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The Society for Clinical Trials opposes US legislation to permit marketing of unproven medical therapies for seriously ill patients

Society for Clinical Trials Board of Directors

On 3 November 2005, US Senators Brownback and Inhofe introduced proposed legislation, U.S. Senate Bill S.1956, to modify the system by which new drugs, biological products and devices are considered for marketing approval by the Food and Drug Administration (FDA). Entitled the "Access, Compassion, Care and Ethics for Seriously Ill Patients Act", the Bill seeks substantial changes, primarily with respect to drugs that are intended for use by a patient whose physician has documented that the patient has exhausted all approved treatment options. The Bill would permit (Tier I) marketing approval on the basis of data from a Phase I trial and other supporting evidence.

The Society for Clinical Trials is a non-profit organization committed to the development of appropriate and reliable study designs for conducting tests on drugs or devices to be used in patients. It was founded in 1978, and its membership consists of representatives of academia, the pharmaceutical industry and the government, with a scholarly journal entitled *Clinical Trials*. As a society we are greatly concerned about the proposed legislation and its potential for substantial adverse effects on the public's health in the event that it becomes law. The following statement expresses the collective and unanimous view of the Society's Board of Directors.

Essential features of the Bill

The Bill is directed primarily towards expedited access to investigational drugs for patients who have "exhausted all treatment options approved … for the condition or disease", based on the premise that the "current standards of the Food and Drug Administration for approval of drugs … deny the benefits of medical progress to seriously ill patients who face morbidity or death from their disease". The Bill proposes Tier I marketing approval after Phase I clinical testing in these settings. Recognizing that Phase I trials are not designed to establish efficacy, approval is also to be based on "preliminary evidence that the product may be effective", using evidence based on "case histories, information about the pharmacological mechanism of action, data from animal and computer models, comparison with historical data, or other preliminary information, and may be based on a small number of patients". Subsequent Tier II approval is to be based on data demonstrating that the drug "has an effect on a clinical endpoint or on a surrogate endpoint or biomarker that is reasonably likely to predict clinical benefit". The sponsor is required to conduct post-marketing clinical investigation to obtain Tier III approval, which is based on existing regulations. This is facilitated by the requirement that these seriously ill patients, "as a mandatory condition of receiving the product", must provide "consent for the manufacturer … to obtain data … about the patient's use of the product". Patients must also provide "a written waiver of the right to sue the manufacturer or sponsor" in order to receive the treatment.

The decision to approve a drug at Tier I is to be "primarily based upon clinical evaluation, not statistical analysis". The Secretary is instructed to make the decision regarding approval based on the "totality of the information … regarding the safety and effectiveness … as compared to the risk of morbidity or death", and is instructed to "approve

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the application" if there is "more benefit than risk". Although the proposed legislation would restrict the need for clinical testing for marketing approval to Phase I data, there are seemingly gratuitous additional regulations. Notably, the Bill prohibits the use of "placebo-only or no-treatment-only concurrent controls in any clinical investigation conducted under this chapter … where reasonably effective therapies exist for the specific indication". Also it is stated that the Secretary "shall give equal weight to clinical judgment and statistical analysis in the evaluation of the safety and effectiveness of drugs … and shall not disapprove a product application solely on the basis of a statistical analysis or rigid use of the 95% confidence level convention".

Why should a seriously ill patient not have access to an experimental drug?

The goal of the Bill is to provide access for desperately ill patients to experimental treatments that may offer hope of saving the patients' lives. The language of the Bill gives the impression that the primary impediments to such access are bureaucratic obstacles, an unconscionably slow approval process, and the over-reliance on excessively conservative (statistical) criteria for approval. Why should a patient who has exhausted all other treatment options be denied the chance to try an experimental treatment even if it has not yet been determined to be effective? The answer is that the approval process advocated in the Bill is not in the best interests of the patients. To see this we need to contemplate what would happen if the Bill becomes law. First we must recognize that the proposed new hurdle for approval is a very low one. Sponsors would only need to complete a Phase I trial to establish a reasonable estimate of a tolerable dose, and to obtain preliminary information about side effects. They then would need to demonstrate using preclinical data that the promise of clinical benefit exceeds the likely risks. However, every drug that reaches Phase I testing looks promising from a preclinical perspective: otherwise its sponsor would not have selected it for testing in patients. By this yardstick, many hundreds of anti-cancer drugs have had preliminary hints of benefit. However, it is *not* the case that most experimental agents for desperate illnesses actually work and that only regulatory bureaucracy inhibits their availability to the public at large. Rather, the unfortunate reality is that there are only a handful of breakthrough agents among the hundreds under development at any one time. The large majority of drugs ultimately fail to reach the market, the principal reasons being toxicity or lack of efficacy. Among drugs that reach the stage of being tested in patients in large pharmaceutical companies only 11% are ultimately approved: the success rate is 20% in cardiovascular disease but only 6% in cancer. Even among cancer drugs that pass Phase I testing, only about one in 10 are ultimately approved [1]. Clearly, if the proposed Bill becomes law, large numbers of these drugs will be made available, very few of which will actually be effective, with some substantially harmful.

As a result, the seriously ill patient will not simply be given the chance to try one more promising experimental therapy as the proposed Bill implies, but instead will very likely be faced with a large pharmacopeia from which to choose, with the vast majority of the choices being ineffective or harmful drugs, and with no good evidence on which to base the choice. This is not a desirable outcome, and it is a major reason why many patient advocacy organizations, such as the National Breast Cancer Coalition through its advocacy of clinical trial participation [2], and the Treatment Action Group (TAG) [3] for AIDS research through its advocacy of "sound regulatory policy … which balances the need for access to new agents and the need for reliable information about their clinical efficacy", are supportive of rigorous clinical testing of new drugs.

Need for an evidence-basis for drug approval based on rigorous scientific testing

As a Society devoted to evidentiary quality in clinical testing, we are concerned at a fundamental level about the repudiation of the scientific method that is embedded in the Bill. The sponsors of the Bill are correct that the regulations surrounding drug approval by the FDA are rigorous, and may be perceived as burdensome or challenging to the pharmaceutical industry. However, there are good reasons for the rigor in the approval process, based on decades of experience in the careful testing of new and existing approaches to the treatment of serious diseases. This long history of drug testing provides overwhelming evidence that the most reliable data for assessing efficacy is that obtained from prospective randomized clinical trials that are sufficiently large to establish efficacy at levels of conclusiveness that are broadly accepted by the scientific community. It is curious that the Bill's authors do not mention the randomized trial specifically, given its frequent requirement for full FDA approval. However, the specific proscription of "placebo-only or no-treatment-only concurrent controls" in clinical investigations "where reasonably effective therapies exist for the specific indication" would appear to be a direct repudiation of the randomized

trial, given that the Bill is ostensibly restricted to patients who have "exhausted all treatment options".

Many people feel instinctively uncomfortable with the idea of giving placebos to patients suffering from serious illness, or indeed with randomization as a means for determining what treatment to administer. This is a concern of doctors as well as patients. The critical importance of randomized trials in separating genuine advances from the optimistic expectations of clinicians, patients, and industry sponsors is something that most doctors only learn by experience. History demonstrates that it is not uncommon for investigational drugs to actually be shown to be inferior to placebo treatment. A prominent recent example is the study of the drug CTNF (Regeneron Inc.), designed as a treatment for the crippling and inevitably fatal disease amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) [4]. This agent was brought to clinical testing on the basis of preclinical evidence that it could stimulate nerves to regenerate. In fact the trial had to be stopped early because the drug was having the opposite of the hoped-for effect – it significantly reduced patient weight and strength, adverse outcomes that could only be determined by using a placebo-controlled study. Similarly, in the 1980s it was widely believed on the basis of observational studies that arrhythmias were predictors of risk of death from a heart attack. A class of antiarrhythmic agents emerged that was shown convincingly to reduce arrhythmias, and was presumed to reduce mortality. However, when a definitive placebo-controlled randomized trial was conducted to confirm the effects on mortality (the CAST study) [5] the drugs were shown to significantly increase the risk of death.

The sponsors of the Bill have confidence in evidence about drug efficacy that is obtained from comparisons that are not based on randomization. However, the history of clinical investigation is rife with examples where such comparisons have led to broad support for a scientific theory, or a class of drugs, that has subsequently been shown to be ineffective or worse on the basis of rigorous testing in a randomized trial. The theory that beta-carotene could prevent lung cancer was widely accepted based on retrospective (uncontrolled) epidemiologic studies of dietary beta-carotene consumption, yet two very large cancer prevention studies in the 1990s demonstrated convincingly that beta-carotene supplementation to smokers actually increases the incidence of lung cancer, to the great surprise of the medical community [6,7]. Combined estrogen and progestin therapy was widely believed to reduce the risk of coronary heart disease (CHD) in post-menopausal women, yet the Women's Health Initiative Study showed convincingly the opposite conclusion, that the treatment actually increased risk of myocardial infarction and CHD death compared to placebo treatment [8].

The sponsors also seek to permit the use of surrogate endpoints or biomarkers that are "reasonably likely to predict clinical benefit" as replacements for the ultimate clinical benefit that the drug is intended to ameliorate or cure. Although it is reasonable to approve agents that are shown to provide direct clinical benefit, the recent history of clinical investigation provides sobering examples where drugs demonstrated strong effects on the surrogate endpoints, but the anticipated benefits on the clinical endpoints failed to materialize. Indeed, as the science of clinical research has learned through experience, it is rare to find a biological measure that can truly serve as a surrogate for improving longevity or quality of life of patients. In cardiology, a class of drugs known as inotropic drugs was developed to treat a population of chronic heart failure (CHF) patients. CHF patients have hearts that do not function efficiently, and the disease can severely restrict daily activity and increase the risk of death. Annual mortality rates can vary from 15% to 40%, depending on the severity of CHF. Drugs in this new class often demonstrated an improvement in cardiac function, and some even showed improvement in exercise testing. However, many of these were tested in large randomized placebo controlled trials (best care plus the new drug or a matched placebo) which demonstrated an increase in mortality. An example is milrinone, a phosphodiesterase inhibitor that was shown to increase the risk of death by 28% and the risk of cardiovascular death by 34% [9]. While the adoption of new drugs on the basis of surrogate endpoints offers the promise of faster approval, the long-term risks of this strategy may well exceed the potential benefits.

Access of patients to experimental agents

The Bill is based on the premise of denied access. Under current law it is possible, however, to obtain compassionate access to experimental drugs in cases of life-threatening illness. The new law would *require* access for all seriously ill patients. By permitting approval for marketing the drug, the sponsor would charge for the drug where currently it must be supplied pro-bono. Furthermore, significant coercion is to be applied to the patient, who is necessarily in a very vulnerable position. The patient would be required by law to sign a waiver of the right to sue the manufacturer, and also to permit access to personal health information to assist the manufacturer in obtaining final (Tier III) approval. Ironically, the best interests of the public's health are served by more widespread participation of

patients in legitimate, scientifically valid clinical trials as part of the pre-approval process. The new law would appear to be part of an effort to undermine this well-tested system of scientific evaluation.

Summary

The proposed Bill S.1956 is a bad law. Wide early access to minimally tested treatments cannot be expected to lead to better or more compassionate care of the seriously ill patient. The long history of medicine is replete with treatments that initially seemed promising to patients, doctors, and especially to their own inventors, but which careful study revealed to be worthless or harmful. We understand the desperate plight of these patients and the importance of hope for them and their families. However, although the proposed law is portrayed as an effort to help patients in desperate need of treatment, in fact its effect would be to undermine the system of scientifically valid testing of new drugs that has been a bulwark of health care for several decades. The effect of the law would be to provide many more possible choices of treatment but much less information upon which to make the choice. Patients would be very unlikely to end up receiving an effective treatment. They would be much more likely to receive useless or possibly harmful treatments in the last days of their lives. The Society for Clinical Trials strongly opposes this legislation.

References

1. **Parexel Sourcebook** Parexel Corporation, 2005: 188–89.
2. http://www.natlbcc.org/bin/index.asp?strid=22&depid=1&btnid=1. (Last accessed 01/06/06.)
3. http://www.aidsinfonyc.org/tag/about.html. (Last accessed 01/12/06.)
4. **ALS CNTF Treatment Study Group.** A double-blind placebo-controlled clinical trial of subcutaneous recombinant human ciliary neurotrophic factor (rHCNTF) in amyotrophic lateral sclerosis. *Neurology* 1996; **46**: 1244–49.
5. **The Cardiac Arrhythmia Suppression Trial (CAST) Investigators.** Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *New England Journal of Medicine* 1989; **321**: 406–12.
6. **The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group.** The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *New England Journal of Medicine* 1994; **330**: 1029–35.
7. **Omenn GS, Goodman GE, Thornquist MD** *et al*. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *New England Journal of Medicine* 1996; **334**: 1150–55.
8. **Roussouw JE, Anderson GL, Prentice RL** *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; **288**: 321–33.
9. **Packer M, Carver JR, Rodeheffer RJ** *et al*. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *New England Journal of Medicine* 1991; **325**: 1468–75.