Memorandum

To: Alan Cornwall, President, CATIE
Darien Taylor, Sr. Co-Chair, AAN
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Christopher Cockrill, CAS

From: Sean Hosein, CATIE

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Subject: Getting sucked in; a problem of awareness of issues related to clinical trials, product testing, drug approval/regulation and ethical behaviour.

Alan, there is a serious deficiency of awareness of the issues revolving around the testing of drugs in Canada. I have been made aware of this in observing the Glaxo meeting as well as other events. This is not a problem confined to Toronto. Indeed, Ian Thom (from Vancouver) of CAS is also aware of this. I will give examples of the what I have seen and outline some ways in which we may begin to deal with them.

In summary, what is happening is that community representatives are confusing the issue of research with treatment. This would not be so bad if the results stayed in their own minds, unfortunately it is reflected in their dealing with the community and more critically with pharmaceutical companies and the government. It would result in policies that, ultimately, do not protect the interests of people with HIV infection. As examples:

1. Exhibit A:'X' is a young social activist who has taken to working with AIDS issues. His politics are generally good. However, take the behaviour of X with the issue of protocol development and product testing. Instead of trying to fight/lobby for compassionate access to product AB 123 he is desperately trying to have entry criteria for a certain trial to be relaxed so that more people may get in to the trial. This is not out of any concern for research or that the trial succeed. Rather X just wants more people to be able to get exposed to the drug because he (and others think) that this is something good to do. They think that this is how to go about getting 'access' to the drug. In part, the pressure on X is due to favourable media reports of a highly preliminary nature. Being a "good activist" X particularly noticed one criterion for the study which does not allow pregnant women into the trial. He objects to this criterion on political grounds. Given the way women have historically been treated, and continue to be treated, by the medical-research establishment, X's concern seems justified. However, further examination of the issue reveals his utter lack of understanding of why protocols are structured in a particular way. X does not understand that pregnant women (in this case) are excluded for very good reasons; they would confound the results of the trial. Moreover, even if the bearing parent were to give informed consent to being in the trial, should "an adverse event" occur, the company testing AB 123 is under tremendous legal liability. If X were really concerned about the health

of HIV+ pregnant women he would see that his approach is not really in the best interest of such people. Were X to have basic understanding of the issues, he would see that compassionate access for pregnant women to AB 123 would allow their doctors to adjust the dose to suit the condition of their patients and reduce its harmful effects. In his zeal to weaken the entry criteria X forgets that in many trials the dose is fixed regardless of people's condition. And if perhaps he was interested in research, he might suggest that the protocol be amended to study the effect of AB 123 on pregnant women in the 1st, 2nd and 3rd trimesters of pregnancy. X does not really understand that there is an interplay between the immune system of the bearing parent, the developing fetus and HIV. Pregnancy is a complex condition that has varying effects on the immune system as the fetus progresses to term. X does not see this. Nor does X appear to realize how the media can be used by pharmaceutical interests to exploit the fears and hopes of people with HIV, not to mention stockholders. X does not understand that the whole raison d'être for having a drug in testing is not out of a pharmaceutical manufacturer's particular concern about people with HIV; it is so that the drug may ultimately win approval from regulatory authorities. The trial's entry & exclusion criteria are structured so that agent AB 123 has a chance of working in a certain population, so that it has a better chance of being approved despite its side effects. Weakening the inclusion criteria has the effect of exposing people to AB 123 who are not likely to show benefit. Drug companies know this, they have profit targets and timelines and don't want to be seen pushing a drug that cannot be shown to work. They do not need bad publicity which may later affect the attitude of regulatory authorities or the value of a firm's class A shares. But X does not understand this. He thinks that drug firms, being multinational corporations, act in a strange and irrational manner. X is so carried away by the collapsing weight of the desperate needs of people with HIV, the agenda of a greedy and incompetent drug company (whose research priorities are 5 years out of date), and his sense of social responsibility, that he acts in a way that is not, ultimately in the best interests of people with HIV. See attached document (a general interest story from the journal Science). He is so caught up in events that he cannot see the long-term effects of what he is doing. Unfortunately X is not alone in this. Without some strategy or blue print, so are most community activists.

2. Exhibit B: 'Y' also has become politicized with AIDS. Moreover Y is a person with AIDS. He has good politics in a general way. Unfortunately, Y is even more dangerous than X because he gets around not just the province, but the country as well. Y has a picture of things only a little larger than X. Thus Y sees that part of the reason that drug companies are unwilling to release products under development in the USA for compassionate use in Canada is the fear that these companies have of the FDA (Food and Drug Administration). The USA represents, outside of Japan and the European Community, the richest drug market in the world. The imprimatur of the FDA can usually be used to successfully sway the opinion of licensing bodies in other parts of the world. Pharmaceutical companies are loathe to irritate the bureau that grants a license for their products targeted to this market. Their concerns may be justified as the FDA has acted, in the past, in an inconsistent and unfair manner when it comes to certain companies. Instead of investigating why the FDA operates the way it does (or even better, organizing other people to study this) Y thinks that the thing to do is to weaken that regulatory agency (and our own) so that we can have access to non-approved drugs once safety and preliminary efficacy has been shown in phase I/II trials (here I am being charitable to Y). In part, the weakening of regulatory requirements is so that conditional licensing offers an alternative to having patients pay for the drug. Conditional licensing could be used to push insurance companies in the USA or provincial

health departments (in Canada) into paying for the cost of the drug. What Y does not see is that9 out of 10 drugs which are discovered do not end up being licensed. This is because along the path of drug development they have been found to be too toxic or that in long-term studies do not work. Y is also blind to the implications of this in the context of his actions. Nor does Y know that a good friend and personal physician to President Bush is a former CEO of Brystol Myers Squibb. Pharmaceutical companies love the line espoused by people like Y. This is on their agenda (see attached article discussing proposed changes to the FDA, ostensibly in the guise of speeding up and streamlining operations). Weakening drug regulatory agencies would allow pharmaceutical companies to pollute the market with useless drugs. Unfortunately these drugs would not be found out to be useless or worse, ultimately toxic, until years down the road when by then it would be too late. Already, this is what appears to be happening when the status of standard of care is prematurely conferred upon a drug which has not been properly tested. Instead of organizing community-based groups to effectively lobby the government to pay for non-approved therapies, Y is simply taking the easiest way—in the short-term—out of a highly problematic situation. Y thinks that by having input into protocol development he is on his way to solving part of this problem of drug access. Y has no idea why it is that pharmaceutical companies do placebo-controlled trials. He thinks that this is a requirement forced on them by the FDA. He is partly correct, the FDA is mandated to make sure that the drug actually works. Regrettably, Y does not see that randomized, placebo-controlled trials are employed because of the statistical design of trials. If a different statistical methodology were to be used, perhaps placebo controls might not be necessary. It is not Y's fault that he does not see this. His colleagues have not fully addressed the issue nor have other community-based groups around the country done this either. Tackling these issues requires a lot of hard work. Y is simply taking the current "line". And, as he travels around the province and country other people in community-based groups are also taking up his line of thinking. These other people in smaller communities do not have the time nor energy to do the kind of analysis necessary for this sort of work. Much of their time is taken up with the business of surviving and caring for their communities. They rely heavily on people like X and Y for information and leadership about the politics of clinical trials.

X and Y are not bad people. They do not receive money from pharmaceutical companies placing themselves in a position of conflict of interest (unlike other people associated with community groups), moreover, they care deeply about what happens to people with HIV and are well intentioned. X and Y are thought of, at least in other parts of Ontario, as people who have a sophisticated understanding of pharmaceutical companies and drug development related issues.

Thus their mistakes will continue and more and more people will attempt to mimic the stand taken by X and Y on certain issues because they don't know any better. This does not bode well for the future. And people will compound these mistakes, not out of any malice, but because no one has properly studied what is to be done. Unless we develop a strategic blue print for ensuring that the interests of people with HIV are safeguarded, people like X and Y will go along their merry way unchecked, sucked straight into the jaws of the pharmaceutical companies. What we will end up with are drugs which ultimately do not have any efficacy and may even increase the chance of death. Both situations are unacceptable. Moreover, as X and Y sit on bodies representing "the community" unless they can properly take up the issues presented before them, they will be unable to defend the interests of people with HIV.

Darien and Kalpesh feel, and I agree with them, that what is needed is a consensus conference on these issues by AIDS activists so that the standard of knowledge can be raised, these issues discussed and people educated.