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Office of the Dean

Mr. Jean Saint-Pierre
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Re: Inspection Strategy for Clinical Trials involving Human Subjects
under the authority of R.S. 1985, C.F-27, s.23

December 1 2002

Dear Mr. Saint-Pierre,

We are pleased to see the amendment to the Food and Drug Regulations (Schedule No. 1024 – Clinical Trials) located in Division 5 of the Regulations. The amendment incorporates, among other things, the implementation of an inspection system for Canadian clinical trials involving human subjects utilising internationally accepted principles of good clinical practice (GCP). We have closely reviewed the HPFBI's policy on the new inspection strategy for clinical trials, which is supported by the compliance and enforcement policy (POL-0001). These are important documents for helping to ensure that there is consistency as to how clinical trials will be inspected and how the regulations will be enforced. It is our understanding that the inspection strategy, which focuses mainly on compliance to the Regulatory framework, is under your authority.

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The ability to inspect clinical trials is important because it allows for review of sponsors' and investigators' adherence to the principles of GCP as well as to other requirements in Division 5 of the Regulations. We were particularly pleased to see at C.05.010 in the Regulations the incorporation of Health Canada's GCP: Consolidated Guidelines (1997) based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

The Regulations as amended recognise the importance of REBs in protecting the rights, safety and welfare of trial subjects. We suggest that neither the process to accredit REBs nor a regulatory structure concerning their mandate for ensuring good clinical practices, offer complete safeguards for the integrity of clinical research, including appropriate publication rights for investigators and prevention of the adverse effects of conflict of interest (COI) in the conduct and reportage of clinical studies. COI generally pertains to private financial or other personal gain and refers to the opportunity to gain, directly or indirectly, either from the outcome of one's research or from one's activities with external organisations. REBs seem to be viewed as a mechanism to help ensure that COI situations are avoided (see Regulatory Impact Analysis Statement, TPD, Policy Division, Bureau of Policy and Coordination). But given the paramount importance of patient safety in clinical research and the need for timely acquisition of valid and reliable data from clinical studies, we believe that multiple safeguards ought to be the rule.

We therefore suggest that the HPFBI has an important role to play in monitoring clinical trials for COI in four main areas. To cover these areas, there needs to be a review of the clinical study agreement, investigators' brochure for the drug, and any related financial agreements. While neither at C.0510 or at C.05012 do the Regulations refer to clinical trial agreements or financial agreements, Health Canada's GCP was integrated (at C.05.010) which presumably allows for the incorporation of Section 8 of those guidelines that outline essential trial documents, including trial agreements (8.2.6) and financial agreements (8.2.4).

The reason why relevant elements of the overall clinical study agreement must be formally reviewed by HPFBI is that the terms and conditions outlined therein are recognised by law as a contract. As such, they take precedence over other trial documents (e.g., policies, study protocols) unless there is explicit language in the clinical study agreement to the contrary. Financial agreements, in particular, must be reviewed as they are not always clearly broken down by service or by activity. The clinical agreement may include a more detailed financial plan or it may be possible to require such detail during an inspection.

The four areas that we believe require review by HPFBI follow.

a) **No Physician Financial Incentive to Recruit Patients or for the Successful Completion of the Trial**

We believe the offer or acceptance of finders' fees or of completion fees ought to be

prohibited in clinical trials. Finders' fees refer to money or other compensation given by the sponsor to a physician in payment for recruiting a patient into a trial while completion fees refer to payment for the successful completion of the trial. These do not include compensation payments to a physician for the services he or she provides (e.g. for determining the eligibility of a patient to participate in the research or for services provided to a patient enrolled in a research study) or to the holdback sponsors maintain until trial completion.

Our reason for proposing this prohibition is that these fees create a conflict of interest between the physician's private interests and his or her obligations to ensure that the patient is recruited appropriately and has given fully informed consent to participate in a particular study. We believe that simple disclosure of the finders' or completion fee to a REB and to patients is insufficient.

It is possible that a sponsor's convention is to incorporate finders' or completion fees into other aspects of the financial agreement rather than to provide a separate line item for each. It would be prudent for the HPFBI to examine the financial agreement to ensure that payment received for the work provided is reasonable compensation for the services or activities performed.

b) **No Inappropriate Inducements to Investigators or Sites for their Participation in a Trial**

This point is similar to (a) above, except it refers to the offer or acceptance of inducements that provide benefits financial or otherwise for investigators or sites to participate in trials. The concern arises when those inducements are at a level that causes concern about undue influence on the independent judgement of the investigators or site administration. A participating site, like an individual investigator, should receive compensation for the direct and indirect services provided by the site. This site compensation is often paid in the form of an institutional overhead charge and a fee to offset the administrative REB costs. We urge that a critical eye be cast on other benefits that may create potential or actual conflicts of interest, and that some of these benefits may best be prohibited. These benefits include, but are not limited to, bonuses and personal gifts, gratuities, donations, property, equipment and special considerations such as offers of products (e.g., pharmaceutical agents) or services outside the trial. To identify the existence of bonuses or gifts, the HPFBI may need sites and sponsors to declare in writing whether either party has, by words or conduct, made a promise or assurance to provide or to accept benefits for participation in a trial. The institutional overhead charge should be consistent with usual and customary charges in other sites that are similarly organized.

c). **Freedom of Investigators to Communicate Directly and without Delay or Censorship to our Regulatory System if there is a Discontinuance of a Clinical Trial at their Site or if there are Serious Unexpected Study-related Adverse Events**

The Regulations at C.05.014 and C.05.015 require sponsors to inform the Minister of

serious unexpected adverse drug reactions or if the trial is discontinued in its entirety or at a particular site. Health Canada's GCP (4.11 and 4.12) outlines the responsibilities of the investigator and site in safety reporting and in the case of premature termination or suspension of a trial. Investigators and sites are also required to comply with the applicable regulatory requirements related to the reporting of these events. In Canada, investigators and sites do not have a regulatory obligation to report directly to the Minister in the same way as sponsors do. However, the Minister does receive complaints about clinical trials and these reports may come from investigators or sites (as well as from others, such as research subjects). It is essential that the clinical agreement does not hinder the rights of the investigator or the site (e.g., hospital board; REB) to report directly, without delay or censorship to the Minister if they determine that reporting is necessary.

d) **Freedom of Investigators to Communicate Directly and without Delay or Censorship to the Scientific Community**

Researchers ought to have independence from the sponsor with respect to the scientific dissemination of the trial result, so that corporate industry interests do not interfere with scientific integrity. It is reasonable for an industrial sponsor to insist that it have some brief period of time either to offer comments on work that will be published or presented, or to seek protection of intellectual property. However, the ultimate right to publish, without censorship, must be retained by the investigators. To this end, the absence of an independent steering committee should be seen as calling into question the likelihood that a study will be published in a biased fashion.

Health Canada's GCP says that there should be a publication policy (6.15), however, there is no mention as to what ought to be included in it. Our own recent work in this area (see Can Med Assoc J 2002; Feb 19; 166(4):453-454) has involved the adoption of new standards for industry-sponsored research that requires all contractual agreements to allow investigators to publish the results of the trial and to do so without undue delay or actual censorship.

In conclusion, HPFBI is in a unique position through its inspection strategy to take a leading role in identifying COI in Canadian clinical studies. Bodies such as the Canadian Institutes of Health Research are debating how they can participate in promoting high standards of conduct in clinical research, but much clinical research is now done outside of academic centres and is therefore outside the reach of granting councils. Only Health Canada has the authority and national mandate to intervene definitively here. While we agree that a wide variety of institutions and agencies should work to achieve the same end, we suggest that Health Canada has the required authority and a special responsibility to address these issues directly and quickly.

Please do not hesitate to contact us if you would like elaboration on these observations and suggestions.

Yours sincerely

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