**Mr Mark Reid** 12 September 2018
**Supplementary Submission**
Response to QVFA supplementary submission 16.7

Ms Lyn Beverley
Committee Secretary
Senate Foreign Affairs, Defence and Trade references Committee
PO Box 6100 parliament House
Canberra ACT 2600

Dear Lyn,

**Re Senate Inquiry – Use of the Quinoline anti-malarial drugs Mefloquine and Tafenoquine in the Australian Defence Force – Supplementary Submission made by Major McCarthy (retired)**

I understand Major McCarthy (retired) has made a supplementary submission in relation to my oral testimony presented to the Committee on the 30th August 2018. The date of Major McCarthy (retired) submission is 6th September 2018.

Allegation of misleading the Committee:

- I'm not sure why receiving a salary under a legitimate employment contract with Clinical Network Services (CNS) Pty Ltd to compile the tafenoquine dossier is misleading the Committee. Presumably, I'm still obligated to pay taxes in Australia after leaving the ADF in 2007.
- As already stated to the Committee during my oral testimony, I have no financial interest in the registration of tafenoquine.
- Further, I have no equity interest in 60 degree Pharmaceuticals.
- The Therapeutic Goods Administration is an independent regulatory body, tasked with ensuring drugs, devices and biologicals are qualified, safe and efficacious. My role as an employee of Clinical Network Services was to provide all the scientific and medical evidence to the FDA and TGA to independently evaluate with their own independent expert committees.
- I do not make any decision about Tafenoquine approval for the TGA or FDA.
- The views I expressed to the Committee in written evidence and during oral testimony were as an Australian army veteran that coordinated Study 033 in East Timor and Townsville in 2000/2001 and my own personal views as per the Committee's Terms of Reference.
- I made this clear in both written evidence and oral testimony and the views I expressed do not represent the views of Australian Defence Force or Clinical Network Services. I believe I submitted an "individual" submission to the Senate Committee and not an organisational submission on behalf of 60P, the ADF, USAMMDA or Clinical Network Services.
- Further, I do not make purchasing decisions about anti-malarial drugs for the ADF or the US military.
- I resigned my commission with the Australian Defence Force over 11 years ago (12th May 2007). I also resigned from Clinical Network Services effective from the 9th October 2017. The tafenoquine dossier was submitted to the TGA prior to October 2017 while I was still employed by Clinical Network Services.

- As I have previously submitted to the Committee (Submission 71.2 Mark Reid), I was never involved in the mefloquine vs. doxycycline studies in the ADF. I stated during my oral testimony that the only malaria assignment I ever performed for the Australian Army was Study 033. I have not misled the Committee about these mefloquine studies despite this also being alleged by Major McCarthy's father.
- I note Major McCarthy's twitter comment (@StuartMcCarthy) about my Submission 71.2. "*Apparently he has a brother with the same initials. Seems a solid defence: 'wasn't me, it was my brother. One brother poisoned us with tafenoquine, the other poisoned us with mefloquine"*.
- **For the record – Michael Patrick Reid and Mark George Reid have both taken tafenoquine and/or mefloquine, primaquine and doxycycline. Therefore, I am unclear how I selectively "poisoned" Major McCarthy but not myself. I would be more than happy to take these anti-malarial drugs again in the future. All of them are safe and effective.**

**Dow GS, Brown T, Reid M, Smith B, Toovey S. Tafenoquine is not neurotoxic following supertherapeutic dosing in rats. Travel Med Infect Dis 2017; 17: 28-34.**

Competing Interest Declaration:

*"TB and MR have no financial interest in the registration of Tafenoquine. TB and MR are employees of Clinical Network Services (CNS) Pty Ltd and have acted as paid consultants to 60P and the US Army Medical Materiel Development Activity (USAMMDA). MR was the former study coordinator of the 033 clinical study (Nasveld et al., 2010) and a former uniformed, serving member of the Australian Defence Force."*

Author Contribution:
*All authors contributed to the conception of the study or drafting of the manuscript, and read approved the final manuscript.*

**Dow GS, McCarthy WF, Reid M, Smith B, Tang D, Shanks GD. A retrospective analysis of the protective efficacy of tafenoquine and mefloquine as prophylactic anti-malarials in non-immune individuals during deployment to a malaria-endemic area. Malar J 2014; 13: 49.**

Competing interests:
*The authors have a personal and professional interest in ensuring the regulatory approval of tafenoquine for malaria prophylaxis but no competing interests.*

Author's contributions:
*MR extracted records from the Central Malaria Registry and conducted the analysis of attack rates from prior deployments.*

**Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C, Prescott W; Tafenoquine Study Team. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother 2010; 54(2): 792-8.**

Acknowledgements

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**Charles BG, Miller AK, Nasveld PE, Reid MG, Harris IE, Edstein ED. Population pharmacokinetics of tafenoquine during malaria prophylaxis in healthy subjects. Antimicrob Agents Chemother 2007; 51(8): 2709-15.**

Acknowledgements:
*Financial support for the study was provided by USAMMDA, GlaxoSmithKline, and the Australian Defence Force.*

*The opinions expressed are those of the authors and do not necessarily reflect those of the Australian Defence Health Service or any extant Australian Defence Force policy.*

Vertigo and other ear/labyrinth disorders during Study 033

- Major McCarthy (retired) has expressed a view that chronic vestibular symptoms occurred among the Study 033 trial (1st Battalion) participants including dizziness, vertigo, balance problems, hearing problems and tinnitus.
- I reject this allegation having personally reviewed most, if not all the study records during monitoring of the study files by a third party clinical research organisation (CRO) that was engaged to verify all the data in the study database and to ensure the study was conducted in accordance with ICH Good Clinical Practice. This monitoring occurred while I was a member of the ADF.
- I recall the vertigo and other ear/labyrinth disorders were almost all mild, self-limiting, usually associated with motion sickness or gastroenteritis. These events were generally considered "not related" or "unlikely related" to blinded study medication. Given the quality of the winding roads in Bobanaro district and the use of helicopters and other military vehicles; motion sickness was expected during the deployment and noted in the medical records appropriately. These symptoms were managed on the boarder with standard therapies and these symptoms did not persist after the battalion returned home from East Timor. I cannot recall any situation where a chronic vertigo and other ear/labyrinth disorder was reported during the post-deployment follow-up period for Study 033.
- I note that Major McCarthy (retired) was never enrolled in Study 033 and we are in a situation where Major McCarthy is insisting that his evidence is correct based on the accounts of others in 1 RAR.
- The Committee could consider recommending an independent evaluation of all Central Medical Records by an independent panel of medical doctors (independent of the ADF, RMA, SMRC, TGA, FDA and any pharmaceutical company that has developed an antimalarial drug) for all those soldiers (**including Major McCarthy [now retired])** that made submissions to the Committee. I believe from public statements by DVA that this includes 42 soldiers (Submission 2 DVA) out of the thousands that received tafenoquine or mefloquine in East Timor or Bougainville as part of ADHREC approved clinical trials (either pre-registration for Tafenoquine, or post-registration phase IV studies for mefloquine). These 42 soldiers are a discrete analysis population that is amenable to review of paper medical records before the Committee provides their report by the 29th November 2018. The conclusions of this independent medical evaluation should be made public but not the individual findings

in relation to each person. The independent review should not seek to influence DVA compensation claims for veteran gold cards but to specifically address the matter of whether tafenoquine or mefloquine are likely to have resulted in "chemically acquired brain injury" in these 42 soldiers. I am confident the conclusions from this independent medical panel will not contradict what has already been submitted to the Committee, acknowledged by RMA, the SMRC review of the RMA findings (when known), published medical evidence in the medical journals about tafenoquine or mefloquine or the scientific evidence that is documented in the TGA and FDA approved prescribing information for these drugs.

<u>Misleading the Committee on "Crude [Malaria] Attack Rates"</u>

- I disagree with this allegation.
- The crude attack rate figures I presented to the Committee are from the ADF MIDI Central Malaria Register for each infantry battalion that deployed to East Timor. These figures are presented in Table 1 (reproduced below) of Dow et al. A retrospective analysis of the protective efficacy of tafenoquine and mefloquine as prophylactic anti-malarials in non-immune individuals during deployment to a malaria-endemic area. Malar J 2014; 13: 49.
- Major McCarthy (retired) cites the "Official ADF data on the 40,571 personnel who served in East Timor from 1998 to 2007[1]". Citation 1 in the Major's supplementary submission dated 6 September 2018 relates to Nasveld et al, 2010. A publication I co-authored. The incidence of malaria in East Timor in infantry battalions deployed prior to 1st Battalion is not specifically discussed in Nasveld et al, 2010.
- Citation 1 in Nasveld et al, 2010 is Bernstein HN. Ophthalmologic considerations and testing in patients receiving long-term anti-malarial therapy. Am J Med 1983; 75(suppl. 1a): 25-34. It also does not discuss malaria incidence in Australian Infantry Battalions deployed to East Timor.

**Table 1 Details of Australian infantry deployments to Timor Leste***

| Battalion | Dates | Regions of Timor Leste | Battalion strength | Months deployed | Pf attack rate (%) Monthly/Cumul *** | Pv attack rate (%) Monthly/Cumul | All malaria attack rate (%) Monthly/Cumul | Prophylaxis |
|---|---|---|---|---|---|---|---|---|
| 2 RAR** | Sep 99 through Jan 00 | Dili, Bobanaro district | 681 | 4.33 | 0.31/1.32 | 2.04/8.81 | 2.34/10.13 | Doxycycline 100 mg q.d |
| 3RAR‡ | Sep 99 through Jan 00 | Dili, Bobanaro district and Oecussi province | 634 | 4.33 | 0.29/1.26 | 2.11/9.15 | 2.59/11.2 | Doxycycline 100 mg q.d |
| 5/7RAR | Nov 99 through Apr 00 | Dili, Bobanaro district | 522 | 6.83 | 0.11/0.77 | 0.81/5.56 | 0.83/6.71 | Doxcycline 100 mg q.d |
| 6RAR | Apr 00 through Oct 00 | Dili, Bobanaro district | 619 | 6.16 | 0.03/0.16 | 0.24/1.45 | 0.26/1.62 | Doxycycline 100 mg q.d |
| 1RAR | Oct 00 through Apr 01 | Dili, Bobanaro district | 723 | 6.00 | 0.00/0.00 | 0.18/1.11 | 0.18/1.11 | Tafenoquine 200 mg or Mefloquine 250 mg weekly |
| 4RAR | Apr 01 through Oct 01 | Dili, Bobanaro district | 750 | 7.00 | 0.00/0.00 | 0.08/0.53 | 0.08/0.53 | Mefloquine 250 mg weekly |
| 2RAR | Oct 01 through May 02 | Dili, Bobanaro district | 681 | 6.83 | 0.00/0.00 | 0.11/0.73 | 0.11/0.73 | Mefloquine 250 mg weekly |
| 3RAR | Apr 02 through Oct 02 | Dili, Bobanaro district | 634 | 7.00 | 0.02/0.16 | 0.14/0.95 | 0.18/1.26 | Doxycycline 100 mg q.d |
| 5/7RAR | Oct 02 through Dec 02 | Dili, Bobanaro district | 536 | 2.57 | 0.00/0.00 | 0.28/0.71 | 0.28/0.71 | Doxycycline 100 mg q.d |

*Values for dates deployed, battalion strength and period deployed are approximate.
**RAR = Royal Australian Regiment.
‡Both 3 RAR and 5/7 RAR soldiers participated in post-exposure prevention studies (Elmes, 2008).
***Monthly attack rate (%) = (Cases/total person-months) x 100; cumulative attack rate (%) = (cases/strength) x 100.

<u>Misleading the Committee on "risk of P. vivax malaria in field"</u>

- I do not understand this allegation of how I misled the Committee.
- If the Committee doubts my evidence they could discuss my personal view with Professor Dennis Shanks at the ADF Malaria and Infectious Disease Institute, Brisbane; Associate Professor Harin Karunajeewa at the Walter and Eliza Hall Institute of Medical Research, Melbourne; Professor Kevin Baird, Eijkman-Oxford Clinical Research Unit, Jakarta; Professor Ric Price at the Menzies School of Health Research, Darwin or any other malariologist of the Committee's choosing who has actually conducted clinical trials in malarious areas.
- Doxycycline is a suppressive drug of pre-erythrocytic and asexual blood stage malaria parasites and has no activity against P. vivax hypnozoites. This is the reason the ADF

uses it in combination with primaquine to reduce the risk of relapsing malaria cases when soldiers return to Australia. This requires a 14 day course of primaquine twice daily at doses of 15 mg/day or up to 30 mg daily where resistant malaria strains occur or where treatment has failed at lower doses (Primacin Prescribing Information). The Chesson strain of P. vivax present in PNG and the Pacific is widely reported to be insensitive to the lower primaquine dose and therefore the 30 mg dose is recommended. The exact mechanism of this resistance is unknown.

- 100 mg doxycycline for malaria prophylaxis has a relatively short half-life of approximately 12 hours. At double the malaria prophylaxis dose (200 mg), the serum half-life of doxycycline ranges from 18 to 22 hours (Doryx Prescribing Information). Therefore, if a soldier misses a dose, he/she starts to lose their suppressive cover before the next daily dose of doxycycline is consumed and they can present with clinical malaria (irrespective of the human malaria species) in the field if doses are missed concurrent to asexual blood parasitaemia developing in the area of operation.
- In a high intensity operation, this is a risk for the ADF service personnel when meal and sleep times are irregular. This raises the concern about the effectiveness of daily suppressive regimens without causal (liver) stage activity in preference to weekly drugs such as tafenoquine with longer half-lives and both blood schizonticidal and causal (liver) drug activity.

The TGA approved Doryx Prescribing Information states the following:

*Doxycycline is active against both pre-erythrocytic and asexual blood stages of Plasmodium falciparum. The tetracyclines are only partially active against the pre-erythrocytic stages of Plasmodium vivax and protection depends on drug suppression of the blood stages. Doxycycline has no activity against the relapsing forms (hypnozoites) of Plasmodium vivax. Doxycycline is indicated, in adults and children older than 10 years, as chemoprophylaxis for malaria caused by Plasmodium falciparum and, in combination with other antimalarial agents, against malaria caused by Plasmodium vivax. Doxycycline is only able to suppress malaria caused by P. vivax. As there are relatively few locations where P. vivax does not co-exist to some extent with P. falciparum, it is recommended that doxycycline should be used routinely with other agents, for example chloroquine.*
https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-02155-3

The TGA approved Primacin Prescribing Information states the following:
*Dosage and administration*
Primaquine should be taken with food.

(a) 15 mg daily for 14 days.
**(b) Up to 30 mg daily for 14 days in areas where resistant malaria strains occur or where treatment has failed with lower doses**
(c) **The WHO advises that the treatment of 21 days should be employed to achieve *radical cure* in most of South East Asia and the Pacific regions**. Other antimalarial agents may be used concomitantly.

https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2014-PI-03203-1&d=201809121016933

For the record. The World Health Organisation (WHO) report – Interregional work on the control of vivax malaria in East Asia explains the concern of the WHO about primaquine resistance here: http://www.wpro.who.int/mvp/documents/docs/Vivax_Mal_EastAsia.pdf

Misleading the Committee on the Importance of CYP 2D6 for the Metabolism of Tafenoquine

- With due respect to Major McCarthy (retired), he has made some very broad and inaccurate claims regarding CYP 2D6 metabolism in terms of safety and efficacy of tafenoquine. This view is not shared by international regulators, including the US Food and Drug Administration. **This is why FDA approved both GSK and 60P indications (relapse treatment and chemoprophylaxis) with no recommendation for CYP 2D6 genetic screening. Subject to TGA's expert opinion, nor should the ADF consider this CYP screening either. There is no scientific evidence to warrant this CYP screening and the ADF needs to be able to deploy the majority of its force on a single anti-malarial drug for command simplicity and logistics reasons. It is only a scenario where a soldier is contraindicated or cannot tolerate a drug, should they be moved to an alternate chemoprophylaxis from the 1st line therapy. As I stated in my oral testimony, this would not affect their military deployment.**
- There are no known mechanisms for drug resistance to tafenoquine. Part of the reason tafenoquine is urgently needed is to manage multiple-drug resistant parasites in SE Asia before they arrive in sub-Saharan Africa. This is especially important for artemisinin resistance. **Multiple-resistant malaria in sub-Saharan Africa will be a public health disaster.** I have already stated this in my oral testimony to the Committee and this point cannot be reiterated enough.
- **I'm not aware of any human data that shows CYP450 2D6 significantly metabolises tafenoquine. Period.**
- The US prescribing label for Arakoda (tafenoquine) states "*Negligible metabolism of tafenoquine was observed in vitro in human liver microsomes and hepatocytes. Following administration of tafenoquine orally, once daily for three days to healthy adult subjects, unchanged tafenoquine represented the only notable drug-related component in plasma at approximately 3 days following the first dose of tafenoquine*". https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210607lbl.pdf
- No clinically significant effects on the pharmacokinetics of dihydroartemisinin, piperaquine, artemether, lumefantrine or substrates of cytochrome P450 isoezymes (CYP) 1A2 (caffeine), **CYP 2D6 (desipramine),** CYP 2C8 (chloroquine), CYP 2C9 (flurbiprofen), or CYP 3A4 (midazolam, chloroquine) where observed following coadministration of tafenoquine in healthy subjects (in a human clinical trial [drug-drug interaction study]). This suggests that tafenoquine is not inhibiting or competing for the CYP 2D6 enzyme in clinical trial subjects because the ratio of desipramine to the major metabolite of CYP 2D6 (2-OH-desipramine) is not changing (FDA Drug Approval Package: KRINTAFEL [tafenoquine] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210795Orig1s000TOC.cfm)
- Dr Sean Marcisin's study was in genetically engineered mice. Not humans and it is not appropriate to make extrapolations to humans on this evidence alone. Marcisin even states this in his publication "*Additionally, despite NPC-1161B and tafenoquine belonging to the same structural class as primaquine, there is little information on the metabolism of these longer half-life molecules by CYP 2D6. It still remains uncertain if there are any other CYP enzymes capable of metabolising NPC-1161B and tafenoquine, however, under the experimental conditions described above [in gene knock in mice], the CYP 2D family is of primary importance for anti-malarial activity in mice and likely in humans. Further studies are required to understand the*

*mechanism by which CYP 2D6 activates NPC-1161B and tafenoquine*" (Marcisin et al. Tafenoquine and NPC-1161B require CYP 2D metabolism for anti-malarial activity: implications for the 8-aminoquinoline class of anti-malarial compounds. Malar J 2014; 13: 2). Again, these underlined statements are consistent with the negligible metabolism statement for CYP enzymes in the Arakoda label approved by the FDA (paragraph above).

- The really important human data is from Dr Pamela St Jean. **St Jean et al showed in a pharmacogenomic assessment of human clinical trial data from the GSK DETECTIVE study that relapse efficacy of tafenoquine was not affected in CYP2D6 poor/intermediate metabolisers and the tafenoquine drug levels in these poor/intermediate CYP2D6 metabolisers was unchanged suggesting no effect of this CYP 2D6 enzyme on tafenoquine** (St Jean et al. Tafenoquine treatment of Plasmodium vivax malaria: suggestive evidence that CYP2D6 reduced metabolism is not associated with relapse in the Phase 2b DETECTIVE trial. Malar J 2016; 15: 97).
- The poor CYP 2D6 metabolisers, who happened to have relapses of vivax malaria and were treated with chloroquine/tafenoquine vs. chloroquine/primaquine in a clinical trial are limited (n=3/treatment arm). However, the FDA statistician reviewed the peer reviewed data of St Jean et al and concluded: "*The point estimate for relapse/recurrence-free efficacy at 6 months is higher for primaquine/chloroquine than tafenoquine/chloroquine in intermediate [CYP 2D6] metabolisers and there are only 3 subjects per arm in the poor metaboliser group. These results are not statistically significant and do not provide adequate support for the applicant's [GSK's] argument that tafenoquine may have an efficacy advantage over primaquine in subjects who are CYP 2D6 poor/intermediate metabolisers. Presently, there is no evidence that the CYP 2D6 polymorphisms impact tafenoquine efficacy; however, a potential tafenoquine advantage over primaquine in this subgroup would need to be further evaluated* (FDA Drug Approval Package: KRINTAFEL [tafenoquine]).
- To be clear – tafenoquine is a slower acting blood schizonticide so it is used in combination with a faster acting drug (i.e. chloroquine or artemisinin) to achieve a clinical cure at the same time as a radical cure (removal of hidden liver hypnozoites) in a P. vivax patient. This slower action does not affect tafenoquine's efficacy for preventing malaria (chemoprophylaxis) as the parasite encounters drug as soon as it enters the liver and blood.
- What Marcisin et al did show from a theoretical perspective is that if you "knock in" the human CYP 2D6 gene into mice – it does not restore causal (liver) drug activity of tafenoquine against malaria parasites. So, in theory, based only on a genetically engineered mouse model, a risk exists that CYP 2D6 could affect tafenoquine efficacy for relapse for vivax malaria (Marcisin 2014). Again, this has never been shown in humans. However, if you double the tafenoquine dose in this mouse study, the prophylactic activity is restored. In other words, compensate for the loss of putative CYP 2D6 activated tafenoquine metabolites in genetically engineered mice by increasing the parental tafenoquine drug concentration and the effect of CYP 2D6 deficiency is corrected in terms of drug activity against parasites in the liver.
- Dr Chau Vuong showed that plasma pharmacokinetics in the CYP 2D6 knock-out mice had an effect on the terminal elimination kinetics of tafenoquine (53.8±3.5 hours vs. 72.4±15.5 hours), resulting in higher overall exposure of the unmodified tafenoquine parent molecule (Vuong et al. Differential Cytochrome P450 2D Metabolism Alters Tafenoquine Pharmacokinetics. Antimicrob Agents Chemother 2015; 59: 3864-3869). **This altered pharmacokinetic effect was not seen in humans in two, independent human clinical trials. See St Jean 2016 for relapsing**

**P. vivax patients who were CYP 2D6 poor/intermediate metabolisers [paragraph above]. The levels of tafenoquine did not change in these CYP 2D6 poor/intermediate metabolisers. There was no evidence that the metabolism of desipramine (a CYP 2D6 substrate) to 2-OH-desipramine was changed in the presence of tafenoquine during a human drug-drug interaction study.**

- Dr Erin Milner showed that CYP 2D6 does not affect blood stage efficacy of tafenoquine (Milner et al. Cytochrome P450 2D-mediated metabolism is not necessary for tafenoquine and primaquine to eradicate the erythrocytic stages of *Plasmodium berghei*. Malar J 2016; 15: 588). **This is the important part in protecting ADF soldiers in the field when using tafenoquine as a chemoprophylaxis because only blood stage infection causes disease and death. Infection of the liver is asymptomatic.**
- We tested Dr Milner's hypothesis in humans and showed in a human malaria challenge study with the more dangerous malaria form – P. falciparum (submitted for peer review in an international medical journal) **that parent tafenoquine kills all P. falciparum parasites when they enter the blood stream.** Using a very sensitive PCR method we could not detect any parasites in the blood. This data was submitted to the TGA and FDA for evaluation.

Misleading the Committee on the Profitability of Tafenoquine, PRV and Financial Incentives.

- Again, I'm unsure how I misled the Committee here.
- I've seen no evidence to suggest GSK or 60P ever "short cut the pharmaceutical registration process". All the scientific evidence for 60P was assembled and submitted for review by the FDA and TGA. The concerns of the anti-quinoline drug community were considered in the chemoprophylaxis dossier and investigated with money spent on actual scientific research to address these concerns (i.e. the rat study that Major McCarthy (retired) pointed out earlier **that showed that tafenoquine was not neurotoxic** [Dow 2017]). I don't apologize for making sure the tafenoquine dossier was comprehensive, complete and for declaring my perceived conflict of interest in making this evidence available to the scientific community.
- The PRV system has incentivized companies to look again at drugs for the developing world that only affect poor people and harm soldiers, and this is a good thing. The market drives this at no direct cost to the tax payer. The reason soldiers also suffer from tropical diseases is because we deploy soldiers to conflict zones in tropical countries and they have no naturally acquired immunity to mosquito, water and food borne diseases. Study 033 certainly proved this for food borne disease effects (Nasveld-2010).
- The GAIN Act was introduced in the USA to incentivize pharmaceutical companies to develop more antibiotics. Right now, we are running out of antibiotics to treat and prevent bacterial infections due to multiple drug resistant bacteria. Antibiotics like most drugs cost hundreds of millions of $US dollars to develop over > 12 years (on average) and when they are finally approved, the drug companies are restricted in their capacity to sell them because of the risk of drug resistance in the remaining years of the patent. These last lines of defence are kept in reserve. However, these antibiotics are really vital (especially for children and elderly people) and I think any scheme that incentivizes the safe and effective development of pharmaceutical drugs for infectious diseases, at no additional direct cost to the tax payer is good for the Australian people and the world community in

general.

Major McCarthy's (retired) Conclusions about Improper Conduct

- I have never claimed I am an expert in written evidence or oral testimony to the Committee.
- In my written submission I addressed the Committee's Terms of Reference. In my oral testimony – I answered the Senator's questions to the best of my ability as an individual witness, who has experience taking tafenoquine, mefloquine, primaquine and doxycycline personally, has conducted tafenoquine clinical trials in the field and compiled the scientific and medical evidence for tafenoquine (as a civilian) for submission to the TGA and FDA. I did not make a submission to the Committee on behalf of any organisation (government or private).
- **Major McCarthy (retired) asserts that anyone that disagrees with his belief system is misleading the Committee, guilty of criminal negligence, criminal offences, scientific fraud, medical negligence, lying, deceit, denial and coercion. See Major McCarthy's original Submission 94, his follow-up submissions and social media commentary on twitter @Stuart McCarthy.**
- I do not believe any level of evidence will alter Major McCarthy's beliefs nor should it have too. However, I note tafenoquine and it's use, as well as development during compliant clinical trials has now been subjected to the following reviews or investigations:
    - Australian Federal Police review of complaints lodged on the 6 November 2015 and May 2017 to AFP-hosted Fraud and Anti-Corruption Centre (Submission 94 attachments)
    - Inspector General ADF review (report dated 08 September 2016)
    - Repatriation Medical Authority review (declaration and statement of reasons on the 18 August 2017)
    - Specialist Medical Review Council review (ongoing)
    - Therapeutic Goods Administration review (ongoing)
    - TGA's Advisory Committee on Medicines review (completed)
    - Joint FDA/TGA clinical trial audit (21 May -1 June) of ADF tafenoquine studies 049 and 033 including consenting processes and compliance with ICH Good Clinical Practice.
    - Antimicrobial Drug Advisory Committee review (recommended 12th July [relapse indication] and 26th July [chemoprophylaxis indication])
    - Food and Drug Administration review (both relapse treatment and chemoprophylaxis indications [approved 20th July and 8th August respectively])
    - Senate Inquiry (ongoing)
    - Royal Commission (proposed)
- Based on the tafenoquine example, **I don't believe this extensive list of reviews and investigations based largely on subjective claims from 42 individuals will incentivize industry to collaborate with the ADF in future.** Especially for drugs, medical devices and biologics that only support the health of poor people and western militaries exposed to infectious diseases or specifically for militaries - chemical, biological, radiological or nuclear threats during military deployments where the prospect of making a return on investment is limited. **This will not be in the Australian national interest despite the objectives of the Defence White Paper of 2016.** I made this point in my original submission to the Committee.