QUINOLINE VETERANS AND FAMILIES ASSOCIATION

SUPPLEMENTARY SUBMISSION TO THE FOREIGN AFFAIRS, DEFENCE AND TRADE REFERENCES COMMITTEE INQUIRY INTO THE USE OF THE QUINOLINE ANTI-MALARIAL DRUGS MEFLOQUINE AND TAFENOQUINE IN THE AUSTRALIAN DEFENCE FORCE

Mr Stuart McCarthy, 6 September 2018

Introduction

QVFA thanks the Committee for their continued efforts with this inquiry. The purpose of this supplementary submission is to draw the Committee's attention to misleading testimony provided by Mr Mark Reid at the Brisbane hearing on 30 August 2018. Mr Reid misled the Committee in responding to questions regarding the efficacy of antimalarial drugs, the profitability of tafenoquine and the financial interests of 60 Degrees Pharmaceuticals (60P).

Mr Reid, Clinical Network Services (CNS), 60 Degrees Pharmaceuticals (60P), the U.S. Army Medical Materiel Development Activity (USAMMDA) and Tafenoquine

From October 2011 to September 2017 Mr Reid was an employee of Clinical Network Services (CNS) (Attachment 1), which was engaged by 60P and the U.S. Army Medical Materiel Development Activity (USAMMDA) as a consultant in the development of tafenoquine, for the purposes of registration with the Therapeutic Goods Administration (TGA) and the U.S. Food and Drug Administration. During this period Mr Reid co-authored tafenoquine papers with Dr Geoff Dow (CEO, 60P), Professor Dennis Shanks (Director, Australian Army Malaria Institute [AMI]) and Colonel Bryan Smith (USAMMDA) (Attachment 2) for this purpose, as a paid employee of CNS.

60P was founded by Dr Dow in 2010 while he was an employee of the U.S. Army, directly involved in the development of tafenoquine. While Dr Dow was working on the development of tafenoquine for USAMMDA in August 2014, 60P entered into a cooperative research and development agreement (CRADA) with USAMMDA for the continued research and development of tafenoquine for malaria prophylaxis (Attachment 3). As part of this contractual agreement, USAMMDA awarded 60P with an exclusive license for tafenoquine.

At the time this license was awarded to 60P, Dr Dow's supervisor was Colonel Bryan Smith, the USAMMDA product manager for antimalarial drugs including tafenoquine. Prior to the award of this contract (as per my original submission, including documentary evidence), Colonel Smith was requested by Commander (ret) Bill Manofsky to approve a follow up vestibular study of the AMI "Study 033" tafenoquine subjects from the 1 RAR Battalion Group in East Timor, to be conducted by Captain (USN) Michael Hoffer a medical doctor specialising in vestibular disorders. Commander Manofsky had already secured the agreement of Captain Hoffer to conduct the study and the necessary funding from U.S. Army Special Operations Command. Colonel Smith simply needed to approve the conduct of this study. The original Study 033 report found that 5% of the tafenoquine and mefloquine subjects experienced vertigo, a vestibular condition. This Committee has heard extensive first-hand evidence of chronic vestibular symptoms among the 1 RAR trial subjects including dizziness, vertigo, balance problems, hearing problems and tinnitus. The reason that Colonel Smith did not approve this follow up study is that the evidence obtained during the proposed study may have undermined his prospects for successfully registering tafenoquine.

Colonel Smith retired from the U.S. Army at the end of 2015 and was then employed by CNS in Washington D.C. (the same consulting company as Mr Reid), where he continued to work as a consultant on the development of tafenoquine. Mr Smith is now the 60P Chief Medical Officer.

Efficacy of Antimalarial Drugs

During the Brisbane hearing Mr Reid provided the following testimony in relation to the efficacy of antimalarial drugs:

> ***CHAIR:*** *You mentioned another drug, Malarone, which I might have taken myself. Is that a commonly prescribed antimalarial treatment for travellers?*
>
> *Mr Reid **:** It is.*
>
> ***CHAIR:*** *What's the difference? Is it part of a suite of drugs?*
>
> *Mr Reid **:** It is a suite of drugs. Malarone is not indicated for preventing vivax infection, which, as Major McCarthy indicated, it is the predominant strain of malaria in South-East Asia. It is currently a second-line therapy for the ADF. Mefloquine is our third-line therapy and doxycycline is our first-line therapy. The danger with doxycycline is that it is a suppressive drug. It allows the infection to occur in the liver, and then what happens is that you are basically just managing the blood infection by just knocking down the parasitemia. It has a half-life of 12 hours. The reason we saw such high **crude attack rates** in our East Timorese battalions is that, if a soldier misses his dose, he isn't protected and then he **could come down with clinical malaria in the field**. And then we use primaquine to eradicate what is living in the liver at the end. We need to move away from this ideology of using suppressive therapies to protect our soldiers. We need drugs that are **safe and effective** but kill what is in the liver as well as in the blood. This is what, hopefully, **tafenoquine will offer in the future**.*

Mr Reid's answer was factually correct, however it was misleading for two reasons. Firstly, he misled the committee with his emphasis on "crude attack rates" of *P. Vivax* malaria and the *risk* of "clinical [P. vivax] malaria in the field", while omitting to mention the published data on *actual* reported cases of clinical *P. vivax* malaria among ADF personnel who served in East Timor. Official ADF data on the 40,571 personnel who served in East Timor from 1998 to 2007[1] shows:

- Of the 501 total cases of clinical malaria (all species) among personnel who had served in East Timor, 416 (83%) of these cases were relapses of *P. vivax* occurring **after** those individuals **returned to Australia**.

- Of the 374 persons who failed post exposure prophylaxis (PEP) (either with the registered PEP drug primaquine or the experimental drug tafenoquine) by having an initial presentation of P. vivax or a mixed *P. falciparum* and *P. vivax* infection, **after** leaving the malarious area, 114 (30.5%) went on to develop one or more relapses of vivax malaria. **Note**: these were individuals who complied with the PEP/treatment regimen **while under medical supervision**.

- Of those who relapsed, 25-28% had **successive relapsing episodes** of *P. vivax*, with some individuals having **up to five documented relapses**.

Secondly, Mr Reid omitted to inform the Committee of key scientific facts in relation to primaquine and tafenoquine, specifically that the efficacy of primaquine and tafenoquine are affected by CYP2D6 drug metabolism. As I have emphasised in my previous submissions, the most plausible explanation for the high rate of *P. vivax* malaria infections among ADF personnel who served in East Timor is reduced CYP2D6 function, which affects around 12-23% of Caucasians. This is supported by a 2014 paper **co-authored by Mr Smith** (former USAMMDA tafenoquine product manager, now 60P Chief Medical Officer), which concludes in part:

> *… it is reasonable to conclude several things about ... tafenoquine. 1). The anti-hypnozoite activity of ... tafenoquine is dependent on CYP 2D6 activation. 2). ...* ***tafenoquine will likely fail for either causal prophylaxis and/or treatment indications in patients with CYP 2D6***

> ***genotypes resulting in the PM phenotype*** *and may require dose modification in some patients with an IM phenotype ...*
>
> *There have been numerous reports in the literature of* ***primaquine failures*** *that are associated with primaquine resistance. This* ***"resistance"*** *refers to the inability of primaquine to clear the hypnozoite form of the Plasmodium parasite. There has been* ***confusion around the idea of primaquine resistance*** *as there are many confounding factors associated with the various reports, such as patient population, patient adherence, dosing regimen, and concurrent blood schizonticidal therapy. The requirement of* ***CYP 2D6 activation for primaquine activity*** *is another factor that needs to be taken into consideration when reporting primaquine resistance. Interestingly, the* ***reported primaquine failure rates seem to align with CYP 2D6 polymorphic allelic frequencies for the PM genotype as individuals with this genotype will likely fail primaquine therapy****. This is not a likely coincidence and* ***calls into question the existence of primaquine resistance and/or Plasmodium resistance to the 8AQ class in general, particularly since the results reported herein suggest that 8AQs likely have a similar mechanism(s) of anti-malarial activity which is mediated through CYP 2D6 activation****. ... Because tafenoquine ... requires CYP 2D6 activation for activity,* ***rates of treatment/prophylactic failures would likely be in line with those noted for primaquine use for both compounds when administered to humans****. If insurmountable,* ***this would present a major pharmacogenomic liability for the 8AQ class of anti-malarial compounds****. New drugs with anti-hypnozoite activity are desperately needed to combat relapsing strains of malaria and* ***future research and development efforts should ensure the complete dissociation between CYP 2D6 metabolism and anti-hypnozoite activity*** *of new potential anti-malarial agents.*[2]

As I have highlighted in a previous submission, this issue has moved beyond an arcane academic argument. Doctors are now proactively using this scientific discovery, in a clinical setting, to ensure the 8-aminoquinolines are being used safely and effectively, for example in this recent case report of relapsing *P. vivax* malaria which is similar to many of the above ADF cases from East Timor that were misattributed to "drug resistance" or "poor compliance":

> *Primaquine (an 8-aminoquinoline malarial therapy) is the only FDA-approved therapy to treat the hypnozoite stage of P. vivax. We think of relapse occurring because of parasitic resistance or poor compliance secondary to drug toxicities. However, in patients with repeated treatment failure, we must consider CYP-450 mutations affecting drug metabolism as an important cause of relapse. A 47-year-old man who travelled to a jungle in Venezuela was diagnosed with P. falciparum and P. vivax in July 2015. He was treated with seven rounds of primaquine-based therapy in the following year, all resulted in relapse without further exposure to endemic areas. On his eighth presentation, he was found to have CYP-4502D6 mutation that affected the metabolism and activation of primaquine. Thereafter, he was treated without relapse. Primaquine efficacy depends on many factors. Understanding the mechanism responsible for malaria relapse is paramount for successful treatment and reduction in morbidity and mortality. This case illustrates the importance of considering cytochrome mutations that affect drug efficacy in cases of relapsing malaria.*[3]

I again emphasise the need for the Committee to challenge the unsubstantiated assertions by various "expert witnesses" regarding "drug resistance." There is clear, published, scientific evidence that the 8-aminoquinolines are ineffective and potentially dangerous for a significant proportion of the population, not because of "drug resistance" but because of reduced CYP2D6 function. *CYP2D6 screening is readily available*, indeed the similar G6PD screen has been a standard test for all ADF personnel for many decades, *specifically to prevent serious adverse reactions to the 8-aminoquinoline drugs primaquine and tafenoquine.*

The Profitability of Tafenoquine and the Financial Interests of 60P

During the Brisbane hearing Mr Reid provided the following testimony in relation to the profitability of tafenoquine and the financial interests of 60P:

> ***CHAIR**: So, because there's not a great market in the poor nations of the world and in the military for these drugs, there's no money in it for any pharmaceutical provider?*
>
> *Mr Reid : That's correct.*
>
> *Senator O'SULLIVAN: I just want to try and get these relationship lines, because they're important, as you'd appreciate, as we give weight to the various testimonies that are provided. Is it the case that the US military, using public funding, socialised funding, paid 60 Degrees to embark on this journey?*
>
> *Mr Reid : No. They're not allowed to.*
>
> *Senator O'SULLIVAN: Did they have a partnership with 60 Degrees?*
>
> *Mr Reid : It's a data-sharing agreement.*
>
> *Senator O'SULLIVAN: But, in the event that the drug miraculously becomes a perfect drug and has a turnover of a billion dollars a year, where would the US Army sit in that circumstance?*
>
> *Mr Reid : The US Army would be paid royalties. If it ever achieved a billion-dollar sale, I would be extremely surprised.*
>
> *Senator O'SULLIVAN: Of course. I appreciate that. When I give my examples, I give them in the extreme, because it saves spending a lot of time trying to explain them.*
>
> *Mr Reid : Sure. Dr Geoff Dow has raised his own private funds to try and get tafenoquine approved so we can do something about the malaria problem globally. It is the only drug that has a prospect of helping eliminate malaria. He is millions of dollars in debt.*

With this testimony, Mr Reid misrepresented the financial interests of 60P by attempting to portray Dr Dow's efforts to register tafenoquine as an act of philanthropy. On 21 September 2015 Dr Dow publicly stated that his motivation in seeking to register tafenoquine was to obtain an FDA priority review voucher (PRV) valued at up to US$350 million:

> *I think that probably in terms of hot topics in this space the focus and investor interest is really around the priority review voucher. That is basically a voucher granted by the FDA if you succeed in getting regulatory approval for a drug for a tropical disease. Those vouchers can be sold to another company that allows fast track review at the FDA of an unrelated therapeutic. They are freely salable on the open market. The most recent sale was for three hundred and fifty million by United Therapeutics to Abbvie. Three out of four of our products are eligible for the PRV and it is a financial incentive independent of your actual development program or the therapeutic you are moving forward. Therefore, that definitely has interest for individual investors, but also big pharma who have an interest in molecules that happen to be in your portfolio.*[4]

Regardless whether 60P was awarded the FDA PRV, the company continues to have a financial interest in tafenoquine because of the license it was awarded by USAMMDA, based largely on the data from the ADF tafenoquine trial subjects (many of whom have testified to this Committee about the adverse effects of tafenoquine). For example, 60P now has a commercial arrangement with Knight

Therapeutics (KT) to sell tafenoquine in Latin America and possibly elsewhere. The KT 2018 first quarter financial results state:

> *Furthermore, 60P and Knight will enter into an exclusive license agreement granting Knight the right to commercialize tafenoquine in Latin America.*[5]

The clear conflicts of interest in the recent development of tafenoquine are emblematic of the controversial FDA PRV program, which in creating artificial value for shortcutting the pharmaceutical registration process has also created an avenue for highly profitable financial speculation. In June 2016 Associate Professor Aaron Kesselheim of Harvard Medical School said of the PRV program:

> *I think it's problematic and potentially dangerous to use this crucial process as a lever to try to artificially create value for a for-profit company.*[6]

This potential danger recognised by Professor Kesselheim should now be one of the central considerations of this inquiry.

Conclusion

A number of the "expert" witnesses to this inquiry, including Mr Reid, have offered very "selective" testimony regarding the efficacy of the 8-aminoquinoline antimalarials, including broad assertions about "drug resistance" and "poor compliance" which are unsupported by scientific evidence. All of the malaria "experts" have studiously avoided the published scientific research which establishes a link between CYP2D6 metabolism of primaquine and tafenoquine. The evidence provided in this supplementary submission suggests that 60 Degrees Pharmaceuticals and their partners who have a stake in the successful registration of tafenoquine have deliberately ignored this important scientific discovery, to protect their own financial or reputational interests at the expense of public health and safety. I trust that this will assist the Committee with its ongoing inquiry.

Attachments

1. LinkedIn profile - Mr Mark Reid
2. Author Affiliations - G. 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," *Malaria Journal*, 2014
3. *Cooperative Research and Development Agreement* between 60 Degrees Pharmaceuticals and U.S. Army Medical Materiel Development Activity, August 2014

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2. S. Marcsisin et al., "Tafenoquine and NPC-1161B require CYP 2D metabolism for anti-malarial activity: implications for the 8-aminoquinoline class of anti-malarial compounds," *Malaria Journal*, vol. 13, no. 2, 2014. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3893421/
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5. Knight Therapeutics, *Knight Reports First Quarter 2018 Results*, 10 May 2018. https://globenewswire.com/news-release/2018/05/10/1500096/0/en/Knight-Reports-First-Quarter-2018-Results.html
6. E. Silverman, “Congress tries to fix a drug voucher program, but critics say it’s not enough”, *STAT News*, 9 June 2016. https://www.statnews.com/pharmalot/2016/06/09/congress-vouchers-rare-diseases/

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I work with an team of superb staff to deliver preclinical drug development solutions including chemistry, manufacturing and control (CMC), toxicology and clinical consultancy for our clients in Europe, the USA, Australia, SE Asia and New Zealand. The BioDesk team also provide dossier writing and submission services for marketing applications in Australia, Europe and New Zealand from our offices in Brisbane, Canberra and London with team members also located in Adelaide and Melbourne.

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In this role, I work with my 7-person team and consultants to deliver preclinical drug development solutions including chemistry, manufacturing and control (CMC), toxicolgy and clinical consultancy for our clients in Europe, the USA, Australia and New Zealand. I also provide standard regulatory affairs services for registration of products in Australia with the TGA and MedSafe in New Zealand. In addition, regulatory services are also provided for the US and Europe from the team offices in Brisbane, Australia and London.

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I now head up a preclinical development desk that supports biotechnology and small pharmaceutical clients develop their products for the international market.

I'm also providing standard regulatory services for registration of products in Australia with the TGA and MedSafe in New Zealand.

Malaria Journal
BioMed Central

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

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