Urgent changes needed for authorisation of phase I trials

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For the **interim report** and **selected parts of the protocol**, **investigator's brochure**, **investigational medicinal product dossier**, and **assessment report** see http://www.mhra.gov.uk

For the **previous Editorial on TGN1412 trial** see *Lancet* 2006; **367:** 960

For the **position paper from Academy of Medical Sciences** see http://www.acmedsci.ac.uk

How clinical trials are regulated is under review after the release of an interim report by the UK Medicines and Healthcare products Regulatory Agency (MHRA). The UK Secretary of State for Health will establish an expert group, led by Prof Gordon Duff from Sheffield, to review the evidence from the TGN1412 trial and to advise on the future authorisation of similar first-in-man trials.

While this new group deliberates, the MHRA, which authorised the disastrous phase I first-in-man trial of TeGenero's TGN1412 in which six healthy volunteers developed serious adverse events, will seek additional expert opinion before approving any further first-in-man trials of any monoclonal antibody or other novel molecules that target the immune system. The Paul-Ehrlich-Institut in Germany, which had approved clinical trials of TGN1412, is also considering introducing restrictions for trials of drugs that might provoke a large immune response.

The MHRA's interim report concludes that there was no evidence of a fault with the quality of the test drug, no contamination, no dosing error, and "it was run according to the agreed protocol", suggesting that the life-threatening cytokine-release syndrome that occurred in all six volunteers given TGN1412 was an effect in man not seen in animal tests. Despite the recognised risk of massive release of cytokines that is clearly described in the product dossier and investigator's brochure, there is no mention in the published documents of any precautionary dosing interval between volunteers. As the Academy of Medical Sciences suggests: "it would be usual practice to administer a single dose in a single patient, who would then be observed for an appropriate period of time".

Prof Patrick Vallance, an author of the Academy's report, told *The Lancet*: "Predicting toxicity of activating antibodies from animal models is not the same as predicting toxicity of conventional small molecule drugs, and this difference must be considered when taking the crucial and essential step of moving into clinical studies." The TGN1412 events indicate that urgent change is needed in the approval processes and regulation of phase I trials of biological agents. ■ *The Lancet*

Reviving research into psychedelic drugs

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For the **case report of intensive ecstasy use** see *Psychosomatics* 2006; **47:** 86–87 doi: 10.1176/appi.psy.47.1.86

That psychedelic drugs, such as LSD and MDMA (ecstasy), can be effective treatments for various psychiatric illnesses is an old idea. Once considered wonder drugs for their effects on anxiety, depression, alcoholism, and other mental illnesses, they have been effectively banished from medical practice after legal rulings banned their sale and use. Although such bans were largely put in place to quash concerns about rampant recreational drug use fuelling the counter cultures of the 1960s and 1980s (LSD and MDMA, respectively), criminalisation of these agents has also led to an excessively cautious approach to further research into their therapeutic benefits.

So do illicit drugs have therapeutic benefits that outweigh their substantial social harm? The evidence is scant. But the case of a man who emerged from a decade-long period of intensive MDMA use—during which he is estimated to have taken 40 000 pills—with no signs of the profound neurotoxicity that has long been feared to result from even limited consumption of ecstasy, has re-energised calls for more research into the real side-effects, and therapeutic potential, of psychedelic drugs. Although some small-scale research projects using LSD, MDMA, and the active components of cannabis are now underway, the blanket ban on psychedelic drugs enforced in many countries continues to hinder safe and controlled investigation, in a medical environment, of their potential benefits.

Exaggerated risks of harm have contributed to the demonisation of psychedelic drugs as a social evil. But although this dangerous reputation—generated and perpetuated by the often disproportionately stiff penalties for their use—is helpful for law enforcement, it does not correspond to the evidence. Rather, the social prescription against psychedelic drugs that hinders properly controlled research into their effects and side-effects is largely based on social and legal, as opposed to scientific, concerns. To maximise research into therapeutic benefits without exacerbating real social harms a legal structure that recognises this distinction is sorely needed. ■ *The Lancet*