f. why is the effective dosage of mefloquine taken by Canadian Forces stronger than the equivalent dosage given U.S. military personnel and what are the possible adverse effects of such stronger dosages?

"The specific policy regarding the consumption of alcohol is left to the Field Commander who determines the amount of alcohol permitted per day during deployment. In Somalia, members were not permitted any alcohol during the first six weeks of their deployment, following which each member was allowed tow beers per day, except on special occasions where no restrictions were imposed, e.g. regimental birthday. In Rwanda, members are permitted tow beers per day four days of the week with no alcohol one day a week."

"Until quite recently, there was no scientific evidence that personnel taking mefloquine were at an enhanced risk of a serious adverse interaction when drinking alcohol. Further, the prescribing information for mefloquine does not mention concern about such an interaction. Thus when [CF] members were deployed to Somalia and Rwanda, there was no evident need to warn those taking mefloquine about an interaction with alcohol..."

Hansard, April 3, 1995 (asked on November 14, 1994, answered on April 2, 1995), Hon. Fred Mifflin, Parliamentary Secretary to Minister of National Defence and Minister of Veterans Affairs.

November 17, 1994: DND says adverse effects may reach 40%:

"Severe psychiatric effects have been reported in the literature and some of our members have anecdotaly reported problems while taking this drug. The incidence of adverse effects may approach 40%. Clearly such adverse effects may have a significant impact upon the operational capabilities of our forces. Rigorous assessment of this potential problem has not been done and is clearly indicated. This study is needed to fill this gap...Typical adverse reactions include irritability, fatigue, vivid dreams with potential sleep disturbances and/or nightmares. While it may be posited that these effects can have an adverse impact upon our operationally deployed personnel this has never been formally studied. The popular press has suggested that these adverse effects may be responsible for some of the critical events that have occurred in recent peace keeping missions. While this is unlikely it does become important to know what sort of impact Mefloquine might have upon the cognitive and psychomotor functioning of our members." Research Proposal: Military mefloquine Adverse Drug Reaction Study, Maj R. Boddam

December 1994: Media report indicates Scott Smith had problems with mefloquine:

"One commando I talked to at length typifies the soldiers doing double duty as escorts

and drivers. CPL Scott Smith suffered six months of dysentery during his last tour in Somalia and is one of the unfortunate ones to react to the malaria medicine everyone has to take. He experiences hallucinations. But in Rwanda he is prepared to endure these side effects and risk dysentery again because he believes his effort, and everyone's effort makes a difference...What carries you on is knowing people have survived some of their ordeal because you were there." Transportation Logistics, Bonnie Toews (December 1992 issue ?)

December 2, 1994: Hoffmann La Roche note on *interaction between Lariam and alcohol, body building steriods, stimulants and other related drugs.*

"This letter is in response to your *request for information concerning Lariam and interactions with alcohol, body building steriods, stimulants and other related recreational drugs.*

A literature search was initiated but failed to retrieve any relevant references in Medline, RoPu, EmBase, REPG, Coof Papers Index, Current Contents, ans Toxline databases. Please note, this information is subject to the limitations inherent in the searched databases and cannot be considered exhaustive.

A Drug Safety of Spontaneous Evetns associated with Lariam since introduction unitl January 1, 1994 was conducted...*Fifty-four spontaneous adverse event have been received in which concomitant use of alcohol was reported. It is difficult to evaluate these cases, since a patient is more liekly to be questioned about alcohol consumption if her presnets with such symptioms as hallucinations, delirum, confusion, or ataxia. Four patients reported "excessive " alcohol use prior to the onset of symptoms. One patient with myalgia felt repeatedlt worsening of his pain after alcohl consumption.*

Of the 54 patients reporting concomitant alcohl consumption, 111 adverse events were reported and are summarized as follows.

Type of Adverse Event	***No.***
Psychosis, hallucination, delirium	14
Convulsions	6
Ataxis, dizziness	8
Sensory, mortor disturbances	5
Headache	7
Anxiety, agitation, concentration impaired	9
Depression	6
Sleep disorders	6
Weakness, arthalgia, myalgia	11
Circulatory disturbances	4

Hepatic disroders	4
GI disorders	13
Eye disorders	4
Skin disorders	4
Others (hypoglycemia, menstrual disorder, palpitation, Wt. decrease, tinnitus, incr. creatinine, fever, dyspnea)	10
Total No. of Adverse Events	**111**

Based on the available information an interaction between lariam and alcohol is not supported. The events which occurred after excessive use of alcohol could be attributed to the alcohol alone or to mefloquine.

An alcohol interaction study in volunteers is in progress in the Netherlands. However, data are not yet available from this study.

Regarding your question on the interaction between Lariam and recreational drugs we do not have data at this time to support a possible interaction with these drugs. However this does not exclude a possibility of neuropsychiatric reactions or cardiac arrhythmias, which are possible with each drug alone occurring as additive effects. Since these drugs are usually illegal it would be difficult to do studies. All that I can say is that we are not are not aware of any supportive data.

Lariam Interactions, Antoinette Meinders, Professional Services, Hoffmann La Roche Canada [written as a fax transmission on fax stationary]

December 28, 1994: **"DHPP has learned today, after telecon from *LCol L. Scott* about the subject case, 23 years old male, from the Airborne Regiment, CFB Petawawa who committed suicide...on Xmas day, 25 Dec 94 at 03:30 hrs in Kilgali, Rwanda...Apparently this patient had a history of hallucinations during his tour in Somalia, which he related to the antimalarial drug that he was taking (mefloquine). Before going to Rwanda he gave interview to the media on mefloquine and it was released in the Canadian Transportation Logistics, vol 97, issue No 10, 94..."** Capt R.C.D. Climie DHPP (Minute Sheet, Suicide Case - Op lance, Kigali, Rwanda, December 28, 1994)

January 6, 1995: **Possible interaction between Lariam and alcohol and other recreational drugs.**

"As discussed during today's telephone conversation, please find attached the response that was prepared to a questions that was recently forwarded to us regarding the potential for an *interaction between Lariam and alcohol and other recreational drugs*."

[the attachment referred to is the notation for December 2, 1994 above]

Lariam NDS - Control #08278, fax from Hoffmann La Roche to Dr. D. Burns - I & I BHPD, HPB.

January 10, 1995: Mefloquine used in Rwanda by CF:

"All personnel received predeployment preventive medicine briefings and immunizations...

"Mefloquine 250mg was taken as a malarial prophylaxis with very few side effects reported. Doxycycline 100mg daily utilized as the alternate prophylaxis...

"No Canadian personnel have been confirmed with malaria.

"To date 193 personnel have reported to the Unit Medical Section with a history of diarrhoea. Of these cases, 120 were CF, 35 other UN military personnel and the remaining 36 were UN civilian employees...

"In theatre health education was provided periodically to Cdn pers... by LCol Scott...on topics such as HIV, Hep B...Malaria, Mefloquine...

"The general health and morale of 1 CDHSR personnel was high throughout OP Lance despite the apparent suicide of an Airborne soldier on Christmas morning...

1 CDHSR Preventive Medicine Post Deployment Summary Rwanda, from LCol K Scott OC Med PI 1 CDHSR, to DHPP

February 2, 1995: Newspare report on possible link to mefloqine in the death of Scott Smith:

"The family and friends are now wondering what role was played by thte anti-malaria drug mefloquine which doctors agree can cause erratic behavior...

"Dr. Barry Armstrong, who served in Somalia as part of a Canadina Forces platoon, has deep concerns about the drug and has suggested a suicide attempt in 1993 "may have been in part mefloquine reated." The soldier in question although facing discipline tried to hang himself."

"Armstrong has also suggested the drug may have played a role in the well-publicized difficulties experienced by the Canadian Airborne Regiment in Somalia including the beating death of a teenager.

"I think there is a problem with it," Armstrong said..."

"The miliary is investigating Smith's death but won't say directly if mefloquine is being explored as a factor in his suicide. A spokesman in Rwanda, however, doubts it will be disregarded.

"The drug...was issued to Canadian soldiers in Rwanda every Thursday.

"Family wants to know if soldier's death linked to drug: The military is investigating Cpl. Scott Smith's death, but won't say directly if mefloquine is being explored as a factor in his suicide", Dan Nolan, The Ottawa Citizen, February 2, 1995 (p. A3).

February 16, 1995: "Based on this new information, the additional advice that will be given to CF members taking *mefloquine* in the future will be that, while excess *alcohol* is never recommended, they should exercise particular caution while on this medication." MGen W.A. Clay, Surg Gen (Comments on SI of Scott Smith's death)

February 20, 1995: Tepper comments on role of mefloquine in suicide in Rwanda

"The antimalarial drug *mefloquine* is explored in the SI as a possible contributor to Cpl Smith's state of mind and *suicide*. The following comments are provided: Until very recently, I would have said that a contribution of *mefloquine* to this suicide was marginally possible but unlikely. *Mefloquine* can cause mood changes, including depression, although these changes are usually mild and decrease as more doses are taken...in light of the report at ref B and Cpl smith's *suicide*, DHPP will issue instructions to CFMS to ensure that members put on *mefloquine* are cautioned about the need for responsible drinking..."

LCol Martin Tepper, DHPP2 (comments on SI of the death of Scott Smith)

February 20, 1995: HPB speaks to Hoffmann La Roche on possible interaction between mefloquine and alcohol:

"Discussed potential for etoh. interaction [with Hoffmann La Roche]. She will review CMAJ article...and look into Netherlands study...notify"

hand written note on the May 1994 Roche Research Report, Review of Adverse Events Associated with Lariam, note at page 37 where interaction between alcohol and mefloquine is considered, signed by P.M. McDonald

February 21, 1995: **Interaction Between Alcohol and Lariam:**

"This is an issue that was discussed with the manufacturer at the time that the Notifiable Change was submitted in response to their HPB letter of 26 July 1994. The response from the manufacturer was as follows:

> 'No data as yet to substantiate an interaction between Lariam and alcohol. The events which occurred after excessive use of alcohol use could be attributed to the alcohol alone or to mefloquine.
>
> An alcohol interaction study in volunteers is in progress in the Netherlands. Until further data are available we not support a warning in the package.'

The current Product Monograph for Lariam has a statement in the Patient Information section suggesting that the consumer avoid alcohol when taking mefloquine.

Further to the recent article in the CMAJ...[by Wittes and Saginur], the manufacturer was contacted...I suggested that the case discussed in the CMAJ article be included in the 'Adverse Reactions' section of the Product Monograph...

Potential for Interaction Between Alcohol and Lariam, from Dr. P.A. McDonald to R. R.E.A. Gadd, Acting Chief of Infection and Immunology Division, HPB

February 27, 1995: **Interaction between Alcohol and Lariam:**

"[Hoffmann La Roche] called me. Netherlands study still ongoing...So far no clear interaction between mefloquine and Etoh. CMAJ article to be sent to headquarters in Basel.

Also discussed issue with Dr. Pless, BPS. Will do international data search for interaction and get back to me. Besides the one case in CMAJ no other local cases in their data base."

hand written note by D. P.A. Mcdonald, attached to note to Dr. Gadd

March, 1995: **"Although we have not gathered routine data regarding mefloquine side-effects among those taking mefloquine, medical personnel deployed with these troops estimate that perhaps 10-20% of those on mefloquine complain of such side-effects as vivid dreams. However most members do not seek medical attention among those taking mefloquine."**

"As Dr. Tepper of my staff discussed with you on 23 February 1995, it is requested

that CATMAT review the situation regarding the efficacy and side-effects of mefloquine as an antimalaria prophylaxis."

"While applicable CF medical personnel have reviewed the situation regarding the CF use of mefloquine, it is important for various reasons, including public perception, that an external credible body provide feedback to us regarding mefloquine."

Maj Gen W.A. Clay Surg Gen, to HPB, Review of Mefloquine by CATMAT

March 2, 1995: **"The conclusion of report authors (CMAJ, Wittes) is quote the circumstances of this case strongly suggest that it was a combination of mefloquine and ethanol that caused (his) two episodes of severe psychiatric disturbance...whatever the mechanism of adverse reactions to mefloquine, it may be prudent to warn patients taking mefloquine prophylactically to avoid excessive ethanol intake while taking the drug and for several weeks thereafter...This report causes some concern. In light of this report, members who are prescribed mefloquine are to be warned against the concurrent excessive use of alcohol."** DHPP 3, message to medical service units, Mefloquine and Alcohol

March 3, 1995: **Dutch study result for Hoffmann La Roche:**

"We did in fact discover a mefloquine-ethanol interction but of a totally uinexpected sort: the drug antagonized the adverse effect of ethanol on volunteers' driving performance..."

"In direct answer to your question, our study was apparently the first to address the question of a possible mefloquine-alcohol inbteracgtion. Instead we found the opposite for the group as a whole..."

letter to Drug Safety at Hoffmann La Roche Canada, from Dr, James F. O'Hanlon, Director of Institue for Human Psychopharmacology, Masstricht, The Netherlands.

March 5, 1995: **"The CAR was disbanded on March 5, 1995**, only a few weeks before this Inquiry was established." (page 350, volume 1, *Report*)

April 3, 1995: **Response to Parliamentary Question Q-105:**

"a. (what clinical or field studies did the Department of national Defence undertake into the possible adverse effects including the impairment of judgement of the mandatory use of mefloquine by Canadian Forces while in somalia, both while in Somalia and on their return to Canada?) None was conducted and none was deemed necessary."

"b. (What clinical or field studies did the Department of National Defence undertake or fund into the possible adverse effects including impairment of judgement of the mandatory use of mefloquine in Rwanda...?) None was conducted and none was deemed necessary."

"c. (what amount of alcohol was available on a daily basis to Canadian Forces personnel in Somalia and later in Rwanda who had received the mandatory dosage , what adjustments or precautions were made to the dosages by those administering the drug and what advice was given to persons required to take mefloquine who might be expected to use alcohol during their tour of duty?) The specific policy regarding the consumption of alcohol is left to the field commander who determines the amount of alcohol permitted per day during deployment. In Somalia members were not permitted any alcohol during the first six weeks of their deployment, following which each member was allowed two beers per day, except on special occasions where no restrictions were imposed, e.g. regimental birthday..."

Hansard, question by John Cummins, answered by Hon. Fred Mifflin, Parliamentary Secretary to Minister of National Defence.

April 5, 1995: Hoffmann La Roche on changes in product monograph to reflect possible interaction between mefloquine and alcohol:

"Further to your requests concerning 1) dosage 2) interaction with alcohol we can now provide the following information.

2) **Alcohol/Mefloquine Interaction**

Attached is the only information we have available at this time on study #MK 10600 being conducted in the Netherlands by Dr. O'Hanlon.

No case of an adverse reaction to the combination was observed.

We believe that, at this time, there is no evidence to justify a change in our product monograph."

Lariam, Hoffmann La Roche letter to Dr. P. McDonald, Infection and Immunology Division, Bureau of Human Prescription Drugs, HPB

April 19, 1995: HPB considers Hoffmann La Rcohe's to request for changes in product monograph to reflect possible interaction of mefloquine and alcohol:

"Discussed with Dr. E. Gadd 18/4/95. Acceptable colurse of action for now. Will await full study report."

hand written notation on Hoffmann La Roche letter of April 5th above, signed by Dr. P. McDonald of HPB

May 2, 1995: CF responds to Access to Information request on its use of mefloquine.

"There is no central registry of each member who was placed on mefloquine for operational reasons since the CF began using mefloquine in 1992...

"The best that can be provided at this time is a list of the major operations where mefloquine was recommended as the first line antimalarial drug; it is presumed that the very large majority of personnel on these operations would have taken mefloquine. Mefloquine has been recommended for the following major CF operations (where know, number of persons who participated in the operation is noted in parentheses): Angola (13), Cambodia (mefloquine was used early in this deployment but was discontinued in favour of doxycycline because of a problem with resistance of malaria to mefloquine in Cambodia), Somalia (1205), Rwanda (634), Mozambique (30), and Ethiopia.

"Copies of all records pertaining to the investigation of mefloquine treatment ordered by the Defence Minister in 1994. A search has failed to uncover any records pertaining to this item.

"It is estimated that additional search and preparation fees will amount to $605,000.

from Coordinator Access to Information and Privacy at DND

May 3, 1995 **Deputy Chief of Defence Staff, mefloquine a contributing factor in suicide.**

"I concur in the DHPP3 suggestion that alcohol was likely a significant contributing factor to Corporal's death. Based on DHPP3's comments and the findings, it is possible to conclude that mefloquine was also a contributing factor, but with less probability. I recommend that the Surgeon General actively look for evidence to establish whether mefloquine and alcohol together affect individuals' metal balance, dangerously more, than do those drugs taken separately."

Summary Investigation Death , CPL Smith S.F. Infmn 031, Comments of the Commander of a Command, VAdm L.G. Mason, Deputy Chief of Defence Staff

September 29, 1995: **Testimony on mefloquine in Somalia:**

"(Did your Platoon use that?) Everyone in the Airborne Regiment had to take it."

"We took it a month before and every week until a month after.

"(Any side-effects, effects?) It's hard to say because we were all taking it. Subsequently to well the last year, I've heard instances where alcohol has triggered a sycosis in people that had taken mefloquine. But over there we were the first ones to use so."

Testimony of WO Murphy *(Somalia Inquiry)*

December 6, 1995: **Results of Dutch study of interaction of mefloquine and alcohol and its effect on driving performance:**

Subjects:

Exclusion criteria were...evidence of drug or alcohol abuse, excessive alcohol or nicotine use...All were ethnic Caucasians...

Design and Treatment:

...Ethanol (70%) was given in seven 3.9 g doses at approximately 30 min intervals...The alcohol dosage regimen was developed...fro achieving and sustaining a blood alcohol concentration between 0.3 and 5.0 mg/ml, the latter being the legal limit for drivers.

Dropouts and Missing Data

Two female subjects dropped out of he mefloquine group after taking tablets on days 1-3 and were replaced. One experienced nausea and vomiting accompanied by dizziness on day 4. Her complaints were deemed to be drug related. The other experienced malaise, fever, headache and cough and was diagnosed as suffering from a flu.

Adverse Events

Including the dropouts, 11 (50%) and 9 (45%) subjects in the mefloquine and placebo groups reported at least one adverse event...The number of events were 21 and 13, respectively. Events occurring more than one in mefloquine/placebo groups were as follows: nausea (accompanied by vomiting in the dropout) 4/2; dizziness 3/2; fatigue 2/2; headache 4/0; lightheadedness 3/0; and diarrhoea 2/1.

DISCUSSION AND CONCLUSIONS

To our surprise, the mefloquine group drove better than the placebo group in the Highway Driving test on day 4 and maintained their advantage, albeit not significantly,during its subsequent repetitions. It is especially noteworthy that the mefloquine group better than the placebo group after the alcohol challenge, particularly during the second half of the Highway Driving test. These result do not contradict a case reported of na individual who experienced psychotic episodes after drinking o.6L if whisky on tow occasions during mefloquine prophylaxis...Anyone who consumes similar quantities of alcohol in one sitting while taking mefloquine may experience similar reactions. But the results of this study show no pharmacokinetic interaction between these agents and nothing that would suggest mefloquine potentiates the adverse effects of alcohol in blood concentrations below o.5 mg/ml.

...Mefloquine...more commonly produces aniety, nervousness and insomnia in ordinary ones [patients]....Clearly the work to elucidate any mechanism of drug's CNS activity has hardly begun.

Test that would not be expected to show any adverse effect of a mean BAC of 3.5 mg/ml after a bolus oral dose, showed highly significant effects of the same concentration achieved by multiple dosing. Only the Critical Instability Tracking Test failed to show impairment due to alcohol. The results obtained in both driving tests were of greater practical relevance. Apparently driving performance impairment is not simply related to the momentary blood alcohol concentration. It also depends upon the time-integral of concentrations that exist beforehand. The implications of this unexpected result will receive the attention they deserve in another article."

Hoffmann La Roche Research Report No. B-164'282 Mefloquine and placebo effects, with and without an alcohol challenge, on psychomotor and actual driving performance in healthy volunteers, E. Vuurman et al, Institute for Human Psychopharmacology, University of Limburg, Maastricht, The Netherlands

Dec. 21, 1995 **Decision in Matchee case at Entitlement Review stage (Veterans Review and Appeal Board, rejected entitlement, found Matchee had taken mefloquine as a preventive rather than as a response to malaria, therefore interpreted the information given it that neuropsychiatric effects arose only when taken to combat malaria, furthermore they noted there was no record of Matchee complaining about the effects of mefloquine, therefore he could not have suffered a problem with it.**

- "The Advocate commenced his presentation by stating that, for the purposes of this Hearing, he would be arguing that no person other than Mr. Matchee himself was involved in his attempted suicide and that no one aided or abetted Mr. Matchee in his attempt to hang himself while in a detention cell in Belet Uen,

Somalia, on 19 March 1993.

- With respect to the necessary evil mind, the mens rea, the Advocate submitted that the authorized drugs that Mr. Matchee was taking while in Somalia, which drugs had been provided by competent medical authority did not permit him to form the necessary mens rea, or evil mind, which is required before a finding could be made by this Panel that Mr. Matchee's self-inflicted wounding was "willful" as required to fall within the-definition of "improper conduct in subsection 3 (1) of the *Pension Act.*

- The Advocate contended that because of the drugs that were taken by the applicant as part of his Military duties to protect him from local diseases, especially malaria, his Mind may have been so clouded that he could not form the necessary mens rea (the evil mind) to know what he was doing when he was hanging himself.

- The Advocate referred to the drug Mefloquine which he submitted was taken by Military members in Somalia as an anti-malarial agent. The Advocate contended that there was the the possibility that the applicant could have had an adverse reaction to this drug and submitted as exhibit "ER-M8" a copy of a relevant portion of the 1995 Canadian Pharmaceutical Association Report respecting Mefloquine. In part, that Report states:

> *"Adverse Events: When Lariam (Mefloquin) is used as malaria prevention, the most frequently 'observed adverse reactions have been nausea, vomiting, abdominal pain, and dizziness. These events usually subside within time after drug, a short period of time administration. If these adverse events are not severe in nature and are tolerable, it is in your best interest to continue Lariam prophylaxis since the consequences of contracting malaria are a cause for greater concern.*
>
> *"As doses given for malaria treatment adverse reactions to Lariam were not distinguishable from the symptoms of malaria. The most frequently adverse reactions included dizziness, muscle aches, nausea, fever, headache vomiting, chills, diarrhea, skin rash, abdominal pain, fatigue, loss of appetite, and ringing of the ears. Other complaints include a slowing of the heart, emotional problems (Panel's underlining), itchy skin and seizures. After taking Lariam to treat a malarlia attack you may become faint. Bed rest should help to alleviate this effect."*

- While the Advocate contended that Mefloquine could cause emotional problems, the Board notes that this has been diagnosed only with respect to malaria treatment and not with respect to malaria prevention. There is no evidence

available to indicate that the applicant suffered from malaria and therefore the Mefloquine he was taking for malaria prevention does not have one of its noted side effects emotional problems. The Panel does note that the information continues that "If You experience unexplained anxiety, depression, restlessness, or confusion, stop taking Lariam and consult a doctor immediately." In this regard, there is no indication provided to this Panel that the applicant suffered from any such symptom or contacted any doctor about any problems with Mefloquine prior to his arrest.

- In summary, this Panel finds, based on a full and careful, review of all of the evidence presented to it, that the applicant's actions in attempting to commit suicide were "willful", that his injury was self-inflicted and, as such, that this constitutes the improper conduct" referred to in subsection 3 (1) of the *Pension Act*.

- As the Panel has determined that the claimed condition is solely the result of the improper conduct of the member, in that he displayed both the necessary mens rea and actus reus this Panel, while mindful of its duties and responsibilities pursuant to subsections 3 and 3.9 of the *Veterans Review and Appeal Board Act* to resolve any questions-of doubt in favour of the applicant, has found that no such doubt exists in the circumstances of this case.

- The Board therefore finds that the claimed condition arose solely from the improper conduct of the applicant as referred to in subsection 22 (1) of the *Pension Act* and, therefore, that entitlement is not indicated."

February 9, 1996: Result of Dutch study using driving tests to consider the effect of mefloquine and alcohol interaction:

"The results of this study showed not detrimental mefloquine effects in any test but rather the opposite in two. It reduced the rise in road tracking error which normally occurs as a function of driving time in the 60 minute test, resulting in significant overall drug-placebo difference. It also antagonized alcohol's effect on postural stability in the Body Sway Test. Mefloquine did not impair coordinated psychomotor activities necessary for safe driving, rather it sustained them through a provigilance effect.

Due to the above results, we are not recommending any changes to the product monograph."

Lariam Tablets Interaction with Alcohol (Report #B-164'282, "Mefloquine and placebo effects, with and without an alcohol challenge, on psychomotor and actual driving performance in healthy volunteers"), Hoffmann La Roche to Dr. Phillipa McDonald, Infection and Immunology Division, Bureau of Human Prescription drugs, HPB

February 14, 1996: WHO comments on mefloquine related problems amongst military personnel:

"In *International Travel and Health - vaccination requirements and health advice 1992* Cambodia is mentioned as a "C" category country, for which the published recommended malaria prophylaxis is "doxycycline or mefloquine, in order of preference" and "no prophylaxis in case of very low risk". Relating to doxycycline it is further stated that "there is relatively little experience with these drugs, and knowledge of their efficacy and toxicity is limited"...

In the first half of 1992, the Malaria Unit of the World Health Organization prepared a brochure Malaria Information for *UNTAC Staff in Cambodia.* In the earlier draft of draft of this brochure, doxycycline was recommended for the Thai-Cambodian border and western Cambodia, while mefloquine was recommended for those stationed in Eastern Cambodia. Those staying only in Phnon Penh and Battambang were advised that they would not need to take malaria prophylaxis. In the revised version of April 1992 mefloquine is taken out of the recommendations, based mainly on a concern about neuro-psychiatric side-effects of mefloquine. Such side-effects are relatively rare, but were considered of particular concern in military personnel. Thus, as of late April 1992 the WHO recommended malaria prophylaxis for UNTAC staff in all endemic areas in Cambodia became doxycycline...

Malarian Prophylaxis 1992 Cambodia, Dr. A.E.C. Rietveld, Malaria Unit, Division of Control of Tropical Diseases, World Health Organization, February 14, 1996.

March 18, 1996: HPB evaluation of the Hoffmann La Roche Duthc Study on the effect of the interaction of mefloquine and alcohol on driving performance.

Background:

"The HLR conclusion was that on the basis of this data an interaction was not supported, and that all events noted to date could be attributed to the effect of the alcohol alone or to mefloquine. The company also notified the Bureau that a study was underlay in the Netherlands to look at mefloquine...with and without an alcohol challenge, on...driving performance..."

"After discussion with BHPD a statement was included in the Information to the Consumer section of the PM in January 1995 to read as follows: "It is best to avoid alcoholic drinks during treatment with Lariam.""

"...This article in the CMAJ was discussed with the manufacturer. The general consensus at that time was that this was probably and idiosyncratic reaction....The

manufacturer made a commitment to provide the complete data from the [Dutch] study after its conclusion and analysis, and in the interim to continue tracking any potential for an interaction between mefloquine and alcohol. No further changes were made in the product monograph at that time."

"The data from the Netherlands study are now available for review."

"Conclusion: ...These findings are of relevance for travellers taking mefloquine who drink moderately before proceeding to drive..."

Recommendation:

1. Discuss study design and results with Bureau statistician to confirm the conclusions of the authors.

2. Send a letter to the manufacturer requesting that they include i the Precautions section of the Product Monograph the one recorded case where an adverse reaction occurred after ingestion of large quantity of alcohol on the same day that the mefloquine prophylaxis was taken (Wittes et al). Suggest that a brief summary of the results from study #B164'282 be included in this section in order to keep this single case in perspective.

3. Send copies of the abstract from study...to Dr. C.M.Wray, Bps, ADR Monitoring Division and to Dr. B. Gushulak, LCDC

05/07/96: Awaiting response from HLR on this issue.

Lariam tablets Interaction with Alcohol (study no. B-164'282), Dr. P. McDonald of Infection & Immunology Division, to Dr. Ed Gadd Acting Chief of Infection & Immunology Division, HPB

April 16, 1996: Testimony on mefloquine in Somalia:

"(With regard to mefloquine, were you aware of any problems, any side effects from that either from your personal experience or form stories from others?) Yes. Wednesday was mefloquine day. PMS, there was pre-mefloquine and post-mefloquine syndrome. I personally had one experience where I went from in the course of the day having taken my pill from a very high almost euphoric type of feeling to a very low to the point I was ready to burst into tears and I couldn't quite understand. I started snapping at people and crazy. Whether it was the particular time whatever I'm not sure or if it was the mefloquine. One stands out in my mind. We did have one incident of a soldier in 3 Commando in the early stages, in fact, not long after we'd got there, Major Magee could probably go into more detail or the medical officer, who was evacuated and there some

suspicion that he was having a reaction to the mefloquine. He was in severe depression, couldn't take the pressure and the stress of the situation."

Testimony of Maj R. MacKay *(Somalia Inquiry)*

April 18, 1996: Testimony on mefloquine in Somalia:

"Some people, they called them the dream pill or the nightmare pill. Some people had a hard time sleeping the night they took it but I was never...did in that way."

Testimony of MWO J. Franklin *(Somalia Inquiry)*

April 18, 1996: Testimony on mefloquine in Somalia:

"(What side-effects did you experience?) Usually it was just the inability to sleep, some I guess you'd call it *feeling of euphoria.* In Service Commando the term we used was mefloquine Wednesday, where ...of the Commando would take their pill on wednesday and that portion would be up all night doing various things like listening to music, just shooting the breeze. A loot of people had the problem where the time period afterwards sleep was not attainable." *(Somalia Inquiry)*

"(Any experiences with vivid dreams?) Yes."

"(How long did these side effects or symptoms last? For the entire duration, just for the first part of your deployment?) It was for the whole time."

Testimony of Capt John Powell

May 28, 1996: Testimony on mefloquine in Somalia:

"(What were the complaints?) Weird dreams."

"(Did it lead to anything other than that you are aware of? You know any kind of irrational behaviour when they were awake?) Not that I can recall. We sued to joke about it, and it's not funny in retrospect. We use to joke about walking to someone you didn't like, putting 3 rounds into him."

Testimony of Maj Mansfield *(Somalia Inquiry)*

June 26, 1996: HPB analysis of Hoffmann La Roche study of the interaction of mefloquine and alcohol on driving.

"The test for treatment difference is not particularly powerful by design. If it is in the interest of the sponsor to show no difference, then the issue of power of the test becomes important."

Notes on Mefloquine Review, appears to be by Dr. P. McDonald, HPB.

July 17, 1996: Review of Notifiable Change in Product Monograph regarding the potential for an interaction between mefloquine and alcohol:

"In response to BPA's letter of March 15, 1996, [HLR] has submitted a Notifiable Change for the Lariam Product Monograph regarding the potential for an interaction between mefloquine and alcohol. In the interim, the Bureau statistician has provided an informal comment on the study as follows:...

"This comment was referred back to HLR on 3/7/96 for their comments. Since the manufacturer has had to refer this issue back to the study's author's, insufficient time will be available to respond by the due date of August 1, 1996. A "Notifiable Change - Refusal Letter" will therefore be sent to Hoffmann La Roche to allow more time for their response on this statistical issue...

"2. Incidence figures (where available) should be provided in the Product Monograph for the most frequently reported adverse events associated with mefloquine use -see paragraph 1, "Adverse Reaction" section PM.

"Conclusion: A "Notifiable Change - Refusal Letter" will be sent to Hoffmann La-Roche to allow more time for their response to the statistical issue raised by Bob Li. Other issues that have arisen during the review of this Notifiable Change will be included in the letter for the hoffmann La Roche's consideration and response in the re-submitted Notifiable change.

Review of Notifiable Change for Lariam: Summary and Evaluation of the Notifiable Change, Dr. P.A. McDonald (Infection & Immunology Division) to Dr. Ed Gadd, Acting Chief, Infection & Immunology Division, HPB

July 19, 1996 **Hearing and decision of the Veterans Review and Appeal Board at Entitlement Appeal stage; finding no medical evidence to indicate that mefloquine caused emotional problems for Matchee; further that there is no evidence regarding Matchee's use of the drug, side-effects etc.; the Board therefore refused to consider mefloquine was a factor in Matchee's attempted suicide.**

- "The Advocate contended that the Entitlement Review Panel made an error in

dismissing the contention that the drug taken by the Appellant to protect himself from local diseases, Mefloquine could have had adverse effects such as creating emotional problems.

The Entitlement Review Panel dismissed this claim on the basis that emotional problems resulting from Mefloquine only occur in situations where it is being used in the treatment of malaria and not as a result of the prevention of malaria.

The Advocate contended that "the combination of the drug effects and the severe mental stress the appellant was under at the time could most certainly have combined to effect adversely his entire mental being'.

- The Board has found no medical evidence to indicate that the drug Mefloquine caused any emotional problems for the Appellant which would effect his decision-making capabilities.

  There is no evidence regarding his use of the drug, side effects, etc..

  Therefore, the Board will not speculate on this being a factor in the Appellant's behaviour leading to his attempted suicide.

- Based on the review of all the evidence presented to it, the Board has concluded that the Appellant's attempted suicide was a "wilful self-inflicted wounding" and thus constituted improper conduct as per subsection 22 (1) of the Pension Act. Consequently, a pension cannot, for this reason, be awarded to the Appellant."

(heard July 19, 1996, decision rendered in June of 1997)

January-June 1997: India approved the manufacture and marketing of mefloquine.

August 27, 1997: Changes in Product Monograph:

"...in support of the supplemental New Drug Submission for Lariam fro a revised Product Monograph, we are submitting herein revised pages for a monograph, using as a baseline the SNDS version submitted April 21, 1997 and including the additional safety information June 4, 1997...."

Response to Telephone Request of August 17, 1997 Lariam Tablets - SNDS Product Monograph, Hoffmann La Roche to Dr. Philippa McDonald, Bureau of Pharmaceutical Assessment, HPB, Health Canada

September 8, 1997: **Lariam Safety Monitoring Study & Lariam in Somalia**

"As per your request, attached is the order form which accompanied the October 6/1992 shipment of 800 bottles of Lariam tablets sent to the Central Medical Equipment Deport at CFB Petawawa."

"As indicated on the form, the shipment of 800 bottles was made to Dr. Saginur for the *Lariam Safety Monitoring Study*."

Hoffmann-LaRoche, to Dr. Ed Gadd of HPB, Health Canada.

September 16, 1997: **(Request for Clarification) Changes in Product Monograph:**

"in accordance with the Drug Directorate Policy of Drug submissions - May 3, 1993, we request clarification of the points on the following pages so that we can continue our evaluation of the safety & efficacy of your Supplemental New Drug Submission for lariam, Control Number 050461."

"...you have included a new indication for 'Self-Treatment' in the 'Indications and Clinical Use' section for the Product Monograph and claimed that this was supported by the safety information submitted on June 4, 1997. The information was not solicited by us and is not considered to be safety information...in order to include this indication in the Product Monograph a separate Supplemental New Drug Submission must be filed with the appropriate supporting data for self-treatment of malaria with mefloquine. Therefore please delete the self-treatment indication from the current draft Product Monograph for lariam."

It should be noted that [CATMAT] has not recommended mefloquine for the treatment of malaria on the basis that mefloquine is less well tolerated at treatment doses and serious neuropsychiatric reactions are reported to be 10-60 times for frequent..For this reason a specific indication for lariam self-treatment may not be appropriate in Canada..."

Request for Clarification, Dr. Phillippa McDonald, Bureau of Pharmaceutical Assessment, HPB, Health Canada, to Hoffmann La Roche.

September 19, 1997: **Lariam Safety Monitoring Study:**

"Further to yesterday's telephone conversations with yourself and Dr. Philippa McDonald, we are sending you the following information on the Safety Monitoring Study:

1) A 3 page listing of Doctors/# of patients and # of pills for 1991 (table dated 28-July-93), for 1992 (table dated 31 May 93) and 1993 (table dated 31-May-93).

2) An 8 page print-out dated 18 Aug 1993 of the adverse events reported in the study arranged by organ category. You will note that this print-out is more up to date than the one submitted to the NDS on July 30, 1993, as preliminary data."

Hoffmann-La Roche, to Dr. Ed Gadd of Health Protection Branch, Health Canada

October 7, 1996: Hoffmann La Roche responds to HPB Refusal Letter on product monograph:

"This letter is in response to the Refusal Letter dated July 17, 1996 for the Notifiable Change to the Product Monograph of Lariam. The comments will be addressed in the order as per you letter:

1. In general, the Statistician responsible for the statistics in the report, agrees with the comments from your statistician. Report No. B-164'282 filed February 12, 1996 contains all individual data which would permit the additional statistical analysis. Plots of power curves for each variable and the comparison of the effects of alcohol can certainly be performed. Due to time constraints and priorities it is not possible for our statistician to do it at this time, however, we are enclosing a diskette with the individual data to facilitate the analysis by your statistician.

3. From the data available, it is not possible to derive incidence figures for the most frequently reported adverse events associated with mefloquine...

4. No interactions have been noted between quinolone and Lariam. Although this is not included in our product monograph, it has been evaluated in the annual safety reports. At no time has there been evidence to suggest there is an interaction...

6. The Australian prescribing information is enclosed. However, please note Australia is currently revising it further as per tem updated International Product Information...

Lariam Notifiable Change, Control #042979, Response to Refusal Letter, Hoffmann La Roche to Mary Carman (Attention of Dr. P. McDonald) Director of Bureau of Pharmaceutical Assessment, HPB

December 20, 1996: HPB statistician reports on Dutch drug study (Lariam and alcohol interaction):

"Methods & Results: ...Due to weakness of the design that Alcohol effects and Day effects were confounded, the two-alcohol days were combined to achieve a better comparison for the alcohol effect...Again, there was no significant Drug by Day interaction....

The Issue of Power: As mentioned in the first report in June 1996, when it is in the interest of the sponsor to find no difference, the issue of power becomes important. It was also observed at that time that power was probably not all that bad...

Sex Differences: ...It appears that the females on Lariam were not affected by alcohol whereas the males were relatively speaking, more affected by alcohol while on Lariam..."

Summary: There does not appear to be much to be concerned about the alcohol effects based on the examination of the driving performance outcome SDLP. The design of the study leaves something to be desired, such as lack of a true baseline, confounded effects, etc. However after adjusting for the differences in the study sample, there does not appear to be much of a differential alcohol effect between drugs."

Lariam Notifiable Change - Control No. 048254, Statistical Investigation Report, K.Y. Robert Li, HPB

July 14, 1997 (signed September 16, 1997): Consideration by HPB of changes to the Product Monograph (rejection):

3. Preclinical & Clinical Evaluation Report

3.2 "This S/NDS is in support of a revised Product Monograph for Lariam..."

4.0 NDS Conclusions and Recommendations

4.2 "A statement remains in the "Warnings" section regarding concomitant administration of mefloquine and various drugs as relates to electrocariographic abnormalities and the potential for cardiac arrest. This issue will be discussed with the manufacturer since the 1997 CATMAT recommendations for mefloquine use state that mefloquine is contraindicated in patients with underlying conduction disturbances,a s does an article by Drs J. Keystone and K. Lain "Mefloquine dangers - fact or fancy?...

Conclusions:

Note 2: "In the manufacturer's response to my telephone request of August 14, 1997 regarding the proposed changes to the Product Monograph, the manufacturer has included a new indication for "Self-Treatment" in the "Indications and Clinical Use

Section" section of the [PM] supported by safety information submitted on June 4, 1997. This is not safety information, and Roche will be requested to delete this information from the draft monograph."

"A fax was sent to Patricia Norman from Submission Management on June 12, 1997, stating that the additional safety data submitted by Roche was not acceptable for review, and indicating that Roche should re-file the information as an S/NDS if wish to pursue the self-treatment indiction for mefloquine. ...[CATMAT] has not recommended mefloquine for the treatment of malaria (on the basis that mefloquine is less well tolerated at treatment doses and serious neuropsychiatric reactions are reported to be 10 - 60 times more frequent...For this reason a specific indication for Lariam self-treatment may not be appropriate in Canada.

Evaluator's Submission Disposition Recommendation: Not recommended for clearance.

Pre-Clinical & Clinical Evaluation Report, Philippa McDonald, I&L Bureau of Pharmaceutical Assessment, to Mary Carmen, Director of Bureau of Pharmaceutical Assessment, HPB, (signed on September 16, 1997)

Sept. 8, 1997: Shipment of Lariam to DND under LSMS:

"attached is the order form which accompanied the October 6/1992 shipment of 800 bottles of Lariam sent to the Central Medical Equipment Depot at CFB Petawawa."

"As indicated on the form, the shipment of 800 bottles was made to Dr. Saginur for the Lariam Safety Monitoring Study."

Memo to Dr. Ed Gadd, HPB from Hoffmann La Roche, September 8, 1997

September 25, 1997: HPB review of adverse reaction reports:

"The review considered reports entered into the DARRP database (8 reports) and those not yet entered due to the CADRIS conversion (17 reports), total 25 reports. Fifteen reports involved reactions related to the Central Nervous System. These are summarized in the above table. We have reviewed the CPS 1977 and note that apart from suicide (which was from an unconfirmed newspaper majority of the CNS adverse events appear to be mentioned. Of note with respect to the "toxic confusional state", the actual psychiatric manifestations were delusions and hallucinations and these are mentioned in the CPS."

Review of Adverse Events, prepared by Amal Helal, HPB, Updated September 25, 1997 (provided to the Auditor General on October 26, 1998 by Cummins).

October 20, 1997: Parliamentary question on mefloquine (Cummins to Rock, Minister of Health:

"(Canadian troops in somalia were administered the experimental drug mefloquine. DND got the antimalarial drug because it agreed to participate in a *safety monitoring study*. It ignored its commitment. Has the Minister taken any action against either the manufacturer who is responsible for supervising the *safety monitoring study* or the military who acted illegally in prescribing the drug?) The facts are not yet clear. As the member should know, efforts are being undertaken at the moment to determine the facts of the matter. I can tell the hon. member that at the time the drug was put in use, those responsible for supplying it believed on the evidence at the moment and in good faith that it was appropriate for the indicated conditions. The responsible thing to do is to await the outcome of the investigations which, as the hon. member should know, are continuing."

"(The facts were clear at the time the drug was administered and it was clear there was a problem. DND participation in the *safety monitoring study* would have alerted Health Canada of the sometimes intolerable side-effects of the drug mefloquine which were well documented at the time by Canadian military doctors. Can the Minister tell the House why his department did not insist that DND participate fully in the *safety monitoring study* before licensing mefloquine for general use by Canadians?) Hindsight affords the hon. member the luxury of characterizing the facts as he sees fit. As I have already said, investigations are continuing to determine all the facts of the matter, I think the responsible thing to do is to wait until all the facts are at hand before coming to any judgment."

Hansard, Question by John Cummins to Allan Rock, Minister of Parliament (October 20, 1997)

October 20, 1997: Advice to Minister that *Somalia Inquiry* mislead on mefloquine:

"ISSUE: On 14 Oct 97, CTV-W5 reported that the military administered illegally mefloquine...to CF troops in Somalia in 1991-93. CTV-W5 noted that, while the CF had access to mefloquine through a safety monitoring study, they failed to follow the rules of seeking informed consent and monitoring the side-effects of the drug and reporting them to the manufacturer.

"IF PRESSED ON ILLEGALITY OF ADMINISTERING MEFLOQUINE"

- "Mefloquine was acquired legally...
- "Mefloquine was licensed in Europe and could have been acquired outside

Canada for use in Somalia...

"**BACKGROUND:**

- "**Somalia Commission of Inquiry - Mefloquine:** The Commission examined the possibility that severe side effects caused by mefloquine, including abnormal and violent behaviour, may have had an impact on operations in Somalia. Noting that they were not able to explore fully the possible impact of mefloquine, the commission's report states that they were not able to 'reach a final conclusion on this issue' and that "DND's decision t in 1992 to prescribe mefloquine for CF personnel deployed in somalia appears to be consistent with the medical practice of that time." Finally, while stating that 'mefloquine use could have been a factor in the abnormal behaviour of some troops in Somalia,' the commission concedes that 'further investigation is warranted before any firm conclusions about the rile of mefloquine [in Somalia] can be drawn.'"

- "In addition, evidence before the Somalia Inquiry indicates that all approvals had been obtained for the use of mefloquine. It must be noted that there was no intention to mislead the Commission. Until very recently, it was believed that the Surgeon General Branch had informed Health Canada that the mefloquine was being dispensed without the consent for individuals--even the directorate which authorized the use of mefloquine in Somalia was under this misconception. These actions appear not to have taken place as no documents requesting or approving the change can be found."

Advice for the Minister: Mefloquine, LCol Cook, D Med Svc 3 (dated October 20, 1997 and faxed to HPB on October 21, 1997)

November 20, 1997: Auditor General Asked ot Audit Licensing

The Department of Health ignored the illegal use of mefloquine and the shortcomings of the *Safety Monitoring Study* when it licensed the drug," said John Cummins, M.P. (Delta-South Richmond)

Cummins today called on the Auditor General to audit the licensing of the anti-malarial drug mefloquine by the Department of Health's *Health Protection Branch* (HPB).

The drug was illegally administered to Canadian troops bound for Somalia.

DND's use of the drug provided the only opportunity for Canadian doctors to directly observe the drug's possible adverse effects. HPB ought to have shown a keen interest in the findings of DND's participation in the *Safety Monitoring Study*. Sadly that was not the case.

Even after the problems associated with DND's use of mefloquine became highly publicized, HPB showed little or no interest in the illegal use of the drug or the failure to comply with the *Safety Monitoring Study* protocol. In fact, HPB has since hired the officer at DND who was responsible for the illegal use of the drug and who refused to comply with the requirements of the *Food and Drug Act*.

What use was made by HPB of the results of the *Study* in its decision to license the drug? Did the department monitor the *Study* and critically assess its findings prior to the licensing of the drug? Were there similar problems amongst other participants in the Study?

Did other participants treat the legal requirements of the *Safety Monitoring Study* as lightly as did the Department of National Defence?

Did HPB take any action against those participants who used the drug illegally prior to licensing and who undermined the pre-licensing study?

Auditor General Asked to Audit Licensing of Mefloquine, press release from John Cummins, M.P., November 20, 1997.

Jan. 23, 1998: **Further request to Auditor General:**

"As you are aware the Department of National Defence illegally administered mefloquine to its soldiers bound for Somalia. The *Health Protection Branch* failed to respond to the breakdown in the *Mefloquine Safety Monitoring* or in any wayway enforce the requirements of the *Food and Drug Act*.

"By 1993 Canadian military doctors had produced a number of reports detailing adverse effects observed when the drug was administered to soldiers under their care. I want to bring to your attention the information available to *HPB* through these reports.

"As the use of mefloquine by Canadian soldiers provided the only opportunity to observe first hand the effects of the drug, the military use of mefloquine ought to have been of keen interest to *HPB*, since it was at this time that decisions were being made about the licensing of the drug.

"From the beginning military doctors had concerns about mefloquine. Citizens could fairly assume that, as the licensing authority and the body ultimately responsible for the Safety Monitoring Study, *HPB* was aware of these concerns. The military protocol for the use of mefloquine dated March 18, 1991 states:

> *"Regarding the potential central nervous system (CNS) side-effects (eg. dizziness) and the precaution related to 'pilots, divers and others with occupations requiring fine coordination and spatial discrimination where the onset of dizziness/vertigo can be hazardous or life threatening'...**The US Army, which developed mefloquine, has some lingering concerns about***

***CNS side-effects and infrequently uses mefloquine, favouring daily doxycycline use instead...For now in light of inadequate data, no Canadian Forces experience with the drug, and the lingering US army concerns, the Director of Preventative Medicine is uncomfortable with the use of mefloquine in critical safety situations**, for example, piloting, diving, parachuting, rappelling, rock face climbing and live fire exercises."*

"Canada participated in the fall of 1992 in a relief mission to Somalia. The ***"Medical Post-Op Report"*** for the mission dated January 21, 1993 describes

> ***"intolerable side-effects from mefloquine**, including severe abdominal cramps up to four days after ingestion of the drug, insomnia, headaches, depressed mood, dizziness, diarrhoea and nausea."*

"Due to the adverse reactions mefloquine was "discontinued and replaced with doxycycline."

"Following the relief mission to Somalia, Canada participated in a military. The ***"Post Deployment Report"*** from *HMCS Preserver* for the period of November 16, 1992 to April, 1993 of the military mission to Somalia observed:

> ***"Numerous reactions to mefloquine were reported**...A large percentage of the reactions were gastro-intestinal related: with nausea, burning epigastric pain and diarrhoea...Ten patients experienced nightmares, with one patient having feelings of unease and paranoia. One patient heard voices and talked to himself. All were switched to doxycycline with no subsequent problems."*

"In conclusion I would refer you to a paper presented at a military medicine conference in October 1993 entitled, **"Medical Operations in Somalia, Surgical Section"**:

> *"Abstract: **Mefloquine malarial prophylaxis caused one psychiatric repatriation and may have had a role in a suicide attempt. Members of surgical section, amongst others, suffered neuro-psychiatric side-effects...It is perhaps causing previously unrecognized, widespread, sub-clinical impairment of cognition. Pending definitive research, alternatives to mefloquine prophylaxis could be considered for those in jobs needing judgement, including military command roles.***
>
> *I believe that the UN's failures in Somalia are rather exceptional, considering previous peace-keeping successes. I believe a simple reason may exist. Canadian and American troops may have been impaired by the use of mefloquine.*
>
> *Mefloquine is well known to have neurologic side effects...*

We had one psychiatric hospitalization in Belet Uen, which did not respond to the usual treatment of battle stress. ***The diagnosis made by the psychiatrists at NDMC, after he was evacuated, was an organic brain syndrome, probably due to mefloquine. The suicide attempt in theatre may also be mefloquine related.***

There are three of us presenting on Somalia today: Two of us had minor neuropsychiatric problems which occurred regularly in the 24 to 48 hours after our weekly mefloquine doses...

I believe that mefloquine causes sub-clinical adverse effects on cognition. The usual soldier taking the drug is not aware of any problems. Nevertheless, his thinking could be impaired...he would not recognize that his judgement was diminished. He would not recognize this because the adverse effect is on cognition, including impaired insight...

I would suggest a further restriction on mefloquine use...

The real difficulty in Somalia might be drug side-effects. ***It would be wise to conduct such a study of mefloquine..."***

"I would ask that your audit consider this failure by HPB to show even minimal oversight or interest in the only opportunity to observe the effects of mefloquine first hand either as part of pre-market evaluation or post approval surveillance.

"Where was the oversight mandated by the *Food and Drug Act*?

Letter to Auditor General from John Cummins, M.P., January 23, 1998

February 10, 1998 — Another request to to the Auditor General

Today I want to bring to your attention another example of *HPB's* disregard for both compliance with the *Food and Drug Act* and with its own mandate to protect the public. *HPB* hired the individual at the centre of the military's illegal use of mefloquine, **Dr. Martin Tepper.** How can HPB be respected as a regulator if it hires someone who apparently broke the very rules that underpin *HPB's* authority with the public?

The Department of Defence (DND) gained access to the drug by agreeing to the requirements of the *Mefloquine Safety Monitoring Study (the Study)* as set out in regulations under the *Food and Drug Act.* **Dr. Tepper** was designated under the *Study* as *"co-investigator"*, the doctor responsible for the use of the drug at DND.

When on March 25, 1991 **Dr. Tepper** signed the *HPB "Statement of Investigator of New Drugs"* as required under the *Food and Drug Act,* he agreed to be bound by certain requirements of the Act. The *"Statement of Investigator"* listed specific obligations that as

a co-investigator **Dr. Tepper** had agreed to accept:

> "5. The undersigned realizes that the new drug is being sold or distributed by the manufacturer for the sole purpose of the clinical testing to obtain evidence with regard to safety, dosage and effectiveness of the new drug."
>
> "7. The undersigned agrees:
>
> (i) not to permit the new drug to be used except by myself or under my direction and for the investigation;
> (ii) to report immediately to the manufacturer and if so required to the Assistant Deputy, *Health Protection Branch*...regarding all serious adverse reactions encountered;
> (iii) to maintain adequate records of all investigations and to furnish reports at appropriate intervals to the manufacturer on all quantities of the new drug received."

The *Study* required that information on the adverse effects of the drug be "distributed to the patients." and that safety data "be collected and efficacy" be "monitored for each subject receiving" the drug. (term 7)

The *Study* stated unequivocally that it was "understood that the drug supplies are exclusively for use in patients under the auspices of this study." The continued supply of the drugs were "dependent upon the receipt by Hoffmann-La Roche Ltd., and by the *Health Protection Branch* on request, of dispensing records for Lariam, and of safety data on all travellers who received Lariam." (term 10)

The *Study* (in a section entitled *"Ethical Considerations")* indicated the "study and the provision of the drug, [were] subject to all applicable requirements of the *Canadian Food and Drug Regulations*." And further that "any clinical adverse event or abnormal laboratory test value that [was] serious, or unexpected and potentially relevant, must be reported immediately to the responsible personnel at Hoffmann-La Roche and to the *Health Protection Branch* (telephone contact)." (terms 11 and 12)

Dr. Tepper respected neither the terms of the clinical study nor his responsibilities as an *"investigator of new drugs"*. As you are aware **Dr. Tepper** would have been in receipt of reports from military doctors describing "intolerable side effects", of attempted suicides, of halicunations and the like. **Dr. Tepper** failed to report these adverse events to either the manufacturer or *HPB*, as was required by the *Food and Drug Act*.

HPB would have known of *Dr. Tepper's* illegal use of mefloquine before hiring him. On October 20, 1994, *HPB* made demands on the manufacturer as to the administration of the drug and it was to **Dr. Tepper** that Hoffmann-La Roche turned, on October 20, 1994, to make an urgent information request in regard to the release of mefloquine:

"In September and October of 1992 shipments of [mefloquine] were made to [DND] under the auspices of the *[Mefloquine] Safety Monitoring Study*. You were a co-investigator in that study...

"In reviewing our records we are unable to find distribution accounts of the tablets shipped to [DND]. One of the requirements of the study was that investigators maintain logs of the distribution of lariam and forward these logs to Hoffmann-La Roche Ltd.

"We have received a written request from [HPB] for the following information regarding the use of Lariam that was provided under the *Safety Monitoring Study*...

"The HPB request was received today October 20, 1994 at 14:50. The HPB has asked that this information be provided to them within 24 hours."

On October 24, 1994, **Dr. Tepper** responded and I interpret that response as an admission that he had not met his obligations under the *Food and Drug Act* and had illegally administered an unlicensed drug to Canadian soldiers.

Once they were formally made aware (by Hoffmann-La Roche) that **Dr. Tepper** might have been directly involved in DND's illegally administering of mefloquine, I fail to understand why the department took no disciplinary action against him.

Not only did they fail to take disciplinary actions against **Dr. Tepper**, they actually hired him.

If the department does not take the requirements of its own clinical licensing studies seriously, then we can hardly expect the hundreds of other doctors who are involved in such studies to take their own obligations seriously.

Letter from John Cummins, M.P. to the Auditor General, February 10, 1999

March 18, 1998: **Auditor General to consider mefloquine:**

"My staff have asked Departmental officials to look into this matter and report back to my office with the results of their investigation."

Letter from Auditor General to John Cummins, M.P.

May 21, 1998: **Auditor General to consider mefloquine:**

"My staff has asked Health Canada to review the manner in which this drug was licensed. We expect to receive the Department's response soon and will review it carefully. We also look forward with interest to the Department's reply to your questions on the topic in the

House of Commons on March 27th.

Sept. 24, 1998 **Parlaimentary Question Q-138 posed on neuro-psychiatric side effects experienced by those taking mefloquine**

With reference to the neuro-psychiatric side-effects experienced by those taking the anti-malarial drug mefloquine (Lariam):

(a) Of those Canadians administered mefloquine prior to the date of its licensing for general use by the Health Protection Branch in 1993, how many persons committed suicide or attempted to commit suicide and how many of these incidents were associated with alcohol use;

(b) Of those Canadians administered mefloquine after the date of its licensing for general use by the Health Protection Branch in 1993, how many persons committed suicide or attempted to commit suicide and how many of these incidents were associated with alcohol use;

(c) Of those members of the Canadian forces who were administered mefloquine since 1992, how many have attempted suicide or committed suicide; in what year; in Canada or abroad and if abroad name the country;

(d) Of those members of the Canadian forces who were administered mefloquine since 1992 and attempted suicide or committed suicide, how many of these incidents were associated with alcohol use;

(e) Has the Health Protection Branch reviewed the international experience concerning suicides, suicide attempts, and suicidal ideation associated with mefloquine use, and if so when, and what were the results and recommendations of the review, and what steps have been taken to implement the recommendations;

(f) Has the Health Protection Branch reviewed the scientific literature with regard suicides, suicide attempts and suicidal ideation associated with mefloquine use and if so when, and what were the results and recommendations of the review and what steps have been taken to implement the recommendations;

(g) Has the Health Protection Branch revised the administering instructions for mefloquine to include warnings regarding suicides, attempted suicides, suicidal ideation, or the combination of mefloquine and alcohol and if so when. and what action taken, and if not does it plan to do so and if so when;

(h) Have the Canadian forces taken actions in regard to suicides, suicide attempts or suicidal ideation associated with mefloquine use or the combined ingestion of mefloquine and alcohol and if so what was the action and when was it taken, if not why

not and when do the forces plan to do so;

(i) Has the Health Protection Branch taken special steps to warn Canadian physicians of the hazards of combining mefloquine and alcohol, when were they taken. and if no action why not, and when does the Branch plan to act and what do they plan to do;

(j) Have the Canadian forces noted or otherwise received letters, doctors reports or other complaints from military families of miscarriages or infant deaths where either the father or mother were administered mefloquine prior to or at the time of the child's conception?

Hansard, September 24, 1998, Q-138 by John Cummins, M.P.

September 29, 1998: Q-138 - suicide and alcohol use amongst mefloquine users:

"b) After NOC in Canada:

i. Two cases in the BDS search (limited to Canadian cases I think. Copy faxed to you earlier:

> -case #2863, 25/12/94: Canadian soldier committed suicide while taking Lariam. History of alcoholism. Unconfirmed newspaper report.
> -case#2614, onset of suicidal ideation 2/6/95 after 2 doses of Lariam taken for malaria prophylaxis. Was drinking 6 beers/week during episode.

ii. One additional case I have on record in my files: 23 year old male from Manitoba with no previous psychiatric history and no history of alcohol use who experienced suicidal ideation after 3 does of mefloquine. This is form a copy of a manuscript planned for publication (where?) and sent to me...in Aug 1997. This particular patient continued to take Lariam even after noticing moderate depression and significant insomnia after the first dose of mefloquine."

e) HPB : No formal review of the international experience of which I am aware. Informal information provided by BDS in Sept 1997 indicated that there were 19 cases worldwide of suicide attempt in people taking mefloquine. This would need confirmation with the manufacturer. I have one additional case since then - the 37 year old lawyer form the UK...Roche is reviewing the case. There are possibly other cases of which I am unaware.

f) HPB & Scientific Literature: No formal review by BPA. Informal reading of the literature.

from Dr.Philipa McDonald of Infection and Immunology Unit to Ed Gadd, Head of

Infection and Immunology Unit, Response to Parliamentary Question Q-138 (mefloquine), September 29, 1998

September 30, 1998: Q-138 - suicide and alcohol use amongst mefloquine users:

a. i. "A summary by the manufacturer of the adverse reactions from the SMS (complied in August 1993 by the manufacturer) did not indicate any suicides, suicide attempts or suicidal ideation were reported to the manufacturer by the clinical investigators. An interim report was received by BPA prior to issuance of the NOC. The manufacturer was requested by telephone (September 28, 1998) to confirm whether or not their records are in agreement with ours. There was no data that at the time of filing of the New Drug Submission by the manufacturer to indicate a potential for an interaction between Lariam and alcohol.

ii. "...The Infection & Immunology Unit of BPA has not received from DND a summary of any drug reactions observed in the Canadian forces in Somalia.

(b,e,f and g) Lariam was approved for marketing in Canada on January 22, 1993 and introduced onto the market in April 1993. BPA is not responsible for post-marketing surveillance.

(c and d) DND has not provided Infection & Immunology Unit of BPA with this information

(g) PM Revisions since NOC was issued:

i. There has been no revision to the Product Monograph relating specially to suicide. Depression is a contraindication to use of the drug (monograph revision of January 1997). The "Precautions" section of the monograph states that "During prophylactic use, if signs of unexplained anxiety, depression, restlessness or confusion are noticed, these may be considered prodromal to a more serious event. In these cases the drug must be discontinued." Similar information is repeated in the "Adverse Reactions" section of the monograph and in the "Information to the Consumer" section of the monograph.

ii. Mefloquine and alcohol: In January 1995 a statement was included in the "Information to the Consumer" section of the monograph to read as follows: "It is best to avoid alcoholic drinks during treatment with Lariam." This was not based on any specific evidence/data at that time, but was suggested to the manufacturer by the Bureau because both alcohol and mefloquine are known to have CNS effects. The manufacturer agreed to the suggestion and also informed the Bureau that a study was underway in the Nether lands to look at mefloquine and placebo effects, with and without alcohol challenge, on the psychomotor and actual driving performance in healthy

volunteers. The results of this small study indicated that moderate alcohol consumption (within legal driving limits) did not impair coordinated psychomotor activities in healthy people taking Lariam. These results were included in the monograph in January 1997. A statement went into the monograph at that time to the effect that "A single case in the literature reports a transient severe psychiatric disturbance, suggesting an adverse reaction to mefloquine associated with a heavy ingestion of alcohol (600ml of whisky).

h) DND has not advised Infection & Immunology Unit of BPA whether they have undertaken any such actions.

Prepared by Dr. Ed Gadd, Head of Infection and Immunology, Response to Parliamentary Question Q-138, "based on knowledge as of September 30, 1998".

October 7, 1998: Response to parliamentary Question Q-91:

"a. Prior to market release...mefloquine was available to Canadians as of August 1990 through a Safety Monitoring Study...When the Lariam SMS was initiated, mefloquine was already on the market in the United Kingdom,the United States and many other countries around the world...

"b. For the most part, the Canadian Forces participated in the Health Canada authorized lariam SMS between March 1991 and January 1993. In 1993, mefloquine was licensed in Canada. CF personnel deployed to Somalia in 1992 did not participate in the Lariam SMS.

"c. For those CF members participating in the lariam SMS, mefloquine was administered as per the rules of the SMS.

CF members deployed to Somalia did not participate in the Lariam SMS, since the guidelines of the SMS were not compatible with the operational requirement to deploy to Somalia...

"f. Lieutenant-Colonel Martin Tepper was a co-investigator in the Lariam SMS, and worked under Dr. Raphael Saginur. Lieutenant Colonel Tepper fulfilled his role as co-investigator for he Lariam SMS by submitting the required information related to the dispensing of mefloquine under the Lariam SMS within the CF to Hoffmann LaRoche and Health Canada. This information included a dispensing record for mefloquine and safety data (adverse events) on all travellers who received mefloquine within the Lariam SMS...

"i. Mefloquine was available to Canadian Forces personnel under the Lariam SMS Protocol...

"j. Under the Lariam SMS, Lieutenant-Colonel Tepper as co-investigator was to

provide information to the company at approximately six-month intervals. This included dispensing information for mefloquine in the CF and reports of any adverse events...

Under the Food and Drug Act & Regulations, the [CF] were required to report to the manufacturer of mefloquine the results of the use of the drug...

"k. ...although CF members deployed to Somalia did not participate in the Lariam SMS, all CF procedures used in the administration of mefloquine in 1992 abided by the spirit of the Food and Drug Act & Regulations by providing information to individuals receiving mefloquine."

"l. The [CF] did fulfil their responsibility to the manufacturer under the lariam SMS for all CF members registered in the Study. Lieutenant-Colonel Tepper fulfilled his responsibility as per the procedures...

"n. For the participants registered by the [CF] in the Lariam SMS, the {CF] did fulfil their pre-licensing responsibilities with Health Protection Branch. The [CF] through Lieutenant Tepper...provided reports on study participants, maintained the required file of all consent forms for study participants, and reported information on adverse effects as requested by the company.

Regarding the Food and Drug Act & Regulations, it is now recognized that the [CF[] did not fulfil the pre-licensing responsibilities to the [HPB] for those individuals deployed to Somalia in 1992...

"r. ...Health Canada that the sponsor has conducted the trial as per the agreed upon protocol. The sponsor responded to inquiries in a timely manner, and on the basis of the response, no disciplinary action was taken against the sponsor."

"w. An interim analysis of the data from the Lariam SMS was received in July of 1992 and *did not reveal reporting deficiencies* in relation to the SMS. The final report of the study was submitted by the sponsor in March 1994 and again *did not reveal reporting deficiencies.* Therefore no action was taken.

Sessional Paper No. 8555-361-91, October 7, 1998

October 20, 1998: Regulation of Lariam:

- "Lariam was approved in January 1993 for the prophylaxis against and treatment of malaria...and was introduced onto the Canadian market in April of that same year.

- In 1990...A new antimalarial drug Lariam was already marketed in many

countries, including the US and UK. At that time the manufacturer...had not yet made an application to Health Canada to make Lariam available on the Canadian market.

- "The SMS was developed by Hoffmann La Roche, the Committee to Advise on Tropical Medicine and Travel (CATMAT) and the then Bureau of Human Prescription Drugs, Drugs Directorate.

Safety Monitoring Studies

- "Safety monitoring studies are clinical trials that are subject to prior approval by the Therapeutic Products Programme (TPP) of Health Canada in advance of enroling patients. The review and approval of these studies and indeed all clinical trials on non-approved drugs, are carried out in accordance with the current regulations (c.l08.005 of the Food and Drug Regulations) and the Clinical Trial Review and Approval Policy.

- "As with all clinical trials on non-approved drugs, the sponsor is required to submit to the TPP and approved and Investigational New Drug submission prior to commencing a trial...

- "The responsible for monitoring the conduct of the trial rests with the sponsor and the clinical investigators...

- "Investigators are required to report any and all serious and unexpected adverse drug reactions according tot he current TPP guidelines...

Lariam Safety Monitoring Study

- "An interim analysis of the results from the SMS was received by the TPP in July 1992. This analysis was reviewed by the TPP who by that time had received an application for a new drug submission (NDS) from Hoffmann La Roche to seek approval of the drug fort he Canadian market...

- "The final report of the SMS was submitted to the TPP in March 1994, after the drug was approved for marketing...

- "One of the principal investigators ...was Dr. R. Saginur. Dr. M. Tepper was designated to be the responsible physician at the DND as co-investigator under Dr. Saginur. Records available to the TPP indicate the Dr. Tepper signed a Statement of Investigator, as co-investigator in March of 1991.

- "In October of 1994, the TPP first became aware of the media reports alleging behaviour associated with the use of Lariam by Canadian Forces personnel in

somalia, as presented by defence counsel in well publicized court martial and inquiry events.

- "In response to the allegations concerning the [CF] in Somalia, the TPP took immediate and affirmative action by requesting the sponsor of the SMS trial, Hoffmann La Roche to provide all information and adverse drug reaction reports, as required under the terms of the SMS.

- "In seeking clarification from the DND, the sponsor was advised by a letter subsequently made available to the TPP, that although DND had not yet found the specific supporting documentation, it was believed that the Lariam issued for Somalia was purchased separately from the SMS."

Briefing Note: Regulation of the Drug Lariam, Therapeutic Products Programme, HPB

October 26, 1998: Further request to the Auditor General:

"Today I want to being to your attention HPB's troubling lack of awareness of a mefloquine-related suicide by a Canadian soldier on December 25, 1994. The Canadian Forces conducted a Summary Investigation and concluded that mefloquine was a contributing factor in the suicide. Yet HPB's only knowledge of a highly publicized suicide triggered by long term mefloquine use was "an unconfirmed newspaper report".

That Summary Investigation also revealed that a significant number of soldiers were having troubling reactions to the drug.

HPB claims to have mechanisms for monitoring adverse drug reactions and ensuring post-approval surveillance. With regard to mefloquine, these mechanisms are clearly not working. While HPB is to be congratulated for reading the newspapers, surely the media reports on Scott Smith's suicide and the assumed mefloquine role in his suicide ought to have triggered follow-up by the Branch. The newspaper report might have been the beginning of the matter but it ought not to have been the end of the matter. This is not the first time long term mefloquine use by a Canadian has led to suicide or attempted suicide.

HPB failed in its responsibility to monitor adverse reactions to mefloquine. HPB does not appear ware of the evidence and findings of the Summary Investigation into Scott Smith's suicide in Rwanda.

HPB's "don't ask, don't tell" policy on adverse reactions to mefloquine is not credible and has lead to unnecessary suicides and suicide attempts. Your audit has the potential of saving lives. (The Summary Investigation into Scott's Smith's suicide is enclosed. I will follow-up with further documented failures in the handling of the Lariam

Safety Monitoring Study.)

Letter from John Cummins, M.P. to the Auditor General of Canada, October 26, 1998.

November 2, 1998: Further request to Auditor General:

"How could HPB loose track of 69,000 mefloquine tablets that were ordered and shipped under a clinical study? That is enough to last 1000 men for more than a year. If the Study did not lose track of the tablets, how else can the fact that 69,000 tablets were missing and the regulator made no efforts to account for them either during their review of the Study's findings or during licensing?

"Hoffmann-LaRoche consistently confirmed to HPB that the 69,000 tablets were ordered and shipped under the clinical study. Not only did Hoffmann-LaRoche inform HPB that the drugs were shipped under the Study, the company provided HPB with a copy of the order form which accompanied the shipment. That order form clearly states that the drug was for use under the "Lariam Safety Monitoring Study". The missing tablets were therefore always counted under the Study by those conducting the Study.

"The Minister of Health has assured Parliament that Dr. Martin Tepper of the Canadian Forces "fulfilled his role as co-investigator for the Lariam SMS by submitting the required information related to the dispensing of mefloquine under the Lariam SMS within the CF to Hoffmann-La Roche and Health Canada. This information included a dispensing record for mefloquine and safety data (adverse events) on all travellers who received mefloquine within the Lariam SMS. Any serious adverse drug reactions (ADRs) were reportable immediately to both the Health Protection Branch and Hoffmann-La Roche."

"HPB failed in its responsibility under the *Food and Drug Act*. It has put the health of Canadians at risk. It showed a callous disregard for 69,000 tablets missing from under a clinical study. Your audit has the potential of saving lives.

Letter to the Auditor General from John Cummins, M.P., November 2, 1998.

November 3, 1998 Further request to the Auditor General

Today I want to bring to your attention another aspect of HPB's "don't ask, don't tell" policy on adverse reactions to mefloquine: a failure to monitor adverse reactions either during pre-market evaluation or as part of post-approval surveillance.

HPB has been only able to account for a total of 25 adverse reaction reports.

Their 1997 list of adverse reactions fails to include the hundreds of often disabling adverse reactions suffered by Canadian soldiers in Africa between 1992 and 1995. The

Forces could have provided several hundred such reports but were apparently never asked to do so. Even if such requests had been refused, the publicly available CF medical reports reveal a vast problem for the regulator. Such documents are likely to be as reliable as "unconfirmed newspaper" reports. HPB's job is to document adverse reactions rather than hiding from them.

The report of the *Summary Investigation* into Scott Smith's suicide included an amazing amount of detailed testimony showing wide spread adverse reaction to the drug as well as a signed statement from a CF medical doctor, expert in mefloquine issues. CF records reveal a 1995 acknowledgement of the reality of adverse reactions by the Deputy Chief of Defence Staff.

In addition there are now a significant number of publicly available CF medical reports outlining the adverse effects of mefloquine in Somalia. These reports detail "intolerable side-effects" involving "paranoia", "attempted suicide", "brain disorders", "hallucinations", "mood alteration", and "severe depression".

HPB's file of adverse reactions fails to record or show any awareness of these well documented events by CF doctors in the field. Nor does the record show the adverse effects that occurred prior to soldiers leaving or after they returned to Canada.

HPB failed in its responsibility under the *Food and Drug Act*. It has put the health of Canadians at risk. Your audit has the potential of saving lives.

Letter from John Cummins, M.P. to Auditor General, November 3, 1998

February 4, 1998: Auditor general acknowledges January 23, 1998 letter from Cummins:

"[My] office is in the process of conducting a preliminary assessment of the Health Protection Branch to develop detailed audit plans. I believe that my audit staff will find information you provided to be of assistance in planning their audit work."

February 11, 1998: Further letter to Auditor General:

"I want to bring to you attention a comment by Hoffmann La Roche, the manufacturer of mefloquine, in the February 9, 1998 edition of the Defence Policy review.

Hoffmann La Roche claimed that its Lariam Safety Monitoring Study conducted under the requirements of the Food and Drug Act for the Health Protection Branch's pre-licensing review of the drug "was not a rigorous study."

The article goes on to say that Hoffmann La Roche "made clear, from the company's point of view, that they had no problem with the way DND had handled the mefloquine

issue."

It is obvious that the climate of drug regulation in Canada is so lax that companies publicly flout their duty and the duty of their own investigation to obey the Food and Drug Act when conducting studies of new drugs."

Letter by John Cummins, M.P. to the Auditor General of Canada, February 11, 1998.

February 16, 1999: Response to Parliamentary Question Q-132:

"b. Reviews indicate that the experience of the Australian, British and Dutch Forces with mefloquine is similar to the Canadian Forces experience...

"c. Health Canada did not undertake any formal investigations in October 1997. In October of 1994, there were media repots of claims of involvement of Lariam in several incidents in somalia. Health Canada took immediate and repeated action by requesting the manufacturer to provide all information and adverse drug reaction reports as required under the [SMS] on the possible use by DND of SMS supplies of Lariam in [CF] deployed to Somalia.

Hansard

February 18, 1999: Response to Parliamentary Question Q-138:

"a. There has been only one case reported in Canada prior to 1993 of a patient with a medical history of alcoholism experiencing tow episodes of hallucinations, depression and suicide ideation while taking mefloquine...

"b. There have been tow additional cases reported in Canada after 1993. Two cases of suicide and tow cases of suicidal ideation have been reported. Of these, tow were potentially associated with alcohol use.

"c. Of the Canadian forces members who were administered mefloquine since 1992, there has been one attempted suicide, Somalia 1993, and one suicide, Rwanda 1994.

Hansard, February 18, 1999

April 20, 1999: Auditor General reveals that DND did not follow the prescribed safety monitoring protocol and that HPB made no attempt to ensure that the protocol, with its reporting requirements to protect patients well being was being followed.

May 6, 1999: **HPB official tells Parliamentary that DND did submit adverse event reports under Lariam Safety Monitoring Study:**

John Cummins: Back in October of 1994 I raised this issue in Parliament and it was raised in the media as well and you requested of the manufacturer that they provide you information on the safety monitoring study.

You found out in 1994 that the protocol had not been complied with and yet you did nothing and that's frightening, because the fact that you did nothing at that time after there had been serious problems with that drugs in Somalia suggests that the Canadian public were not well served by the Health Protection Branch.

Jan Pound: ...DND did submit those to us and we did see them also when the manufacturer made the formal application for approval of this drug in Canada.

Jan Pound is Manager, Office of Strategic Planning, Communications and Quality, Health Canada.

Proceedings of the Standing Committee on Health, Hansard, May 6, 1999