

## Research Integrity: **Selling the Stem Cell Dream Stopped in the Netherlands** Telegraaf Fall 2006

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### **1. Introduction**

Several companies offer "stem cell therapy" for a multitude of diseases, like MS, or conditions, like paralysis after an accident, on unproven scientific evidence and with unproven results. These 'therapies' are offered outside the normal health care system, meaning in private clinics and without reimbursement from the health care insurance system. This is – by the way - not unique for stem cell "therapy". Many so called 'alternative therapies' are being administered outside the normal health care system to often desperate cancer patients without proven efficacy or even safety.

In this report we will first address the possible regulatory approach for unproven stem cell therapy at the European level. Next we will address how the Dutch government has reacted when it became clear that two Dutch private clinics were particularly involved in selling this stem cell dream.

### **2. European loopholes**

First, some background on the European regulatory environment. The European Community can only legislate on points, which have been specifically assigned to it. The health care system as such is excluded from this attribution of competences (art. 152 EC Treaty, ECT). However, section 4 of art. 152 did make the EC competent on measures by which high quality and safety standards are set for organs and tissues and of blood and blood-components of human origin. The quality standards for human organs and tissues have been set in Directive 2004/23/EC, recently followed by Commission Directives 2006/17 EC and 2006/86/EC. Earlier the EC regulated blood and blood components in several Directives, most notably Directive 2002/98 EC. These Directives do not regulate therapies. They only stipulate that if human tissue or blood (components) is used, these will have to be in accordance with certain safety standards, most of all the absence of transmittable pathogens from the donor.

The EC and the former EEC (European Economic Communities) has issued an extensive and complicated body of legislation regarding pharmaceuticals. The basis of this legislation is again not therapies, but neither is it safety as such. The legal rationale comes from art. 28, and following ECT, the free trade of goods within the community. Free trade would be seriously hampered if the market approval of a medicine in one country would not be valid in another EC country. Therefore the EEC could intervene with harmonising measures. Once it intervenes with such harmonising measures they should be set at a high level of health protection (art. 95.3 ECT).

So in spite of all the emphasis on safety and efficacy of medicines, free trade within the EC countries is the basis of these regulations. This can be clearly seen from Directive 2001/83/EC and its following amendments. Medicinal products have always been defined broadly in the European pharmaceutical Directives. However, medicines which are prepared in the pharmacy for a particular patient (so called 'magistral formula' and 'official formula' medicines) are excluded from its scope (art. 3.1 and 2 of Directive 2001/83/EC). There is no cross border, so free trade aspect involved in these medicines and the community would not have been legally competent to regulate this issue.

The proposed Regulation on advanced therapeutic medicinal products again intends to regulate the products, and its market authorisation, but not the therapies as such, for which these products could be used

Directives must be implemented in national legislation.

Depending on the origin and nature of the Directive, the national legislator may set higher safety standards than those which are set in the European Directive. This can be the case with the tissue and blood Directives, which set minimum standards. The European pharmaceutical legislation is meant to be all-inclusive and there is no room for higher national standards. National pharmaceutical legislation can of course regulate what is not regulated in the European pharmaceutical legislation, like the safety around magistral and officinal medicines. However, the legislation will usually follow the European definition on medicinal products. Whole blood, plasma or blood cells fall outside the scope of the European pharmaceutical legislation except for blood plasma which is prepared by a method involving an industrial process. For that reason, a 'stem cell brew' which is often made for a particular patient usually escapes national pharma legislation. The national implementation of the blood Directives would also not be applicable as these exclude stem cells (art. 2.4 of Directive 2002/98/EC).

The 'stem cell brew' does fall under the tissue Directive 2004/23/EC and its national implementation. That Directive encompasses nearly everything where human tissue or cells are used, except when this would be regulated by another Directive. The tissue Directive holds other exemptions as well. The exemption for 'solid organs as used in organ transplantation' is not relevant here. The exemption for the autologous graft which is used in the same procedure where it is taken out, could be relevant in other circumstances, however, the alternative stem cell clinic seem to use other methods. The tissue Directive therefore also applies to stem cells or putative stem cells. However, safety and quality in the context of that Directive means that the process from procurement until preparation should be safe, in the sense of the absence of contamination and preparation in an appropriately competent laboratory. There is nothing in the Directive that prescribes that the prepared cells must be safe in the sense of achieving the intended therapeutic effect and not an unintended effect, like uncontrollable proliferation of the transfused stem cells. As the Directive sets minimum standards, member states may set higher standards. However, this will usually be done in the context of regulating certain therapies, not the tissue establishment and the quality chain from procurement to preparation, which is regulated by the Directive and its national implementation. We will come back to that in the context of the Dutch regulations. It might be argued that this 'therapy' is experimental and therefore is regulated by the European clinical trials Directive (2001/20/EC). Two remarks about this point: First, this Directive only regulates the upstream development of a medicinal product in the sense of the pharmaceutical Directives. If the product is not intended to be a medicinal product it would fall outside the scope of this Directive and its national implementation. However, most European countries have legislation on medical trials, which have a much less limited scope. But here comes the second, and more important, point. This stem cell 'therapy' is not offered as being experimental at all. It is offered as 'new' and 'promising', but not as being in the very early stage of development. The paradoxical situation exists that when conscientious researchers try such therapies, these researchers will adhere to the strict regulations of medical trials but when such therapies are administered on patients on the basis of unproven theories, they seem to escape nearly all regulation. It goes without saying that these private companies, which sell

bogus therapies, are even less likely to adhere to international recommendations without binding force.

#### **How did the Dutch authorities react?**

Though it took some time, the Dutch authorities took adequate measures, based on two legislative instruments. Both are typical for the Dutch health care system but interesting enough to discuss in this context.

The first is the Act on health care establishments. Originally the scope of this Act was limited to establishments offering health care within the social health care insurance system. After incidents with 'alternative' cancer clinics the scope of application was broadened and also 'alternative' clinics like these stem cells clinics fall under it. The Act does not give detailed instructions as to how a health care establishment should be organised and neither are there by-laws on how to do so. It basically says that a clinic or hospital should have a quality system compatible with the standard for the procedures concerned. If the Inspectorate for Health concludes that a clinic fails, it may – as an ultimate resort – issue an administrative Order to which the clinic should comply. Mainly this Order involves that the clinic should terminate certain activities or close the department concerned. If the problems are not resolved within the time mentioned in the order, the Minister of Health may continue this order for a longer period. The Inspectorate found that one of the clinics did not comply with the safety standards for handling human tissue, which had been laid down in Dutch law which was in force already before the arrival of the EC tissue Directive. Hence it issued the order to stop these activities immediately. As this order should be able to withstand the possible challenge by the clinic before a Court, it took some time to finish the investigation leading to the order. During this period, the Inspectorate sent a letter to patient organisations concerned. This letter warned them that the stem cell 'therapy' offered by private clinics is not based on proven scientific evidence and might even be dangerous. At the same time the Inspectorate conceded that patients are free to make use of certain therapies, even if unproven.

This is one of the more interesting underlying points in the discussion. Should government 'only' protect against unsafe treatment, or should it be more paternalistic and should it prevent that treatments are being offered which – even if they are safe – do not offer any benefit either?

The safety of whole procedure leading to the stem cell 'therapy' of the private clinic, which was investigated by the Inspectorate of Health, could not be proven. That ended the discussion for this clinic at that point.

Before the termination of this order, the Minister of Health issued a Decree based on the Act on special medical treatments.

This Act is a type of safety valve for the admission of therapies in the Dutch health care system. Based on this Act, the Minister of Health may forbid certain treatments or designate who may administer it and under what circumstances.

Originally, the predecessor of this Act had a mere financial goal. Special medical treatment meant especially expensive medical treatment. But the scope has been expanded and, at this moment, also encompasses ethical and quality control aspects (concentration in certain specialised medical centres) which make intervention necessary in the rather liberal Dutch regime of controlling medical treatments.

On the 25th of October 2006, the Minister of Health used this Act to put a ban on stem cell therapy unless it would be offered at a university hospital or the National Cancer Institute in the context of an approved medical trial. The explanatory notes emphasise that mainly the possible negative side effects of stem cell therapy, like unintended proliferation of the stem cells, were the reason behind this measure.

## Conclusion

For a ban on unproven stem cell 'therapy' help will not come from above, in such cases the European Union. Safety standards can be based on European legislation, but it is the national legislator who must do the trick when regulating therapies.

The Dutch system is not based on the principle 'every therapy is forbidden unless approved' but rather on the contrary. Within the normal health care system, this works, as there are many safeguards in that system against offering unproven therapies. Originally the government was empty handed when unproven stem cell 'therapy' was offered by alternative clinics. That loophole has been cut off.

However, clinics could still be based in a country with much less regulations and offer their services to desperate patients in Western countries. A total ban on such advertising would easily contravene the freedom of expression and would also be very difficult to control in the Internet age. The main challenge for physicians and researchers in our opinion is to show the same kind of compassion to those patients as seems to be shown by those alternative clinics, not only to listen to and to truly understand their fears and hopes but also to respond with a realistic story at the same time. Apart from contacts with individual patients, more contacts with patient organisations could be useful in fostering a high ethical standard in the delivery of novel therapies. Usually physicians and researchers wait for their patients. We would suggest that this case would be better served if patient organisations were invited in order to form an alliance to achieve these standards and to communicate clearly to the patients concerned.