MP John Cummins
CANADA

Time Line/Chronology

1985: **Lariam approved in Switzerland ("launched")**

1986: **Lariam approved in France ("launched")**

1987: **Lariam approved in Australia and Germany ("launched")**

1998: **Lariam apporved in Austria ("launched")**

1989: **Lariam approved United Kingdom (?)**

August 29, 1989: **Intention of CF to use mefloquine in Cambodia:**

"It is the intention that malaria prophylaxis for this UN peacekeeping deployment will consist of mefloquine, a drug which is not marketed in Canada (or the USA to date) but which is being imported for CF use under the *Emergency Drug Regulations*. this drug will probably be prescribed for those finally chosen for this operation during the anticipated predeployment briefings at NDHQ.

"...To ensure that the above relative drug contraindications for use of mefloquine are observed, addresses are to review the medication status of persons in ref, Annex A who are in their area of medical responsibility and who have been found fit for this operation as well as any other personnel who have been screened for peacekeeping duties in Cambodia and have been found fit for such duties. Any of these persons who are taking the drugs mentioned in para 2 are to be identified to NDHQ/DPM 2 by message no later than 06 Sep 89 so that alternate antimalarial medication can be considered. It is rather unlikely/unlikely that any of the persons who have been screened as fit are on the contra indicated medication since such medication would not/not normally be compatible with fitness for peacekeeping duties.

drafted and signed by M. Tepper, to CF medical service units.

September 6, 1989: **Planned Use of Mefloquine Under Emergency Drug Regulations:**

"This letter is to confirm the arrangements for the importation of the antimalarial drug, mefloquine under the Emergency Drug Regulations...Hoffmann La Roche in Toronto is in the process of bringing the drug into Canada for the Canadian Forces use."

"Mefloquine has been recommended tot he CF by several tropical medicine consultants

in both Canada and the USA a the antimalarial prophylactic drug of choice for an anticipated deployment of CF peacekeepers to Cambodia. While the CF has no experience with this drug, the European and (draft) US package inserts are available and offer germane advice regarding the use of this drug.

"For your purpose, the 'attending physician' for this release ca be listed as Dr. M.L. Tepper, Directorate of Preventive Medicine."

Release of Mefloquine, Signed Col C.A. Burden, Director of Preventive Medicine.

February 1990: Letter to Martin Tepper of DND informing him of mefloquine, a new antimalarial (from Hoffmann LaRoche):

"Appearance of chloroquine resistant P. Falciparum is making prophylaxis against malaria more complex...more effective agents against this strain have been unavailable to U.S. physicians..until now. Announcing *Lariam* 250 mg tablets... a new antimalarial agent developed as a collaborative effort by the U.S. Army, the World Health Organization and Hoffmann LaRoche."

February 1990: Lariam was launched in United States in February 1990. (?)

March 1990: Lariam recommended by Centers for Disease Control in Atlanta for malarial chemoprophylaxis:

"In March 1990, mefloquine was recommended by the Centers for Disease Control as malarial chemoprophylaxis for Americans travelling to areas of endemic chloroquine-resistant Plasmodium falciparum."

D. Phyllis Kozanky, *"Use of Mefloquine for Malarial Chemoprophylaxis in Its first year of Availability in the United States"*, Clinical Infectious Diseases, 1993; 16: 185-6

May 1990: Lariam became publicly available in the United States:

"The drug first became available in pharmacies in the United States in May 1990."

D. Phyllis Kozanky, *"Use of Mefloquine for Malarial Chemoprophylaxis in Its first year of Availability in the United States"*, Clinical Infectious Diseases, 1993; 16: 185-6

June 6, 1990: Invitation goes out to doctors inviting them to become principal investigators under the *Lariam Safety Monitoring Study*, letter from *Robert C. Wittes* of HPB and copied to *Drs. Ed Gadd and Phillippa MacDonald.*

"I am writing to solicit your application to be a PI for MFQ in Canada."

July 25, 1990: Hoffmann La Roche agrees that Tepper of CF can be principal investigator for LSMS:

"We are pleased that you have agreed to act as a principle investigator for this study with 'Lariam'. We have reached an agreement with the Health protection Branch whereby you may prescribe this compound to your patients..."

"In accordance with our obligation to HPB, please submit this documentation to your ethics committee for approval..."

"Enclosed also please find HPB Form 3005...These documents are required to that I may formally register you with the HPB as a principle investigator."

"We expect to have all details finalized and 'Lariam' available to you in early September..."

Lariam Safety Monitoring Study, letter to Dr. Tepper from Hoffmann La Roche.

August, 1990: Invitation goes out to doctors inviting them to become co-investigators under the *Lariam Safety Monitoring Study*, letter from Robert C. Wittes of HPB

"I am writing to inform you of the possibility of becoming a co-investigator for MFQ in Canada...The terms of the protocol will require active surveillance of adverse drug reactions (ADR's) to MFQ. Periodic reporting of drug usage and of minor ADR's will be required to both BHPD and HLR."

November 1990: LSMS began (according to Hoffmann-LaRoche letter to Dr. Ed Gadd of HPB dated July 30, 1993.

November 29, 1990: RS at Ottawa Civic Hospital that LSMS will proceed but RS cannot participate until he returns a copy of the protocol agreement signed:

"We are pleased to inform you that all arrangements are now complete and we are in a position to proceed with this study. There are still some principal investigators who have not returned to us the documentation needed to register them for inclusion in the study. We cannot supply study drug to you without this documentation.

"1. Adverse Events

Adverse events reported to you which have occurred while the patient was taking 'Lariam' must be reported to 'Roche' by completing an *Adverse Event Case Report Form*...

"2. Co-investigators

...You are responsible for reporting relevant details as indicated on the Patient Record....Please note that you are still responsible to ensure your co-investigator reports patients by completing and returning, either to you or directly to 'Roche', the completed Patient Records.

"4. Informed Consent

'Lariam' is not an approved drug in Canada and is made available under a study protocol. Therefore Canadian regulations require that informed consent must be obtained from each patient...and these documents must be retained by you. Please note that designated monitors either form 'Roche' or the Health Protection Branch retain the right to audit for the presence of these consents, and must withdraw study medication from you if this regulation is not met...

"7. Reporting Requirements

"This protocol is designated to monitor 'Lariam' usage at major travel clinics...Under protocol regulations we must both account for study drug usage and follow-up for the occurrence of adverse incidents. The simple Patient Record has been designed for this purpose. You are required to complete the information for every patient entered into this study. Each reporting page must be signed by you (or by your designated co-investigator) and returned to 'Roche'. Completed pages must be returned to us on a regular basis, at least every other month...The detailed case report forms which must be completed for patients reporting are to be returned to 'Roche' as soon as possible...

"We look forward to working with you on this important study. With your efforts we will collect a large and unique data base which will serve to more fully detail the safety and efficacy of 'Lariam'.

Safety Monitoring Study with Limited Distribution of 'Lariam', letter to RS of Ottawa Civic Hospital a PI and copied to LCol Tepper a CI.

December 21, 1990: Possible CF participation on LSMS:

"Canadian Forces member may well deploy (operationally) to areas endemic for chloroquine-resistant Plasmodium falciparum (CRPF) malaria...Hence there is a need for CF members to have access to the antimalarial mefloquine. We are aware that a study ("Mefloquine Safety Monitoring Study") has been put in place to allow the dispensing of mefloquine as an Investigational New Drug and to document the adverse effects of the drug (and we have the protocol for the study)."

"As you and Dr. tepper of my staff have discussed several times recently, it would be useful if designated physicians of the Canadian Forces Medical Services (specifically Dr. Martin Tepper of this directorate and Dr. Ken Scott, Infectious Disease Consultant at National Defence Medical centre) were authorized to be CTs in this study with you as PI. Our intent would be to distribute, to our base/field medical officers (physicians), the prescribing information about mefloquine, information about the study (eg. consent, reporting adverse effects), and the CATMAT malaria guidelines (soon to be published in the CDWR). If a base/field medical officer feels that mefloquine is indicated as chemoprophylaxis, then he/she would contact one of the CFMS CIs, who would discuss the matter with the physician, and if applicable authorize release of mefloquine from NDMC/Pharmacy."

"Enclosed please find a [cv] and completed HPB form for Dr. Tepper. Dr. Scott will submit his documentation after he receives approval to participate from his superiors."

"...the CF mefloquine supply would be held at the Central Medical Equipment Depot/Canadian Forces Base Petawawa...and be released from that pharmacy when authorized by a designated CFMS CI. Barring specific *operational deployment* to a CRPF area, it is anticipated that our use would be perhaps 100 does a month."

Letter from RCD Climie Captain, Director of Preventive Medicine, to [RS?] Director/Tropical and Infectious Disease Clinic, Ottawa Civic Hospital.

December 21, 1990: Possible CF participation in LSMS:

"Mefloquine i snot licensed for use in Canada. However it is available as an Investigational New Drug through a network of "principal investigators who are co-operating with the manufacturer...in an adverse effects study which is required in preparation for licensure."

"While DPM had considered joining the study as a [PI], this would have required review of the protocol by an ethical review committee (ERC). Unfortunately, an ERC does not exist at this time at NDHQ. However, it is possible (and perhaps preferable) to join the study as a [CI] by aligning with a PI. In this circumstance, there is no need for ERC review by the CI's institution since the PI's ERC review encompasses the CI."

"Contact has been made with [RS?] infectious disease consultant at Ottawa Civic Hospital, who is a PI...appears quite willing to have CIs from the CF. This would allow the CF to have access to mefloquine in a controlled manner where we can document centrally the use of and experience with mefloquine by CF personnel..."

Malaria Chemoprophylaxis/Mefloquine Availability, RCD Climie, Captain, Director of Preventive Medicine

1991: Lariam approved in Italy ("launched")

January 23, 1991: Possible CF participation in LSMS:

"Prior to NDMC's participation in this study it is requested that the protocol be reviewed by NDMC's Research Review Committee, with Bioethics Committee input, and the decision forwarded to this headquarters."

"It is understood...that should a member refuse to sign the consent form they do not jeopardize their tasking or access to other chemoprophylactic agents."

Malaria Chemoprophylaxis/Mefloquine Availability, Brig Gen JJ Laliberte, Commander

March 14, 1991: Statement on mefloquine availability in CF:

"DPM will soon issue to CFMS units the protocol for prescribing mefloquine in the CF. This protocol will mention that the drug will be authorized for release from CMED by DPM 2/LCol Tepper (and eventually NDMC/Maj Scot as well after he is authorized by CFHMSSHQ) and then will be sent from CMED to the supporting base pharmacist for dispensing to the patient." Mefloquine Availability in CF, RCD Climie Director of Preventive Medicine (signed by Tepper for Climie) to medical service units

March 18, 1991: Military protocol on use of mefloquine:

"1. ...Mefloquine is not yet leicenced for use in Canada. However, it is available through a network of "principal investigators"...in an adverse effect stuyd which is required in preparation for licensure and has been approved by [HPB]...

2. It is important for CF members, travelling to...areas...on duty to have access to mefloquine...To assist in this access and to allow for acquiring some cumulative experience with the drug , DPM 2/LCol tepper has become a "co-investigator"...

3. Access to mefloquine for CF members in Canada is through the following mechanism:

b. if mefloquine is indicated for the specific travel and not contraindicated for the specific patient, then the attending physician should contact DPM 2/LCol Tepper...

c. if agreement is reached that mefloquine is indicated, then the attending physician must brief the traveller regarding the use of mefloquine..

d. if mefloquine is refused, no medical/administrative/disciplinary consequences are to occur, and the patient should be prescribed and alternate...

f. if any side effects that might be related to taking mefloquine come to the attention of CF medical personnel, these are to be reported to NDHQ/DPM 2 by telephone. If these side effects are felt to "serious or unexpected and potentially relevant", then reporting must be urgent. It is anticipated that DPM will soon provide a questionnaire to gather adverse effects data from all CF patients given mefloquine

6. Regarding the potential central nervous system (CNS) side-effects (eg. dizziness) and the precaution requiring fine coordination...it is impossible, other than for pilots and divers, to provide definitive rules as to who can or cannot take mefloquine, especially on deployment. Ultimately each case will need to be decided on its own merits. The US Army, which developed mefloquine, has some lingering concerns about CNS side-effects and infrequently uses mefloquine, favouring daily doxycyline use instead...For now, in light of inadequate data, no CF experience with the drug, and the lingering US Army concerns, DPM is uncomfortable with the use of mefloquine in critical safety situations, for example...live firing.

Malaria Chemoprophylaxis/Mefloquine Availability, R.C.D. Climie, director of Preventative Medicine for CDS

March 18, 1991: Issuance of military protocol governing the use of mefloquine:

"Mefloquine is not yet available for use in Canada. However it is available through a network of 'principal investigators" who are cooperating with the manufacturer...in an adverse effect study which is required in preparation for licensure and has been approved by Health and Welfare Canada.

"It is important for CF members... to have access to mefloquine...to assist in this access and to allow for acquiring some cumulative experience with the drug, DPM 2/LCol Tepper has become a 'co-investigator'...

"Access to mefloquine for CF members in Canada is to be through the following mechanism: (c) ...the attending physician must brief the traveller regarding the use of mefloquine, including contraindications, precautions, and dosage and the need for the traveller to report any significant side-effect which might be related to the drug...;(f) if any side-effects that might be related to taking mefloquine come to the attention of CF medical personnel (whether or not these personnel are the original attending medial personnel who prescribed the mefloquine), these are to be reported to NDHQ/DPM 2 by telephone. If these side effects are felt to 'serious or unexpected and potentially relevant' (see para 12 of the study protocol mentioned in para 4b below), then reporting must be urgent. It is anticipated that DPM will soon provide a questionnaire to gather adverse effects data from all CF patients given mefloquine; "

"Regarding the potential central nervous system (CNS) side-effects (eg. dizziness) and the precautions related to pilots..., it is impossible, other than for pilots and divers, to provide definitive rules to who can or cannot take mefloquine, especially on deployment. Ultimately each case will have to be decided on its own merits.

"The US Army, which developed mefloquine, has some lingering concerns about CNS side-effects and infrequently uses mefloquine, favouring doxycycline use instead. To address these lingering concerns, the US Army is planning to run a comparative trial...regarding side-effects on deployed troops.

"For now, in light of inadequate data, no CF experience with the drug, and the lingering US Army concerns, DPM is uncomfortable with the use of mefloquine in critical safety situations, for example, piloting, diving, parachuting, rappelling, rock face climbing and live fire exercises.

March 18, 1991: Issuance of military protocol governing the use of mefloquine (Information Sheet for soldier):

"When taken to prevent malaria, mefloquine may occasionally cause stomach upset, headache, dizziness. lightheadness, restlessness, confusion and sleeplessness...Those taking mefloquine should exercise caution if operating vehicles or other machinery requiring mental alertness. Seizures, and serious emotional or mental changes are when mefloquine is taken to prevent malaria. However, persons taking mefloquine who experience unexplained anxiety, emotional upset, restlessness or confusion, should stop taking mefloquine and promptly consult with a health care professional. Should this situation arise, alternative measures to prevent malaria, including other drugs, must be considered...

"There are certain persons who should not take mefloquine...:

- pilots, divers and others with occupations requiring fine coordination and

spatial discrimination where the onset of dizziness/vertigo can be hazardous or life threatening

- those with a significant compromise in kidney or liver function

- those taking certain other drugs, eg. quinine, chloroquine, quinidine, calcium channel blockers, beta blockers, valproic acid, oral anticoagulants and oral antidiabetics...

"For those who agree to take mefloquine, it is important that they report any significant adverse effects that they or their physician feel may be related to mefloquine."

March 21, 1991: Dr. Martin Tepper signs the HPB Statement of New Drugs form (Lariam)

The form states and Tepper by signing attested to:

"The undersigned realizes that the new drug is being sold or distributed by the manufacturer for the sole purpose of clinical testing to obtain evidence ...to the safety, dosage and effectiveness of the new drug."

"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 terminate investigations and return all available supplies as soon as a request from the manufacturer has been received;
(iii) to report immediately to the manufacturer and if so requested to the Assistant Deputy Minister, Health Protection Branch, Health and Welfare Canada, regarding all serious adverse reactions encountered;
(iv) 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."

March 25, 1991: Dr. Martin Tepper of DND becomes a co-investigator under the Lariam Safety Monitoring Study (date Tepper signed the "Statement of Investigation of New Drugs"). Military now has access to mefloquine under the LSMS.

April 3, 1991: Dr. Tepper sends signed form to Dr. Saginur, Ottawa Civic Hospital:

"In relation to your kindly given assistance in having certain Canadian Forces physicians

as coinvestigators on the mefloquine study, enclosed are: (a) a signed copy of the necessary HPB form for Dr. tepper (he neglected to sign the copy previously sent to you); (b) the letter we have sent to our medical personnel outlining the procedure for obtaining/prescribing mefloquine in the CF. This letter includes our consent form."

from RCD Climie, Director of Preventive Medicine, signed by Tepper, to Dr. Saginur at Ottawa Civic Hospital

April 5, 1991: Mefloquine now available to military personnel:

"Mefloquine is now available form the Ottawa Civic Hospital."

"The drug will be authorized for release by LCol Tepper (DPM 2) or Maj Scott ."

Malaria Chemoprophylaxis - 6505NIC Mefloquine, LCol C. Heard, Senior Staff Officer Medical Supply (CF Hospital and Medical Supply System Headquarters)

August 25, 1991: Hoffmann La Roche review of reports of severe psychiatric reactions and convulsions:

"This paper reviews all severe neuropsychiatric adverse events reported to Roche Drug safety up May 1991. During this time 59 serious neuropsychiatric adverse reactions have been reported (26 convulsions, 1 toxic encephalopathy, 12 depressions and 20 psychotic episodes)....An estimated 2-4 million people were given mefloquine for prophylaxis during this time.."

"...The precise mechanism of serious neuro-psychiatric reactions is unknown. The relative frequency of occurrence of such reactions in association with other drugs remains unclear...neuro-psychiatric reactions

"SOURCES OF REPORTS

"As of 1 May 1991, Roche Drug Safety has received a total of 613 adverse event reports in association with all the uses of Lariam. Of the 613 patients, 430 had used Lariam for prophylaxis of malaria.

"241 reports (56%) of all reports associated with prophylactic use of Lariam were of neuropsychiatric nature (WHO system organ class 0410: 'necrologic disorder' and 0500: 'psychiatric disorders'). This includes well-known reactions as transient dizziness, headache, paraesthesias, weakness, fatigue, sleep disturbances and nervousness.

"SERIOUS DEPRESSION OR MANIC-DEPRESSIVE REACTIONS

"There was a total of 12 reports of depression or manic depression associated with prophylactic use of Lariam which were rated serious [life-threatening, requiring hospitalization, or resulted in severe disability] according to the CIOMS-criteria.

1. Clinical Presentation

Five patients had *suicidal ideas*, four of them attempted to commit *suicide*.

Three has non-specific depression....

Two patients exhibited symptoms of mania or panic.

In two further patients the depression was accompanied by agitation, anxiety and restlessness. One patient's depression had also psychotic features such as hallucinations and delusions.

SERIOUS PSYCHOTIC REACTIONS

"There was a total of 20 reports of psychotic reactions associated with prophylactic use of Lariam which was rated serious [as defined above] to the CIOMS-criteria.

"1. Clinical Presentation

Thirteen of the 20 patients were reported to have typical psychiatric symptoms such as hallucinations, schizophrenia, delusions or paranoia.

"TOXIC ENCEPHALOPATHY

"There was one report of a 43-year-old female who developed encephalopathy on Day 6 after one tablet of Lariam while on the plane returning from Thailand. She had dizziness, diplopia, frontal headache, amnesia, stupor, photophobia, lethargy and memory deficit...She recovered within three months.

Mefloquine: Review of Spontaneous Reports of Severe Psychiatric Reactions and Convulsions, J.L. Bem, L. Kerr, D. Sturchler, Roche Research Report No. B 117 397

October 2, 1991: "As noted the U.S. Army and navy's policy for prophylaxis in south-east Asia is Doxycyline daily. Mefloquine is used for treatment of acute falciparum." Malaria Prophylaxis. LCol James Anderson, Canadian Forces Medical Liaison Officer in washington, to Director Health Protection and Promotion (notation by Tepper on November 17, 1991)

November 21, 1991 Problems with Lariam Safety Monitoring Study

"From discussions with the Co-investigators many of the individuals receving teh Mefloquine have no further contact with the Travel Clinic prescribing the drug. Can you comment on how effective this passive (report to the clinic if you have an adverse reaction) surveillance is expected to be."

Lariam Safety Monitoring Study, letter from Dr. N.M. Arnott, Communicable Diseases Epidemiology Service, B.C. Centre for Diseases Control, Miniistry of Health and Minister Presponsible for Seniors, Vancouver to Hoffmnan La Roche

December 12, 1991: Request for *fast-tracking* of Lariam NDS:

"Enclosed please find a five volume New Drug Submission for Lariam...

"It is quite apparent that there is a definite need for Lariam on the Canadian market. Therefore, we ask that this NDS be fast tracked."

"This NDS is based on the information previously submitted in the IND filed June 8, 1990."

Lariam NDS, Hoffmann La Roche to Dr. C.A. Franklin, Acting Director of Bureau of Human Prescription Drugs, HPB, December 12, 1991.

January 28, 1992: Hoffmann La Roche requests fast-tracking of the Lariam New Drug Submission.

April 1992: "The first response to a request in April 1992 for a commitment of military observers to participate in UNOSOM was negative." (page 765, volume 3, *Report)*

"Beginning in the spring of 1993, Gen de Chastelain ordered his staff officers to begin planning for another United Nations operation in Somalia." (page 803, volume 3, *Report*)

June, 1992: Study suggests that *mefloquine* might interact adversely with *alcohol*:

"(risk factors) In four cases, the reporting physician mentioned exertion, fatigue, sun exposure, or *alcohol* as potential co-factors....*Alcohol* abuse was suspected in one patient."

see Table 4 "Clinical features of patients who developed psychotic episode during prophylaxis with mefloquine."

"Mefloquine Prophylaxis: An Overview of Spontaneous Reports of Severe Psychiatric Reactions and Convulsions", Journal of Tropical Medicine and Hygiene, 1992, 95:167

July 1992: **"Commander Land Force Command formally decided that the CAR [Canadian Airborne Regiment] would go to Somalia."** (page 242, volume 1, *Report)*

July 18, 1992: **Review of New Drug Submisson:**

"This NDS is considered to comply with the requirements of section C.08.002 of the *Food and Drug Regulations* and is recommended for clearance."

Review of New Drug Submission, from Dr. R.A. McDonald to Dr. R.E.A. Gadd, Acting Chief of Infection & Immunology Division, HPB, Health Canada, July 18, 1991

July 28, 1992: **"Gen de Chastelain [Chief of Defence Staff, CDS] directed staff at NDHQ to conduct a feasibility study to determine the capability of the Canadian Forces (CF) to provide a battalion to Somalia."** (page 239, volume 1, *Report)*

October 9, 1992: **Revision of Product Monograph:**

"Further to our meeting of September 30, 1992 with Drs. E.Gadd and P. McDonald, enclosed plese find one highlighted coopy of the revised product monograph for 'Lariam'"

Lariam NDS Revised Product Monograph, Hoffmann La Roche to Dr. J. Messier, Director of Bureau of Humand Prescription Drugs, HPB

August 13, 1992: **Canada agreed...to participate in an airlift of relief supplies**, designated Operation Relief, even before it commitment to the UNOSOM mission." (page 240, volume 1, *Report)*

August 24, 1992: **Safety data for safety study is incomplete:**

"An estimated...patients have received Lariam over the period November 1990 to June 1992 through the open treatment IND in Canada. Of the ...patients...case report forms were received, in which...adverse events were reported. Obviously many investigators are not returning their completed case record forms. This was a prerequisite for continued supply of the drug from the company. This issue will be discussed further with the company.

"Unfortunately many investigators have failed to return their completed case record forms to Hoffmann-La Roche. This indicates that the safety data from the Canadian study i s

incomplete. In addition, since the majority of the investigators collected their safety data by means of passive surveillance, the data is less useful than collected by active surveillance...

"To date the neuropsychiatric side-effects following the use of mefloquine are of the most concern...

"A meeting will be held with representatives form Hoffmann-La Roche. Issues of concern will be discussed, and the Product Monograph will be revised to satisfy concerns during the review of this drug.

Review of Safety Report Update for the Lariam Safety Monitoring Study, from Dr. P.A. McDonald to Dr. R.E.A. Gadd, Acting Chief of Infection and Immunology Division, Health Protection Branch, Health Canada.

August 25, 1992: "NDHQ received an informal request for troops from the UN that set out a general outline of the battalion that would later be requested formally." (page 719, volume 3, *Report)*

August 26, 1992: "The CDS and the DM recommended, in a letter to the Minister of National Defence dated August 26, 1992, that the CF should undertake relief operations in Somalia as requested..." (page 729, volume 3, *Report)*

September 1, 1992: "An *initial warning order* was issued by Force Mobile Command Headquarters, stating in general terms that the government had announced a willingness to participate in a UN mission to Somalia." (page 577, volume 2, *Report)*

September 1, 1992: Control of alcohol use in Somalia by CF

"**Injury Avoidance:** nonoperational injuries are predicted to be the commonest cause of serious injury or death in this operation. Safety is important both on and off duty. *Alcohol consumption* is well recognized as associated with unsafe behaviour and should be discouraged." [punctuation added]

NDHQ Ottawa to RCCXAAE/AIG 1704 AL, Preventive Medicine Recommendations for Somalia

September 3 (and/or 1), 1992: Use of mefloquine in Somalia by CF:

"1. CF May/may support relief or peacekeeping operations in Somalia. DHPP has received a number of calls regarding prev med recommendations for such

deployments. This message provides the preliminary prev med recommendations for deployment to Somalia. The same recommendations are made for those who may operate our of Kenya (eg Air Transport Element).

"3. Malaria prophylaxis: All of Somalia is considered malarious with Falciparum predominating and chloroquine resistance reported. Mogadishu is said to present a lower but still present risk IAW REF C, Mefloquine weekly recommended. DHPP 2 hereby provides blanket approval for mefloquine to be provided to personnel deploying on this mission however, a consent form IAW REF D is not repeat not to be used for this operation however dispensing pharmacists are to record, in a readily retrievable format, a line listing of those personnel who have been dispensed mefloquine under this blanket approval. Personnel for whom mefloquine is medically contraindicated as per REF D, eg. pilots, can be given doxycycline 100 milligrams per day."

"6. Medical intelligence upon request, DHPP 2/LCol, Tepper or DHPP 2-2/Maj Nowak (613-995 9206) can provide relevant medical intelligence regarding the disease threats in the area of deployment. Such intelligence has already been provided to FMCHQ/CSURG and AIRCOMHQ/CSURG. [colon and periods added throughout]

[at this point and until mid December it was believed that the Canadian contingent was to be further north west. In Dec it was decided that the CAR BG was to be a drier area further south, with less malaria threat. No indication that the preventive medicine recommendations were ever revised.]

NDHQ Ottawa to RCCXAAE, Preventative Medicine Recommendations for Somalia

September 3, 1992: **Information on Adverse Reactions Requested:**

"The documentation enclosed is this submission is in response to Dr. MacDonald's request of August 27, 1992. This documenation includes:

1) the Adverse Reaction Reports for the deaths reported in the NDS (December 12, 1992) and in the Safety Update (July 15, 1992);

2) spontaneous adverse events reported by pregnant woment exposed to Lariam;

There were a total of ...deaths most of them neonatal or intrauterine..."

Lariam NDS Control #5HN916108 Additional Information, Hoffmann la Roche to Dr. J. Messier, Director of Bureau Prescription Drugs, HPB, Health Canada

September 4, 1992: **"A formal Warning Order for Operation Cordon, Canada's contribution to UNOSOM, was made... on September 4, 1992."** (page 576, volume 2, Report uses September 5, 1992: Although the warning order for Operation Cordon was not issued until September 5, 1992, rumours had been circulating about a possible mission, and plans were being formulated in late August.")

September 9, 1992: **Hoffmann-LaRoche ships 100 bottles of Lariam to DND** (Regional Medical Equipment Depot, Debert, Nova Scotia)

September 15, 1992: **Hoffmann-LaRoche ships 480 bottles of Lariam to DND** (Central Medical Equipment Depot, CFB Petawawa)

September 21, 1992: **DND informs Dr. Saginur (investigator) under the LSMS** that since "March 1991, the CF has obtained 3,500 tablets of mefloquine...Of these tablets had been dispensed by the end of February 1992." (signed by Tepper) DND did not provide patient case reports, only a list showing how many took the drug.

"Under the arrangements with you, Dr. Tepper is required to submit certain information related to the dispensing of mefloquine within the [CF]...

"All of [the 3500 tablets of mefloquine] had been dispensed by the end of February 1992..."

"As is seen from the enclosure:

a. only four women are among the 96 patients;

b. the travel destinations are as follows: Southeast Asia - 38 (all for cambodia); Africa - 55 (including Angola - 17, Nigeria - 22 and Zaire - 10); South America - 1; and unknown - 2. Of course, these destinations largely reflect *operational deployments* for CF members as opposed to leisure travel;

"As regards adverse effects reported to Dr. Tepper among the CF patients provided mefloquine, only tow such effects have been reported as follows...: a male with feelings of 'not giving a damn' occurring within 12-24 hours after a second and a fourth dose of mefloquine and lasting for some six months..."

"I must take this opportunity to thank you for your readily given cooperation in allowing

access to mefloquine through the study and I look forward for continuing this relationship until mefloquine is licensed in Canada."

letter from RCD Climie, Director of Health Protection and Promotion, signed by Tepper for Climie, to RS at Ottawa Civic Hospital, no patient case reports were submitted as required by the study protocol.

September 22, 1992: **CATMAT advises HPB on mefloquine use:**

"c. Mefloquine resistance **Dr. Jay Keystone**

"Mefloquine resistance in P. falciparum has been reported sporadically from Africa, but no change in recommendations for chemosuppression are warranted at this time. In the Thai-Cambodian and Thai-Myanmar border areas...although data is lacking on chemosuppression failures in this area **several military services have changed their primary recommendation for chemosuppression to doxycycline.**

"THE SUBCOMMITTEE ADVISES that notice be given of sporadic mefloquine resistance in Africa...

"d. Safety of Mefloquine

"It has come to the attention of CATMAT that **some non-governmental organizations and their cooperants have been recommending that mefloquine not be used for prophylaxis because of the dangers posed by the drug** or because of the concern that prophylaxis will promote drug resistance in the area.

"Large scale studies involving tens of thousands of tourists have shown that approximately 25% of travellers will experience side effects from mefloquine, most of them transient and mild...The most frequent minor side effects are nausea, strange dreams or nightmares, dizziness, mood changes, insomnia. headache and diarrhoea. Severe neuro-psychiatric reactions such as convulsions and psychosis are estimated to occur in approximately 1: 10,000 travellers.

Report of the Malaria Subcommittee to the Committee to Advise on Tropical Medicine & Travel (CATMAT), September 22, 1992

October 5, 1992: **Cpl Matchee, Pte Brocklebank, and a third person approached WO Murphy to report they had participated in a party in Algonquin Park, where they consumed alcohol** and fired off pyrotechnics." (page 444, volume 2, Report)

October 6, 1992: **DND ships 800 bottles of Lariam to DND** (Central Medical Equipment Depot, CFB Petawawa)

October 12, 1992: **A CF reconnaissance [advance party], to support deployment to Somalia, left Canada for Somalia on October 12, 1992."** (page 265, volume 1, *Report)* (page 251, volume 1, *Report)*

November 3, 1992: **Adult Treatment Dosage for Mefloquine**

"Adult treatment dosage for lariam are not standard at the present time. For example, the US recommends a single dosage of 1250mg, the WHO recommends a single dosage of 1000mg, the Canadian open treatment IND recommends 750mg as a single dose of 1250 mg in two divided doses...

"Taking into consideration the fact that mefloquine is associated with a much higher incidence of neuropsychiatric adverse drug reactions when used at the higher dosage (1 in 215 patients for the treatment dose...), it would seem prudent from the risk benefit perspective to keep the treatment dose as low as possible...

"I therefore elected to base the prescribing information in the Canadian Product Monograph for mefloquine on the approach taken by Switzerland and by the United Kingdom...This decision was reached after reviewing the data available to me from the trials submitted in the US NDA, after discussion with the manufacturer, and after discussion with Dr. J. Keystone and Dr. D. MacPherson (members of the Lariam Subcommittee for CATMAT).

Review of Adult Treatment Dosage Information For Lariam, from Dr. P.A. McDonald to Dr. E.E.A. Gadd, Acting Chief of Infection and Immunology Division.

November 30, 1992: **"Cpl Matchee was appointed to master corporal."** (page 513, volume 2, *Report)*

December 1992: **"Canadian personnel...were deployed for service to Somalia,** mainly in December 1992." (page 1, volume 1 of the *Report of the Commission of Inquiry*, hereafter *Report*)

December 6, 1992: **"Canadian contingent was assigned initial responsibility for maintaining security at Baledogle airport."** (page 261, volume 1, *Report)*

December 8, 1992: **Final Revision of Product Monograph:**

"Enclosed please find three copies of the final revised 'Lariam' product monograph. The latest requested rvisions are highlighted and only the pages for which thees revsions are requested are enclosed."

Lariam NDS Final Product Monograph Contol #HN916108, Hoffmann La Roche to Dr. P. McDonald, Infection and Immunology Division, Bureau of Human prescription Drugs, HPB

December 11, 1992: **Col Labbe, Commander of Canadian Forces in Somalia, arrives in Mogadishu.** (page 283, volume 1, Report)

December 15, 1992: **"It is requested that once any investigation into the efficacy (or lack thereof) of mefloquine as a malaria prophylactic is completed, those who were believed to have contracted malaria while in Angola be given a definite answer whether they did or did not contract the disease. As a former Commanding Officer of this contingent, I do not consider the "no news is good news" philosophy to be an adequate response by the CFMS."** CCIMAVEM - Current Location of First Contingent, LCol E. Fafard, D Mil E 2,

December 19, 1992: **"Canada's ultimate mission was finally assigned. The Canadian contingent was to be responsible for security in the Belet Huen Humanitarian Relief Sector."** (page 261, volume 1, *Report)*

December 21, 1992: **Mefloquine experience in Somalia**

"Several anecdotes of G1 upset, headache, or thought disturbance, temporally related to mefloquine use."

CDN JFHQ Somalia to RCCPJSA/NDHQ - Weekly medical sitrep, 13-20 Dec 92.

December 28, 1992 - January 1, 1993: Flights to Somalia of main body of CAR. "The advance body of CARBG landed at the Belet Huen airstrip on board eight Canadian Hercules C-130 aircraft on December 28, 1992." (page 283, volume 1, *Report)*

1993: **Lariam approved in Hong Kong ("launched")**

January 11, 1993: **"A CARBG soldier had surgery to repair a wound in his**

forearm caused when he shot himself while cleaning his pistol. (page 290, volume 1, *Report)*

January 21, 1993: **"At least five experienced intolerable side effects from *Mefloquine*, including severe abdominal cramps up to four days after injection [ingestion] of the drug, insomnia, headaches, depressed mood, dizziness, diarrhoea and nausea. Medication was tried for a least 3-4 weeks before it was discontinued and replace with Doxycyclyne...no major problems with Doxyclycline."** Medical Post-Op Report-Op Relief, Nairobi, Kenya 24 October-20 December, Capt Jussak-Kiellerman.

January 22, 1993: **Lariam approved for marketing:**

"An interim report [LSMS] was received by BPA prior to issuance of the NOC."

"The infection & Immunology Unit of BPA has not received from DND a summary of any adverse reactions observed in Somalia."

"DND has not provided Infection & Immunology Unit of BPA with this information [of those members of the Canadian Forces who were administered mefloquine sine 1992, how many have attempted suicide...]"

"Lariam was approved for marketing on January 22, 1993 and introduced onto the market in April 1993. BPA is not responsible for post marketing surveillance."

Dr. E. Gadd, Head of Infection and Immunology Unit, Biopharmaceutics Evaluation Division, Bureau of Pharmaceutical Assessment, Therapeutic Products Directorate, Health Protection Branch, Health Canada (Dr. Gadd's response to Cummins' Inquiry of Ministry Q-138, September 30, 1998)

February 16, 1993: **Lariam New Drug Submission approved by HPB:**

"The Lariam New Drug Submission has been approved by the Health Protection Branch (HPB). We are currently preparing for the introduction of Lariam. All components should be complete by the beginning of March 1993. The Lariam Safety Monitoring study will be closed at that time...We would appreciate receiving any remaining patient and drug distribution records from you within a month of study closure."

Lariam Approval, letter to Ottawa Civic Hospital (RS?), from Hoffmann-LaRoche

February 17, 1993 (Wednesday):

"An unidentified, unarmed Somali killed on February 17, 1993 during an encounter with the Mortor Platoon." (page 288, volume 1, *Report)*

Mid-March 1993: **LSMS ends** (according to Hoffmann-LaRoche letter to Dr. Ed gadd of HPB dated July 30, 1993.

March 2, 1993: **"The seeming high prevalence of reported (alleged) intolerable side effects from mefloquine causes some concern. However, there was no similar observation in the Op Relief report submitted by Capt Banner. Further, we have not had any similar reported problem among the 1,000 or so CF personnel taking *mefloquine* in Somalia."** comments on Post Op Report/ Op Relief, signed approved by *LCol Tepper* on March 2, 1993 (see notation for January 21, 1993)

March 3, 1993: **"An American soldier died when a U.S. vehicle struck a mine near the village of Matabaan, approximately 80 or 90 kilometres north-east of Belet Huen..."** (page 661, volume 2, *Report)*

March 5, 1993: **CF (Tepper) informed that Lariam New Drug Submission has been approved:**

"As per your request, please find attached leter sent by Hoffmann-La Roche to [?RS, Ottawa Civic Hospital] regarding 'Lariam.'" [apparently a copy of the letter sent to the Principal Investigator, at the Ottawa Civic Hospital on February 16, 1993 (as above)]

March 4, 1993 (Thursday):

"Death of a Somali citizen at the hands of Canadian soldiers." (page 31, volume 1, Report); "Mr. Aruush, killed during an encounter with the Reconnaissance Platoon." (page 288, volume 1, Report)

March 16-17, 1993 (Tuesday, night):

Beating death of Shidane Arone near Belet Huen, Somalia.

Witness [Giasson]: "At that time the man in the bunker, like, he sounded pretty crazy to me and I was scared of my...for my personal safety...." *[vol. 2, page 255]*

Assistant Prosceutor: "What made you think he was crazy?"

Witness: "The ways...the samll talk he was talking, he was more talking like...a laugh,

like, he was sort of laughing at the same time he was talking." *[page 255]*

Assistant Prosecutor: "Was he talking like a soldier?"

Witness: "No, not like a soldier." *[page 256]*

Prosecutor: "Giasson testified that the man in the bunker [Matchee] seemed crazy. The accused did not even describe the behaviour of Matchee that led him to even think he was drunk." *[Brocklebank Court Martial, vol. 5, page 757]*

* * * * * *

Defence Counsel: "What was Master Corporal Matchee's condition at that time, Corporal Pusch?"

Witness [Corporal Pusch]: "He was under the influence of alcohol at the time. *[vol. 4, page 684]*

Defence Counsel: "That appeared obvious to you did it?"

Witness: "Yes. There was also a beer can in the pit with him." *[page 684]*

Defence Counsel: "And would you describe his condition as being fired up?"

Witness: "He was charged up, yes." *[page 684]*

Judge Advocate: "He described Matchee as under the influence of alcohol, charged up and hyper. He saw Matchee strike the prisoner." *[vol. 4, page 755]*

Court Marshall of Kyle Brown

* * * *

Prosecutor: "What was his condition as you observed him at that point as to being influenced by alcohol or not?

Witness: "He didn't seem to be influenced by alcohol, sir. From what I can ascertain, Master Corporal Matchee was pretty much in the same state that I had seen him earlier when I had gone to the access point to retrieve him." [page 387]

Prosecutor: "Now, at that time, when that was said, you have described what Matchee was doing and that you were telling to stop, could you see any indication at that time of any effect of alcohol?" *[page 390]*

Witness (Private Kyle Brown): "At the time Matchee had returned, I think he had a beer with him and I think it was still in the plastic ringlet, if you will, and he'd been sipping from it. There wasn't much in that I could see, but at one point I'd actually taken a sip of it myself. Other than the smell of alcohol I couldn't accurately give you any kind of estimation as to what effect it had on him, sir. *[vol. 2, page 390]*

Private Kyle Brown, Court Marshall of Captain Sox

March 16, 1993, 2045 hours:

"An unarmed 16-year old Somali youth, Shidane Abukar Arone, was captured in an abandoned U.S. Seabees compound." (page 320, volume 1, *Report)*

March 17, 1993 (Thursday):

"An unidentified person killed during a confrontation at the International Committee of the red Cross compound in Belet Huen on March 17, 1993." (page 288, volume 1, *Report)*

March 18, 1993: **Arrest of *MCpl Matchee* on suspicion of the murder of a Somali prisoner.** (volume 325, volume 1, *Report)*

March 19, 1993, 1300 hours (Friday): **Suicide attempt of *MCpl Matchee.*** (page 325, volume 1, *Report)*

March 19, 1993, 1300 hours plus:

"Major Armstrong and Cpl Adkns arrived within minutes, along with an ambulance. Major Armstrong and a U.S. medic who was in the vicinity began recusitation." (page 325-6, volume 1, *report)*

March 20, 1993: **"*MCpl Matchee* was evacuated via Hercules aircraft to the U.S. 86th Evac Hospital in Mogadishuu."** (page 326, volume 1, *Report)*

March 24, 1993: **Mefloquine now licensed:**

"The antimalarial mefloquine is now a licensed drug in Canada. Therefore, the provisions for access to this drug through DHPP 2 at ref no longer repeat no longer apply."

"Pharmacists are to retain the line listing of persons dispensed mefloquine under ref study for six months from the date of this message."

Mefloquine Licensure, from LCol Tepper, DHPP 2 (signed by Tepper)

March 29, 1993: **Events of March 16th:**

"that just before his shift he was woken by Matchee and told by Matchee that he had a surprise for him. At this time he noted that MCpl Matchee had alcohol on his breath;"

Statment Analysis Pte Brocklebank, DND014932, volume 38, tab I 15 , *Somalia Inquiry*

April 1, 1993: **Events of March 16th:**

"On the 16th of March I ws woken up at...2345..As I came up to the trench Tpr Brocklebank was standing above the pit and Mcpl Matchee was in the pit with the prisoner. Mcpl Matchee came out of the pit and told me that he had been beating the prisoner for three hours. That is when I noticed the alcohol in his breath and I said to myself that he was drunk..."

"I took Sgt Skipton aside and told him that Mcpl Matchee did this along with Tpr Brown taking pictures and Mcpl Mathcee was drunk because I could smell alcohol on his breath..."

Statement by Tpr Robert Glass *(Somalia Inquiry)*

April 7, 1993: **"Numerous reactions to mefloquine were reported...A large percentage of the reactions were GI related: with nausea, burning epigastric pain and diarrhoea. Several patients were switched to Doxycycline. 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."** *HMCS Preserver*, Post Deployment Report of Op Deliverance, 16 November 1992 - 7 April 1993

May 2, 1993: **Cpl Abel, killed by an accidental weapon discharge by another CARBG member on May 2, 1993."** (page 288, volume 1, *Report)*

June 1993: **"The question is now raised as to the use of primaquine prophylaxis for CF personnel who have returned for or will soon return form Somalia. After discussion with CAT BG MO, HMCS Preserver MO, MARLANTHQ/RSURG, NDMC/HEAD OF INF DIS, and CF Med Council in TROP MED, Primaquine Terminal Prophylaxis is not repeat not recommend at this time.**

Reasons for this decision include:

A. **Few if any CF members deployed to Southern Somalia (the seeming high risk area) for even moderate (a few weeks) periods of time;**

B. **There is no evidence of vivax activity in the Belet Huen area where the CAR BG is located;**

Regardless of the primaquine issue, the following are important points to note:

A. All personnel returning to Canada from the OP Deliverance theatre to continue to take malaria prophylaxis for four weeks after leaving the theatre;

Malaria from Somalia, DHPP 2, to medial service units

June 16, 1993: **"All Canadian troops had left Somalia by June 16, 1993"** ("with the exception of a small number of CF members assigned to UNOSOM II") (page 333, volume 1, *Report)*

June 17, 1993: **"Redeployment of CARBG back to Canada completed."** (page 324, volume 1, *Report)*

July 16, 1993: **Canadian travellers complain to HPB of problems experienced with mefloquine:**

"In the middle of April a group of 20 Canadians, including myself, travelled to the Solomon Islands...we all went on a prophylactic treatment of mefloquine..."

"As time went on, about 50% of us had severe reactions to mefloquine and subsequently switched to chloroquine for prophylaxis. During the second week of the expedition, one of our group members was mentally unstable and had suicidal tendencies. Others experienced milder side effects, ranging from nausea and constipation. to emotional duress."

"I contacted malaria...despite being on mefloquine...While on mefloquine prophylaxis, I had myself been feeling abnormal, and had bouts of depression and emotional upheaval, occurrences that do not normal[ly] happen...But these imbalances increased with time, and during the treatment for...malaria with mefloquine, I experienced severed nightmares. In addition I had no sense of balance, and my frame of reference kept changing during sleep, that is I could not distinguish my feet from my head since they kept switching continuously."

"Therefore, on behalf of myself and the group I would like to request that approval for mefloquine for malaria prophylaxis be re-evaluated, since neither it s safety nor efficacy is any better than of chloroquine, and in fact more severe side-effects have occurred. I would strongly oppose any recommendation by physicians at Canadian travel clinics to prescribe mefloquine for malaria prophylaxis, and would go as far as to say that it is better to contact malaria and be treated for it than to take mefloquine for prophylaxis. ...we have all suffered severe emotional, psychological, and physical duress.

"I hope that these comments will be seriously considered, and that the approval of mefloquine in Canada will be reconsidered.

Letter from Hari A. Venkatacharya to Dr. Claire Franklin, Acting Director of Bureau of Human Prescription Drugs, HPB

July 30, 1993: Informed of possible relationship between **alcohol** and mefloquine (letter to Dr. E. Gadd of HPB from Hoffmann LaRoche.

Sept. 20, 1993: **"Mefloquine is now licensed in Canada and is the drug of choice for travellers exposed to the risk of acquiring chlorquine-resistant malaria. However, mefloquine is specifically contraindicated in aircrew therefore doxycycline in a dose of 100 mg is substituted."** Advisory Publication 61/58B Aircrew Malaria Prophylaxis, Maj H.J. O'Neill, CA Project Officer PG 115, Directorate of Medical Operations

October 26, 1993: **"We had one psychiatric hospitalization in Belet Huen, which did not respond to the usual treatment of battle stress. The diagnosis made by psychiatrists at NDMC [National Defence Medical Centre], after he was evacuated, was an organic brain syndrome, probably due to *mefloquine*. The suicide attempt [*MCpl Clayton Matchee*] may also be *mefloquine* related."** Medical Opeations in Somalia, Surgical Section, Op Med 93 Conference, *Maj Barry Armstrong*

February 1, 1994: **Requests advice on comments on Maj Armstrong's analysis of problems associated with mefloquine use in Somalia:**

"As you discussed by phone today with Dr. Tepper of my staff, it would appreciated of you consider the question of subtle cognitive effects of prophylactic mefloquine use. To this end, enclosed are:

a. the abstract of a presentation given by Dr. B. Armstrong...This presentation subsequently stimulated media interest and ultimately resulted in you CBC interview;

c. a draft letter regaling this matter which lays out the Surgeon General's response tot this issue.

We would appreciate your review and comment on this letter and any additional comments that may be germane to the topic."

Capt Climie to Tropical Disease Unit, Toronto Hospital (signed by LCol tepper for Climie), Subtle Cognitive Effects of Prophylactic Mefloquine.

February 7, 1994 **DND statement to JAG (Petawawa) on impairment (mefloquine)**

"We are not aware of any data to support the suggestion that *melfoquine is perhaps cuasing previously unrecognized, widespread, subclincial impairment of cognition."*

Attention DJA, Prophylactic Mefloquine Use and Impairment Judgement, from RCD Climie, Director of Health Protection and Promotion.

February 7, 1994: **Dr. Keystone advises the Surgeon General on issue of possible subtle cognitive effects of mefloquine.**

"Based on my experience with hundreds of returned rteavellers who have used mefloquine ans an examination of the medical literature on the subject, I fully concur wity the conclusions reached by your staff concerning the potentila adverse efects of mefloquine. I too am not aware of any data which support the suggestion that mefloquine causes 'previously unrecognized, widespread impairment of cognition.'"

Dr. Keystone to Capt Climie, Letter regarding Surg Gen response to issue that mefloquine might cause subtle cognitive effects.

February 8, 1994: **"Enclosed is our considered view of this subject as you requested from LCol Tepper of my staff."** RCD Climie, Captain, Director of Health Protection and Promotion, to attention DJA [Judge Advocate], CFB Petawawa, Prophylactic Mefloquine Use and Impaired Judgement

"We are not aware of any data to support the suggestion that '(mefloquine) is perhaps causing previously unrecognized, widespread, subclinical impairment of cognition' (reference H [Barry Armstrong paper, Medical Operations in Somalia])."

February 24, 1994: **Events of March 16, 1993:**

"3. Under cross-examination, Push: ...d. Matchee was under the influence of alcohol,

there was beer inside the bunker. Matchee was hyper, full of adrenalin and was slurring his words, 'a bit'. Matchee was 'always aggressive but now pumped up, full of piss and vinegar'. Brown was quiet, not smiling and didn't seem to want to be there."

"The last witness for the day was Cpl MacDonald. He was the radio operator on duty at the CP on the night of 16 Mar 93. He stated the following:...i. Matchee was in a 'chipper mood, answering clearly'. Brown didn't say anything.

GCM Pte Brown, Sitrep #25 - 241630 Feb 94, Court Activities, DND015505, *Somalia Inquiry*

March 21, 1994: Adverse reactions to mefloquine:

"Further to our recent discussions at the March 18, 1993 FDA Antinfectives Advisory Committee Meeting on the U.S. Megalone NDA, please find enclosed a selection of literature on 'Lariam' that was recently retrieved, specifically dealing with adverse reactions and tolerability."

"The most recent analysis of the data collected in the Canadian 'Lariam' Safety Monitoring Study is also included."

"Please note that while there are no reports of amnesia there are reports of forgetfulness, and memory impairment/loss."

Lariam General Information NDS Control #08278, from Hoffmann La Roche to Dr. Ed Gadd, Chief of Infection and Immunology Division, bureau of Human Prescription Drugs, Health Protection Branch, Health Canada

March 21, 1994: Submission of draft of *"Safety Report for the Lariam Safety Monitoring Study":*

"The following report summarizes briefly the study and the safety data reported from November 1990 to March 19, 1993. The study was terminated March 1993 and CRF's collected for one month following termination...

The organ systems with the most reportable adverse events (AE) were the gastrointestinal system;...events(...of the...AEs), cental and peripheral nervous system; ...events (...of the..AEs)...

"Some of the most frequently reported adverse events in the ...patients were nausea (..of the..patients)headache..., dizziness..., sleeplessness..., diarrhoea..., vertigo...; abdominal pain...insomnia...;...anxiety."

Lariam General Information NDS Control #08278, from Hoffmann La Roche to Dr. Ed Gadd, Chief of Infection and Immunology Division, bureau of Human Prescription Drugs, Health Protection Branch, Health Canada

April 1994: **"GCM of *MCpl Matchee found* him unfit to stand trial."** (page 120, volume 1, Report)

April 6, 1994: **Events of March 16, 1993:**

"He [Brocklebank] described Matchee as excited (giddy, laughing, smiling) pumped up, and Glass could smell alcohol on his breath. Brocklebank looked nervous."

GCM Sgt Gresty Sitrep #10 -061700 Apr 94, DND 015572 , Court Activities, Somalia Inquiry

April 14, 1994: **"...from the Tropical Disease Unit in Toronto has proposed that the military participate in a *Mefloquine Adverse Drug Reaction Study.* The objective of the study to document neuropsychiatric adverse effects of Mefloquine (if any). Information from this study would clearly be of operational relevance to the Canadian military and our participation would enhance our efforts to become more active in practical research."** Mefloquine Adverse Drug Reaction Study, Maj K.C. Scott, Hd Inf Dis

May 1994: **Hoffmnan LaRoche report on adverse events to January 1, 1994:**

1. INTRODUCTION

"This is a cumiulative safety update on Lariam compolied for regulatory authorities in the format proposed by CIOMOS Working GroupII. It sumarizes the safety data received by the International Drug Safety Department of f. Hoffmann La Roche from worldwide sources between introduction on 18 Sepember 1985 and 1 Jan. 1994...

"...Mefloquine is taken up largely in the livers, but also into the lungs, muscles, brain and retina. The average half-life of mefloquine in Caucasians is 21 days...

3. LICENCED STATUS

"Lariam has been approved for prophylactic use and treatment of malaria in 30 countries and has been launched in 20 countres.

4. UPDATE ON REGULATORY OR MANUFACTURER ACTIONS TAKEN FOR SAFETY REASONS

In the first half of the Seventies, emefloquine has been selected by the US Army Antimalarial Drug Development Program by the Walter Reed Army Institute of Research as a candidate for the preventative (and curative) treatmetn of all forms of human malaria...It has been developed by WRAIR to the stage of clinical and field testing, and handed over in 1975 to Hoffmnann La Roche...for furhter developometn and worldwide commercialization.

6.1.3 Characteristrics of Adverse Events

"The majority of evetns were neuropsychiatric disorders...

6.2.1.2 Photosensitivtiy Reactions

Mefloquine was originally chosen by the US-Army from among its congeners because of its low photoxicity in early studies.

6.2.4 Central and Peripheral Neurologic and Psychiatric Disorders

Distribution of Adverse Events: **[HPB removed all numbers]**

Centr. & Periph Neurological Disorders
Dizziness, vertigo, drowsiness
Ataxia
Headache
Sensory disturbances
Neuropathy
Twitching, tremor, spasms
Convulsions, seizures

Psychiatric Disorders
Anxiety
Agitation, restlessness
Feeling strange, psychiatric disturbances
Depression
Suicide attempt, tendency
Hallucinations
Psychosis
Paranoia, fear
Manic, aggressive reaction
Panic reaction
Behaviour disturbance
Memory disturbance, confusion
Concentration impaired
Sleep disorder, insomnia

Dreaming abnormal
Euphoria

Headaches and dizziness or vertigo are the most common complaints with an incidence ....

In a US-Army study...32% of 22 mefloquine users complained of insomnia and/or dreams.

6.2.4.6 Confusion/Memory Disturbance

The acute confusional state is a common neuro-behavioral syndrome in which global impairment of cognitive function is accompanied by impairment of attention and consciousness. The impairment of cognition usually include disorientation, abnormal perception, disordered reasoning and poor memory...

8. OVERALL SAFETY EVALUATION

8.1 Drug Interactions

8.1.4 Concomitant Use of Quinolones

'Lariam must not be administered concurrently with quinine or related compounds e.g. quinidine, quinoline, chloroquine) since these could increase the risk of convulsions.'

This statement in the core data sheet is based on theoretical grounds because of the structural similarities and the fact that psychic disturbances and convulsions have been associated with all of these compounds.

A possible additive effect cannot be substantiated by spontaneous adverse event reporting: *A total of [deleted] patients (including [deleted] from the Canadian study*) had taken concomitantly cifloxacine or norfloxacine. [deleted] patient who had also received chloroquine, quinine and Fansidar developed severe memory disturbance and speech disorder requiring hospitalization. Neurologic examination, CSF and CT-scan were WNL [deletion] other patients had non-serious events such as headache, dizziness or GI-complaints.

8.1.5 Concomitant Use of Alcohol

Drug Safety has received [deleted] adverse event reports in which concomitant alcohol use was reported.

It is difficult to evaluate these cases, since a patient is more likely to be questioned about alcohol consumption if he presents with such symptoms as hallucinations, delirium, confusion, or ataxia.

8.4 Conclusions

...Roche Drug Safety has received [deleted] spontaneous event reports mainly from industrialized countries such as Germany, France, USA and Switzerland. The majority of evens were neuropsychiatric disorders [deleted].

Review of Adverse Events Associated with Lariam, Introduction to Jan 1, 1994, The Department of Drug Safety, F. Hoffmann La Roche, Basel Switzerland, signed by Lydia Kerr, Dr. Martine Streb, approved by Dr. Bart Vannauwere.

June 1994: Ontario Criminal Code Review Board...decided that MCpl Matchee was unfit to stand rial by court martial." (page 120, volume 1, *Report)*

July 4, 1994: Further review of Canadian safety data (LSMS):

"After a review of the data submitted...Some revisions may be required to the Product Monograph. The following issues will be discussed with the manufacturer:

1. The Adverse Drug Reaction section of the monograph is vague, and should be updated to reflect the more common reactions seen after both prophylaxis and treatment with mefloquine. For prophylaxis these should include nausea, vomiting, abnormal pain, diarrhoea, dizziness, insomnia and anxiety.

2. The sponsor will be requested to took into the possibility of drug interactions with quinolone class of antibacterials. This is especially relevant considering the potential use of the quinolones in the self-treatment of traveller's diarrhoea."

Review of Requested Additional Data For Safety Update for Mefloquine, Dr. P.A. McDonald to Dr. R.E.A. Gadd, Acting Chief of Infection and Immunology at HPB

July 26, 1994: Possible changes in the product monograph:

"Further to our telephone conversation of June 30, 1994, I am writing to confirm the discussion of the following issues:

1. The Adverse Drug Reaction section of the current Product Monograph is vague, and should be updated to reflect the more common reactions seen after both prophylaxis and treatment with mefloquine. For prophylaxis these should include

nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, insomnia and anxiety...

3. The possibility of drug interactions between mefloquine and the quinolone class of antibacterials. This is especially relevant considering the potential for use of the quinolones in the self-treatment of traveller's diarrhoea.

...In the interest of patient safety, could you please respond to this letter within sixty days."

Lariam NDS Control #08278, letter to Hoffmann La Roche from Dr. Ed Gadd, Acting Chief of Infection and Immunology Division, HPB

September 30, 1994: Hoffmann La Roche responds to July 26, 1994 letter:

"1. In response to your Point #1, the adverse events list in the Adverse Reaction section of the Product Monograph, has been reorganized into, 'most frequently reported', and 'less frequently reported'...[HPB made an undated handwritten notation as this point: "Ref # 1 pg. 36-37: Alcohol issue]

The adverse events reported with 'Lariam' has recently been reviewed by our company based upon the most recent and relevant publications, and a summary document entitled: "Review of Adverse Events Associated with Lariam-Introduction to January 1, 1994, has been prepared. This document was used in updating the Adverse Reactions section of the Product Monograph.

The following adverse events have been added to the Product Monograph:

Central and Peripheral Nervous System: loss of balance; somnolence; sleep disorders (insomnia, abnormal dreams); anxiety, restlessness, depressive mood as specific examples of 'emotional problems', the general term used n our current Product Monograph; forgetfulness; confusion; hallucinations...

Loss stools has been added as a further description of diarrhoea.

A specific statement regarding the 'most frequently observed adverse experiences'...has been retained. We have included all of the adverse events suggested in your letter in this statement except abdominal pain, insomnia, and anxiety. These are reported under the general list of the 'most frequently reported' adverse events....

3. The list of adverse drug reactions has recently been revised based on the most recent and relevant publications as discussed in the response to Point #1. In this

review no clinically relevant interactions between 'Lariam' and quinolone antibiotics were observed. Section 8.1.4 (p.36) of Reference #1, 'Review of Adverse Events Associated with Lariam, discusses concomitant use of quinolones...

In addition to the Product Monograph revisions required to address the Points in your July 26, 1994 letter, the following additional Product Monograph updates were done:

3. The 'PRECAUTIONS, drug Interactions' section was revised to include statements regarding possible interactions between mefloquine and halofantrine, anti-arrhythimcis, H-1 blocking agents, tricyclic antidepressants, phenothiazines, carbamazepine, phenobarbital, phenytoin, oral live typhoid vaccines.

Lariam Tablets NDS Control #08278 - Response to Letter of July 26, 1994, Hoffmann La Roche to Dr. Claire Franklin, Director of Bureau of Human Prescription, HPB.

October 18, 1994: Parliamentary Statement on Mefloquine by Cummins:

"The Minister and the military establishment ignored the well known effect of mefloquine, a malaria drug administered to Canadian troops in Somalia. Side-effects include violent dreams, hallucinations, confusion, anxiety and mental depression. Mefloquine could have precipitated the murder of the prisoner and Master Corporal Matchee's attempted suicide."

"Statement on Mefloquine", John Cummins, M.P., Hansard, October 18, 1994 (p.6847)

October 19, 1994: Note to Minister further to Worthington article:

"As a result of the Peter Worthington article in Tuesday's Ottawa Sun which suggested that the use of the prophylactic drug mefloquine may have contributed to the behaviour which lead to the death in Somalia, we have prepared a BN to provide the MND with the facts as we know them."

LGen Addy to DM/CDS, Use of Mefloquine

October 19, 1994: Note to Minister further to Worthington article:

"The issue raised by CDS has been addressed and the BN has been reworded accordingly. Request that file be forwarded to DM after CDS is briefed on the change."

LCol JRR Besner(initialed)

October 19, 1994: **Note to Minister due to Worthington article:**

"What is made clear from the BN is when the drug(?) was administered (?) to Canadian troops in Somalia. The BN says the drug was approved for use in Canada in the Spring of 93. It also says the drug was chosen as the drug for the deployment to Somalia. The deployment to Somalia took place in Dec/Jan 92/93. When was it administered to our troops?

(on CDS stationary of AJGD de Chastlelain, initialed by AGD)

October 20, 1994: **HPB makes formal request to Hoffmann LaRoche** "regarding the use of mefloquine by the co-investigator Dr. Martin Tepper under the auspices of the protocol entitled *Safety Monitoring Limited Distribution of Lariam* (control no. 902095)" -- mefloquine taken by Canadian soldiers deployed to Somalia.

October 20, 1994: **Hoffmann LaRoche notifies DND of the HPB request, and that HLR is unable to find receipt of dispensing records, and requests answers to HPB's three questions:**

"In September and October of 1992 drug shipments of "Lariam" were made to the Central Equipment Department at CFB Petawawa...under the auspices of the "Lariam" safety Monitoring Study...

"In reviewing our records we were 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 LaRoche.

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

Hoffmnan LaRoche, to Dr. M. Tepper DND, Lariam - Releases of Drug under the Safety Monitoring Study - URGENT

October 21, 1994: **DND prepares Q and A regarding mefloquine and Somalia:**

"(What are the side-effects of mefloquine?) Approximately 25% of those taking mefloquine will have side-effects, most of them transient and mild. The most frequent minor side-effects are nausea, dreams or nightmares, dizziness, mood changes, insomnia, headache and diarrhoea..."

"(Does mefloquine impair 'thinking' or judgement?) A close review of the relevant scientific literature does not indicate any such side-effects from mefloquine sued to

prevent malaria. This conclusion is shared by Dr. J Keystone...Discussion with relevant medical authority indicates that there is no concern about mefloquine-related effects on cognition/behaviour among the CF units deployed in *Rwanda*."

Questions and Answers Regarding Mefloquine and Somalia, prepared by DHPP 3 /LCol Tepper Immediately preceded ministerial briefing note, may have been part of it.

October 24, 1994: DND responds to Hoffmann LaRoche regarding the dispensing of mefloquine/status of mefloquine used in Somalia:

"While we have not yet found the specific supporting documentation, the firm intent was and, till now, the belief was that the mefloquine issued for Somalia was purchased separately from the Safety Monitoring Study; this was partly because a decision had ben made that a consent form, mandatory under the SMS, would not be (and was not) used for operational deployments. Sine the SMS was not to be involved, the requested list is not relevant."

RCD Clemie, Captain, Director Health Protection and Promotion (actually signed by LCol M. Tepper for Clemie), to Hoffmann LaRoche

October 24, 1994: Defence Minister informed on the use of mefloquine by the CF in Somalia:

"Administration of the drug was started one week prior to deployment in Dec 92/Jan 93, continued weekly during the deployment, and given weekly for 4 weeks post-deployment. Although at the time of its initial administration it was still not licensed for general use in Canada, Health Canada was recommending its use among travellers to endemic area for falciparum malaria, and was making it available for such use...Mefloquine was subsequently licensed for general use in Canada in the spring of 1993.

"A number of allegations with respect to adverse effects of mefloquine, and their relationship to the death of a Somali prisoner, have been made by Mr, John Cummins.

these are the subject of an article in the Ottawa Sun by Peter Wothington, which contains statements of a number of CF personnel who report untoward effects of the drug."

"It is not intended to deny the perceptions of those who served in Somalia that there were drug effects associated with mefloquine use. The weight of scientific evidence, however, suggests that the possibility of there being adverse effects severe enough to have an impact on the behaviour of our troops, and to constitute a contributing factor to the tragic events that occurred, is very low indeed.

"At the present time, the CFMS is not aware of any data to support the suggestion that mefloquine is causing either previously unrecognized, widespread, subclinical impairment of cognition, or behaviours that are consistent with those associated with the death of the Somali prisoner. Dr. J.S. Keystone, Director of Tropical Disease Unit, Toronto Hospital and advisor to the Surgeon General, however, to investigate further the statements made by the CF personnel quoted in the Wothington article on the effects of mefloquine."

Briefing Note for the MND: Prophylactic Mefloquine Use, Gen AJGD de Chastelain, CDS,

November 14, 1994: Parliamentary Question by Cummins In Regard to Mefloquine, Q-105 (alcohol use):

"With regard to the mandatory use of mefloquine by canadian Forces personnel:

a. what clinical or field studies did the Department of National Defence undertake or fund into the possible adverse effects including the impairment of judgement of the mandatory use of mefloquine by Canadian Forces while in Somalia, both while the personnel were in Somalia and on their return to Canada;

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 by Canadian forces while in Rwanda, both while the personnel were in Rwanda and on their return to Canada;

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 of mefloquine, 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;

d. what screening and other precautions were taken by those administering mefloquine, and what advice was given to Canadian Forces personnel in regard self-administered recreational bodybuilding drugs that it could be reasonably be expected that personnel might be taking concurrent to their usage of mefloquine;

e. what ranks and occupations in the Canadian Forces were not subject to the mandatory use of mefloquine in either Somalia or Rwanda and why were they not subject to the mandatory in either Somalia or Rwanda and why were they not subject to the mandatory requirement to take mefloquine; and