HOUSE OF COMMONS
CANADA

Pursuant to Standing Order 108(3)(*e*), the Standing Committee on Public Accounts has the honour to present its

THIRD REPORT

The Standing Committee on Public Accounts has considered the April 1999 Report of the Auditor General of Canada – Other Audit Observations *(National Defence and Health Canada: Non-compliance with conditions and inadequate monitoring with respect to the pre-licensing use of an anti-malarial drug)* and the Committee has agreed to report the following:

INTRODUCTION:

The health and safety of the men and women who serve Canada in its armed forces is a matter of ongoing concern to the Standing Committee on Public Accounts. In recent years, the Committee has examined the results of audits performed by the Auditor General of Canada on the Department of National Defence (DND) and its management, procurement, and planning systems. The reports tabled by the Committee following these examinations have placed a strong emphasis on measures aimed at reinforcing the safety of armed forces personnel.

Based on its continuing interest in the Department of National Defence, the Committee decided to examine an audit note included under Other Audit Observations in the April 1999 Report of the Auditor General of Canada. This note reported the results of an audit that was done of circumstances surrounding the administration, in the fall and winter of 1992, of an (at that time) unlicensed drug to Canadian peacekeepers by DND under conditions established by Health Canada.

In order to develop a better understanding of what had happened and to inquire into corrective measures taken since April 1999, the Committee met with witnesses on 18 November 1999. Mrs. Maria Barrados, Assistant Auditor General, and Mr. Ronald Campbell, Principal, Audit Operations Branch, represented the Office of the Auditor General of Canada. Mr. Dann M. Michols (Director General, Health Protection Branch and Mr. Ian MacKay (Manager, Special Access Programme, Bureau of Pharmaceutical Assessment) represented Health Canada. Brigadier General Claude Auger (Surgeon General and Commander, Canadian Forces Medical Group) and Lt. Colonel Greg Cook (Head, Public Health, Directorate of Medical Policy) appeared as witnesses for the Department of National Defence (DND).

BACKGROUND

In the fall and winter of 1992, Canadian armed forces personnel were sent on a peacekeeping mission to Somalia, a country in which a drug-resistant form of malaria was prevalent. In order to protect its personnel, DND dispensed an anti-malarial drug – mefloquin – that was known to be effective when traditional drugs were not and was already approved for sale in 29 countries. At that time, however, mefloquin was unlicensed in Canada and only available under a clinical trial (called a Safety Monitoring Study).

DND was under obligation to adhere to the conditions imposed by the trial, conditions approved by the federal department that licences drugs for sale in Canada – Health Canada. These conditions, collectively known as a protocol, required DND to obtain informed consent from its personnel and to keep careful records of the drug's use and possible side effects on a regular basis. These records and data were to be submitted to the drug's manufacturer – which was responsible for conducting the trial – at six-month intervals. This data would be used to better understand the drug's effects under field conditions and to establish its safety and efficacy before its manufacturer would be granted a licence to sell mefloquin to the general Canadian public.

Although the Department had obtained mefloquin for its personnel in the past and had met the conditions imposed by the trial, it did not do so on this occasion. The approximately 900 troops deployed to Somalia were given an oral briefing on mefloquin and its possible side effects prior to departure. No written documentation was given to them and their consent was not obtained. DND did not systematically monitor the drug's efficacy or adverse reactions among its personnel while in the field and, consequently, did not provide the manufacturer with the required records or data.

DND stated that it was of the opinion that it had the approval of Health Canada to waive the requirements of the protocol. In fact, no such

authorization was sought or obtained. According to the Department, poor communications between two of its divisions were at fault; each thought that the other had applied for and received permission to set the protocol aside, but neither had checked or informed the same.

Apart from establishing the protocol for the drug trial, Health Canada took a hands off approach, in conformity with its procedures regarding all such trials. It approved the study design and protocol for the Safety Monitoring Study and the manufacturer conducted the trial.

In January 1993, Health Canada licensed mefloquin and the drug became available on the market in March 1993. In October 1994, after the media raised questions about the use of the drug on the Somalia deployment, the Department asked the manufacturer for its records on the 69,000 doses of mefloquin provided DND in 1992. The manufacturer responded that it had no such records and Health Canada pursued the matter no further. In its final report on the drug trial issued in April 1993, the manufacturer indicated that other participants in the trial had also failed to provide information required by the protocol.

Neither the Department of National Defence nor Health Canada disputed the Auditor General's description of the circumstances surrounding DND's acquisition and use of mefloquin.

OBSERVATIONS AND RECOMMENDATIONS

In testimony before the Committee, DND acknowledged its responsibility for what happened and explained that at the time of the Somalia deployment, mefloquin was the most effective drug available to protect its personnel against malaria. DND then described the actions it has taken to prevent a reoccurrence of the 1992 event. The Department has:

Established a regulatory affairs position to serve as a single contact point with Health Canada and produce better documentation of the discussions between the two departments; and

Confirmed, via a directive, a requirement and procedure for acquisition, distribution, use, and recording of unlicensed medical products.

The Department is now developing a detailed drug and vaccine sheet for the benefit of the Canadian forces health care provider and Canadian Forces members, and is also developing an adverse effect monitoring and reporting database.

The Department of National Defence failed to adhere to the protocol established for the clinical trial when it dispensed mefloquin for use on the Somalia deployment, an error that it has acknowledged. It must shoulder its share of the blame for what occurred, especially with regard to the breakdown in inter-divisional and inter-departmental communication. The Committee acknowledges the extraordinary circumstances surrounding deployments, accepts the Department's explanations and finds that the corrective actions it has taken appear to be appropriate. The Committee fully expects that this incident will not be repeated and recommends:

RECOMMENDATION 1:

That when it participates in trials of unlicensed drugs, the Department of National Defence take every necessary measure needed to ensure that its inter-divisional and inter-departmental communications function properly and that the protocols for such trials are adhered to scrupulously.

In addition, the Committee recommends:

RECOMMENDATION 2:

That the Department of National Defence include a discussion of its efforts to improve its control over, and use and monitoring of, unlicensed drugs supplied under the terms imposed by clinical trials in its annual Departmental Performance Report for the period ending 31 March 2000. If the Department has obtained and administered unlicensed drugs during this period, it must clearly link the results obtained with the measures it has taken.

In his testimony, Mr. Michols suggested that Health Canada's involvement in clinical trials is an active one. He indicated that the Department sought to ensure that Canadians had access to mefloquin by "working with the manufacturer to sponsor a special clinical trial" for the drug, (1540) a statement that implied an ongoing interaction between them. This impression of a department actively engaged in the trial process, or at the very least, actively aware of the trial as it unfolded, was reinforced by this subsequent statement:

> In a general way, drug development relies on an effective partnership between Health Canada as the regulator, the pharmaceutical industry, physicians and other health care professionals and the institutions with which research is conducted as well as with the patients themselves. Within this partnership, Health Canada is responsible for ensuring that clinical trials are designed according to national and international scientific and medical standards and that the patients are not exposed to undue risk. (1545)

In this instance, however, if Health Canada was a partner, it was largely a silent one. Health Canada was unaware that the manufacturer had not received records required by the protocol. In particular, Health Canada was unaware that a significant number of records from a large federal government department (DND) participating in the trial were not being submitted to the manufacturer. Claims to partnership with the manufacturer seem limited, therefore, to the period during which the protocol was developed and afterwards when the drug was licensed. Any partnership between Health Canada and DND regarding this trial simply did not exist and, therefore, cannot be said to have existed between Health Canada and this group of patients either. Health Canada did not ensure that these patients were not exposed to undue risk, or at the very least, did not assure itself of that fact. While Mr. Michols testified that Health Canada "does monitor adverse drug reactions submitted by the sponsor of a clinical trial through the course of that clinical trial," that works only if the trial participants are submitting the required reports. The absence of a significant body of data – including potential data on adverse affects – could not have benefited this trial or the reliability of the conclusions drawn from it. Mr. Michols' assertion that Health Canada "has confidence in the partnership it has with clinical trial sponsors and physicians"(1545) concerns the Committee greatly in light of the failure to obtain the required reports and data during this trial and to ensure the existence of an effective partnership between itself and all trial participants. These concerns must be seriously addressed by the Department.

Health Canada testified that when it licensed mefloquin in January 1993, it received a "comprehensive data package" that included data from well-designed clinical trials. (1540) However, this comprehensive package did not include records for, or data derived from, 33.8 percent of the 501,424 pills dispensed during the trial or records for 34.9 percent of the patients. (15) And it contained no records whatsoever of the 69,000 pills dispensed to the approximately 900 Canadian peacekeepers deployed to Somalia.

Health Canada claims that it compensated for gaps in the Canadian data with information derived from trials conducted elsewhere and from international post-marketing data. If this is so, and if these data were considered sufficiently reliable as to obviate the necessity of having complete data from the Canadian trial, one might well ask why Canadian trials are deemed necessary in the first place. The Committee is seriously concerned about Health Canada's failure to obtain complete data from the Canadian clinical trial when it considered licensing mefloquin for sale in this country. Health Canada must also take this concern of the Committee's into serious consideration.

Health Canada licensed Mefloquin in January 1993. In March 1993, the drug became available for sale on the Canadian market. In April 1993, the manufacturer issued its final report on the drug trial. That report indicated that the manufacturer had not received the records for all of the pills dispensed or all of the patients who had received them. (15) In October 1994, 21 months after mefloquin had been licensed, 19 months after it went on sale, 18 months after the manufacturer's final report, and after use of the drug during the Somalia mission became an issue in the media, Health Canada approached the manufacturer in search of the data from DND. The manufacturer did not have these records and was unable to get them from DND. Health Canada took no further action. (16) Mr. Michols testified that this was "primarily because there was no further action to be taken" since the drug had already been licensed. (1545)

Health Canada licensed this drug despite the fact that it had not verified the full status of the trial as it unfolded and despite the absence of complete data once the trial had ended. If it was indeed aware that a full set of data from the Canadian trial was not available and that the protocol had not been completely followed, it went ahead and issued a licence anyway, based in part on the fact that the drug had been tested and licensed elsewhere.

Health Canada has no procedures for monitoring the conduct of studies or clinical trials and Mrs. Barrados testified that "there is a need to strengthen measures for ensuring compliance with the approved protocols" for these trials. (1540) Mr. Michols reflected Health Canada's agreement with this when he indicated that the Department is

> In the process of considering several reforms to the clinical trial review process…reforms [that] will increase the protection of research subjects participating in clinical trials and implement more efficient review processes. (1540)

Mr. Michols went on to state that these proposed reforms "will include development of an audit system of clinical trials with regard to compliance with international guidelines on the conduct of clinical research." (1540) Mr. Michols added that the implementation of an audit system "will ensure that research in Canada is conducted in accordance with these high [international] standards, and increase the integrity of data generated in support of drug marketing applications." He then noted that such a move would require regulatory change and that the Minister of Health is proposing to make those changes within two months. (1550) Mr. Michols did not clarify what kind of audit the Department has in mind nor did he offer any reasons why this should require regulatory change.

When questioned as to why an audit procedure is still not in place five years after this incident came to light, Mr. Michols suggested that the problem was "one of resources and priorities." (1650) In further testimony, he indicated that those resources will be made available to the Department. (1655) He concluded by stating that "now is the time to do it." The Committee is relieved to learn that the Department intends to take action and recommends:

> RECOMMENDATION 3:
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> That Health Canada independently develop an audit system to monitor clinical trials of unlicensed drugs randomly and at regular intervals;
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> > a) That Health Canada proceed to make the necessary regulatory changes in order to implement this audit system;
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> > b) That Health Canada develop a timetable for the implementation of an audit system to be used to monitor clinical trials. This timetable should include benchmarks for the completion of various components of this process and should be submitted to the House of Commons Standing Committee on Public Accounts no later than 31 March 2000; and
> >
> > c) That Health Canada describe, in its Plans and Priorities document for fiscal year 2000 – 2001, the audit system it proposes to implement and the human, technological, and financial resources it intends to dedicate to it.

Mr. Michols indicated that Health Canada was also considering other, unspecified, reforms to the clinical trials review process. The Committee believes that these proposals should be made available to Parliament in order that Parliament may review and comment on them and, where appropriate, support their timely adoption. The Committee therefore recommends:

> RECOMMENDATION 4:
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> That Health Canada include a discussion of the proposed overall changes that it is considering to the clinical trials review process in its Departmental Plans and Priorities document for fiscal year 2000 – 2001.

Because the Committee sincerely hopes that the implementation of an audit system and other reforms will help prevent a situation similar to the one reported in this audit note, it also recommends:

> RECOMMENDATION 5:
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> That Health Canada include reports on its audits of clinical drug trials, as well as the outcomes generated by other reforms to the clinical trials review process, in its annual Departmental Performance Reports, beginning with the Report for the period ending 31 March 2001. Where appropriate, a discussion of measures taken to correct problems brought to light by audits and other measures must also be included

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The results that were reported in this audit note and the evidence provided by witnesses raise a number of serious questions about Health Canada's role in drug development and licensing. Accordingly, the Committee recommends:

> RECOMMENDATION 6:

That a Standing Committee of the House of Commons be given the task of reviewing the manner in which drugs are developed, tested, and licensed for sale in the Canadian market.

CONCLUSION:

The Committee places high importance on the health and safety of men and women in Canada's armed forces and, indeed, on the health and safety of all Canadians. Canadians expect that Health Canada will take all reasonable measures to ensure that the drugs that are offered for sale on the Canadian market are safe and effective. Canadians also expect that the Department of National Defence will take every measure to protect the health and safety of those who place their lives at risk in the service of their country. In these matters, there can be no room for compromise, no room to assign secondary priorities, no room to allocate insufficient resources, and no room for breakdowns in inter-divisional or inter-departmental communication.

The steps taken by the Department of National Defence as well as those planned by Health Canada, although belated, are welcome. The Committee accepts the sincerity of those involved and has noted Health Canada's belief that the system is a safe one. Nevertheless, systems are only safe to the extent that their rules are adequate and are scrupulously implemented. And all witnesses agreed that a safe system could be made even safer. To repeat the words of Mr. Michols, "the time to do it is now."

Pursuant to Standing Order 109, the Committee requests that the Government table a comprehensive response to this Report.

A copy of the relevant Minutes of Proceedings *(Meetings Nos. 4 and 9)* is tabled.

Respectfully submitted,

JOHN WILLIAMS

Chair