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The Swiss Regulatory Framework for Paediatric Health Research

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Abstract
Medical research on minors entails both risks and benefits. Under Swiss law, clinical trials on children, including nontherapeutic drug trials, are permissible. However, ethics committees must systematically verify that all clinical studies have a favorable risk-benefit profile. Additional safeguards are designed to ensure that children are not unnecessarily involved in research and that proper consent is always obtained. Federal Swiss law is undergoing revision to extend these protections beyond clinical trials to a broad array of health research. The Swiss drug agency also seeks to improve the incentives for pharmaceutical firms to develop new paediatric drugs and relevant paediatric drug labels.

Keywords
Paediatric studies; clinical trials; drug research; pharmaceutical regulation; data protection; ethics committees; Swiss law

Introduction

Medical research on minors raises similar concerns throughout the world. On the one hand, children should enjoy the benefits of scientific discoveries as soon as possible. On the other hand, children should be protected from harms to their health and well-being. These two objectives are partly incompatible.[1] If children are excluded from clinical trials, they will be administered treatments which safety and efficacy have only been tested on adults and which may therefore be hazardous to them. If children do participate in trials, they may suffer the unknown or unavoidable side effects of treatments that may additionally prove ineffective. It is difficult to balance these two concerns, and various countries have chosen

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[1] For a review of the pros and cons of research on children, see e.g., M. Oberman & J. Frader, Dying Children and Medical Research: Access to Clinical Trials as Benefits and Burden, 29 American Journal of Law & Medicine 301 (2003).

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somewhat different rules.[2] In Switzerland, medical research on children is broadly admissible, but with reinforced safeguards.

Jurisdiction over human research is shared among the Swiss federal government and the 26 States (called cantons). Since 2002, clinical research involving a therapeutic product is regulated at the federal level;[3] since July 2007, trials of transplanted organs, tissues or cells follow a similar legal regime.[4] All other kind of health research is presently within the province of the cantons, with some constraints derived from mandatory federal law principles. However, a draft federal law covering the entire scope of human health research is under discussion; it would operate a significant transfer of powers from the cantons to the federal government.

This article will start by analyzing the most *comprehensive* body of current law, *i.e.* the federal law on therapeutic products and its ordinance on clinical trials of therapeutic products. This first chapter will also describe the incentives offered to promote paediatric research.[5] The second chapter will provide a short overview of how *cantons* regulate other health research. The third chapter will explain how the draft law on human research, if implemented, would alter the current situation.

1. Federal Regulation of Clinical Research on Therapeutic Products

1.1. *Overview*

On January 1, 2002, a new federal law on therapeutic products (hereafter abbreviated "LTP") entered into force.[6] Its chapter 4, section 2, (article 53-56) regulates — for the first time at the federal level — clinical trials of therapeutic products.[7] Other research projects (*e.g.*, studies based on data review, epidemiological studies, purely observational trials, studies of surgical procedures, health surveys) are outside the scope of this federal regulation.

[2] For a comparison of Swiss, German and E.U. law, see Franziska Sprecher, Medizinische Forschung mit Kindern und Judendlichen (Springer, Berlin 2007).

[3] The Federal law on therapeutic product (LTP) applies to drugs, medical devices, standardized transplants, blood products, narcotics used for medicinal purposes as well as other therapeutic therapies involving a therapeutic product; *see* article 2 LTP and also article 2 of the Ordinance on clinical trials (abbreviated "OClin").

[4] *See* article 36 and 38 of the Federal law on transplantation, in force since July 1, 2007. However, the Federal Office for Public Health takes on the role of Swissmedic for transplantation trials. *See also* article 1.3. of the Federal law on research with stem cells, in force since March 1, 2005; article 1.3 of the Federal law on human genetic analysis, in force since April 1, 2007.

[5] Research on embryos, foetuses and still-born babies is outside the scope of this article, even though the proposed future Federal Law on human research (abbreviated "dLHR") would regulate it.

[6] For a detailed commentary of the LTP, article by article, see Eichenberger et al., Heilmittelgesetz, Basler Kommentar, (Helbing & Lichtenhahn, 2006).

[7] *See supra* note 3 for the list of products falling within the scope of the LTP.

Before 2002, clinical trials were regulated by the cantons.[8] By convention, the 26 cantons had pooled their regulatory powers and set up a country-wide system of drug regulation.[9] Through an administrative body set up under the convention, the cantons adopted in 1993 the regulation on drugs at the clinical trial stage.[10] That system was replaced in 2002 by the LTP and its ordinances.[11] However, many of the intercantonal provisions were copied into the 2002 federal law and its ordinance on clinical trials of therapeutic products (hereafter abbreviated "OClin").

Furthermore, the LTP and the OClin take into consideration regulatory developments in the European Union, in particular Directive 2001/20/EC.[12] The OClin also incorporates by reference ICH's E6 Guideline on good clinical practices.[13] Finally, several provisions of the federal regulation, in particular the one on paediatric research, were inspired by the Council of Europe's Oviedo Convention on human rights and biomedicine.

Before recruitment of trial subjects can start, a clinical trial must be approved by the competent research ethics committee;[14] the committee must base its opinion on a full examination of scientific and legal documents provided by the investigator;[15] it has 30 days to do so.[16] The committee pays special attention to the clinical research protocol, the informed consent documents,[17] the insurance

[8] For a review of clinical trial regulations in Switzerland *before* the 2002 LTP, see D. Sprumont, La protection des sujets de recherche notamment dans le domaine biomédical, Staempfli (1993), partie III, pp. 183-279; G. M. Zanini, Swiss regulations for controlling clinical trials, 37 Pharmacological Research p. 321 (1998).

[9] The intercantonal convention started in 1900, but did not bind *all* cantons until 1942.

[10] *See* "Règlement de l'OICM sur les médicaments au stade d'essai clinique du 18 novembre 1993", which entered into force in 1995. Article 5 and points 1.13-16 of its annex 1 applied to trials on minors.

[11] For a review of clinical trial regulations in Switzerland *after* the 2002 LTP, see V. Junod, Clinical drug trials, Schulthess (2005); D. Sprumont & M.-L. Béguin, La nouvelle réglementation des essais cliniques de médicaments, 83 Bulletin des médecins suisses pp. 894-906 (2002).

[12] The E.U. Directive is however not applicable — whether directly or by indirect reference — in Switzerland.

[13] *See* article 4.1 OClin. ICH stands for International Conference on Harmonisation. Trials of *medical devices* must comply with by E.U. directives (article 4.2. OClin).

[14] Ethics committees must be endorsed by the cantonal government; joint committees operating for two or more cantons are admissible. The list of the 15 approved committees (not including the subcommittees of university hospitals) is available on Swissmedic's website. Ethics committees reviewing paediatric trials must have members with relevant expertise (article 30.1 OClin), but there are no further guidelines on this topic. *See also* the report by Sprumont, Baume & Neuvecelle, "Réglementation et organisation des commissions d'éthique de la recherche (CER) en Suisse", p. 12 (June 2007).

[15] Articles 9 and 10 OClin. Ethics committees must have internal bylaws (article 34 OClin). They usually set forth their own requirements as to the format and content of the documents to be prepared (e.g., the detailed website of the Bern ethics committee).

[16] *See* article 11 OClin.

[17] The minimal information set to be given to trial subjects is described in article 54.1 LTP. Moreover, Swissmedic has prepared a check-list of information that must be provided (see "File rouge" of August 2005).

coverage policy and, of course, the risk-benefit balance.[18] A clinical trial positively reviewed by the ethics committee must then be submitted to the federal administrative authority created by the LTP.[19] This authority, the Swiss Agency for therapeutic products (commonly called Swissmedic), has powers approximately comparable to those of the American FDA or the European EMEA. Upon submission by the sponsor, Swissmedic reviews essentially the same documents previously evaluated by the ethics committee.[20] If Swissmedic raises no objection within 30 days, the sponsor and the investigator can begin the trial.[21] In 2006, 360 drug trials were given the green light.[22] Both the ethics committee and Swissmedic are supposed to exercise supervision throughout the trial; yet, this supervision is essentially limited to the review of adverse event reports, protocol changes and annual updates.[23] When the trial is completed, the sponsor must provide copy of the study report to Swissmedic.[24]

1.2. *Clinical Research on Minors*

Trials of therapeutic products that involve minors as research subjects follow the same assessment route as summarized above. However, article 55 LTP sets forth additional requirement, mainly pertaining to when such trials are admissible.[25] It applies to three groups of persons: minors (anyone under the age of 18[26]), adults whom the courts have declared legally incapable (judicial disability) and adults

[18] *See* article 7 OClin. Standard insurance documents and explanations are available from Swissmedic's website.

[19] *See* article 13 OClin and its limited exception for medical devices. The cooperation between ethics committees and Swissmedic has been difficult. Despite a 2003 recommendation regarding the collaboration between Swissmedic and cantonal ethics committees, a 2004 Parliamentary intervention (04.3231), as well as a 2004 Parliamentary report on the problems facing Swissmedic (FF 2005 pp. 298-99), there are remaining tensions between Swissmedic and cantonal ethics committees as to their respective scope of powers.

[20] *See* article 14 OClin.

[21] *See* article 15 OClin. Formal authorization by Swissmedic is required for certain risky trials (e.g., trials involving somatic genetic therapy, genetically modified micro-organisms). See articles 16-18 OClin; article 38 of the federal law on transplantation.

[22] Swissmedic, annual report 2006, p. 45 (381 proposed drug trials had been submitted). The 2004-2006 report from the Bern ethics committees states that some 1'500 research projects are conducted each year at the five Swiss university hospitals. Obviously, only a minority of trials have to be submitted to Swissmedic.

[23] *See* articles 19, 20 and 22-24 OClin. According to the Swissmedic 2005 annual report (p. 52), some 2300 changes were received that year. Inspections are possible (article 27 OClin), but infrequent.

[24] *See* article 21.3 OClin.

[25] The OClin contains few implementing provisions. Article 10 OClin does require that ethics committees ensure that *vulnerable* trial subjects are protected; moreover, they should verify whether the inclusion of subjects incapable to provide informed consent is justified and how these people (implicitly competent minors) give their consent.

[26] *See* article 14 of the Civil code.

whose decision-making ability is markedly impaired at the time of the trial.[27] However, this article only focusses on the first group. Article 55 LTP reads as follows:[28]

> **Art. 55** Clinical trials on minors, persons under judicial disability or persons incapable of judgement
>
> [1] Clinical trials on minors, persons under judicial disability or persons incapable of judgement may only be carried out if:
> a. trials on persons of adult age and who are capable of judgement would not produce comparable insights;
> b. if the legal representatives of the trial subjects have given their informed consent;
> c. if persons capable of judgment, but who are minors or persons under judicial disability, have given their consent;
> d. if there is no indication to suggest that persons incapable of judgement would refuse to participate in the trials.
> [2] Exceptionally, clinical trials not bringing a direct benefit to the trial subjects may be carried out on minors, persons under judicial disability or persons incapable of judgement if, in addition to the conditions specified in paragraph 1:
> a. the trials are expected to produce important knowledge concerning the status, illness or suffering of the trial subjects, and if this knowledge would bring long-term benefits for the trial subjects concerned or for persons of the same age group, or for persons suffering from the same illness or presenting the same characteristics;
> b. the risks and the unpleasantness that the trial subjects must endure are minor.

The provision introduces a distinction between two classes of clinical trials: those that confer a *direct benefit* to the minors involved (paragraph 1; sometimes referred to as "therapeutic trials") and those that do not (paragraph 2; "non-therapeutic trials"). Trials belonging to the second class must satisfy additional conditions. Although this is not apparent from the letter of the law, the distinction hinges on the *potential benefits*.

- Trials are viewed as *therapeutic* if they *could* confer a benefit to *some* subjects (for example those reacting positively to the experimental product, as opposed to those on the placebo).[29] Similarly, a trial that compares two active drugs will also satisfy this condition, even if the same benefits can be obtained without participation in the trial. Phase 2 trials that explore the

[27] Decision-making ability is appreciated on the basis of article 16 of the Civil Code and interpretative case law. Children over 15 are ordinarily presumed to be capable of judgment, while children under 10 are supposed to lack it. *See* Groupe de travail "Coordination de l'Evaluation des Essais Cliniques" (GT CEEC), Recherche en situation d'urgence avec des personnes provisoirement ou durablement incapables de discernement, p. 4 (May 2006).

[28] Unofficial English translation, available from Swissmedic's website. Article 55 was modelled on article 17 of the 1997 Convention on Human Rights and Biomedicine. *See also* the Federal government's Message of 1999 (FF 1999 p. 3231).

[29] Ethics committees will nonetheless check that the risks borne by the placebo or control group are minimized.

effectiveness of the experimental product are usually viewed as conferring a direct benefit; phase 3 trials are typically therapeutic. Vaccine trials on healthy patients normally entail direct benefits.

- Without direct benefits are trials that purport to investigate preliminary safety or to select an appropriate starting dose (phase 1), especially if conducted on healthy volunteers.[30] Similarly, trials on patients suffering from diseases that can be neither cured nor improved are nontherapeutic. The psychological benefit of contributing to the progress of research is insufficient to qualify the trial as therapeutic. Similarly, giving trial subjects more attentive health care or general medical check-ups will not suffice.

In practice, this requirement's exclusiveness generates some unease among ethics committees members. In Geneva, the majority of the trials conducted at the public university hospitals (HUG) are classified as therapeutic.[31]

1.2.1. *Trials with Direct Benefit*

Clinical trials with a direct benefit can be carried out if the four requirements of article 55, paragraph 1, are met. The first requirement (letter a) reveals a policy choice: research on minors can take place only if research on competent adults would not produce equivalent results. This is referred to as the "subsidiarity" principle. Its meaning is regrettably ambiguous.

According to one reasonable interpretation, children should be excluded from research if the product's *general* safety and efficacy can be established by trials conducted on an adult population; trials would hence be possible only against diseases affecting children exclusively. Another reasonable interpretation would have the words "equivalent results" refer to *specific* safety and efficacy in a *paediatric population*; trials on children would then be allowed whenever there is a need for better therapeutic treatments in this population.

In practice, a middle-of-the road approach has been retained. Unless the medical condition affects children exclusively, trials are first conducted on adults. Once safety and efficacy on this population are confirmed (large phase 2 or phase 3 trials), research can start on children. Risks and benefits are weighed to determine when paediatric research should begin. ICH Guideline E11 provides helpful advice and Swissmedic has declared it applicable.

[30] In practice, many trials can be hard to classify (e.g., a trial on sick paediatric subjects with a control group made up of healthy children).

[31] The list of all HUG trials approved since 2005 (about 30 every year) is available on-line (http://ethiquerecherche.hug-ge.ch/protocoles_actifs/gynecologie_obstetrique.html). However, most of the HUG trials do not involve a therapeutic product and are therefore outside the scope of the LTP. Based on the trials' titles, 14 out of 81 listed trials involved a drug. The main reason for the small number of paediatric drug trials is the small size of the Swiss population: with 7.5 million inhabitants, recruiting children of different relevant age groups is difficult. Yet, the number of trial subjects enrolled is a key factor determining the statistical significance of the clinical trial results. Hence, drug trials conducted in Switzerland are often part of international multicentric studies. The number of children enrolled at a Swiss research site may therefore be quite small (1 or 2 children).

Once this first hurdle is overcome, the next two requirements of article 55 paragraph 1 are easier to understand and satisfy. The law mandates that the legal guardian of the child (typically the father or mother, depending on who has legal authority)[32] should give his or her informed consent. This consent is obtained in the same manner as if the guardian were the intended trial subject: The investigator and her team will provide a full information package and, once the guardian has had the time to absorb the information, review the documents and ask her questions, the guardian will sign and date the informed consent document.

If the child who is to be enrolled is deemed capable of judgment (based on his age, maturity level and health status), then his own consent must be obtained *in addition* to that of his guardian. Article 55, paragraph 1, letter c, uses the word "consent" (instead of assent), yet does not explicitly require that the child be informed. In practice, whether or not the child is deemed competent, he will receive information adapted to his age and level of understanding. The older he is, the more detailed will be the information. Information in writing is given past a certain age; signed consent is then sought. There is no official guideline specifying the age threshold for oral information, written information and signed forms. At the Geneva university hospitals, children over 12 usually receive written information and sign forms; for cancer research, the threshold may be set at an even younger age. Interestingly, Swiss law allows no exception for teenagers close to adulthood, regardless of the risks or the topic of research (e.g., sexual matters),[33] and even though these teenagers may receive ordinary care from doctors without their parents' involvement.[34]

If the child lacks judgment capacity, his consent is not sought. However, article 55 paragraph 1 letter d states that there should be no sign suggesting that the child refuses participation.[35] This requirement has been criticized as dangerously vague. What exactly is to qualify as a sign of refusal? Is a child crying and adamantly refusing an injection to be excluded from the trial, even though his health

[32] When both parents have legal authority, both should agree to have their child participate; however, the investigator may assume — unless the circumstances indicate otherwise — that the parent who gave consent is acting with the agreement of the other. When legal authority over the child has been awarded to one parent (*e.g.*, after a divorce), only that parent is entitled to give consent. *See, e.g.*, GT CEEC, *supra* note 27, p. 4.

[33] On this topic, see e.g., Sprumont, *supra* note 8, pp. 209-210.

[34] *See* article 19.2 of the Civil code. Hence, without her parent's knowledge and approval, a teenage girl would not be allowed to participate in a trial testing a new contraceptive. When research does not involve a therapeutic product, exceptions to this principle of parental consent are sometimes made in the case of teenagers.

[35] *See similarly* point A.1. of the (usually non-binding) 1997 Directive on experimental human research prepared by the Swiss Academy of Medical Sciences (SAMS). *See however* Mercurio et al., American Academy of Pediatrics Policy Statements on Bioethics, Part 1, 29 Pediatrics c2 (2008).

is to gain from participation? In practice, the provision is not given this severe interpretation: investigators and researchers rather weigh the benefits and the risks of the research and respect the wishes of the parents.[36]

1.2.2. *Trials with no Direct Benefit*

Under Swiss law, non-therapeutic trials are not prohibited, but are subject to two additional requirements. First, *important new knowledge* relevant to the children population must be expected to flow from the trial and this knowledge should lead, in the future, to therapeutic benefits for this population. Second, the *risks* incurred by the research subjects must be *minor*.

The language of article 55, paragraph 2, letter a, reveals the intention of the legislator to encompass as many situations as possible. The new knowledge can pertain to the medical state of the trial subjects, their disease or their suffering. The future benefits may concern the same children who participated in the research, children of the same age group, people (including adults) with the same disease or even people exhibiting the same characteristics. Such broadly outlined benefits could sanction most clinical trials, with the exception of those whose outcomes are viewed as trivial. Once again, in practice, the provision is understood as signalling the need to apply caution. The ethics committee should review carefully the protocol's stated objectives and make sure that the anticipated gains in knowledge are sufficiently worthy.

Even if the trial is to produce vital knowledge, the children enrolled must not incur more than minimal risks and "unpleasantness". There is no list of interventions entailing minimal risks. In its explanatory report, the government indicated that this refers to the risks that a reasonable person would tolerate in the course of ordinary life or of an ordinary medical check-up.[37]

1.2.3. *Trials in a Situation of Emergency*

Article 56 LPTh applies when a trial of a therapeutic product is performed, in a situation of *emergency*, on subjects (adults or minors) who are *not capable* of judgment. These trials must fulfil three additional conditions. First, these trials, even if they are therapeutic, must promise significant new knowledge which will benefit the trial subject or persons in similar situation.[38] Second, they must be supervised by a physician who is not the investigator or part of her team and whose task is to provide medical assistance to trial subjects and to defend their interests. Finally, they must incorporate a process whereby the informed consent of the legal guardian (in case of a minor) is obtained "within a useful time period"; this aspect must be specifically approved by the ethics committee. The last condition is remarkably nebulous.

[36] *See also* point 2.6.3 of ICH Guideline E11.

[37] *See* Federal government's Message of 1999, FF 1999 p. 3232.

[38] This requirement of article 56 letter c is very similar to that of article 55 paragraph 2, letter a, except that the latter applies only to non-therapeutic trials whereas the former applies even if the urgent trial entails a direct benefit.

1.2.4. *Incentives for Paediatric Research*

As is true everywhere, children in Switzerland lack therapeutic products suitable to their needs.[39] Most available therapeutic products have not been scientifically tested on children; their efficacy and security when used on children of various ages are poorly understood.[40] Appropriate dosage forms (e.g., syrups instead of hard-to-swallow pills) may also be lacking. Given the relatively small number of patients (furthermore segmented by age groups), pharmaceutical companies see little profits in investing in paediatric drugs. Besides, companies know that the absence of a paediatric label does not necessarily dampen the sale of their "adult-approved" drugs to minor patients.

Hence, as do other governments, Swiss authorities are looking for ways to bridge this gap in knowledge and products. So far, this task has been devolved to Swissmedic,[41] which employs a mix of pull-push mechanisms.

First, Swissmedic construes article 12 LTP so as to grant *data protection*[42] to sponsors conducting paediatric studies if these lead to a change in the drug's label.[43] As do most countries, Switzerland grants data protection to clinical trial data; data gathered for an entirely new drug application will receive ten years of exclusivity; data gathered for several important changes in the drug label will receive a minimum of three years of protection and a maximum of five years if the change is significant. Pharmaceutical companies may receive either the three or

[39] *See e.g.*, Di Paolo et al., Incidence des prescriptions hors autorisation de mise sur le marché dans le département médico-chirurgical de pédiatrie d'un CHU suisse, poster 2003, Congrès annuel de la Société Suisse de Pédiatrie.

[40] The problem is more serious for the older than for the newer drugs. Nowadays Swissmedic takes pain to include all available paediatric information in the professional drug label (i.e., the notice of use intended for physicians). For older drugs, the label frequently holds no information and may even be misleading. *See* Swissmedic, Information sheet on drugs for children: situation overview ("Médicaments pour enfants : état des lieux") (December 2006).

[41] The government is also trying to improve the social reimbursement of orphan drugs. Presently, public mandatory insurance covers drugs if three conditions are met: the drug has received marketing approval, it was prescribed to the patient *in accordance with its approved label* and it is included in the positive list of reimbursed drugs. Drugs prescribed off-label are sometimes reimbursed under an exception crafted by the Supreme Court.

[42] For the duration of the protection, a generic competitor will not be allowed to refer to the data produced by the company enjoying data protection. The generic competitor must either wait for the end of the period of protection or generate its own data in support of marketing approval (or the change to the initial marketing approval). *See further* D. Bachmann, Der Erstanmelderschutz in der Schweiz und in der EU, 3 Revue suisse de droit de la santé pp. 31-40 (June 2004); decision of the Federal administrative tribunal of November 7, 2007, C-2263/2006.

[43] *See* the Swissmedic information sheet, *supra* note 40; also article 17 of the 2002 Ordinance on drugs.

the five-year exclusivity[44] if they submit paediatric trials that result in the inclusion of paediatric information in their drug's labels (*e.g.*, a paediatric recommended dosage). The exclusivity only encompasses the changes brought to the label.[45] If the trial results show that the drug is *not* appropriate for children, no data protection will be granted.

Second, if a sponsor seeks marketing approval for a paediatric label, it must provide Swissmedic the *same clinical trial data* that it submitted (in support of this same change) to the E.U. or U.S. drug agencies. In other words, to authorize the paediatric change, Swissmedic wants to review the same clinical trials that its counterpart agencies reviewed. Thus, Switzerland will benefit from the information generated thanks to the more extensive incentives offered by the European Union and the United States.[46]

Third, when a drug targets a rare disease (i.e., a disease affecting 5 or less patients out of 10'000 people in Switzerland), it can receive marketing approval following the *simplified* pathway created for orphan drugs.[47] This procedure is available both for drugs against diseases affecting children exclusively and for already-approved drugs seeking a paediatric indication. Sponsors of drugs awarded orphan status may be exempted from the payment of reviewing fees.[48] They may also request Swissmedic's scientific guidance so as to better plan their preclinical and clinical studies.[49]

Fourth, Swissmedic encourages pharmaceutical companies to submit applications for paediatric labels. To maintain international harmonization, it has espoused ICH Guideline E11.[50] However, Swissmedic considers that it cannot *force* companies to submit such requests or to initiate paediatric trials.[51] Hence, if a company refuses to provide paediatric data, its drug may nonetheless be approved for adult-only patients.

Finally, Swissmedic is pondering the need to adapt the current legislative framework to further encourage paediatric research, in particular through incentives akin to those of the European Union and the United States. However, nothing has happened so far. Moreover, Swissmedic's public statements on the matter remain timid. Apart from its December 2006 press release, Swissmedic is not actively raising the issue among the public. For example, its website contains no section on children's medicines. Parents and physicians can search in vain for a list of paediatric drugs or paediatric clinical trials.

2. Research not Involving a Therapeutic Product

When research is not aimed at ascertaining the properties of a therapeutic product, it is *outside the scope* of the Federal Law on Therapeutic Products (LTP). In Switzerland, most research projects — whether on adult or paediatric subjects — fall in this category, even though there are no official statistics on the number of health research projects performed in Switzerland, nor on the number of paediatric projects. Clinical trials in Switzerland are hampered by the relatively small size of the population (7,5 million), making recruitment of children even more difficult.

Cantons can enact their own standards to govern research taking place within their borders.[52] They must abide by principles of federal law that essentially mandate informed consent.[53] Most cantons have adopted short statutes applicable to health care and medical research;[54] a few cantons have not updated their statutes following the entry in force of the LTP. About a third require compliance with good clinical practices; four cantons declare the LTP and the OClin applicable by analogy to all human research projects. Statutes rarely distinguish between adult

[44] In a 2002 document titled "Enfants et médicaments: quelle sécurité?", Swissmedic has attempted to clarify when paediatric changes deserve the five years of data protection.

[45] If a generic drug is already available for adults, it may not include the paediatric label approved for the original product until the specific data protection period is expired. Nonetheless, physicians could write off-label generic prescriptions for children.

[46] In the United States, a company can receive a six-month patent extension if it conducts paediatric studies and provides the corresponding reports to the FDA; this incentive has proven remarkably effective. In 2007, the European Union retained a similar system, drugs which are studied in children become eligible for a 6-month extension to their supplementary protection certificate (article 36 of Regulation 1901/2006 of 12 December 2006 on medicinal products for paediatric use; also article 37 for orphan products).

[47] Articles 4-7 and 24-27 of the 2006 Ordinance on the simplified authorization of drugs (abbreviated "OASMéd").

[48] Article 7 of the Ordinance on the fees perceived by Swissmedic; *see also* Swissmedic, *supra* note 40.

[49] Article 25 OASMéd.

[50] *See* Swissmedic, Instructions regarding the presentation of marketing applications for human drugs containing new active substances (December 2006).

[51] One could nonetheless argue that article 3 LTP is sufficient to compel companies to take all necessary measures to prevent harm to human health; in my view, this obligation should encompass providing clinical information to physicians about newly-identified dangers of paediatric (off-label) use.

[52] For trials involving a therapeutic product, cantons cannot enact laws that contradict the LTP and the OClin. It is unsettled to which extent they may adopt laws that contain more severe requirements. *See also* the report cited *supra* note 14, pp. 8-9; Sprumont & Béguin, *supra* note 11, p. 901.

[53] The few *applicable federal* statutes basically require informed consent and carve out exceptions. *See e.g.*, article 321 (physicians' duty of confidentiality) and 321bis (researchers' duty of confidentiality) of the Penal Code; the Federal law on data protection (applicable whenever data on a person are systematically gathered). Article 321bis of the Penal Code is complemented by the Ordinance of 14 June 1993 regarding the authorizations to lift professional secrecy for medical research. Under these regulations, exceptions to the principle of informed consent can be made for important gathering and analysis of patients' personal data. For example, a disease register, such as the childhood cancer registry, can be created and used for research on the basis of patients' *presumed* consent.

[54] Six cantons still refer to the former intercantonal regulations. Furthermore, six cantons declare applicable the (otherwise non-legally binding) SAMS Directive (cited *supra* note 35). *See, e.g.*, article 1.c) Geschäftsordnung der Ethikkommission des Kantons St-Gallen. For a review of the cantonal provisions on paediatric research, see Sprecher, *supra* note 2, pp. 139-153.

and paediatric research;[55] if they do, it is to reiterate the requirement to obtain the guardian's informed consent. However, two cantons have copied nearly *verbatim* the requirements of article 55 LTP. Moreover, two other cantons have imposed further restrictions on paediatric research.[56] Finally, and as can be expected given the wide leeway enjoyed by ethics committees, cantonal *practices* may vary.

3. The Future Law on Human Research

3.1. *Overview*

The lack of a comprehensive *federal* regulation of all biomedical research has long been viewed as undesirable. Therefore, in 2000, the federal government initiated a project for a new federal law on human research (dLHR), along with a change to the Federal Constitution.[57] The dLHR should apply to research on human beings, personal data, human tissues, foetuses, embryos and even still-born babies.

The draft law, the constitutional clause and their explanatory reports were first submitted for public comments in spring 2006.[58] No clear consensus emerged from the consultation: some viewed the law as being overly restrictive, while others found it too lax.[59] To incorporate some of these comments, the federal government has brought changes to the constitutional clause and will also modify the dLHR. The proposed constitutional clause is now before Parliament,[60] whereas the draft law is to be submitted to Parliament in Fall 2008. Given the length of the parliamentary process in Switzerland, a new law is unlikely to become effective before 2011. When it does, it should supplant the corresponding provisions of the LTP and the OClin.

[55] *See* C. Baume, A. Neuvecelle & D. Sprumont, Législation cantonale en matière de recherche impliquant des êtres humains (March 2007). The authors have reviewed and summarized all cantonal laws regarding research. The document is available from the website swisethics.ch.

[56] The Canton of Schaffhausen forbids nontherapeutic studies on incompetent subjects (article 5.3 of the 2002 "Verordnung über Heilversuche und wissenschaftliche Versuche am Menschen"); the canton of Ticino seems to forbid nontherapeutic studies on all minors (articles 11 and 12 of the "Legge sulla promozione della salute e il coordinamento sanitario").

[57] The constitutional amendment transfers subject matter jurisdiction from the cantons to the federal State.

[58] The draft law of February 2006, its accompanying report, the draft constitutional clause, its accompanying report are all available from the website of the Federal Office for Public Health.

[59] A report summarizing the comments received is available on the web site of the Federal Office for Public Health.

[60] The proposed new article 118a of the Constitution and its explanatory report by the Federal government (FF 2007 pp. 6345-6387) were submitted to Parliament in September 2007. Parliamentary debates have not yet started.

3.2. *Health Research on Minors*

With regard to paediatric research, the dLHR resembles the LTP. The subsidiarity principle is retained, and even highlighted by way of repetition.[61] The distinction between research with or without direct benefit is kept.[62] Research on minors *lacking* judgment is regulated likewise, except that the legal representative (guardian) is no longer the only one entitled to give informed consent: relatives ("*proches*") may also do so.[63] Contrary to the LTP, research on minors *capable of judgment* would be possible on the basis of their sole consent if two conditions are satisfied: the research entails a direct benefit and the risks and inconveniences of the research are minimal.[64]

The most significant change brought by the dLHR would be the extension of the rules applicable to drug trials to most, if not all, health research. Health projects which are not biomedical (e.g., research in sociology, psychology, economy with no medical intervention) would become subject to ethics committees' review and oversight.[65] Regrettably, the draft law lacks a *de minimis* exception.

4. Conclusion

Switzerland authorizes paediatric research while incorporating safeguards to protect vulnerable populations. The implementation of these safeguards is largely delegated to ethics committees, and to a lesser extent to the investigator and her team. Incentives to encourage paediatric research exist, but are significantly less generous than in the United States or the European Union. The draft federal law would slightly alter the regulatory framework, mostly by extending the LTP principles to all kinds of health research. Importantly, the draft law would also introduce a central register;[66] having a public Internet database of ongoing and past trials is likely to bring considerable benefits to the many stakeholders involved in paediatric research.[67]

[61] *See* Articles 17 and 20 dLHR.

[62] Articles 18 and 21 apply to research with a direct benefit, whereas articles 19 and 22 govern research without a direct benefit. The requirement that non-therapeutic research on individuals *lacking judgment-making capacity* only entail *minimal risks* would be set in the proposed new article 118a of the Constitution.

[63] "Close relatives" are mentioned because Articles 18 and 19 of the dLHR apply *both* to children and adults lacking decision-making abilities, and incompetent *adults* often do not have legal guardians.

[64] If the risks and inconveniences exceed this low threshold, the legal guardian/close relation must give her consent. The legal guardian/close relation must also give her consent when the research has no direct benefit; moreover, in that situation, the risks and inconveniences must also be minimal — as is already required by the LTP for clinical trials of therapeutic products. The explanatory report of February 2006 (p. 91) gives examples of medical and non-medical interventions carrying only minimal risks.

[65] *See* article 56 dLHR.

[66] *See* article 72 dLHR.

[67] Switzerland has a central register for paediatric *cancers*, but this register is not public and does not list all ongoing or completed trials (see the website of the Swiss Childhood Cancer Registry).