Other Audit Observations

National Defence and Health Canada

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Non-compliance with conditions and inadequate monitoring with respect to the pre-licensing use of an anti-malarial drug

National Defence participated in a clinical trial of an anti-malarial drug, but did not follow the study protocol when the drug was administered to Canadian Forces personnel deployed to Somalia. Despite a requirement in the protocol to do so, the Department did not obtain consent from the personnel who received the drug, did not systematically monitor for efficacy, and did not provide to the study sponsor records of the drug's administration or reports of adverse reactions to the drug.

Once Health Canada approved the conditions for the clinical trial of the drug, it made no attempt to monitor the study to ensure that the trial was adhering to the protocol with its reporting requirements and procedures to protect patients' well-being.

Health Canada is responsible for the regulation and licensing of drugs in Canada. An unlicensed drug may be made available only through special measures, such as a clinical trial when Health Canada has approved the study design and protocol for testing the drug. Some studies test the drug in "real world" conditions and are thus a potentially valuable source of information about adverse drug reactions among specific populations, efficacy problems in certain environments, and so on.

Background

1. Health Canada licenses manufacturers to produce and sell drugs that have been demonstrated to be safe and effective. Only licensed drugs can be sold in Canada, except under specific, controlled conditions. For example, an unlicensed drug may be available through the Special Access Program (whereby Health Canada approves the sale of the drug for a specific patient), or through a "clinical trial", which tests the drug to obtain evidence on its safety, dosage and effectiveness. A clinical trial is conducted under the direction and control of a sponsor (usually the manufacturer), but the study design and protocol must be approved by Health Canada. Once it has approved the protocol and received information about the investigators appointed by the sponsor, the sponsor is responsible for conducting the study and ensuring that the investigators follow the protocol. The sponsor is obligated to inform Health Canada of any serious adverse reactions (other than those already identified) or deaths associated with the drug.

2. As they travel throughout the world and are involved in hostile situations, Canadian Forces members are sometimes exposed to health hazards for which licensed drugs or other protective measures are not available in Canada. These may include diseases, such as malaria, that are not common in Canada or health hazards associated with hostile actions such as biological warfare. As a result, National Defence must sometimes obtain drugs or vaccines through special measures.

3. Canadian Forces members may be subject to discipline under the *National Defence Act* if they refuse to submit to a treatment, drug or vaccine when ordered to do so. National Defence officials told us that it is policy not to seek written, informed consent when preventive drugs or vaccines are prescribed for Canadian Forces members during deployments, since such consent is often not compatible with operational requirements.

4. Mefloquine is an anti-malarial drug that is recommended by the World Health Organization and others for use

against some types of malaria that have become resistant to other drugs. Although licensed in a number of countries since the late 1980s, it was not licensed in Canada until 1993 and in 1992 was available to National Defence only through a Safety Monitoring Study. Use of the drug was conditional on satisfying the requirements of the protocol for the study, including obtaining informed consent.

5. From November 1990 to early 1993, mefloquine was available in Canada only through an ''open label, compassionate access" clinical trial called a Safety Monitoring Study, under the sponsorship of the drug's manufacturer. The objectives of the study were:

- to ensure that the Canadian public travelling to regions where chloroquine-resistant malaria was present had access to mefloquine under controlled conditions; and

- to collect safety data on those travellers.

6. The study was carried out under the direction of 21 principal investigators, who were medical doctors in travel clinics across Canada. The study protocol specified the investigators' responsibilities, including keeping accurate records on dispensing and reporting all adverse drug reactions. It stipulated that informed consent was to be obtained from all participants and specified that "safety data will be collected and efficacy will be monitored for each subject receiving [mefloquine]". All data and records were to be provided regularly to the sponsor (the manufacturer).

7. National Defence participated in the study beginning in March 1991, with a physician at an Ottawa hospital as a principal investigator and a Department physician as a co-investigator.

Issues

National Defence did not consistently follow the protocol for the Mefloquine Safety Monitoring Study

8. From 1991 to July 1992, 96 National Defence officials travelling to Cambodia and Africa were given mefloquine under the provisions of the Safety Monitoring Study. The Department kept records of all but 362 of the 3,500 mefloquine tablets dispensed; obtained consent forms from the travellers; and reported to the study sponsor on the frequency of adverse effects.

9. However, National Defence did not follow the protocol in the fall and winter of 1992–93, when mefloquine was dispensed to approximately 900 Canadian Forces members before they left for Somalia and while there. It did not provide the manufacturer with records of the drug's distribution, nor did it obtain the consent of those receiving the drug, which was not licensed. Canadian Forces members were given an oral briefing on malaria, mefloquine, and the possible side effects, but did not get the written documentation given to other Department travellers who received the drug. Further, even though all supplies of the drug used by National Defence were labelled "for investigational use only", the Department did not systematically monitor efficacy or adverse reactions for each person receiving the drug, as required by the study protocol. It relied instead on a disease surveillance system and a periodic report of activities to provide any indication of side effects or other problems with mefloquine.

10. The manufacturer had identified a number of side effects of the drug for which patients were to be monitored, including gastrointestinal, central nervous system and psychiatric disorders. (While severe side effects were rare, mefloquine was not prescribed for pilots or others in occupations ''requiring fine co-ordination and spatial discrimination, where the

sudden onset of dizziness/vertigo can be hazardous or life-threatening".) Although 69,000 doses of mefloquine had been provided to the Canadian Forces medical unit in Petawawa in September and October of 1992, information on their use and on adverse reactions or side effects was not reported. Thus, neither the manufacturer nor Health Canada benefited from information that might have been obtained about safety and efficacy of mefloquine.

11. National Defence officials told us they did not follow the protocol because they believed at the time that they had received authorization from Health Canada to follow a different set of procedures that would not require informed consent. However, no such authorization was obtained, nor have we been provided with any evidence that such authority was sought, or even discussed in National Defence, with Health Canada or with the manufacturer. National Defence attributes this confusion to a lack of communication between two of its directorates.

12. In an attempt to minimize the likelihood of non-compliance with the *Food and Drugs Act* and Regulations, in July 1998 National Defence established a position with responsibility for all regulatory issues relating to unlicensed medical products. This position serves as a single point of contact between the Department and Health Canada's Health Protection Branch.

Health Canada took no steps to ensure the mefloquine study protocol was followed by National Defence

13. Health Canada officials told us that although they had approved the protocol for the Mefloquine Safety Monitoring Study, they took no steps to ensure that it was followed. They said that monitoring the conduct of the study was the responsibility of the manufacturer, as the sponsor of the study.

14. Health Canada has the right, under the Food and Drug Regulations, to request copies of the records of a study and to terminate the study if it believes it is not being conducted properly. However, it has no procedures for monitoring the conduct of these studies or clinical trials.

15. We found that National Defence was not the only participant in the study who failed to provide the manufacturer with information about patients and the dispensing records of the drug. The manufacturer's final report on the study (April 1993), which included the results reported by all 21 principal investigators, stated that the inability to obtain the actual number of patients receiving mefloquine made it necessary to estimate the number on the basis of pills dispensed. The report noted that:

- 501,424 pills had been shipped to all investigators in the study but there were records for only 331,695 (66.2 percent); and
- there were an estimated 38,747 patients, but records for only 25,235 (65.1 percent).

16. Mefloquine has been available in the U.S. and Europe since the late 1980s, and was licensed in Canada in January 1993, and available on the Canadian market in March 1993. However, not until October 1994, when the use of the drug by Canadian soldiers in Somalia became an issue in the media, did Health Canada ask the manufacturer for copies of the records on the 69,000 doses of mefloquine provided to National Defence in 1992. The manufacturer did not have any such records, although the study protocol called for them to be provided to the manufacturer every six months; it passed the request on to National Defence. When the Department could not provide the information, Health Canada took no action.

Conclusion

17. National Defence did not consistently keep essential records or follow required procedures to fulfil its obligations as a participant in a clinical study of an unlicensed drug. As a consequence, the integrity of the Mefloquine Safety Monitoring Study may have been compromised and potentially valuable information about the safety or efficacy of the drug under "field" conditions was not gathered. We have noted that, as a result of this situation, National Defence has implemented measures to increase monitoring and improve documentation when using unlicensed medical products.

18. Where unlicensed drugs are dispensed through clinical trials, Health Canada has the responsibility to review and approve the trial design and protocol. It needs to assure itself that the conditions of clinical trial protocols are met in order to preserve the integrity of the process and to satisfy conditions set out under the Food and Drug Regulations. "Open label" trials provide an opportunity to test the safety and efficacy of drugs in "real world" situations and thus to identify potential hazards or problems that may not surface under laboratory conditions. They represent a potentially valuable source of information about the drug and its use.

National Defence's response: *Despite the shortcomings identified in this audit observation, cases of potentially lethal malaria were prevented and the health and safety of Canadian Forces personnel were not compromised. At the time of the Somalia deployment, mefloquine was already licensed in 29 countries, including the United States, and the drug had an established record of safety and efficacy. This record is further supported by the recommendations of the World Health Organization and by Health Canada's granting of a Canadian licence in January of 1993, which coincided with the arrival of the main body of Canadian troops in Somalia.*

Health Canada's response: *It is Health Canada's policy that the monitoring of study protocols rests with the sponsor of the clinical trial (usually the manufacturer), as well as associated institutional research ethics boards, and data safety monitoring committees. Physicians conducting clinical trials do so under provincial/territorial jurisdiction and processes are in place to monitor the compliance of medical professionals with established practice protocols.*

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