to ask inspectors of a foreign agency to carry out onsite inspections of production plants in order to ensure the quality of imported drugs. These agreements could be broadened to incorporate the exchange of information on and enquiries into suspicions of violations of ethical standards.

4.4.3. Swissmedic rights and obligations

Swissmedic only has jurisdiction to authorise trials conducted in Switzerland, as well as the legal obligation to consider the conditions in which foreign clinical trials were conducted when evaluating an MA application. Despite provisions on international relations that enable Swissmedic to collaborate with foreign institutions to evaluate compliance with international ethical standards, in practice, the Agency never does this for clinical trials conducted in developing countries.

Provisions for information sharing

Reviewing clinical trials conducted in the past and abroad requires information sharing with regulatory authorities and potentially, local ethics committees.

The LPTh clearly outlines provisions on international relations that give Swissmedic the authority to settle the information sharing issues raised by the implementation of the law:

1. *The services of the Confederation responsible for implementing this law may request information from competent foreign authorities or international organisations.*
2. *They are authorised to provide competent foreign authorities or international organisations non-confidential data collected by virtue hereof.*

3. They are authorised to provide competent foreign authorities or international organisations confidential data collected by virtue hereof if said measure is to prevent serious health risks or to uncover illegal trafficking or other serious violations of this law.

4. They are authorised to provide competent foreign authorities with confidential data collected by virtue hereof at their request, provided: a. that the requesting foreign authorities guarantee that confidentiality will be respected; b. that they use data exclusively within the scope of an administrative procedure associated with the implementation of provisions related to therapeutic products; c. that only the data required to implement provisions related to therapeutic products are communicated; d. that no manufacturing secrets or trade secrets are disclosed unless the communication of data is essential to counteract direct health risks.

5. The Federal Council may enter into international agreements on the communication of confidential data to foreign authorities or international organisations if required by this law.

6. The provisions on international cooperation for penal matters shall be upheld.

LPTh Art. 64 "International administrative assistance"

A similar provision also appears in the new LRH (as from 2014).¹⁸⁹

4.5. Swissmedic actions during the MA process

Swissmedic claims to be well aware of the problems associated with the globalisation of clinical trials. During our meeting¹⁹⁰ with the agency managers, however, they confirmed that no monitoring is conducted in developing countries and that the Agency has no relationship with local players or even local drug regulatory agencies.

It is impossible to monitor based on a file, we would have to be onsite to check. There needs to be greater cooperation.

Françoise Jacquet, Head of Clinical Trials Division, Swissmedic

We would not know where to start in China. We are too small to share information with our Partners.

Petra Dörr, Member of Management Board, Swissmedic

We make no attempt to contact India.

Verena Henkel, Assistant Manager, Clinical Review Division, Swissmedic

Swissmedic currently does not carry out any GCP (or ICH-GCP) inspections abroad.

Swissmedic – Berne Declaration correspondence¹⁹¹

When in doubt, Swissmedic looks for additional information, but in practice, only talks to the promoters¹⁹². The Agency thus relies fully on pharmaceutical companies wishing to market a new drug. In other words, it relies fully on the market players it is supposed to regulate. This conflict of interest must be addressed.

It seems clear that the Agency needs to take a more active role in its efforts to ensure ethical clinical trials. But this aspect is neglected, while the issue of clean data has been successfully addressed (see 4.4.1. *The MA and clean data*, above).

Swissmedic's European counterpart, the EMA, clearly reported in its Reflection Paper its intention to tackle this problem and explicitly declared its desire to "identify those studies that may give rise to special ethical concern (e.g. arising from their design, the local regulatory framework within which they are conducted, the vulnerability of the study subjects) and where applicable, seek additional assurance that the trials have been ethically conducted."¹⁹³ However, Swissmedic has not been able to furnish any proof of concrete action beyond the basic principles. When asked, the agency simply repeats these principles and mentions that it "asks promoters detailed questions" (see Appendix III).

Questions:

- | | |
|---|---|
| 1 | How can Swissmedic ensure that laws are complied with, and that it authorises drugs only when the clinical trials used for the MA comply with ethical standards, when the Agency relies solely on promoters to collect additional information in case of doubt? |
|---|---|

2	How can Swissmedic ensure that ethical standards are complied with when the agency has <i>no contact</i> with authorities in the emerging economies where some clinical trials are conducted?
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4.6. Improving ethical controls

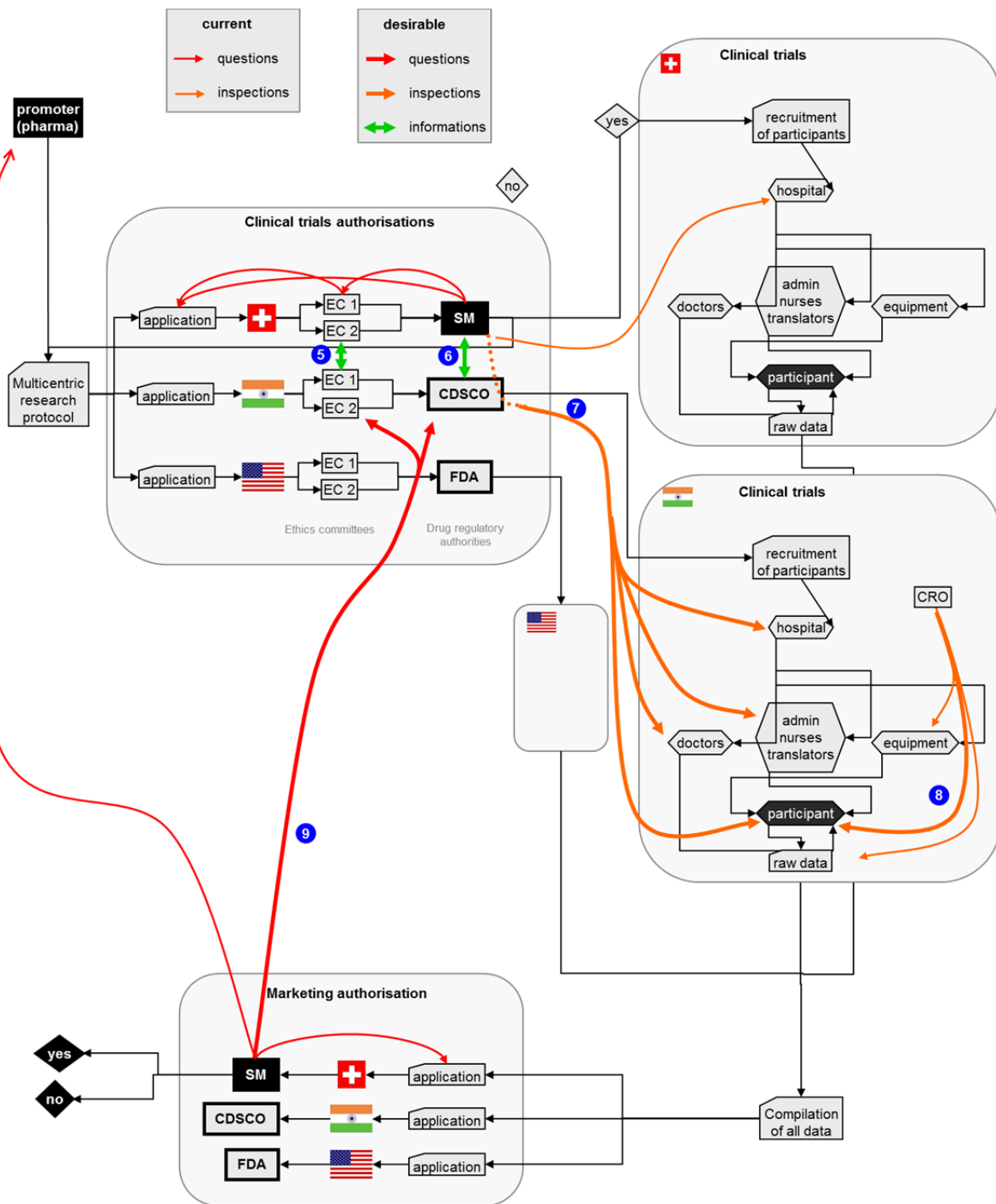
4.6.1. Recommended additional ethical controls

To ensure compliance with ethical standards, a drug regulatory agency ideally should maintain relationships with the following actors, so that they can ask for additional information:

1. the local drug regulatory agency, for details on the clinical trial application submitted for authorisation;
2. the local ethics committee that also examined the application;
3. the research centres that conduct the trials (hospitals, private clinics) and physicians in charge of research in order to be able to request additional information or even organise inspections;
4. the trial participants (difficult from a legal standpoint as their anonymity must be protected, however without any contact with participants it is impossible to ensure that they have a clear understanding of the protocol or have been informed of their rights).

In practice, this probably requires the Agency to send its requests to its foreign counterparts.

The diagram shown in Figure 5 summarises the interventions and additional checks and monitoring that would be useful to ensure better compliance with ethical standards.



- 5 Ethics committees from different countries exchange more information and harmonise their practices, with the support of international organisations and drug regulatory authorities.
- 6 Swissmedic entertains relationships also with its counterparts in developing countries, not only within the EU and with other Western countries.
- 7 Swissmedic encourages their local counterparts to carry out inspections during clinical trials that might serve for a marketing authorisation application in Switzerland. In particular, controls directly with the participants are encouraged.
- 8 The pressure put by drug regulatory authorities during the (forthcoming) procedure of marketing authorisation encourages the promoters to require from CROs to also conduct audits on ethical aspects.
- 9 In case of doubt during the examination of a marketing autorisation, Swissmedic does not limit itself to ask the promoter about ethical questions but enters directly in contact with its local counterparts, if not with the local ethics committees.

Figure 5: Suggested additional checks and monitoring in the process of bringing a drug to market

4.6.2. Difficulties

Implementation of these types of additional checks and monitoring would encounter obstacles, both in practice and in principle.

Objective controls are challenging

In contrast to the process of objectively confirming “clean data”, it is difficult in an MA application to objectively monitor aspects such as informed consent or the pressure¹⁹⁴ experienced by a participant who sees a clinical study as the only way to access certain treatment. Of course, it is possible to check whether information documents are in the right language and comprehensible, and if they have been signed, but it is difficult to be sure if participants have understood them well.

Define criteria

Before being able to control, ethical criteria must be objectively specified in a detailed manner, underlines Valérie Junod.¹⁹⁵ Even the principle of access to post-trial treatment for vulnerable populations fails to be described in sufficiently operational terms in the DoH (see 3.4.2. *Access to post-trial treatment*).

Insufficient interest in Switzerland

Swiss authorities and Swissmedic do not seem particularly concerned with participants’ lack of understanding of clinical trials in Switzerland.¹⁹⁶ The Agency thus is unlikely to be ready to take interest in participants of studies conducted abroad.

FDA difficulties

Despite a budget of \$4.4 billion and 9,300 employees, the FDA itself probably does not carry out the types of checks and monitoring suggested above.¹⁹⁷ How therefore can one hope that Swissmedic and its 400 employees will be able to carry them out?

The new LRH law

The new law on research on human beings (LRH) risks decreasing Swissmedic’s authority with respect to ethical matters (also see 3.3.1. *New legislation: the LRH*).¹⁹⁸ However Swissmedic will continue to be the gateway for trials conducted abroad that are used for MA applications in Switzerland. It therefore remains necessary for the Agency to have an ethics control mechanism (or at least a way of delaying the process in the event of suspicion of ethical violations). With the implementation of new mechanisms under the LRH, including a likely coordination body at the level of the FOPH, the new coexistence between the LPTh and LRH may also be a catalyst for new fields of collaboration between the institutions concerned.

4.6.3. Recommendations

Despite these difficulties, drug regulatory agencies could implement measures to ensure compliance with ethical standards during those clinical trials that are subsequently submitted in an MA application.

Of course the idea is not to systematically control all clinical trials, but to develop additional ways of identifying those that could have potentially violated ethical standards and carry out occasional checks that would serve as a deterrent.

Recommendations:	
1	Drug regulatory agencies in industrialised countries, governments and international organisations support the creation, maintenance, development and training of ethics committees in developing countries. Ethics committees in the North share their knowledge and experience with local counterparts.
2	Drug regulatory agencies in industrialised countries systematically encourage local drug regulatory agencies to carry out inspections of clinical trials in order to monitor ethics criteria by surveying hospitals, physicians, administrative staff and the participants themselves.
3	During the MA process, drug regulatory agencies in industrialised countries verify submitted ethics-related documents with at least as much attention as is paid to clean data issues.
4	Agencies not only address ethics issues with the promoter, but also with the local drug regulatory agencies that authorise clinical trials. If necessary, they ask them to contact CROs, the ethics committee that authorised the trials, the research centre where the trial was carried out and even the actual participants. If necessary, the national agency or another competent body directly contacts the local ethics committee.

5	Additional investigations would be justified in ensuring compliance with international ethical standards and delaying approvals for marketing a drug, thereby increasing financial pressure on pharmaceutical companies.
6	Agencies increase pressure in order to encourage promoters (and thus CROs) to stress the importance of ethical issues in addition to clean data. In addition to clean data monitoring, CROs would then also monitor ethical issues.
7	Authorities encourage research on informed consent of participants in order to determine whether the methods of communication generally used (written documents and forms) are effective in enabling participants to give truly “informed” consent.

5. Conflicts of interest and transparency

5.1. Introduction

The public expects the decisions of the administration to be determined by prevailing public interest, and decisions should reflect careful consideration of the various legitimate interests involved. In order for this consideration to be objective, it is vital for administrative bodies to be – and look – independent.

Les conflits d'intérêts dans l'administration, en particulier à l'OFSP (Conflicts of interest in the administration, and in particular at the FOPH)¹⁹⁹

Swissmedic's independence in decision-making (marketing, clinical trial or production authorisation) is crucial to ensuring that the activities of the pharmaceutical industry adequately comply with the interests of the population. But four areas of conflict of interest weaken this independence and tarnish its image:

1. Swissmedic's mandate makes it serve two masters: the pharmaceutical industry, which the Agency must regulate efficiently and with a minimum of administrative procedures, and the population, which it must protect.
2. The industry's significant financial contribution to Swissmedic's funding creates a situation of dependency.
3. Swissmedic's staff have close links to the industry (problem of the "revolving door").
4. Members of expert committees often have close links to the industry.

5.2. A regulated industry or client?

Industry fees cover 80% of the Swissmedic budget, placing the monitoring authority in a position of financial dependency. Although it seems logical to make the industry pay for the costs of the procedures required for its regulation, this practice can blur the boundaries between a regulated industry and a client who pays for a service.

This type of funding can create conflicts of interests. First, it creates the impression – for the public, civil servants, and fee-paying companies – that those who pay, in this case, the industry, should be treated like clients. However, the industry is not the client, but rather the sector regulated due to the safety risks that its products involve. Nevertheless, Swissmedic sometimes

makes this mistake: several of its annual reports refer to the pharmaceutical industry as a client, or even a "priority client". Fee-based funding also creates the risk of a budget that fluctuates from year to year, because it depends on the number of fee-incurring contracts. In order to maintain a balanced budget, Swissmedic may have to refuse to perform some services that are important but bring in insufficient financial resources.

Les conflits d'intérêts dans l'administration, en particulier à l'OFSP (Conflicts of interest in the administration, and in particular at the FOPH)²⁰⁰

There is a potential conflict of interest with regard to the way in which Swissmedic is funded, which largely relies on fees paid by the industry, particularly for marketing authorisations. This creates a risk that the administrative body becomes dependent on those it is administering and monitoring. Swissmedic's costs mainly involve its many and highly qualified staff, but its freedom to act independently of the industry may be compromised. This is further exacerbated by the fact that a large proportion of Swissmedic staff come from the industry and return to work in the private sector after a period at Swissmedic.

Dominique Sprumont²⁰¹

5.2.1. Situation in Europe

The situation in Europe is similar to that in Switzerland, with fees received by the EMA representing 76% of its revenue.²⁰²

National regulatory agencies in the various European countries can end up competing with one another and be tempted to relax their criteria to ensure that a pharmaceutical company ("client") is not tempted to switch countries in search of a less demanding agency that could also provide access to the European market.²⁰³ The European Parliament is currently discussing new European regulations on clinical trials, with the aim of harmonising procedures to address this problem. The EMA (European drug regulatory authority) is also beginning to take precedence over national drug agencies. Most marketing authorisations are now issued by the EMA, which grants access to the entire European market with a single procedure.

5.2.2. Situation in the USA

Compared with Swissmedic, only a third of the FDA budget is funded since 2007 by industry fees (Barack Obama

announced in 2012 that he wanted to increase this share to 45%).²⁰⁴

This problem is clearly recognised in the USA, as the NGO Public Citizen expressed in 2007.²⁰⁵

So in many ways, the FDA started looking upon the industry as their client, instead of the public and the public health, which should be the client.

Sydney Wolfe (Public Citizen)²⁰⁶

This is the case despite the fact that the industry contribution to the FDA budget is half that of Swissmedic.

5.2.3. Greater financial independence?

Swissmedic says it wants to increase fees in order to provide the additional resources required to perform its work, and particularly to improve collaboration with the EU and the European Medicines Agency (EMA). This change would further increase the industry's share in the Swissmedic budget.

A clearer division between the industry and Swissmedic could be achieved by further separating the Agency's direct financial dependency. A political decision could be made to increase the share of public funding for Swissmedic and thus strengthen its independence.

However, it also seems perfectly reasonable to make the industry bear the costs of its regulation, rather than making citizens pay via taxes. One possibility could be to separate industry payment from the services performed by Swissmedic, by creating, for example, a contribution in proportion with turnover achieved in Switzerland, rather than for each authorisation application submitted to the regulatory agency.

5.3. The problem of the "revolving door"

A second issue created by the close links between the regulated industry and the regulatory body is the "revolving door", i.e., former drug regulatory agency executives who leave to work directly or indirectly (via consultancy services) for the regulated industry. The reverse situation can also occur (the "reverse revolving door"), i.e., pharmaceutical industry employees who are recruited to work in a regulatory agency.

The quasi-commercial nature of the relationship between Swissmedic and the industry mentioned above (section 5.2) encourages special links between people who are active in the two fields and facilitates career progression from one to the other.

Swissmedic has the same weaknesses as most drug regulatory agencies in the world. Swissmedic is faced with legislation, which gives it a mandate

and funding structure that often mean it needs to function within a revolving door system, where experts who work for Swissmedic come from the industry and often return to work in the industry after a few months or years in the administration.

Dominique Sprumont²⁰⁷

The "revolving door" issue creates conflicts of interest. Once in the industry, former managers from public administrative bodies or regulatory authorities are able to share (consciously or unconsciously) their knowledge of administrative procedures or even industrial secrets relating to procedures concerning competing companies with their new employer. There is also the risk that while working for a regulatory agency, an official could behave more leniently towards a company s/he wants to work for in future.

Such job moves create conflicts of interest, and allow officials to potentially abuse their inside knowledge of European decision-making and their access to former colleagues for the benefit of their new corporate employers or clients. There is also risk that the prospect of going through the revolving door could influence officials while in public office, leading them to act, not in the public interest, but in the interest of future employers or clients.

Block the revolving door²⁰⁸

In the opposite case (reverse revolving door), someone working in the regulated industry takes a job within a regulatory authority. This situation creates the risk of a feeling of loyalty towards the former employer, which could influence decisions taken whilst working for the regulatory authority.

5.3.1. The revolving door at Swissmedic

There are frequent examples of the revolving door at Swissmedic:

1. After resigning over the VanTX scandal (see Appendix 1), four Swissmedic lawyers founded Pharmalex, a consultancy company for therapeutic product law, which often represents parties taking legal action against Swissmedic.²⁰⁹
2. After resigning in 2003, Hans Stocker, Swissmedic's first Executive Director, worked for Cytos Biotherapeutics, a company that works in the field of pharmaceutical manufacturing and licenses, before becoming an independent consultant.²¹⁰
3. Before becoming the third Executive Director of Swissmedic, Franz Schneller was Director of the Swiss

branch of the Lundbeck pharmaceutical group.²¹¹ After resigning in 2006, he became a consultant in the health sector.

4. Before being recruited to Swissmedic, the current Executive Director, Jürg Schnetzer, worked as a specialist in healthcare law and medical technology for the Markwalder & Partner consultancy firm.²¹²

5.3.2. Situation in Europe, USA and Switzerland

Both the EU²¹³ and USA²¹⁴ have introduced strict legislation to deal with the “revolving door” issue. For example, regulations prohibit moving between the industry and administrative bodies for a certain period of time or require that managers be informed and authorisation issued before taking up a post in the private sector.

However, Switzerland has no legislation in place to deal with these issues.

Switzerland has chosen not to legislate on the employment of parties who have worked in the private sector as civil servants, or the reverse situation – which is often more problematic – the employment of former civil servants in the private sector (“revolving door policies”). Non-competition clauses (with a limited validity period) are common in the private sector, but unheard of in the public sector. Secrecy rules can only sanction more serious abuses. They do not necessarily forbid the use of networks of contacts (particularly lobbying). At the moment, this type of behaviour is not necessarily considered problematic.

Les conflits d'intérêts dans l'administration, en particulier à l'OFSP (Conflicts of interest in the administration, and in particular at the FOPH)²¹⁵

European examples

Even when revolving door legislation exists, it is not always respected or strictly enforced. Despite very clear European regulations²¹⁶, the NGO ALTER-EU (which is campaigning to stop “revolving door” cases) gives 16 examples.²¹⁷ Pressure from civil society can prove effective in ensuring enforcement, as shown in the case of the European Food Safety Authority (EFSA) in 2011, where the European Ombudsman followed up an NGO's demand and called for more stringent procedures.²¹⁸

One of the most famous examples is that of the former EMA Executive Director, Thomas Lönngren.

Shortly after leaving the EMA, where he had been Executive Director for ten years, Thomas Lönngren informed the EMA in late 2010 that he was going to work as an independent consultant for the

pharmaceutical industry from 1 January 2011. The EMA replied, saying that it had “no objection to these activities given [his] assurance that they create no conflict of interests and comply with procedures”.

NGOs, two members of the European Parliament and the press then expressed their concern that the EMA did not correctly follow the procedures regulating the activities of EU employees. After an investigation into Thomas Lönngren's activities, the EMA declared in February 2011 that none of Thomas Lönngren's activities presented any conflict of interest, but that they would restrict his activities for a period of two years and would particularly ban him from holding any kind of managerial, executive or consultative role in which he could provide advice with regard to any matter related to activities that fall within the remit and area of responsibilities assigned to the EMA.

Adapted from Pharma Times, 2011²¹⁹

According to the NGO ALTER-EU, the EMA should have conducted an in-depth investigation into the activities planned by Thomas Lönngren at the time of his initial request, and not only following media pressure.²²⁰ ALTER-EU believes that the tone of an e-mail sent to Thomas Lönngren by the new Executive Director of the EMA, Andreas Pott, was inappropriate and shows an overly-close relationship.²²¹ Just as close relationships between the regulated industry and the regulatory body can tarnish the image of independence, too close a relationship between someone requesting authorisation (here, a former Executive) and the person who must assess their request (here, the new Executive) can also be problematic.

5.4. The independence of the expert committee

Like any monitoring or decision-making authority, Swissmedic must demonstrate that it is independent and above reproach in order to avoid any suspicion that its decisions may be influenced. The independence of the expert committee – whose opinion plays a very important role in marketing authorisations – is crucial.

5.4.1. RTS investigation in 2011 and Swissmedic reaction

In June 2011, an RTS²²² (Swiss TV) investigation condemned the association of the interests of external experts of Swissmedic's Medicines Expert Committee (SMEC) and the pharmaceutical industry. It says that “over two thirds of experts consulted by Swissmedic when introducing new drugs onto the Swiss market have interests

in the pharmaceutical industry”²²³. After analysing the conflicts of interest declarations obtained via the Freedom of Information Act, journalists concluded that:

1. 25 of the 38 experts who completed their declaration of interests (of the 40 HMEC experts) mentioned links with the pharmaceutical industry (66%).
2. These links primarily consisted of assessment, consulting or administrative contracts for pharmaceutical companies and private-sector funding for research.
3. In at least seven cases (23%), experts declared that they held shares in pharmaceuticals firms, including Novartis, Roche, GSK or Merck.

Another criticism concerned the legibility of declarations (which were often hand-written) and a lack of clarity (the sum of financial links was not given).

This investigation led to political reactions.²²⁴ On 2 January 2012, Swissmedic announced a change to the SMEC member code.²²⁵ The changes relate primarily to the following points:

1. Declarations of interests are made public on the website.²²⁶
2. They are no longer completed by hand or typewriter, but on a computer.
3. Forms have been clarified slightly.²²⁷

5.4.2. Dealing with conflicts of interest

The following interests must be declared:²²⁸

1. investments in the pharmaceutical industry;²²⁹
2. professional activities for the pharmaceutical industry (in the past five years);²³⁰
3. pharmaceutical industry funding for research, assistant positions, grants and sponsorship activities (in the past five years).

Some interests are deemed incompatible with the function of a permanent SMEC member (only points 4. and 5. for temporary members):

4. employment contracts signed or planned with a pharmaceutical company;
5. any involvement (current or planned) in a management or monitoring body, particularly a board of directors;
6. consultancy activities for companies, particularly as a member of a consultant committee or similar body;
7. Significant financial interests held by a member in company investments (investments with a fiscal value of > 50,000 CHF and/or shares > 3% of voting rights).

There are also temporary bans relating to the assessment of a therapeutic product:

8. Employment with the company requesting authorisation;
9. Significant financial interests in the company applying for authorisation (see point 7. above);
10. Holding patent rights on the product;
11. Acting now or in the past as Principal Investigator (PI) in a product trial.

5.4.3. Notable cases

Françoise Brunner-Ferber

The HMEC expert, Françoise Brunner-Ferber, is Head of Brunner Naga Life Science Consulting (Pfäffikon, ZH). The company was founded in 2001 and offers strategic consulting in the field of drug and therapeutic approach development – particularly advice on protocols and phase I and IIa clinical trial reports²³¹. The company also helps assess licensing applications²³². Françoise Brunner-Ferber has declared consultancy contracts for 9 companies (and a university research centre) since 2006. In late 2011, three contracts were still ongoing for the following activities:

1. “Consulting” for Advicenne Pharma (France), since June 2007;
2. “Non-clinical strategy and logistics” for Chiesi Farmaceutici (Italy), since November 2009;
3. “Scientific Coordinator for analytics, non-clinical programme and Phase I. Non-clinical and clinical strategy. Logistics for non-clinical programme and Phase I” for Mylan (Switzerland), since February 2010.

Since October 2008, Françoise Brunner-Ferber has also been on the Advicenne Pharma Advisory Board for “Formulation and Development Strategy” and holds shares greater than 50,000 CHF or 3% of voting rights.

Jürg Messerli

The television programme, *Temps Présent*, revealed that on 26 August 2009, the expert Jürg Messerli (Leitender Arzt Augenklinik, Universitätsspital Basel) declared shares in Roche worth 316,688 CHF and in Novartis worth 109,710 CHF. These shares do not appear in the new declaration forms, even though they require declaration of all investments above 50,000 CHF. We do not know whether Jürg Messerli has sold his shares or not.

5.5. Transparency

5.5.1. Public information and relationship of trust

A crucial part of Swissmedic's work is providing information to the public, politicians, and journalists, and in this way convincing others of its independence and professionalism. This is included in its service mandate.²³³

Swissmedic already uses its website and newsletters to inform the public about:

1. product authorisations for therapeutic product manufacturers and any suspensions;
2. marketing authorisations issued and withdrawn;
3. changes to use or dosage;
4. withdrawal of therapeutic products or drug batches (e.g. announced by a manufacturer);
5. Swissmedic directives concerning advertising for therapeutic products;
6. general information on the safety of therapeutic products;
7. declarations of conflicts of interest for the SMEC (since 2012).

But important information is still missing to ensure the quality of the work of Swissmedic and compliance with current legislation:

8. figures on authorisation applications for clinical trials in Switzerland, including the number of refusals;
9. reasons for refusal;
10. figures on marketing authorisation applications, including the number of refusals;
11. the reasons given by the expert committees for accepting or refusing to issue MA, including ethical aspects;
12. minutes from expert committee meetings;
13. the clinical trials used for MA applications.

5.5.2. The importance of clinical trial registers

Keeping a register of clinical trials is a crucial step in facilitating the work of independent researchers wishing to carry out their own meta-analyses on the effectiveness or safety of a drug. NGOs and journalists also need this information to inform the public about research conducted in Switzerland and elsewhere.

Judging the effectiveness of a drug requires information on all trials that have been conducted. Scientific articles published in research journals often give only positive results and ignore negative data (publication bias). This practice is well known, and makes it impossible for researchers to objectively assess the effectiveness and safety of a drug.

Unkept promises

Even drug regulatory agencies face this problem. In principle a pharmaceutical company should not hide results, but this is difficult to enforce – unless all clinical trials are notified in a register in advance. And despite efforts and promises, the situation remains unsatisfactory.

The leading medical journals made a commitment to only publish articles that are based on registered clinical trials, but have not kept their promises.²³⁴ Drug regulatory agencies such as the FDA promised to only authorise drugs on the basis of the clinical trials declared, but the registers have not always been used correctly.²³⁵ Some pharmaceutical companies have announced that they will systematically record their clinical trials in registers like Clinicaltrials.gov²³⁶, but refuse to make their data public.²³⁷

A comprehensive register

A comprehensive register would not only record the clinical trials performed in Switzerland (before research begins), but all trials (including those performed abroad) whose results are used in applications for marketing authorisation. This is crucial in order to be able to make the link between marketing authorisations issued in Switzerland and a clinical trial performed abroad, and to be able to revisit the ethical issues raised by the clinical trial at a later date.

International registers exist²³⁸ and Swissmedic refers to them, but in practice they are very difficult to use. For example, finding the clinical trials that were used for the assessment of a marketing authorisation application is a laborious task.

Swissmedic developed plans for a clinical trial register, and encountered no significant opposition from the pharmaceutical industry. But the project was discontinued due to the time and human resources involved.²³⁹ Swissmedic has declared²⁴⁰ that the FOPH will keep a register of all studies performed in Switzerland from 2014, but this does not solve the problem of clinical trials conducted abroad which are used for marketing authorisation applications submitted in Switzerland. The LRH (taking effect from 2014) will introduce this type of register in Switzerland²⁴¹, but the initial versions of the related ordinances, which were presented in 2012, suggest that the data publicised in the register will be limited.²⁴²

Several Europe-wide campaigns²⁴³ demand access to all data from clinical trials: not just a summary, as is currently the case for the various existing public registers, but also the clinical study report, and all anonymised patient data (commonly known as raw data). The EMA has announced its desire to publicise all its data after the decision on the MA.^{244,245} Pharmaceutical companies recently announced

that they wanted to increase access to their data, but subject to tight conditions.²⁴⁶

Marketing authorisation (MA)

Public trust in Swissmedic could be increased by publishing the opinions given by experts during marketing authorisation assessments (as the EMA does with European Public Assessment Reports – EPAR²⁴⁷) and would help to better monitor whether ethical issues have been taken into account or checked (e.g. relating to clinical trials performed abroad).

Publishing summaries of expert sessions, like the EMA²⁴⁸ already does, would help prevent conflicts of interest and create a group dynamic better suited to critical discussion.

5.5.3. Trade secrets and the Freedom of Information Act

The law protects trade secrets and seems not to authorise Swissmedic to communicate some information.²⁴⁹ However, the 2004 Freedom of Information Act (FoIA) should give citizens access to the reasons behind administrative decisions.

Swissmedic therefore faces two contradictory requirements: informing citizens and protecting trade secrets. According to Dominique Sprumont, only a legal decision could clarify this situation, by clearly giving precedence to one requirement over the other.²⁵⁰

The situation has changed in the European Union. Following EMA's denial of a citizen request for access to detailed information concerning the suspected serious side effects of Roacutane (a controversial anti-acne drug from Roche), the European Ombudsman recommended that the EMA share this information, which it subsequently did.²⁵¹ In another similar case concerning an anti-obesity drug, the European Ombudsman found that the EMA did not have the right to cite trade secrecy as a reason for refusing access to data.²⁵²

The situation could change in Switzerland. A request under the Freedom of Information Act was sent to Swissmedic requesting details of a marketing authorisation decision. Swissmedic partially refused and legal proceedings have been initiated. This legal procedure has been ongoing for years, but may result in the ruling that data relating to clinical trials is not secret (i.e. protected by a trade secret within the meaning of the FoIA).²⁵³

Ethics Committees

Ethics Committees also do not publish detailed information on trials that they have authorised or refused²⁵⁴, which further increases a lack of transparency with regard to the way in which medical research is conducted.

5.6. Recommendations

Recommendations:	
1	The problem of the revolving door does not apply only to Swissmedic, but to the entire public sector. The Federal Personnel Act (LPers) needs to be adapted to provide Switzerland with the tools capable of dealing with this issue, like the EU and USA.
2	Greater transparency in describing the reasons for Swissmedic refusing or accepting a clinical trial or marketing authorisation request is necessary. This would help civil society to assess how strictly rules are being enforced and notice if ethical abuses could have taken place during the clinical trials used for Swiss MA.
3	This transparency would also help strengthen the appearance of independence of the regulatory agency and would encourage experts to do all they can to be seen as independent.
4	The authorities should keep a clinical trial register ²⁵⁵ for all trials performed in Switzerland and all trials (in Switzerland or abroad) that support a marketing authorisation request, in order to guarantee that the scientific community can check the efficacy of the treatment and any side effects, and so that civil society can check the ethical aspects. Information should not just consist of a summary of the trial, but should include all documents (research protocols, clinical study reports, anonymous patient data) – as is currently being discussed for the EU.
5	A decision from the administrative court is required to give precedence to the Freedom of Information Act over trade secrecy. Otherwise, a political intervention will be required. ²⁵⁶

Conclusions

Like other drug regulatory agencies in industrialised countries, Swissmedic cannot ignore the ethical violations that can and do occur during clinical trials performed in other countries, which are then used to submit a marketing authorisation application for the Swiss market. The law is clear on this subject.

However, the checks and monitoring carried out by Swissmedic appear insufficient, or even non-existent. When in doubt, Swissmedic turns only to the drug promoters, who of course have no interest in investigating any possible violations of ethical rules that occurred during their own clinical trials. Swissmedic has absolutely no contact with its Indian or Chinese counterparts. According to its managers, it “would not even know where to start” to contact them.

The European Union is working on these issues, particularly the EMA, which explicitly mentions the ethical aspects and proposes introducing standards equivalent to those in the 2008 version of the Declaration of Helsinki, in particular in order to regulate the issues of vulnerable populations, access to post-trial treatment and the use of placebo-controlled studies. Swissmedic, on the other hand, is surprisingly passive and does not seem inclined to address the problem.

The introduction of the Law on Research involving Humans in early 2014 does not seem likely to solve these problems and raises other concerns. In particular, it dissociates ethical and scientific concerns, which raises the question of whether it will further absolve Swissmedic of its responsibility for checking the ethical aspects of the clinical trials used for MA for drugs in Switzerland.

Who, then, will be responsible in Switzerland for checking that these ethical standards are respected? Perhaps Swissmedic could report suspicious cases to an external body responsible for analysing the presence and seriousness of ethical violations. This body could function in a similar way to the Swissmedic Medicines Expert Committees, which judges the effectiveness of new

therapeutic products, and could comprise members of Swiss ethics committees.

This report has outlined a number of recommendations for improving the situation, but economic pressure is probably the most influential agent for change. Greater attention to ethical issues, leading to a refusal to consider dubious clinical trials, would place pharmaceutical companies under significant financial pressure, thereby ensuring that they consider ethical aspects from the outset. Even justified additional checks during a marketing authorisation request would probably delay issue of the authorisation, which would have significant financial consequences for pharmaceutical companies. This type of pressure worked for data integrity (clean data) and it is hard to imagine why it would not also work for ethical issues.

Implementing checks seems difficult. However, Swissmedic could at least discuss these problems publicly and begin dialogue on the subject with its counterparts in order to show that Switzerland takes ethical violations seriously. Countries such as India and Brazil want to position themselves as centres for clinical trials and to reap the economic benefit from this. This ambition makes them disinclined to agree to stricter controls over ethical compliance, afraid that such measures could drive pharmaceutical companies away. However, if Northern drug regulatory agencies clearly expressed the importance of complying with international ethical standards and enforced compliance, the situation could change. By performing strict checks and responding to cases of ethical violations, Swissmedic could play an important role in ensuring that these standards are respected.

If nothing is done, ethical scandals are sure to damage the reputation of the Swiss authorities. Several instances of abuse have already been documented and there is no objective reason why Switzerland should be spared. The risk of Switzerland's reputation being tarnished by scandal is too great to be ignored.

Appendix I: Cases of ethics violations in Switzerland

The Van Tx case

The VanTx case represents one of the more serious examples of ethical violations during clinical trials performed in Switzerland. The scandal came to light in the Spring of 1999: for several years, the Basel VanTx CRO (Contract Research Organisation) recruited volunteers from the Baltic States and Eastern Europe – in particular Estonia – to participate in clinical trials in Switzerland.

The trials were performed very rapidly and took place under dubious circumstances.^{257,258} The participants were very poorly informed and given vague explanations either in English or German. The substantial remuneration promised to them placed them under a lot of pressure. The medical monitoring for side-effects after the participants had returned to their home country was poorly organised. The trial was performed without prior consultation with the Estonian authorities, as required by Estonian law, under which a clinical trial begins from the moment of recruitment.

VanTx's clients included the majority of the important international pharmaceutical groups (including the main Swiss companies).²⁵⁹ It was the main CRO in Switzerland, and organised almost one-third of all the Phase I clinical trials performed in Switzerland at that time.²⁶⁰

The clinical trials organised by VanTx were all approved by a private ethics committee, the Freiburger Ethik Kommission International (FEKI). It subsequently emerged that the main researcher from VanTx was one of the administrators at FEKI.²⁶¹

After the scandal broke out, the European medicines agencies insisted that unless new conformant clinical trials were conducted, the results obtained during the trials organised by VanTx would be nullified.²⁶² However, in Switzerland, Swissmedic did not react.

The VanTx affair demonstrated not only that clinical trials can be performed in Switzerland under outrageous conditions, but also that there is a lack of control in the composition and the work of the ethics committees. Since then, the activities of the latter have been formalised with, in

particular, the creation in 2005 of the Kobek ("Koordination der Beurteilung klinischer Versuche").

Due allegedly to the efforts of Swiss pharmaceutical companies involved in the VanTx affair, this remained largely unreported to the Parliament during the entire process of consultation on the new Law on Research on Humans: the pharmaceutical companies were afraid that the Parliament would draw unfavourable conclusions about them from the affair.²⁶³

The Geneva heart implants

At the end of 2008, the Swiss TV programme "Temps présent"²⁶⁴ reported on the case of the heart implants developed by a surgeon²⁶⁵ at the University Hospital of Geneva (HUG).

The surgeon submitted an application issued from developing countries for research involving adults and children to the Ethics Commission of the HUG. The latter refused for three reasons: the implants could not first be tested on adults; the surgeon was the founder of the company sponsoring the research (but no longer its administrator); and the parents of the children singled out for the research lived too far from Geneva to be able to give informed consent.

The surgeon organised trials elsewhere, and two years later obtained the European certification in Paris. Under bilateral agreements, Swissmedic authorised the heart implants in 2005, without reviewing the application again.

It is still impossible to understand the circumstances under which the trials were performed, because the surgeon, the company and the private certification company in Paris refuse to give any details.

This case illustrates the problem of accreditation of medical devices by private organisations, which can refuse to divulge information protected by industrial confidentiality. It also demonstrates how a clinical trial refused for ethical reasons in Switzerland can still be used to obtain accreditation abroad for a product which in the end will be used in Switzerland.

Appendix II: ICH-GCP Ethical standards

Ethical principles that should be respected during clinical trials according to ICH-GCP are the following:

2.1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

*2.2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. **A trial should be initiated and continued only if the anticipated benefits justify the risks.***

*2.3. **The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.***

2.4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

*2.6. **A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.***

2.7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

*2.9. **Freely given informed consent should be obtained from every subject prior to clinical trial participation.***

2.10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

ICH-GCP, The principles of ICH-GCP, p. 8-9

Appendix III: Original correspondence between Swissmedic and the Berne Declaration

1^{ère} correspondance, avril-mai 2012

De: Patrick Durisch
Envoyé: mardi, 24. avril 2012 15:39
À: 'petra.doerr@swissmedic.ch'; 'roland.zwahlen@swissmedic.ch'
Objet: Demande de rencontre Swissmedic-DB

Chère Dr Dörr, Cher Dr. Zwahlen,

La Déclaration de Berne (DB, Erklärung von Bern en allemand, www.ladb.ch) est une organisation non-gouvernementale suisse forte de plus de 23'000 membres et qui s'engage depuis plus de quarante ans pour des relations équitables entre la Suisse et les pays en voie de développement / émergents dans des secteurs variés comme les banques/finances internationales, le commerce international, le négoce des matières premières, l'agriculture, l'industrie du textile et la santé.

Dans ce dernier domaine, la DB s'engage pour le droit à la santé et l'accès aux médicaments vitaux pour tous. Elle demande une recherche pharmaceutique orientée sur les besoins de santé publique, au Nord comme au Sud, et non sur les seules opportunités de profit, et s'inquiète des conséquences du renforcement des droits de propriété intellectuelle sur les médicaments pour la santé des populations défavorisées.

Dans ce cadre, nous nous intéressons aux essais cliniques de médicaments menés en vue de l'obtention d'une autorisation de mise sur le marché en Suisse, en particulier ceux menés dans les pays en développement et/ou émergents. Selon les chiffres à notre disposition, cette délocalisation (offshoring) des tests cliniques hors de l'Europe occidentale (Suisse incluse), des Etats-Unis et du Japon est en constante augmentation, couplé ou non à une sous-traitance (outsourcing) de leur conduite vers des organismes tiers (Contract Research Organizations). Selon nos analyses, ces phénomènes entraînent un risque accru de violations des standards éthiques, les essais cliniques étant menés dans des contextes où les législations et les règles en vigueur varient considérablement d'un pays à l'autre, sans même parler du problème de la traçabilité en cas d'externalisation.

En tant qu'Institut autorisant ou non la mise sur le marché en Suisse de médicaments testés dans des conditions diverses, nous estimons que Swissmedic doit jouer un rôle central en matière de vérification du respect des règles éthiques. Dès lors, nous aurions souhaité vous rencontrer afin de mieux comprendre si et comment Swissmedic s'y prend pour évaluer le respect des standards éthiques universels dans le cas de tests de médicaments menés dans les pays en développement et émergents.

Nous sommes conscients que le Dr Esa Heinonen, nouveau chef du secteur Mise sur le marché de Swissmedic, ne prendra ses fonctions qu'à partir du 1er mai. Nous nous permettons de vous adresser cette demande en tant que responsable ad interim du secteur, afin que nous puissions sans tarder commencer à planifier une date de rencontre dans vos locaux à Berne.

Je me tiens à votre entière disposition pour tout renseignement complémentaire que vous pourriez souhaiter.

Dans l'attente de votre réponse, nous vous adressons, Madame, Monsieur, nos meilleures salutations

Patrick Durisch

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SWISSMEDIC

Berne, le 31 mai 2012

Monsieur,

Par la présente, nous vous remercions pour vos questions et vous prions de nous excuser pour notre réponse tardive.

Vous avez contacté Swissmedic pour requérir un entretien en vue de discuter de questions sur le thème du transfert de la réalisation d'essais cliniques de pays industrialisés vers des pays émergents, ainsi que sur les exigences applicables aux essais cliniques soumis dans le cadre de procédures d'autorisation de mise sur le marché. Vous vous êtes déclaré particulièrement intéressé par la procédure appliquée par Swissmedic lors du contrôle des aspects éthiques des essais cliniques réalisés dans des pays émergents.

Pour ce qui est l'objet principal de votre question, à savoir la délocalisation d'essais cliniques, Swissmedic ne saurait être votre interlocuteur principal. C'est en effet plutôt aux entreprises de l'industrie pharmaceutique qu'il faudrait vous adresser, puisque ce sont elles qui décident, sur la base des conditions générales qui prévalent à ce moment-là, de l'endroit où elles veulent effectuer leurs études.

Dans ce contexte, nous considérons que l'entretien que vous appelez de vos vœux n'est pas pertinent. Nous prenons cependant volontiers position sur les aspects partiels entrant dans notre champ de compétence (les critères éthiques qui sont contrôlés lors de l'examen d'essais cliniques). Vous trouverez nos commentaires ci-dessous.

En guise d'introduction, nous souhaiterions souligner que les exigences relatives aux aspects éthiques d'essais cliniques qui sont réalisés en Suisse sont contrôlées et examinées par les commissions d'éthique cantonales (voir aussi sous <http://www.baq.admin.ch/nekcne/index.html?lanq=fr>), ainsi que par la division Essais cliniques de Swissmedic.

Quant aux essais cliniques présentés dans les documents d'autorisation, ils sont le plus souvent réalisés au plan international, c'est-à-dire dans plusieurs pays. Ils ont pour objet d'attester de la sécurité et de l'efficacité d'un médicament et doivent à la fois satisfaire aux exigences internationales en vigueur et être conformes à l'état des dernières connaissances scientifiques et techniques acquises.

En ce qui concerne les exigences éthiques à remplir par les essais cliniques, il convient de respecter tout particulièrement la Déclaration d'Helsinki¹ et ses diverses révisions et directives, telles que celles de l'ICH-GCP (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). Vous trouverez les directives ICH-GCP en cliquant sur le lien suivant: <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html> Eu égard à ces directives, une importance particulière est accordée au respect des principes éthiques applicables à la recherche médicale sur l'être humain et ce, indépendamment du fait que ces essais cliniques soient effectués dans des pays industrialisés ou dans des pays émergents. Concrètement, Swissmedic examine la documentation soumise par le requérant de la manière suivante:

Lors de l'examen des données provenant d'essais cliniques, Swissmedic examine si ces études ont été réalisées conformément aux BPC, à savoir aux directives de «Bonnes pratiques cliniques», en répondant principalement à des questions telles que:

- Tous les patients étaient-ils suffisamment assurés pour garantir leur protection pendant l'étude?
- Tous les patients ont-ils déclaré par écrit leur consentement (sur la base d'informations suffisamment compréhensibles) avant leur participation à l'étude?
- L'étude a-t-elle été notifiée officiellement avant son démarrage?
- La composition du comité d'éthique local était-elle judicieuse et y a-t-il eu votes pour chacun des centres de recherche impliqués?
- Comment s'est-on assuré pendant l'étude d'un diagnostic correct et du meilleur traitement possible, et comment a-t-on défini ensuite le traitement relais?

- Le design -c'est-à-dire la conception -de l'essai clinique était-il conforme aux aspects éthiques et aux dernières avancées scientifiques?

Du fait d'une possible influence génétique sur le métabolisme -qui peut s'avérer pertinente p. ex. pour la dégradation du médicament -, on vérifie en particulier aussi si les patients choisis pour l'étude permettent de formuler des indications représentatives pour la Suisse. Tous ces documents sont examinés avec soin par nos spécialistes de la division «Clinical Review». Si des questions ou des doutes se font jour pendant l'examen d'une demande d'autorisation de mise sur le marché d'un médicament, ils donnent lieu à l'envoi de ce que l'on appelle une «liste de questions». Cette dernière peut notamment contenir des «major objections» (objections majeures) susceptibles d'entraîner un rejet de la demande d'autorisation. Des questions relatives à l'observation des principes éthiques des essais cliniques peuvent être envoyées à cette occasion aux promoteurs des études.

Dans ce domaine aussi, Swissmedic collabore étroitement avec des partenaires internationaux. L'institut a ainsi participé à un séminaire de l'Agence européenne des médicaments (EMA) sur le thème des aspects éthiques et des BPC lors de la réalisation d'essais cliniques sur des médicaments à usage humain dans des pays tiers. Vous pouvez consulter le document *Draft Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in marketing-authorisation applications to the EMA* en cliquant sur le lien suivant: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/05/news_detail_001255.jsp&mid=WCOb01ac058004d5c1.

Nous espérons que ces informations auront permis de répondre à vos questions.

Veuillez recevoir, Monsieur, nos salutations distinguées.

Swissmedic, Institut suisse des produits thérapeutiques

Responsable secteur Autorisation de mise sur le marché
Dr. Esa Heinonen

Responsable Regulatory Management
PD Dr. Roland Zwahlen

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DECLARATION DE BERNE

Lausanne, le 21 juin 2012

Contrôle du respect des standards éthiques d'essais cliniques réalisés dans des pays en développement/émergents

Cher Dr. Heinonen, Cher Dr. Zwahlen,

Nous avons bien reçu votre courrier du 31 mai dernier en réponse à notre demande de rencontre et vous en remercions.

L'objet principal de l'entretien que nous sollicitons n'est pas d'analyser ensemble le phénomène de délocalisation des essais cliniques, mais bel et bien de mieux comprendre et d'échanger sur le rôle que peut jouer Swissmedic en matière de contrôle des aspects éthiques lors de tests menés dans les pays en développement et émergents. Nous pensons donc avoir frappé à la bonne porte et estimons cette rencontre tout à fait pertinente et opportune.

Dans votre lettre, vous faites référence au processus en cours au niveau européen concernant le renforcement du rôle de l'Agence européenne des médicaments (EMA) et de ses instruments en matière de protection des droits, de la sécurité et du bien-être des patient-es enrôlé-es dans des essais cliniques partout dans le monde. Le processus de consultation, auquel a participé Swissmedic, a abouti récemment à la finalisation [*Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities, European Medicines Agency, 16 April 2012*] du document de travail auquel vous nous avez renvoyé. Dans celui-ci, les multiples défis en matière de supervision des essais cliniques menés dans des pays tiers auxquels doivent faire face les Agences de régulation des médicaments sont clairement mis en avant, que ce soit en matière de coopération internationale, de renforcement des capacités, de transparence ou de consolidation des instruments de contrôle. Les organisations de la société civile ont en outre été pleinement associées au processus et sont considérées comme des acteurs à part entière.

Nous réitérons dès lors notre demande de rencontre dans les meilleurs délais, afin de comprendre précisément le rôle que Swissmedic joue actuellement et pourra jouer à l'avenir en matière de protection des sujets de recherche, notamment dans des pays tiers. Cette rencontre permettra d'aborder également des cas concrets que nous avons compilés concernant des produits testés dans des pays dits non-traditionnels et autorisés sur le marché en Suisse.

Dans le mandat de prestation 2011-2014 entre la Confédération et Swissmedic, il est stipulé que l'Institut s'attache à «accomplir ses tâches de manière transparente» et à «se positionner comme autorité digne de confiance sur le plan national». Nous estimons que recevoir des représentants de la société civile répond à ces objectifs stratégiques.

Dans l'attente de vos nouvelles, nous vous prions de croire, Messieurs, à l'expression de nos sentiments les meilleurs.

Patrick Durisch
Responsable Programme Santé
Déclaration de Berne

Cc: Christine Beerli, Présidente de l'Institut

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SWISSMEDIC

Berne, le 28 juillet 2012

Monsieur,

Nous avons bien reçu votre courrier du 21 juin 2012 et vous en remercions.

Nous serions heureux de vous recevoir, avec nos experts, à un entretien personnel et vous proposons de débattre à cette occasion des thèmes suivants:

- Exigences posées en matière d'essais cliniques en Suisse (p.ex. Bonnes pratiques cliniques (BPC), rôle et tâches de Swissmedic, rôle et tâches des commissions d'éthique)
- Acceptation des essais menés à l'étranger dans les dossiers de demande d'autorisation remis à Swissmedic
- Collaboration de Swissmedic avec l'OMS

Voici des propositions de date de réunion dans nos locaux:

- Mardi 14 août 2012, de 9h à 10h
- Mercredi 15 août 2012, de 16h à 17h

Nous vous serions reconnaissants de bien vouloir nous informer rapidement si l'une de ces dates vous convient.

Dans l'attente de vos nouvelles, nous vous prions de recevoir, Monsieur, nos salutations distinguées.

Swissmedic, Institut suisse des produits thérapeutiques

La cheffe de l'Etat-major

Dr Petra Doerr

2^e correspondance, octobre - décembre 2012

Subject: 2^{ème} rencontre Swissmedic-DB
Date: Tue, 30 Oct 2012 16:04:54 +0100
From: Patrick Durisch <durisch@ladb.ch>
To: <Petra.Doerr@swissmedic.ch>
CC: <Roland.Zwahlen@swissmedic.ch>, <esa.heinonen@swissmedic.ch>, <Cordula.Landgraf@swissmedic.ch>

Chère Dr. Dörr,

Nous vous remercions encore une fois, vous et vos collègues, pour notre rencontre du 15 août dernier dans vos locaux.

Nous avons depuis poursuivi nos travaux concernant le rôle joué par les agences des médicaments – notamment Swissmedic – sur les questions relatives au contrôle des aspects éthiques lors d'essais cliniques menés dans des pays tiers, en particulier dans les pays en développement ou émergents.

M. Saraga et moi-même souhaiterions venir à Berne éclaircir avec vous les quelques points encore en suspens sur les procédures de contrôle et vous offrir l'occasion de prendre connaissance de nos premiers constats.

Serait-il possible de se rencontrer à nouveau à partir de la mi-novembre? Pour votre information, je serai absent du 3 au 15 décembre.

Dans l'attente de votre réponse, meilleures salutations

Patrick Durisch

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De: Cordula.Landgraf@swissmedic.ch [mailto:Cordula.Landgraf@swissmedic.ch]
Envoyé: jeudi 1 novembre 2012 16:08
À: Patrick Durisch
Cc: Petra.Doerr@swissmedic.ch; anna.sieg@swissmedic.ch
Objet: AW: 2^{ème} rencontre Swissmedic-DB

Cher Monsieur Durisch

Merci bien de votre message.

Nous avons regardé pour une date possible à partir du mi-novembre. Malheureusement, nos calendriers se complètent de plus en plus, mais ce que je pourrais encore vous proposer c'est le mardi, 20 novembre 2012, de 15.00 à 16.00 p.ex.

Si cette date ne vous convient pas, on pourrait aussi regarder après le 15 décembre, p.ex. mercredi, 19 décembre 2012, le matin de 10.00 à 11.00.

Serait-il possible que vous nous envoyez les questions/points que vous avez en avance pour qu'on puisse voir avec nos experts qui nous accompagneraient pour le rencontre?

Dans l'attente de votre réponse, je vous envoie mes meilleures salutations

Cordula Landgraf
Swissmedic, Institut Suisse des Produits Thérapeutiques
Responsable Networking

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Von: Patrick Durisch [mailto:durisch@ladb.ch]
Gesendet: Sonntag, 4. November 2012 12:49
An: Landgraf Cordula Swissmedic
Cc: Dörr Petra Swissmedic; Sieg Anna Swissmedic
Betreff: RE: 2ème rencontre Swissmedic-DB

Chère Madame Landgraf,

Merci pour votre réponse rapide avec les propositions de dates.

Nous souhaiterions opter pour le mercredi 19 décembre à 10h. Nous vous enverrons volontiers plus d'informations sur les points que nous voudrions aborder d'ici à la fin novembre.

Nous vous remercions pour votre collaboration et vous adressons nos meilleures salutations.

Patrick Durisch

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De: Cordula.Landgraf@swissmedic.ch [mailto:Cordula.Landgraf@swissmedic.ch]
Envoyé: lundi 5 novembre 2012 10:37
À: Patrick Durisch
Cc: Petra.Doerr@swissmedic.ch; anna.sieg@swissmedic.ch
Objet: AW: 2ème rencontre Swissmedic-DB

Cher Monsieur Durisch

Je vous remercie de votre réponse.

Nous avons réservé le mercredi, 19 décembre 2012, de 10.00 à 11.00, pour notre rencontre.

En attendant les informations sur les points que vous voudrez aborder je vous envoie mes meilleures salutations,

Cordula Landgraf

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De: Cordula.Landgraf@swissmedic.ch [mailto:Cordula.Landgraf@swissmedic.ch]
Envoyé: vendredi 7 décembre 2012 09:12
À: Patrick Durisch
Cc: Petra.Doerr@swissmedic.ch; anna.sieg@swissmedic.ch; Françoise.Jaquet@swissmedic.ch;
claus.bolte@swissmedic.ch
Objet: AW: 2ème rencontre Swissmedic-DB

Cher Monsieur Durisch

Nous nous avons réservé le 19 décembre 2012, 10.00 à 11.00, pour notre deuxième rencontre. Je vous serais très reconnaissante si vous pourriez nous envoyer vos questions le plus vite possible pour que nous puissions nous préparer.

Merci d'avance et avec mes meilleures salutations

Cordula Landgraf

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Von: Patrick Durisch [mailto:durisch@ladb.ch]
Gesendet: Montag, 10. Dezember 2012 17:32
An: Landgraf Cordula Swissmedic
Cc: Dörr Petra Swissmedic; Sieg Anna Swissmedic; Jaquet Françoise Swissmedic; Bolte Claus Swissmedic
Betreff: RE: 2ème rencontre Swissmedic-DB

Chère Madame Landgraf,

Comme convenu, voici notre proposition de déroulement de la réunion, si vous êtes d'accord.

Nous souhaiterions, dans une première partie, pouvoir vous exposer en 10-15 minutes notre point de vue sur la question du contrôle des aspects éthiques d'essais cliniques menés dans des pays émergents / en développement dans le cadre de l'autorisation de mise sur le marché. Suite à notre utile rencontre d'août dernier, nous avons en effet poursuivi nos réflexions sur le sujet et souhaiterions pouvoir échanger sur cette nouvelle base avec vos experts.

Dans un deuxième temps, nous aurions souhaité savoir si et comment Swissmedic entendait mettre en œuvre concrètement et à son niveau des mesures similaires que celles décidées par l'Agence européenne des médicaments telles que reflétées dans le document attaché (Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities, April 2012). Swissmedic a d'ailleurs participé à la consultation à l'origine de ces décisions.

Compte tenu du temps limité à disposition lors de notre réunion, nous souhaiterions vous entendre en particulier sur les questions suivantes:

1. Est-ce que Swissmedic a prévu d'établir un document similaire en vue de décisions à prendre, tenant compte de ses propres spécificités et celui du contexte suisse? Si oui, dans quel horizon temporel?
2. Dans le document de l'EMA, il est beaucoup question de collaboration internationale et de formation (capacity building) pour renforcer les autorités de régulation ainsi que les comités d'éthique dans les pays où ceux-ci sont «insuffisamment développés». Quel rôle Swissmedic peut-il et veut-il jouer dans ce domaine? Un plan d'action concret est-il déjà en discussion? Il est notamment question de mettre en place un «service» ou «centre» d'échanges entre différents acteurs (p. 12): quelle est votre position sur ce sujet?
3. "EU Regulatory Authorities should identify those studies that may give rise to special ethical concern (e.g. arising from their design, the local regulatory framework within which they are conducted, the vulnerability of the study subjects) and where applicable seek additional assurance that the trials have been ethically conducted" (p. 18). L'EMA suggère de procéder de même en cas de doute sur le (non) respect de plusieurs autres aspects éthiques, tels que:
 - Consentement éclairé
 - Compensation
 - Vulnérabilité des participant(e)s
 - Utilisation de placebo
 - Accès au traitement après l'essai

Swissmedic compte-t-il également prendre des mesures similaires? Si oui, vers quelles institutions se tournerait-il afin de s'assurer que les essais cliniques en question ont bien été conduits de manière éthique?

4. L'EMA souhaite publier à partir de janvier 2014 l'ensemble des données d'essais cliniques à sa disposition, une fois l'AMM accordée. Selon leurs propres dires, la question n'est pas «si» mais «comment» publier ces données; des travaux ont encore lieu en 2013 à cette fin. Swissmedic pense-t-il suivre le mouvement et selon quel calendrier?

J'espère que cette proposition vous convient, et me réjouis de vous rencontrer accompagné de M. Daniel Saraga la semaine prochaine. D'ici-là, je reste bien entendu à votre entière disposition.

Meilleures salutations

Patrick Durisch

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De: Cordula.Landgraf@swissmedic.ch [mailto:Cordula.Landgraf@swissmedic.ch]
Envoyé: mercredi 12 décembre 2012 09:21
À: Patrick Durisch
Cc: Petra.Doerr@swissmedic.ch
Objet: AW: 2ème rencontre Swissmedic-DB

Sehr geehrter Herr Durisch

Besten Dank für die Zusendung Ihrer Information und Fragen.

Auf Grund eingeschränkter Ressourcen in der Vorweihnachtszeit kann ich die Fragen leider so kurzfristig nicht bis zum nächsten Mittwoch abklären und muss daher das Treffen nächste Woche mit Ihnen leider absagen.

Wir werden die von Ihnen eingereichten Fragen aber gerne prüfen und wenn es in die Zuständigkeit von Swissmedic fällt, Ihnen bis spätestens Ende Januar 2013 eine Antwort zukommen lassen. Falls Sie bereits eine ausgearbeitete Position von Ihrer Seite vorliegen haben, auch im Entwurf, können Sie uns diese selbstverständlich gerne noch zusenden und wir würde sie zusammen mit den Fragen anschauen.

Für mögliche Rückfragen stehe ich Ihnen selbstverständlich zur Verfügung.

Besten Dank vorab für Ihr Verständnis verbunden mit den besten Wünschen für die Adventszeit,

Cordula Landgraf

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De: Patrick Durisch
Envoyé: mercredi 12 décembre 2012 18:12
À: 'Cordula.Landgraf@swissmedic.ch'
Cc: Petra.Doerr@swissmedic.ch
Objet: RE: 2ème rencontre Swissmedic-DB

Chère Madame Landgraf,

Merci pour votre message.

Nous comprenons la situation, mais nous souhaiterions que cette réunion puisse être refixée dès que possible en janvier, lorsque toutes les personnes concernées seront à nouveau disponibles. Un échange direct comme celui que nous avons eu en août dernier dans vos locaux nous paraît en effet plus efficient et enrichissant qu'un échange de correspondance. Serait-il possible de nous proposer 1-2 dates courant janvier pour fixer une nouvelle réunion à Berne? Je suis absent jusqu'à la fin de

cette semaine mais vous pouvez sans problème me contacter par téléphone à partir de lundi prochain, si nécessaire, ou par email d'ici-là.

Avec mes meilleures salutations

Patrick Durisch

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Von: Patrick Durisch [mailto:durisch@ladb.ch]
Gesendet: Montag, 7. Januar 2013 17:02
An: Landgraf Cordula Swissmedic
Cc: Dörr Petra Swissmedic
Betreff: RE: 2ème rencontre Swissmedic-DB

Chère Madame,

Sans nouvelles de votre part, nous aurions souhaité savoir quelle suite vous pensiez donner à notre requête de pouvoir refixer la réunion annulée de décembre dernier d'ici à fin janvier.

J'en profite pour vous souhaiter, ainsi qu'à tous vos collègues, mes meilleurs vœux pour cette nouvelle année 2013.

Meilleures salutations

Patrick Durisch

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De: Cordula.Landgraf@swissmedic.ch [mailto:Cordula.Landgraf@swissmedic.ch]
Envoyé: lundi 14 janvier 2013 14:50
À: Patrick Durisch
Cc: Petra.Doerr@swissmedic.ch
Objet: AW: 2ème rencontre Swissmedic-DB

Cher Monsieur

Gerne möchte ich auf Ihre Anfrage in Zusammenhang mit dem unten erwähnten Reflection Paper der Europäischen Arzneimittelbehörde EMA zurück kommen und Ihnen wie angekündigt anbei unsere schriftlichen Antworten auf Ihre Fragen zukommen lassen.

Sie finden unsere Antworten im beigefügten pdf Dokument. Wir möchten Sie um Verständnis für unsere rein schriftliche Beantwortung Ihrer Fragen bitten, aber leider erlaubt es uns unsere derzeitige Ressourcen Situation nicht, ein weiteres Treffen zu organisieren.

Wir hoffen, dass unsere Antworten Ihnen weiterhelfen können und sind selbstverständlich gerne bereit, weitere Verständnisfragen zu klären.

Sie können uns auch gerne Ihre Überlegungen/Ihren Bericht (auch im Entwurf) für allfällige Kommentare/Fragen zukommen lassen.

Für Ihr Verständnis möchte ich mich vorab bedanken und stehe Ihnen für Rückfragen jederzeit zur Verfügung.

Freundliche Grüsse / Meilleures salutations

Cordula Landgraf

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3^e correspondance, janvier 2013

SWISSMEDIC

10 janvier 2013

Réponse de Swissmedic aux questions de la «Déclaration de Berne» concernant le document «*Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities, April 2012*»

Question 1: Est-ce que Swissmedic a prévu d'établir un document similaire en vue de décisions à prendre, tenant compte de ses propres spécificités et celui du contexte suisse? Si oui, dans quel horizon temporel?

Swissmedic connaît le document que vous mentionnez (Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities, April 2012) et en tient compte. Nous en avons d'ailleurs parlé avec vous lors de notre dernière rencontre et l'avons intégré dans nos présentations. Swissmedic ne prévoit pas actuellement d'élaborer un document similaire. Il est tout à fait courant que Swissmedic se réfère à des directives scientifiques internationales comme celles de l'EMA ou de la FDA pour l'application des dernières connaissances scientifiques et techniques acquises et qu'il ne rédige pas ses propres directives. Pour ce qui est des activités internationales de Swissmedic, veuillez vous reporter aux réponses à la question qui suit.

Question 2: Dans le document de l'EMA, il est beaucoup question de collaboration internationale et de formation (capacity building) pour renforcer les autorités de régulation ainsi que les comités d'éthique dans les pays où ceux-ci sont «insuffisamment développés». Quel rôle Swissmedic peut-il et veut-il jouer dans ce domaine? Un plan d'action concret est-il déjà en discussion? Il est notamment question de mettre en place un «service» ou «centre» d'échanges entre différents acteurs (p. 12): quelle est votre position sur ce sujet?

Conformément au Mandat de prestations 2011 – 2014, Swissmedic entretient des relations étroites avec des autorités étrangères et des organisations internationales et œuvre à la signature de contrats de coopération. Swissmedic s'est d'ailleurs notamment fixé comme axe stratégique de tirer parti et d'intensifier les collaborations existantes et d'en établir de nouvelles avec un objectif clair. Swissmedic collabore étroitement avec l'OMS et soutient cette organisation dans l'élaboration de lignes directrices, la création de matériel de formation et la réalisation de formations. L'institut a d'ailleurs accueilli en 2008 à Berne la conférence ICDRA (International Conference for Drug Regulatory Authorities), qui est une plate-forme essentielle d'échange d'expériences et d'expertises pour toutes les autorités de contrôle des médicaments des Etats membres de l'OMS, en particulier celles des pays émergents et en développement. Elle permet en effet à ces pays disposant d'autorités reconnues au plan international d'entrer en contact, de discuter d'initiatives et de projets communs et de mettre en œuvre des mesures d'harmonisation. La Conférence s'achève sur la rédaction de ce que l'on appelle un «Recommendation Paper». Les recommandations qui y figurent, ainsi que leur application, contribuent au «capacity building». Voici, à titre d'exemple, le lien vers les recommandations de la 15^{ème} Conférence ICDRA d'octobre 2012: http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/en/. Par ailleurs, Swissmedic met à disposition des intervenants lors de sessions de formation de l'OMS et prend activement part à différents groupes de travail. Toutes ces mesures permettent à Swissmedic de contribuer au «capacity building».

Question 3: «EU Regulatory Authorities should identify those studies that may give rise to special ethical concern (e.g. arising from their design, the local regulatory framework within which they are conducted, the vulnerability of the study subjects) and

where applicable seek additional assurance that the trials have been ethically conducted» (p.18). L'EMA suggère de procéder de même en cas de doute sur le (non)respect de plusieurs autres aspects éthiques, tels que:

- Consentement éclairé
- Compensation
- Vulnérabilité des participant(e)s
- Utilisation de placebo
- Accès au traitement après l'essai

Swissmedic compte-t-il également prendre des mesures similaires? Si oui, vers quelles institutions se tournerait-il afin de s'assurer quels essais cliniques en question ont bien été conduits de manière éthique?

Lors de l'évaluation des données d'essais cliniques achevés soumis à Swissmedic dans le cadre de demandes d'autorisation, l'institut vérifie avec soin si les essais cliniques ont été réalisés en conformité avec les BPC, c'est-à-dire les directives de «Bonnes pratiques cliniques». Il se pose notamment les questions suivantes:

- Tous les patients étaient-ils suffisamment couverts par une assurance pour garantir leur protection pendant l'étude?
- Tous les patients ont-ils fourni, avant leur participation à l'étude, une déclaration de consentement écrite reposant sur des informations suffisamment compréhensibles?
- L'étude a-t-elle été officiellement notifiée avant de démarrer?
- La composition de la Commission d'éthique locale était-elle judicieuse et chaque centre d'étude participant a-t-il fait l'objet de votes de la Commission d'éthique?
- Comment s'est-on assuré de la justesse du diagnostic et du meilleur traitement possible dans le cadre de l'étude et comment le traitement relais a-t-il été réglé?
- Le design de l'essai clinique tenait-il compte des aspects éthiques et des dernières connaissances scientifiques acquises?

Dans cette dernière question, la présence d'un groupe de contrôle placebo ou le choix du dosage du groupe contrôle actif et l'effet sur le traitement de certains patients sont d'une importance capitale pour l'étude. Du fait d'une possible influence de la génétique sur le métabolisme (critère pertinent par exemple pour la diminution des doses du médicament), l'institut vérifie notamment aussi si la composition du groupe de participants à l'étude permet de tirer des conclusions représentatives pour la Suisse. Tous ces documents sont examinés par nos spécialistes de la division «Clinical Review». S'ils ont des doutes, ils posent des questions détaillées aux promoteurs des études et émettent au besoin de sérieuses réserves. Ce qui peut avoir des conséquences notables, notamment la remise en cause de l'autorisation d'un produit.

Les conditions générales qui sous-tendent les mesures précitées ont été énoncées dans la Déclaration d'Helsinki et ses diverses versions révisées ainsi que dans d'autres directives comme les règles de BPC susmentionnées ou les lignes directrices de l'ICH-GCP et du CHMP. Swissmedic ne réalise lui-même actuellement aucune inspection des BPC à l'étranger. Si le besoin s'en fait sentir et à titre de garantie supplémentaire, Swissmedic demande, comme dans d'autres domaines, des rapports d'autres autorités reconnues, et ce, en application de l'article 13 de la loi sur les produits thérapeutiques (<http://www.swissmedic.ch/rechtstexte/00201/00203/index.html?lang=fr>)

Question 4: L'EMA souhaite publier à partir de janvier 2014 l'ensemble des données d'essais cliniques à sa disposition, une fois l'AMM accordée. Selon leurs propres dires, la question n'est pas «si» mais «comment» publier ces données; des travaux ont encore lieu en 2013 à cette fin. Swissmedic pense-t-il suivre le mouvement et selon quel calendrier?

D'une façon générale, les essais cliniques peuvent être enregistrés et consultés dans la base Eudra-CT (<https://www.clinicaltrialsregister.eu/>) ou sous [clinicaltrials.gov](http://www.clinicaltrials.gov) (<http://www.clinicaltrials.gov/>). Swissmedic ne publie à ce jour aucune liste des études soumises dans le cadre d'une demande d'autorisation. Toutefois, avec l'entrée en vigueur de la loi relative à la recherche sur l'être humain, un registre de toutes les études réalisées en Suisse sera mis en place à partir de janvier 2014, pour l'instant sans publication des résultats. Ce registre sera géré par l'OFSP, ce dernier étant chargé de la conduite des activités dans ce domaine.

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Subject: RE: 2ème rencontre Swissmedic-DB
Date: Mon, 28 Jan 2013 16:56:34 +0100
From: Patrick Durisch <durisch@ladb.ch>
To: <Cordula.Landgraf@swissmedic.ch>
CC: <Petra.Doerr@swissmedic.ch>

Chère Madame,

Je vous remercie pour ce document avec les prises de position de Swissmedic sur ces différents aspects et prend note, avec regret, de l'impossibilité pour vous d'organiser une nouvelle rencontre avec la Déclaration de Berne pour en discuter plus avant.

Je n'hésiterais pas à revenir ultérieurement vers vous en cas de besoin et vous adresse mes meilleures salutations.

Patrick Durisch

Appendix IV: Some sources

General literature

- *The Body Hunters*, Sonia Shah (The New Press, 2006)
- *A Bitter Pill*, Wemos (2007)
- *Bad Pharma: How drug companies mislead doctors and harm patients*, Ben Goldacre (Forth Estate, 2012).
- *Promoting ethical standards in globalized drug trials through market exclusion*, Fazal Khan, Popular Media, Paper 81 (2008). http://digitalcommons.law.uga.edu/fac_pm/8
- *Training and Resources in Research Ethics Evaluation*, programme de formation en ligne. <http://elearning.trree.org>

Interviewed persons

Longs interviews

- Valérie Junod, health law specialist and associated professor at the Département de droit des affaires et fiscalité of the University of Lausanne, interviews (9 March 2012 et 28 January 2013) and email (7 January 2013 et 1 April 2013).
- Dominique Sprumont, Professor in Health Law, University of Neuchâtel, interview (21 March 2012) and email (4 January 2013).
- Former employee of Swissmedic, summer 2012.

Meeting Swissmedic –Berne Declaration, 15 August 2012

- Cordula Landgraf, Head of Networking
- Petra Dörr, Head of Management Services and Networking; Member of Management Board.
- Françoise Jaquet, Head of Clinical Trials Division
- Verena Henkel, Deputy Head of Clinical Review Division
- Claus Bolte, Head of Clinical Review Division

Telephone conferences

- Vicky Cann, Alliance for Lobbying Transparency & Ethics Regulation (Alter-EU), 29 March 2012
- Annelies Den Boer, Wemos, 19 March 2012

Informal meetings

- Nathalie Wourgaft, Medical Director DNDi, 18 March 2012.
- Pierre-Henri Bertoye, Assistant Director in charge of clinical trials & pharmacovigilance, ANSM, 18 May 2012.

¹ *The Body Hunters*, Sonia Shah (The New Press, 2006), p.7.

² *Promoting ethical standards in globalized drug trials through market exclusion*, Fazal Khan, Popular Media, Paper 81 (2008). http://digitalcommons.law.uga.edu/fac_pm/81

³ *Informed consent: Enforcing pharmaceutical companies' obligations abroad*, S.B. Lee, Health and Human Rights, Vol 12, No 1 (2010) p.15. <http://www.hhrjournal.org/index.php/hhr/article/viewArticle/200/297>

⁴ See, for example, see the scandal on the Tuskegee trials (USA). Between 1932 and 1972, around 600 people - primarily Afro-Americans on low incomes - were enrolled in a study on syphilis, without informing those suffering from the disease of their illness and without offering any effective treatment. See *The Body Hunters*, Sonia Shah (The New Press, 2006), p. 65 and *Tuskegee syphilis experiment* (Wikipedia) http://en.wikipedia.org/wiki/Tuskegee_syphilis_experiment (perused on 11 March 2013).

⁵ "And yet, we are still seeing consistent violations of ethical standards." *Promoting ethical standards in globalized drug trials through market exclusion*, Fazal Khan, Popular Media, Paper 81 (2008). http://digitalcommons.law.uga.edu/fac_pm/81

⁶ In 2012, The Lancet condemned failures in the regulation of clinical trials in India. For example, a Government investigation had uncovered 81 cases of serious side effects (including 18 involving children) during 73 clinical trials performed on 3300 patients. *Regulation failing to keep up with India's trials boom*, The Lancet, Vol 379 No 9814, p.397 (4 February 2012).

⁷ *Ethical and Scientific Implications of the Globalization of Clinical Research*, New England Journal of Medicine vol 360, p.816 (February 19 2009)

⁸ *A Bitter Pill*, Wemos (2007).

⁹ *SOMO briefing paper on ethics in clinical trials #1: Examples of unethical trials*, F. Weyzig and I. Schipper, SOMO/WEMOS (February 2008).

¹⁰ *Is GlaxoSmithKline Behaving Badly in Argentina?*, ABC News (Sept. 23, 2008) <http://abcnews.go.com/Health/story?id=5735276&page=1>. *GlaxoSmithKline fined over trials on the babies of Argentinian poor*, The Telegraph (11 Jan 2012) <http://www.telegraph.co.uk/science/science-news/9006614/GlaxoSmithKline-fined-over-trials-on-the-babies-of-Argentinian-poor.html>

¹¹ See *The Body Hunters*, Sonia Shah (The New Press, 2006), p. 144; *Bad Pharma: How drug companies mislead doctors and harm patients*, Ben Goldacre (Forth Estate, 2012), p.117 and *Abdullahi v. Pfizer, Inc.* (Wikipedia) http://en.wikipedia.org/wiki/Abdullahi_v._Pfizer,_Inc (perused on 11 March 2013.)

¹² *SOMO briefing paper on ethics in clinical trials #1: Examples of unethical trials*, F. Weyzig and I. Schipper, SOMO/WEMOS (February 2008).

¹³ *The Body Hunters*, Sonia Shah (The New Press, 2006), p.148.

¹⁴ *The Globalization of Clinical Trials: Testimonies from Human Subjects*, Wemos, 2010, p. 16.

¹⁵ *Ethics for Drug Testing in Low and Middle Income Countries, Considerations for European Market Authorisation*, I. Schipper and F. Weyzig, SOMO (Feb 2008), p. 64 et *AstraZeneca* (Wikipedia) <http://en.wikipedia.org/wiki/AstraZeneca> (consulté le 11 mars 2013).

¹⁶ *A Bitter Pill*, Wemos (2007), p. 16.

¹⁷ *India plans to audit clinical trials*, G. Mudur, British Medical Journal 331(7524):1044 (2005) quoted in *A Bitter Pill*, Wemos (2007), p. 16.

¹⁸ *Clinical trials in sub-Saharan Africa and established standards of care: a systematic review of HIV, tuberculosis, and malaria trials*. D.M. Kent, D.M.Mwamburi, M.L. Bennish, B. Kupelnick, J.P. Ioannidis, JAMA 14;292(2):237-42 (14 July 2004).

¹⁹ *Putting Contract Research Organisations on the Radar: An exploratory study on outsourcing of clinical trials by pharmaceutical companies to contract research organisations in non-traditional trial regions*, M. van Huijstee and I. Schipper, SOMO/CSER/SALUD Y FARMACOS (February 2011).

²⁰ Read *Bad Pharma: How drug companies mislead doctors and harm patients*, Ben Goldacre (Forth Estate, 2012), in particular p. 25.

²¹ In 2004, The leading medical journals had made a commitment to only publish articles on the basis of the clinical trials declared, but have not kept their promises. Read *Bad Pharma: How drug companies mislead doctors and harm patients*, Ben Goldacre (Forth Estate, 2012), in particular p. 51.

²² Drugs agencies have introduced clinical trial registers, but they have not always been used correctly. Read *Bad Pharma: How drug companies mislead doctors and harm patients*, Ben Goldacre (Forth Estate, 2012), in particular p. 50.

²³ *GSK have promised to share all trial data: should we trust them?*, Bad Science, Ben Goldacre (11 October 2012). <http://www.badsience.net/2012/10/gsk-have-promised-should-we-trust-them>

²⁴ In the case of AstraZeneca's Seroquel read: *Ethics for Drug Testing in Low and Middle Income Countries, Considerations for European Market Authorisation*, I. Schipper and F. Weyzig, SOMO (Feb 2008), p. 59.

²⁵ Read for example *Clinical Trials in Developing Countries*, Novartis (August 2011). <http://www.novartis.com/downloads/corporate-responsibility/resources/positions/clinical-trials-developing-markets.pdf>

²⁶ "This article suggests that, no matter how robust obligations appear, they will continue to fall short of providing meaningful protection [about informed consent] until they are accompanied by a substantive enforcement mechanism that holds multinational pharmaceutical companies accountable for their conduct." *Informed consent: Enforcing pharmaceutical companies' obligations abroad*, S.B. Lee, Health and Human Rights, Vol 12, No 1 (2010), p.15.

²⁷ *Promoting ethical standards in globalized drug trials through market exclusion*, Fazal Khan, Popular Media, Paper 81 (2008). http://digitalcommons.law.uga.edu/fac_pm/81

²⁸ Read *Bad Pharma: How drug companies mislead doctors and harm patients*, Ben Goldacre (Forth Estate, 2012).

²⁹ *The Body Hunters*, par Sonia Shah (The New Press, 2006), p.3.

³⁰ *Le marché du médicament en Suisse*, Interpharma, 2011 and *Phases of clinical research* (Wikipedia). http://en.wikipedia.org/wiki/Phases_of_clinical_research (perused on 11 March 2013.)

³¹ Source: *Le marché du médicament en Suisse*, Interpharma, 2011.

³² LPTh Art. 54 Para. 1c and Para. 3. Once the LRH comes into force, this article of the LPTh will be modified and will reflect - with regard to the ethics committee authorisation procedure - the extended provisions contained in LRH Art. 45. The principles stated above are fundamentally upheld.

³³ LPTh Art. 54 Para. 4, respectively Para. 1 and Para. 5 following the coming into force of the LRH.

³⁴ LRH Art. 1 Para. 1

³⁵ "Health funds only reimburse drugs prescribed by a doctor under mandatory health insurance if they have been included on the

Federal Office of Public Health (FOPH) List of Pharmaceutical Specialties (LS). Before a drug is entered on the LS, it is checked for safety of use, efficacy and product quality. Swissmedic, the Swiss Institute for Therapeutic Products, is the authority responsible for these checks. In order for a drug to be admitted onto the LS, its effectiveness, therapeutic value and economical nature must then be assessed. The FOPH makes a decision based on the recommendation of the Federal Drug Commission (FDC)" Interpharma, website. <http://www.interpharma.ch/fr/politique/le-marche-pharmaceutique-suisse/Liste-des-spécialités.asp>

³⁶ LPT Art. 10.Para. 1a

³⁷ Interview with Valérie Junod (2012).

³⁸ OEMéd Art. 5 Para. 1

³⁹ OAMal Art. 65.

⁴⁰ "Research and development costs must be appropriately taken into account during assessment of the economic nature of an original preparation. These costs shall be taken into account via an innovation fee, which shall be included in the price, if the drug represents progress in medical treatment." OAMal Art. 65.Para. b.

⁴¹ OAMal Art. 71.

⁴² *Mandat de prestation 2011-2014*, Swissmedic.

<http://www.swissmedic.ch/org/00006/index.html?lang=fr>

⁴³ LPT Art. 51.

⁴⁴ LRH Art. 4 (coming into force from 01.01.2014)

⁴⁵ "All human clinical trials of therapeutic products must be carried out in accordance with the recognised principles of good clinical trial practice." LPT Art. 53 Para.1. Once the LRH has come into force, this article of the LPT will be modified and refer to the extended provisions contained in the new law.

⁴⁶ "The manufacture of medicinal products must conform to the recognised rules of good manufacturing practice." LPT Art. 7.

⁴⁷ "Any person exporting medicinal products intended for use in clinical trials must demand proof that the rules of good clinical trial practice are applied." LPT Art. 22. "Any person engaged in the wholesale trade of medicinal products must respect the recognised principles of good wholesale trade practice." LPT Art. 29.

⁴⁸ "For a large number of medical devices, such as bandages, splints and other supports, the risks are limited and can be managed using a self-check system. An authorisation procedure, which is likely to be similar to drug marketing authorisation, could prove to be disproportionate." Nevertheless, for higher-risk devices, such as pace-makers or breast implants, stricter checks may be necessary. There is a trend to increase requirements for breast implants, which could lead to a system very similar to a marketing authorisation." (Interview with Dominique Sprumont (2012) and e-mail (2013)).

⁴⁹ Medical devices comprise the instruments, substances and medical and technical software used for diagnosis or therapy, such as implants, measuring devices, tests, etc.

⁵⁰ *Mandat de prestations 2011-2014*, Swissmedic, § 9.1.

⁵¹ *Mandat de prestations 2011-2014*; Swissmedic et LPT Art. 10 et Art. 58

⁵² Swissmedic's remit operates in "a field of tensions generated by potentially divergent interests." *Mandat de prestations 2011-2014*, Swissmedic.

⁵³ Swissmedic must accomplish its missions "independently of economic and political influences" and must prevent "any conflicts of interest that could occur in its entities and commissions". At the same time it must also respect the principle that "an authority must act efficiently and avoid excessive application of standards and paperwork in accomplishing its missions" (*Mandat de prestations 2011-2014*, Swissmedic.)

⁵⁴ LPT Art. 68.

⁵⁵ *Les conflits d'intérêts dans l'administration, en particulier à l'OFSP*, Valérie Junod, Ed. Olivier Guillod (IDS/Unine), 2009, p. 102.

⁵⁶ LPT Art. 1.

⁵⁷ LPT Art. 72.

⁵⁸ Illustration taken from *Le marché du médicament en Suisse*, Interpharma, 2011.

⁵⁹ For Swissmedic, drugs are considered "new" when they contain new active ingredients or if key changes have been made.

⁶⁰ *Rapport d'activité 2011*, Swissmedic, p. 20 and *Rapport d'activité 2010*, Swissmedic, p.41.

⁶¹ *Contrat de prestations 2011*, Swissmedic.

⁶² "The total amount of these fees depends on the number of drug packages sold in Switzerland and their factory price." *Redevances de vente 2010*, Swissmedic, website.

<http://www.swissmedic.ch/aktuell/00003/01443/index.html?lang=fr>

⁶³ This mainly involves marketing authorisations, changes to drug use and clinical trial authorisations. Ordinance concerning fees on therapeutic products (OEPT) Art. 1 and Appendix.

⁶⁴ *Rapport d'activité 2010*, Swissmedic and *Rapport d'activité 2011*, Swissmedic, p.63.

⁶⁵ OEPT appendix A.

⁶⁶ "Swissmedic Medicines Expert Committees support Swissmedic by providing assessment and consulting during the scientific analysis of documents submitted for marketing authorisations, monitoring and licensing. These services are answers to specific technical issues, encountered either during or independently of ongoing procedures." *Swissmedic Medicines Expert Committees*, Swissmedic, website.

⁶⁷ He serves as an expert for Swissmedic, the EMA and the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) in Germany. *Registre des membres nommés du Human Swissmedic Expert Committee (HMEC) et déclarations publiques d'intérêts*, Swissmedic (01.12.2011).

⁶⁸ Omal, Art. 37 e.

⁶⁹ Response of the Federal Council on 7 November 2001 to a query by Caspar Baader. (01.3410).

⁷⁰ *Les conflits d'intérêts dans l'administration, en particulier à l'OFSP*, Valérie Junod, Ed. Olivier Guillod (IDS/Unine), 2009, p. 115.

⁷¹ Although authorised by Swissmedic, Myozyme (a drug against Pompe disease) was not initially included on the List of Pharmaceutical Specialties, because its effectiveness is limited and it is very expensive (it is now on the list). Read *Rationnement des soins: Qu'implique l'arrêt «Myozyme»? J.-B. Wasserfallen, V. Junod, Bulletin des médecins suisses*, 2011;92: 45.

⁷² This issue can be seen in some ethics committees. Although the law requires a certain level of diversity in the composition of their members (physicians, nurses, non-medical members, statistician, lawyer, bioethicist), the "scientific voice" can dominate the others. Interview with Valérie Junod (2012) and e-mail (7 January 2013).

⁷³ Interview with Valérie Junod (2012).

⁷⁴ Interview with Valérie Junod (2012).

⁷⁵ *World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects*, 1964-2008. <http://www.wma.net/en/30publications/10policies/b3/>. All articles cited in this report refer to this latest version, revised in 2008.

⁷⁶ *ICH-GCP Harmonised Tripartite Guideline: Guideline for good clinical practice E6*, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-GCP).

<http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>

⁷⁷ "Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects." ICH-GCP, Introduction.

⁷⁸ *Helsinki discords: FDA, ethics, and international drug trials*, J. Kimmelman, C. Weijer, E.M. Meslin, *The Lancet*, Vol. 373, No 9657 (2009), p. 13-14.

⁷⁹ *Does the FDA have the authority to trump the Declaration of Helsinki?*, M.D. Goodyear, T. Lemmens, D. Sprumont, G.D. Tangwa, *BMJ*, 338:b1559 (2009).

⁸⁰ *Clinical trials in developing countries: how to protect people against unethical practices?* Directorate-General for External Policies of the Union/SOMO (March 2009), p.34.

⁸¹ *Helsinki discords: FDA, ethics, and international drug trials*, J. Kimmelman, C. Weijer, E.M. Meslin, *The Lancet*, Vol. 373, No 9657 (2009), p. 13-14.

⁸² "Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible." ICH-GCP, Introduction.

⁸³ "The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. (...) The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee." DoH Art. 15.

⁸⁴ "A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion." ICH-GCP Art. 2.6.

⁸⁵ "For conducting clinical trials, the following requirements in particular must be fulfilled: (...) the competent ethics commission endorses the trial" LPT Art. 54 Para. 1c and OClin Art. 9 sq.

⁸⁶ "Conducting a research project [is subject] to authorisation from the ethics committee with jurisdiction" LRH Art. 45. The LRH will come into force on 01.01.2014. Also see Art. 47 and Art. 51, and forthcoming ordinances relating to the LRH that are currently under consideration.

⁸⁷ "Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject." DoH Art. 19.

⁸⁸ "The clinical trials authorised must have been recorded in a public register" LRH Art. 56 (from 2014). After several years of procrastination, a public register is set to be implemented to record clinical trials authorised in Switzerland. The content of records and when they should be made is still under discussion. Also read 5.5.2. *The importance of clinical trial registers*.

⁸⁹ "Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation." DoH Art. 18.

⁹⁰ "Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks." ICH-GCP Art. 2.2.

⁹¹ "Foreseeable risks and restrictions encountered by people participating in a research project must not be disproportionate to the anticipated usefulness of the project." LRH Art. 12 (from 2014).

⁹² "The health of my patient will be my first consideration." DoH Art. 4.

⁹³ "The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society." ICH-GCP Art. 2.3.

⁹⁴ "The interests, health and well-being of human beings shall take precedence over the interests of science and society" LRH Art. 4 (from 2014).

⁹⁵ Both the DoH and ICH-GCP only mention this possibility of compensation in the event of a problem, without explicitly requiring it. Read 3.4.3. *Compensation in the event of a problem*

⁹⁶ "Full compensation of any damages encountered as part of the trial [must be] guaranteed to research subjects" LRH Art. 54 Para. 1b (from 2014).

⁹⁷ "Anyone who initiates a research project on human subjects shall be responsible for harm suffered in relation to the project." LRH Art. 19 Para. 1 (from 2014). Articles 19 and 20 describe future methods of compensation.

⁹⁸ "...each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given (...) to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing the non-written consent must be formally documented and witnessed." DoH Art. 24.

⁹⁹ "Freely given informed consent should be obtained from every subject prior to clinical trial participation." ICH-GCP Art. 2.9.

¹⁰⁰ "... the following requirements in particular must be fulfilled: a) the trial subjects have explicitly given their free consent in writing, or testified in writing, having been informed in particular on: 1. the nature and purpose of the trial; 2. all of the processes and investigations connected with the trial; 3. the existence of other treatments; 4. the anticipated risks, discomforts and benefits; 5. their rights to compensation in the case of harm attributable to the trial; 6. their right to withdraw their consent at any time without impairment to their therapeutic care" LPT Art. 54.

¹⁰¹ "Research may only be conducted on human subjects if they have given informed consent and have not exercised their right of refusal after being informed in accordance with this law" and "Persons may only be included in a research project if they have given their consent, after having received sufficient information (informed consent)" LRH, Art. 7 and 16 (from 2014).

¹⁰² "Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence." DoH Art. 9.

¹⁰³ "An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects." ICH-GCP Art. 3.1.1. "Vulnerable Subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent." ICH-GCP Art. 1.61.

¹⁰⁴ Chapter 3 of the LRH is dedicated to additional requirements for to research on “particularly vulnerable people”, but does not mention poor populations from developing countries or emerging economies. Read 3.4.1. *Vulnerable populations*).

¹⁰⁵ In principle, this idea rules out the possibility of performing trials on vulnerable “Southern” populations for drugs that will be marketed to fight a “Northern” illness or for medicines that will only be sold in the “North”.

¹⁰⁶ “Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.” DoH Art. 17.

¹⁰⁷ “The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.” DoH Art. 14.

¹⁰⁸ “The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances: The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.” DoH Art. 32.

¹⁰⁹ “Use of placebo or the forgoing of a treatment shall not be authorised unless no additional risk of serious or irreversible harm to the person concerned is expected” and only in the “absence of existing proven therapy” or if “use of placebo is necessary for compelling and scientifically sound methodological reasons in order to determine the efficacy or safety of a therapeutic method.” LRH Art. 13 (from 2014). Read 3.4.4. *Placebo*.

¹¹⁰ “1. All human clinical trials of therapeutic products must be carried out in accordance with the recognised principles of good clinical trial practice. 2. The Federal Council shall specify the recognised principles of good clinical trial practice. In particular, it shall lay down the obligations to which the investigator and the sponsor are subject and shall adopt provisions concerning the control procedure. In doing so, it shall take account of internationally recognised guidelines and standards.” LPTh Art. 53.

¹¹¹ *Org LRH, Ordonnance concernant l'organisation découlant de la LRH, Projet 23.07.2012* chap. 2 Organe de coordination, Art. 9.

¹¹² Interview with Valérie Junod (2013).

¹¹³ Interview with Dominique Sprumont (2012) and email (2013).

¹¹⁴ «Avant-projet de loi fédérale relative à la recherche sur l'être humain: Prise de position», D. Sprumont, 30 mai 2006.

¹¹⁵ “Scientific requirements. 1 Research may only be conducted on human subjects under the following conditions: a. it complies with recognised standards for scientific integrity, particularly the management of conflicts of interest; b. it fulfils the criteria for scientific quality; c. it complies with international rules of recognised good practice for research on human subjects; d. the people in charge have sufficient professional qualifications. 2 The Federal Council shall clarify the national and international regulations that must be complied with.” LRH, Art. 10.

¹¹⁶ Interview with Dominique Sprumont (2012) and email (2013).

¹¹⁷ *Avant-projet de loi fédérale relative à la recherche sur l'être humain: Prise de position*, D. Sprumont, 30 mai 2006.

¹¹⁸ LRH art 51 2.

¹¹⁹ Interview with Dominique Sprumont (2012) and email (2013).

¹²⁰ *Trials on trial: the Food and Drug Administration should rethink its rejection of the Declaration of Helsinki* [editorial], *Nature* 453:427-8 (2008).

¹²¹ *Helsinki discords: FDA, ethics, and international drug trials*, J. Kimmelman, C. Weijer, E.M. Meslin, *The Lancet*, Vol. 373, No 9657

(2009), p. 13-14; *The FDA and the Declaration of Helsinki: A New Rule Seems to Be More About Imperialism than Harmonisation*, M. Goodyear, T. Lemmens, D. Sprumont, G. B. Tangwa, *British Medical Journal*, Vol. 338, pp. 1157-1158, 2009.

¹²² *Does the FDA have the authority to trump the Declaration of Helsinki?*, M.D. Goodyear, T. Lemmens, D. Sprumont, G.D. Tangwa, *BMJ*, 338:b1559 (2009).

¹²³ *Commission directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products*.

¹²⁴ *Proposal for a regulation of the European parliament and of the council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, 2012/0192 (COD)* (17 July 2012).

¹²⁵ *Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities*, EMA/121340/2011 (16 April 2012).

¹²⁶ *Ibid*, 4.5. *Vulnerable populations*, p. 25

¹²⁷ *Ibid*, 4.6 *Placebo and active comparator*, p. 26.

¹²⁸ *Ibid*, 4.7 *Access to treatment post trial*, p. 28.

¹²⁹ Valérie Junod specialises in Health Law and is an Associate Professor in the Department of Business and Tax Law at Lausanne University.

¹³⁰ Valérie Junod, email (1 April 2013).

¹³¹ Valérie Junod, interview (2013) and email (1 April 2013).

¹³² *The Helsinki Declaration and the Law: An International and Comparative Analysis*, D. Sprumont, S. Girardin, T. Lemmens, in *History and Theory of Human Experimentation – the Declaration of Helsinki and Modern Medical Ethics*, Andreas Frewer, Ulf Schmidt, eds., (Franz Steiner Verlag, 2007), p. 234-237.

¹³³ “Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.” DoH Art. 17.

¹³⁴ *Lignes directrices internationales d'éthique pour la recherche biomédicale impliquant des sujets humains*, Conseil des organisations internationales des sciences médicales (CIOMS) avec la collaboration de l'Organisation mondiale de la santé (OMS), 2003.

¹³⁵ *Ibid*

¹³⁶ For example, the International Federation of Pharmaceutical Manufacturers & Associations (which represents companies involved in pharmaceutical, biotechnological and vaccine research) defines vulnerable subjects as “individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.” *Glossary*, IFPMA Clinical Trials Portal <http://clinicaltrials.ifpma.org/clinicaltrials/index.php?id=15&L=0>

¹³⁷ *Does the FDA have the authority to trump the Declaration of Helsinki?*, M.D. Goodyear, T. Lemmens, D. Sprumont, G.D. Tangwa, *BMJ*, 338:b1559 (2009).

¹³⁸ *The battle of Helsinki: Two troublesome paragraphs in the Declaration of Helsinki are causing a furor over medical research ethics*, H. Wolinsky *EMBO Rep.* 2006 July; 7(7): 670-672.

¹³⁹ Valérie Junod notes that the vague nature of this principle makes it impractical as it fails to specify the length of time during which a participant has a right treatment following the end of the trial, in accordance with the DoH (one month, one year, a lifetime). Neither does it resolve the problem of treatment that has not yet been approved, but seems promising. Should it continue to be given freely - and run a possible health risk - or should medical staff await marketing authorisation from a country (and in this case, the question arises of which country should be taken into account)? Valérie Junod, interview (2013).

¹⁴⁰ Résolutions du Conselho Nacional de Saúde 196/96, 251/97 et 404/08.

¹⁴¹ Read *Pharmaceuticals companies vs. the State: who is responsible for post-trial provision of drugs in Brazil?*, D.W. Wang, O.L. Ferraz, J Law Med Ethics 40(2):188-96 (2012).

¹⁴² *Ethical guidelines for biomedical research on human participants*, ICMR (2006). http://icmr.nic.in/ethical_guidelines.pdf

¹⁴³ Particularly resolutions 1490/2007 and 1480/2011.

¹⁴⁴ *The battle of Helsinki: Two troublesome paragraphs in the Declaration of Helsinki are causing a furor over medical research ethics*, H. Wolinsky EMBO Rep. 2006 July; 7(7): 670-672.

¹⁴⁵ "Note of clarification on paragraph 29 of the WMA Declaration of Helsinki: The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances: - Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or - Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm. All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review." Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

¹⁴⁶ ICH-GCP Topic E 10, *Choice of Control Group in Clinical Trials, Step 5, Note for guidance on choice of control group in clinical trials (CPMP/ICH-GCP/364/96)* (January 2001).

¹⁴⁷ <http://www.ema.europa.eu/pdfs/human/ich/036496en.pdf>

¹⁴⁸ *The Body Hunters*, Sonia Shah (The New Press, 2006), p.33.

¹⁴⁹ *Clinical trials in developing countries: how to protect people against unethical practices?* Directorate-General for External Policies of the Union/SOMO (March 2009).

¹⁵⁰ "The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option." DoH (2008) Art. 32.

¹⁵¹ One third of drugs (new molecules) authorised by the FDA between 2001 and 2010 were only tested against placebo. *Availability of Comparative Efficacy Data at the Time of Drug Approval in the United States* N. H. Goldberg, S. Schneeweiss, M. K. Kowal, J. J. Gagne, JAMA. 2011; 305(17):1786-1789, quoted in *Bad Pharma: How drug companies mislead doctors and harm patients*, Ben Goldacre (Forth Estate, 2012).

¹⁵² Interview with Dominique Sprumont (2012).

¹⁵³ Interview with Dominique Sprumont (2012) and email (2013).

¹⁵⁴ Voir *The Body Hunters*, Sonia Shah (The New Press, 2006), p.6-8.

¹⁵⁵ Read *Regulation failing to keep up with India's trials boom*, The Lancet, Vol 379 No 9814, p.397 (4 February 2012).

¹⁵⁶ Interview with Valérie Junod (2012).

¹⁵⁷ "This article suggests that, no matter how robust obligations appear, they will continue to fall short of providing meaningful protection [à propos du consentement éclairé] until they are accompanied by a substantive enforcement mechanism that holds multinational pharmaceutical companies accountable for their conduct." *Informed consent: Enforcing pharmaceutical companies' obligations abroad*, S.B. Lee, Health and Human Rights, Vol 12, No 1 (2010), p.15.

¹⁵⁸ Interview with Dominique Sprumont (2012).

¹⁵⁹ Interview with a former Swissmedic employee, summer 2012.

¹⁶⁰ "There seem to be well-founded reasons for concern with regard to the independence and quality of [Institutional Review Boards] in many foreign institutions." *Ethical Review and the Globalization of Clinical Trials: Defining Policy through Action*, WHO (2001). <http://www.nus.edu.sg/irb/Articles/WHO%20Defining%20Policy%20Through%20Action.pdf>

¹⁶¹ We would like to restate a paragraph from our *Introduction*: "According to a study in 2004, a quarter of clinical trials carried out in India had not been approved by an ethics committee. Only a quarter of Indian ethics committees followed the prescribed guidelines, and conflicts of interest could not be excluded for half of them, according to research in 2005. Only 16% of the 73 clinical trials carried out in sub-Saharan Africa complied with international ethical principles. Finally, a more recent study carried out in India, Brazil, Argentina and Peru confirmed shortcomings in clinical trial monitoring, both on the part of regulatory authorities and the ethics committees in the relevant countries."

¹⁶² *The Body Hunters*, Sonia Shah (The New Press, 2006), p.135, quoting *Letter Criticizing Draft Report on Ethics of Research in Developing Countries*, Public Citizen (6 December 2000), section I <http://www.citizen.org/hrg1550>

¹⁶³ *Double évaluation éthique des projets de recherche menés à l'étranger, en particulier en partenariat Nord-Sud*, Bulletin des médecins suisses (2008); 89, p.511

¹⁶⁴ *Ethical international research on human subjects research in the absence of local institutional review boards*, S.B. Bhat, T.T. Hegde, J Med Ethics (Sep 2006);32(9):535-6.

¹⁶⁵ <http://www.who.int/sidcer>

¹⁶⁶ <http://www.fecis.net>

¹⁶⁷ <http://www.fecap-sidcer.org>

¹⁶⁸ <http://www.flaceis.org>

¹⁶⁹ The TRREE initiative (Training and Resources in Research Ethics Evaluation) brings together Northern and Southern experts to offer free online training for people whose activities involve ethical issues around medical research. The training focusses on the situation in Africa but also includes modules on changes to Swiss law. <http://www.trree.org>

¹⁷⁰ Discussion with Pierre-Henri Bertoye (Deputy Director responsible for trials, devices and pharmacovigilance at the ANSM), 18 May 2012.

¹⁷¹ "Local Ethics Committees make their own assessment according to local [moral and cultural] criteria." Interview with Dominique Sprumont (2012).

¹⁷² Discussion with Nathalie Wourgaft, Medical Director de DNDi, 18 May 2012.

¹⁷³ Discussion with Nathalie Wourgaft, 18 May 2012.

¹⁷⁴ Interview with Dominique Sprumont (2012).

¹⁷⁵ *Présentation du 15 août 2012*, Cordula Landgraf, Head of Networking, Swissmedic.

¹⁷⁶ Prequalification Programme, OMS <http://apps.who.int/prequal/>

¹⁷⁷ Cordula Landgraf, Head of Networking, Swissmedic. Presentation given on 15 August 2012.

¹⁷⁸ Interview with a former Swissmedic employee (summer 2012), who states that Swissmedic managers once questioned participants

to find out what they had understood about how the clinical trial would be conducted and its possible consequences.

¹⁷⁸ "I think Swissmedic never checks whether patients have understood the nature of the trial in which they are taking part. I believe that it hardly ever happens at all either in Switzerland or even in the USA." Interview with Valérie Junod (2012).

¹⁷⁹ Interview with Valérie Junod (2012).

¹⁸⁰ Read *Quality of informed consent in cancer clinical trials: a cross-sectional survey*, Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC, Lancet 358(9295):1772-7 (2001 Nov 24) that concluded: "74% of patients any did not recognise non-standard treatment, 63% the potential for incremental risk from participation, 70% the unproven nature of the treatment, 29% the uncertainty of benefits to self, 35% that trials are done mainly to benefit future patients."

¹⁸¹ A study carried out at the University Hospital of Geneva (HUG) showed that a large majority of participants had not understood. Interview with Valérie Junod (2012).

¹⁸² "All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification." ICH-GCP Art. 2.10. "Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol." ICH-GCP Art. 2.12.

¹⁸³ Interview with Valérie Junod (2012).

¹⁸⁴ Interview with Valérie Junod (2012).

¹⁸⁵ Interview with Valérie Junod (2012).

¹⁸⁶ Interview with Dominique Sprumont (2012) and email (2013).

¹⁸⁷ Interview with Valérie Junod (2012).

¹⁸⁸ Interview with Valérie Junod (2012).

¹⁸⁹ LRH, Art. 60

¹⁹⁰ Interview Swissmedic – Berne Declaration, 15 August 2012.

¹⁹¹ Read Appendix III, 3rd correspondence, January 2013.

¹⁹² Interview Swissmedic – Berne Declaration, 15 August 2012.

¹⁹³ «EU Regulatory Authorities should identify those studies that may give rise to special ethical concern (e.g. arising from their design, the local regulatory framework within which they are conducted, the vulnerability of the study subjects) and where applicable seek additional assurance that the trials have been ethically conducted», *Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities*, EMA (April 2012), p.18.

¹⁹⁴ Informed consent presumes that the participant is capable of making a choice, but there is an implicit pressure due to a lack of choice for poor patients from developing countries, who could be strongly tempted to accept a clinical trial, in order to receive treatment to which they would not otherwise have access. Interview with Valérie Junod (2013).

¹⁹⁵ Interview with Valérie Junod (2013).

¹⁹⁶ Interview with Valérie Junod (2013).

¹⁹⁷ Interview with Valérie Junod (2013).

¹⁹⁸ Interview with Valérie Junod (2013).

¹⁹⁹ *Les conflits d'intérêts dans l'administration, en particulier à l'OFSP*, Valérie Junod, Ed. Olivier Guillod (IDS/Unine), 2009, p.91

²⁰⁰ *Les conflits d'intérêts dans l'administration, en particulier à l'OFSP*, Valérie Junod, Ed. Olivier Guillod (IDS/Unine), 2009, p.108.

²⁰¹ Interview with Dominique Sprumont (2012) and email (2013).

²⁰² *Annual accounts, Financial year 2010*, EMA p. 12.

²⁰³ Discussion with Annelies Den Boer, Wemos, 19 March 2012.

²⁰⁴ *Obama asks for hike in industry funding for FDA*, Reuters, 13.02.2012

²⁰⁵ "User fees have created an untenable conflict of interest in which the Food and Drug Administration (FDA) is literally in hock to the industry it is supposed to be regulating. The result has been a decline in safety standards at the FDA, with a resultant record number of drug withdrawals for safety reasons. (...) The user fee program has demonstrably failed. In a recent open letter, 22 drug regulatory experts, including six former senior FDA staff and four

authors of the Institute of Medicine's drug safety review, opposed the continuation of user fees and concluded that "User fees may appear to save taxpayers money, but at an unacceptable cost to public health."", *Letter Regarding Prescription Drug User Fee Act*, Public Citizen, 4 mai 2007.

²⁰⁶ Interview PBS radio,

<http://www.pbs.org/wgbh/pages/frontline/shows/prescription/interviews/wolfe.html>, published on 13.11.2003

²⁰⁷ Interview with Dominique Sprumont (2012) and email (2013).

²⁰⁸ *Block the revolving door: why we need to stop EU officials becoming lobbyists*, ALTER-EU, 2011.

²⁰⁹ The website of their company, Pharmalex, even boasts of their network of contacts: "Until 2003, we were executive employees of the Swiss Drug Regulatory Authority, Swissmedic (formerly IKS). As part of the legal department our core function was the preparation of the new Federal Law on Therapeutic Products and its by-laws, including the authorship as well as taking care of all legal texts and lawsuits of Swissmedic/IKS. This experience enabled us to acquire an excellent knowledge about the federal legislative procedure and develop an excellent network of, contacts to the authorities, organisations and the pharmaceutical industry. Our firsthand knowledge of the new Law and its by-laws and our long experience within IKS and Swissmedic put us in an absolutely unique position – a valuable asset and advantage for you, for our clients."» *Les conflits d'intérêts dans l'administration, en particulier à l'OFSP*, Valérie Junod, Ed. Olivier Guillod (IDS/Unine), 2009, p. 147 and note 225.

²¹⁰ *Cytos Biotherapeutics*, website Moneyhouse.

<http://www.moneyhouse.ch/en/u/cytos-biotherapeutics-ag-CH-170.3.032.950-3.htm>

²¹¹ *Franz Schneller ab April 2005 neuer Direktor von Swissmedic*, Federal Press release,

http://www.admin.ch/cp/d/4123382e_2@fwsrvg.html

²¹² *CV de Jürg H. Schnetzer*, Swissmedic,

<http://www.swissmedic.ch/org/00074/01135/02108/index.html?lang=en>

²¹³ *Staff Regulations of Officials of the European Communities*, Art. 16, 2004.

²¹⁴ *Summary of Post-Employment Restrictions*, FDA, 2011,

<http://www.fda.gov/AboutFDA/WorkingatFDA/Ethics/ucm071580.htm>

²¹⁵ *Les conflits d'intérêts dans l'administration, en particulier à l'OFSP*, Valérie Junod, Ed. Olivier Guillod (IDS/Unine), 2009, p.146.

²¹⁶ "Officials intending to engage in an occupational activity, whether gainful or not, within two years of leaving the service shall inform their institution thereof. If that activity is related to the work carried out by the official during the last three years of service and could lead to a conflict with the legitimate interests of the institution, the Appointing Authority may, having regard to the interests of the service, either forbid him from undertaking it or give its approval subject to any conditions it thinks fit. The institution shall, after consulting the Joint Committee, notify its decision within 30 working days of being so informed. If no such notification has been made by the end of that period, this shall be deemed to constitute implicit acceptance." *Staff Regulations of Officials of the European Communities*, 2004, Art. 16 p. I-10.

²¹⁷ *Block the revolving door: why we need to stop EU officials becoming lobbyists*, ALTER-EU, 2011, p.18.

²¹⁸ Following a complaint from a German NGO, alleging that EFSA failed to address a conflict of interest arising from the move of an EFSA Head of Unit to a biotechnology company, in December 2011, the European Ombudsman, Nikiforos Diamandouros, called on the European Food Safety Authority to strengthen its rules and procedures in order to avoid potential conflicts of interest in "revolving door" cases. (*EFSA should strengthen procedures to avoid potential conflicts of interest in "revolving door" cases.*) European Union Press release, 14 December 2011).

²¹⁹ *EMA puts curbs on new work by ex-chief Lonngren*, Pharmatimes, 22 March 2011.

²²⁰ The staff regulations at EMA, Open letter, ALTER-EU, 19 December 2011.

²²¹ *Block the revolving door: why we need to stop EU officials becoming lobbyists*, ALTER-EU, 2011, p.18.

²²² *Faut-il avoir peur des médicaments?*, Temps Présent, Radio Télévision Suisse (Swiss television company), 16 June 2011.

²²³ *Intérêts croisés entre Swissmedic et les pharmas*, RTS, website. <http://www.rts.ch/info/3209982-interets-croises-entre-swissmedic-et-les-pharmas.html>

²²⁴ The following day (17 June 2011), the National Councillor, Stéphane Rossini, submitted the parliamentary initiative: *Totale indépendance des expertes et des experts de Swissmedic*.

²²⁵ *Remaniement du code des membres des Swissmedic Medicines Expert Committees et déclaration d'intérêts*, Swissmedic, website. <http://www.swissmedic.ch/zulassungen/00173/01887/index.html?lang=fr>

²²⁶ Available as links in the following two documents: *Registre des membres du Human Medicines Expert Committee (HMEC)* et *Registre des membres du Veterinary Medicines Expert Committee (VMEC)* published in <http://www.swissmedic.ch/zulassungen/01836/index.html?lang=fr>

²²⁷ For example: "Financial Interests, including holding of shares in a pharmaceutical company (tax value > CHF 50'000 and/or voting rights of more than 3 %)".

²²⁸ *Code relatif à la gestion des conflits d'intérêts applicable aux SMEC*, Swissmedic, January 2012.

²²⁹ For example: holding stocks and shares, employee stock options, investments, bonds, ownership rights. Holding shares in stock funds or bonds where the holder has no influence on investment strategy are not deemed an investment.

²³⁰ For example: participation in decision-making processes for a pharmaceutical company, membership of the board of directors, an operational management position, a permanent or temporary staff role, consultancy or any other external activity for the company. For next of kin: membership of the board of directors or operational management of a pharmaceutical company.

²³¹ "Brunner Naga is a Health Science Consulting company dedicated to strategy, logistics, and innovative development of new drugs and new therapeutic concepts" <http://www.brunner-naga.com>

²³² Business activity: "Strategie- und Logistikberatung im Bereich der medizinischen und wissenschaftlichen Entwicklung von neuen Medikamenten, insbesondere präklinische und Phase I-IIa Studien sowie Auswertung von Lizenzdossiers und Durchführung von Inspektionen", *Registre du commerce du canton de Zurich*.

²³³ "Swissmedic shall actively inform the public about drugs in order to protect the population. Swissmedic shall continue to position itself as an authority worthy of confidence at a national level" *Mandat de prestations 2011-2014*, Swissmedic.

²³⁴ *Bad Pharma: How drug companies mislead doctors and harm patients*, Ben Goldacre (Forth Estate, 2012), p. 51.

²³⁵ *Bad Pharma: How drug companies mislead doctors and harm patients*, Ben Goldacre (Forth Estate, 2012), p. 50.

²³⁶ See, for example, the declaration *Position commune sur la divulgation d'informations relatives aux essais cliniques par l'intermédiaire de registres et de bases de données* co-signed in 2009 by the International Federation of Pharmaceutical Manufacturers & Associations (which brings together all pharmaceutical companies, including Novartis, GSK, Pfizer, etc.). http://clinicaltrials.ifpma.org/clinicaltrials/fileadmin/files/pdfs/E/N/November_10_2009_Updated_Joint_Position_on_the_Disclosure_of_Clinical_Trial_Information_via_Clinical_Trial_Registries_and_Databases.pdf

²³⁷ *GSK have promised to share all trial data: should we trust them?*, Bad Science, Ben Goldacre (11 October 2012). <http://www.badsience.net/2012/10/gsk-have-promised-should-we-trust-them>

²³⁸ www.clinicaltrials.gov, www.clinicaltrialsregister.eu, www.who.int/ictpr.

²³⁹ Interview with a former Swissmedic employee, summer 2012.

²⁴⁰ Read Appendix III, *Correspondence Swissmedic – Berne Declaration*.

²⁴¹ LRH Art. 56

²⁴² *ORH 1, Ordonnance sur les essais cliniques (Ordonnance relative à la recherche sur l'être humain 1)*, Projet 23.07.2012 chap. 5 (*Enregistrement*), Art. 72 to 75 and appendix 5 (*Contenu du registre*).

²⁴³ See in particular the campaign by the *British Medical Journal* in partnership with *The Cochrane Collaboration* on the issue of Tamiflu (www.bmj.com/tamiflu) and the *All Trials Registered, All Results Reported* (<http://www.alltrials.net>) petition supported by Sense About Science, Bad Science, BMJ, The James Lind Initiative and the Centre for Evidence-based Medicine. Only one pharmaceutical company has signed it (GSK).

²⁴⁴ *Release of data from clinical trials*, EMA website http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac0580607bfa (perused on 27.03.2013)

²⁴⁵ According to Ben Goldacre, the EudraCT register set up by the EU does not include all of the data required to be considered a clinical trial register and remains inaccessible; read *Bad Pharma: How drug companies mislead doctors and harm patients*, Ben Goldacre (Forth Estate, 2012), in particular p. 52.

²⁴⁶ *Glaxo Opens Door to Data on Research*, The New York Times (October 11, 2012). *GSK have promised to share all trial data: should we trust them?*, Bad Science, Ben Goldacre (11 October 2012) <http://www.badsience.net/2012/10/gsk-have-promised-should-we-trust-them>. The recent declaration by Roche announcing a committee responsible for assessing data access requests was received with scepticism; read *Drug firm Roche pledges greater access to trials data*, BBC (26 February 2013) <http://www.bbc.co.uk/news/health-21595895> (perused on 12.03.2013).

²⁴⁷ *European public assessment reports*, EMA website http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125.

²⁴⁸ Read *CHMP: Committee meeting reports* on

<http://www.ema.europa.eu>.

²⁴⁹ "Swissmedic is bound by official secrecy laws and the duty of secrecy. There are also legislative restrictions concerning the protection of trade secrets". Interview with Dominique Sprumont (2012).

²⁵⁰ Interview with Dominique Sprumont (2012).

²⁵¹ Summary of decision on complaint 2493/2008/(BB)(TS)FOR against the European Medicines Agency. <http://www.ombudsman.europa.eu/en/cases/summary.faces/fr/11740/html.bookmark>

²⁵² European Ombudsman website, decision on complaint

2560/2007/BEH. For a summary, see <http://www.ombudsman.europa.eu/fr/cases/summary.faces/en/5646/html.bookmark>

²⁵³ Interview with Valérie Junod (2012).

²⁵⁴ http://ethiquerecherche.hug-ge.ch/protocoles_actifs/chirurgie.html

²⁵⁵ The LRH/ORH 1 stipulates that the FOPH will be responsible for managing use of an additional data bank with entries made in one of the national languages. This clause currently only applies to clinical trials performed in Switzerland and does not include foreign trials presented during a marketing authorisation application in Switzerland.

²⁵⁶ Interview with Dominique Sprumont (2012).

²⁵⁷ Interview with Dominique Sprumont (2012).

²⁵⁸ *La Suisse importe des cobayes humains humains*, L'Hebdo 20 May 1999 p. 18.

²⁵⁹ Interview with Dominique Sprumont (2012).

²⁶⁰ *La nouvelle réglementation des essais cliniques de médicaments*, D. Sprumont et M.-L. Béguin, Bulletin des médecins suisses 83, 2002, p. 902.

²⁶¹ Ibid

²⁶² Interview with Dominique Sprumont (2012).

²⁶³ Interview with Dominique Sprumont (2012).

²⁶⁴ *Le grand marché des cobayes humains*, Temps Présent, RTS, 11 December 2008.

²⁶⁵ Cross-checking this information with the article *Genève, fuites sur fond de controverse à l'hôpital* (Le Temps, 28 février 2009), we can assume it is about Afksendyios Kalangos.