



The Legal Implications of Phase I Clinical Trials

Anthony Warnock-Smith, Partner and Head of the life sciences group at the London office of Morgan Lewis examines the future role of Phase I clinical trials in the light of the recent disastrous TeGenero experience



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Phase I clinical studies in healthy volunteers are, from a legal perspective, inherently problematic – a fact that was illustrated recently by the life-threatening side-effects experienced by the six healthy volunteers who took part in the now infamous TeGenero Phase I trial of its monoclonal antibody product, TGN1412.

Phase I studies are never without risk, largely because the medicine being tested has, at that stage, only been tested theoretically and in animals. Despite this, there has only been a small level of personal injury among Phase I volunteers since current legal and clinical practice procedures were introduced in the 1970s, including just one recorded death.

The severe reactions of the volunteers in the TeGenero trial are thought to have occurred because the type of drug being tested – a monoclonal antibody which is a form of biological medicine – was designed explicitly to target a specific human protein. The prior animal tests that were conducted using the drug revealed no drug-related adverse events, probably because the artificial antibodies in the drug were designed to latch onto human protein only.

The failure of TGN1412 is a significant blow for what has been regarded as one of the most promising sub-categories of the relatively new monoclonal antibody class of drugs, and could have negative implications for development within this drug category, which is thought to show potential in the treatment of diseases such as cancer, immune and inflammatory disorders. Beyond the potential set-back of this sub-category, the TeGenero incident is likely to have even greater consequences for clinical trials in general, because it has caused the pharmaceutical industry and the regulatory

authorities in the EU to revisit the safeguards put in place for Phase I studies.

Presently, the legal obligations that concern clinical trials in the EU are governed by EU Directive 2001/20/EC (the 'CT Directive'), which has been implemented into national laws in the member states of the EU. The CT Directive requires sponsors of clinical trials to ensure that such trials are conducted in accordance with the international principles of good clinical practice. Interestingly, it brought Phase I studies in the UK into the regulatory regime for the first time.

In addition, the CT Directive dictates that a clinical trial may be conducted only if the foreseeable risks and inconveniences have been weighed against the anticipated benefits to the trial participants and future patients, and that the trial subjects have been adequately informed of the risks, inconveniences and objectives of the trial and have given their informed consent. It also requires clinical trial sponsors in the EU to have safeguards in place with respect to personal data, and these must be in line with EU data protection laws and make provision for insurance or indemnity to cover the liability of the sponsor and investigator.

Complementing the CT Directive is the recently implemented GCP Directive (Directive 2005/28/EC). The CT Directive specifically requires the adoption of principles of good clinical

practice, and GCP Directive was introduced in late 2005 to respond to this requirement. In addition to setting out detailed guidelines in line with those principles, the GCP Directive also sets forth the minimum requirements for authorisation of the manufacture or importation of investigational medicinal products as well as detailed guidelines on the documentation relating to clinical trials to verify their compliance with the CT Directive.

The GCP Directive requires clinical trials to be conducted so that the rights, safety and wellbeing of trial subjects prevail over the interests of science and society. It further requires each individual involved in conducting a trial to be appropriately qualified and the trial itself to be scientifically sound and guided by ethical principles. Such non-clinical and clinical information on an investigational medicinal product as is available must be adequate to support the proposed trial, and the appropriate manufacturing and import authorisation for the investigational medicinal product must be in place. According to the GCP Directive, sponsors may delegate any or all trial-related functions but, in such cases, the sponsor remains responsible for ensuring that the conduct of the trials and the final data generated by those trials comply with the CT and GCP Directives. The TGN1412 study was managed by the well-known CRO, Parexel.

Finally, the GCP Directive requires trials to 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 in 1996 (the 'Declaration of Helsinki'). This statement of ethical principles provides guidance to physicians and other participants in medical research involving human subjects for the protection and safety of people and sets forth a number of basic principles that govern the conduct of clinical trials, together with some additional principles for medical research combined with medical care.

The CT and GCP Directives are further complemented by a number of guidance notes produced by the EU, the European Medicines Agency, and the regulatory bodies in each member state. Although such guidance notes are not binding for

sponsors, it is commonly accepted that adherence to the procedures and recommendations set forth in them will ensure compliance with the legal requirements set out in the Directives.

Most of the guidance notes produced by the regulatory bodies in the EU are based upon or reflect the recommendations of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH brings together the recommendations of regulatory authorities in Europe, Japan and the US and experts from the pharmaceutical industry in the three regions relating to scientific and technical aspects of product registration, including good clinical practice.

As the above summary indicates, the EU has enforced a comprehensive set of rules that govern the conduct of clinical trials within its borders. In light of the TeGenero incident, the question is whether these rules are sufficiently rigorous.

There has been much criticism from the pharmaceutical and scientific community as to the manner in which the TeGenero trial was carried out – namely that it was conducted so soon following the discovery of the antibody (approximately less than one year after it was discovered, and thus before any other results on the same compound that might have revealed a problem were carried out), and that, as this was the first time it was tested in humans, it should have been tested in only one volunteer to begin with to monitor the reaction, instead of simultaneously in six.

Such criticisms are only one element of the aftermath of TeGenero. In terms of continuing work in the monoclonal antibody field of medical research, there has been some suggestion that the industry must look to other, laboratory-based approaches instead of risking clinical trials. Beyond this, in terms of impact on the regulatory and legal rules governing clinical trials in the EU, there been some suggestion that biological medicines (of which monoclonal antibodies are a key subgroup) should be subject to separate clinical trial guidelines drafted specifically with them in mind.

In response to the TeGenero incident, an Expert Scientific Group was set up by the UK health secretary to assess the suitability of the present laws covering clinical trials. The Expert Scientific Group released its interim report in July 2006. Consultation by interested stakeholders in relation to it closed in September and it is anticipated that the full report will have been released by the end of last year.



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The interim report contained a number of recommendations, including the following:

- ◆ In drug trials of this type, the first dose should be given to one person only, leaving sufficient time for any adverse reaction to develop before further doses or administration to more people
- ◆ In some circumstances, and particularly if the drug is to affect the immune system, first studies may more appropriately involve patients being treated for the disease rather than healthy volunteers
- ◆ Earlier dialogue between the drug developer and regulator in the case of higher risk agents to allow thorough review of safety data
- ◆ Better international sharing of information about serious adverse reactions to drugs in trials
- ◆ The development of specialist centres to undertake Phase I studies on higher risk agents

How these recommendations are translated into actual changes to the current legal system, or guidance concerning clinical trials, remains to be seen. However, no doubt the final report of the Expert Scientific Group will be carefully considered by the EU regulatory authorities and the volunteers' legal advisers.

A key implication arising from the particular set of circumstances surrounding the TGN1412 study is how any legal liability for the injuries suffered by the volunteers works out. The immediate and obvious target for legal claims is the study sponsor, but it is by no means clear to the outside observer that, assuming the injuries suffered were caused by the study drug (and that, in principle, would have to be proved by the claimant), any liability at all will have accrued notwithstanding the serious injuries incurred. A claim would have to be based on the legislation on defective products or in negligence or, perhaps even, breach of contract. Although the law on defective products does not require the claimant to show that the injuries were anyone's fault in the sense of negligence, the very essence of the 'defectiveness' which has to be shown is defined by the safety expectations which the consumer of the product (the volunteer) was entitled to have. It must, therefore, be open to a sponsor in such circumstances to defend any claim by arguing that in a Phase I study the volunteer's expectation of safety was conditioned and informed by the experimental nature of the drug and all of the explanations which, under the CT and GCP Directives,

must be given to any participant in a clinical trial as well, of course, to the fact of his having given consent on an informed basis.

The alternative form of claim, based in negligence, would require a claimant to prove that the study was designed or performed negligently regarding the body of knowledge possessed by experienced medical and clinical trial professionals operating in the pharmaceutical clinical environment – and that is by no means an easy legal burden to discharge. If the sponsor company itself were not experienced in conducting clinical studies on its drugs it must engage the services of an internationally known expert clinical trials organisation for that purpose.

The pharmaceutical industry in the UK has promulgated two sets of clinical trial compensation guidelines: one for trials involving healthy volunteers and one for studies on patients. Although there are differences between the two sets of guidelines, in broad principle they recommend that sponsors agree to a simple and expeditious procedure for the provision of compensation for injury caused by participation in clinical trials and that notwithstanding the absence of legal liability the company should pay compensation to study subjects suffering injury or death. Until now, the level of claims received or payments made to these guidelines has, in relation to Phase I studies, been remarkably low.

However, the seriousness of the injuries in the TGN1412 study were, apparently, such that the guidelines (if applied to the particular sponsor and study) could be severely tested even though no sponsor is bound by law to follow them as such unless they have been incorporated into some form of contractual arrangement such as the clinical trial agreement, which is usually made with the particular institution at which the study was conducted.

It seems clear that changes are necessary to take into account the major advances in scientific and medical research that are leading to completely new categories of potential medicinal products and treatments for diseases. In the meantime, the TeGenero incident is likely to lead to closer scrutiny of clinical trial applications in the EU and companies wishing to conduct studies on biological products in particular may find themselves subject to a number of additional recommendations and conditions based on the above conclusions. ◆

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