PUBLIC CONTRACTS APPEALS BOARD

Case 70

CT 2383/2004, Advert No 193/2004, GPS 02.135.T03.MH - *Supply of Statin Preparations*

This call for tenders was issued by the Contracts Department following a request which was originally sent by the Government Pharmaceutical Services (GPS) and subsequently received by the Department of Contracts on 21st June 2004.

The closing date for this call for offers was 28th September 2004 and the global estimated value of the contract was Lm 233,240.

Three (3) different tenderers submitted their offers.

Following recommendations made by the Evaluation Board to the Contracts Committee for the latter to award the tender in caption (with respect to Item 3) to *A.M. Mangion Ltd and their principals Merck Sharp & Dohme Interpharma* (Lm 140,348.30), Messrs *VJ Salamone Pharma Ltd and their principals Novartis Pharma Services Inc.*, filed an objection on 30th January 2006.

The Public Contracts Appeals Board (PCAB) made up of Mr Alfred Triganza (Chairman) with Mr Anthony Pavia and Mr Edwin Muscat, respectively, acting as members, convened two public hearings, one on 15.03.2006 and the other on 24 March 2006, to discuss this objection.

Present for the hearing were:

VJ Salamone Pharma Ltd / Novartis Pharma Services Inc.

Dr Michele Bortolini
Ms Lara Cauchi
Dr Mario Demarco (Legal Advisor)

A.M.Mangion Ltd /Merck Sharp & Dohme Interpharma

Mr Alfred Mangion	Chairman, A.M. Mangion Ltd
Dr Henri Mizzi	Legal Advisor
Dr Francios Chazelle	Technical Specialist, MSD France
Mr Ray Vella	Director, A.M. Mangion Ltd
Mr Roger Aquilina	MSD Medical Rep (A.M. Mangion Ltd)

Government Pharmaceutical Services

Ms Anna Debattista	Director, Government Pharmaceutical Services

Adjudication Board

Ms Miriam Dowling	Chairperson
Mr M Spiteri	Pharmacist
Mr M Haidon	Senior Pharmacy Technician

Witnesses

Dr Stephen Fava
Prof. Frederick F. Fenech
Mr Alex Manche

Dr Lilia Mendizova
Mr Ivan P Micallef
Ms Vanessa Said Salomone
Dr Roland Schomer
Dr Robert Sciberras
Dr Robert G Xuereb
Dr Josette Grech

Other Witnesses

Dr Conrad Azzopardi
Dr Patricia Vella Bonanno
Prof Carmel Mallia
Prof Albert Fenech

After the Chairman's brief introduction, the representatives of *VJ Salamone Pharma Ltd / Novartis Pharma Services Inc.* were invited to explain in brief the motive leading to their objection.

Dr Mario Demarco, the appellants' legal representative, commenced his intervention by stating that this tender was issued for the supply of statin preparations. The tender *Specifications & Conditions* indicated the current annual consumption against the different doses of Fluvastatin 20 mg, Fluvastatin 40 mg and Fluvastatin 80 mg. He said that Items 1 and 2 were awarded to his clients *VJ Salomone Pharma Ltd/ Novartis Pharma Services* Inc who tendered with Lescol® (Fluvastatin) 20 mg (pack x 28 tablets = CHF 5.50) and Lescol® (Fluvastatin) 40 mg (pack x 28 tablets = CHF 10.75) whilst Item 3 was awarded to *A.M. Mangion Ltd / Merck Sharp & Dohme Interpharma* who tendered with Zocor® (Simvastatin) 20 mg.

Mr Ivan P Micallef, who is responsible for Novartis Pharma's business in Malta, said that Lescol® was a trade mark which was produced by Novartis and its active ingredient was Fluvastatin. He said that this product was used to reduce cholesterol in the blood preventing heart attacks which could lead to pre-mature deaths. He said that currently all the three Fluvastatin doses were supplied by Novartis in the form of Lescol 20 mg, Lescol 40 mg and Lescol XL 80 mg and they had been doing so for the past 10 years.

Both Dr Demarco and Mr Micallef said that the appellants felt aggrieved by the decision because they believed that the award was based on an incorrect technical evaluation when Zocor® 20 mg was compared to Fluvastatin 80 mg. They claimed that the efficacy of Fluvastatin 80 mg was comparable to that of Zocor® 40 mg and not to Zocor® 20 mg. They argued that, as a consequence, patients who were being treated with Lescol® XL 80 mg would have to be switched to Zocor® 20 mg and therefore they would need to take two (2) Zocor® 20 mg tablets instead of one to have an equivalent efficacy. Hence, although one pack of Zocor® 20 mg was 6% cheaper than that of Lescol® XL 80 mg, the award of this item to A.M. Mangion Ltd / Merck Sharp & Dohme Interpharma would effectively increase the cost by 88%. They contended that, as a result, the award was not made to the most economically advantageous offer.

Dr Henri Mizzi, legal advisor to A.M. Mangion Ltd / Merck Sharp & Dohme Interpharma, rebutted by stating that the technical people had decided that the two versions of statin under consideration, namely Fluvastatin 80 mg and Simvastatin 20

mg, were equivalent. He claimed that, by their objection, the appellants were effectively requesting the PCAB to substitute the technical decision of the Health Department's Adjudication Board. He insisted that the function of the PCAB was to establish whether the evaluation process was transparent and properly carried out and not to review or substitute the technical decision made by the experts.

On cross-examination by the PCAB, Ms Anna Debattista, Director, Government Pharmaceutical Services (GPS), testified that this tender was issued for statin preparations, that is, statin tablets or capsules as available in different dosages, namely, the Fluvastatin 20 mg, Fluvastatin 40 mg and Fluvastatin 80 mg. She said that the tender specifications were open because there were other statins on the market.

Ms Debattista said that in actual fact they received three tenders and each tenderer offered a different product, namely *Fluvastatin*, *Simvastatin* and *Atorvastatin*. The Director GPS confirmed that the Adjudication Board recommended the award of Fluvastatin 20 mg and Fluvastatin 40 mg capsules to V.J. Salomone and the Simvastatin 20 mg tablets to A.M. Mangion Ltd on behalf of their principals, Merck Sharp & Dohme. She explained that the Adjudication Board based their decision on the cost effectiveness of the product and on the same official equivalence ratios that were used in the previous tender, namely:

Fluvastatin	Simvastatin
20 mg	5 mg
40 mg	10 mg
80 mg	20 mg

Ms Debattista continued by claiming that the parameters of these equivalence ratios were discussed within the Drugs and Therapeutics Committee and the Lipid Sub-Committee and were based on the scientific data available and various international studies. At that time it was the lower doses of statins that were being used. She claimed that they required different doses of statin preparations in order to meet the needs of different patients, depending on their lipid profile. The witness said that patients would not be affected when switching from one statin to the other.

When asked to state on which guidelines were the equivalence ratios based, Ms Debattista said that Dr Conrad Azzopardi was in a better position to reply.

However, on taking the witness stand, Dr Azzopardi testified that he was not in a position to state from where the Drugs and Therapeutics Committee got the data to establish those standards because he was not involved in the process.

At this stage, Ms Debattista clarified that when the equivalence ratios were established, the Chairman Drugs & Therapeutics Committee was Prof Carmel Mallia, who could not attend for these proceedings because of his clinical commitments at SLH. Ms Debattista presented the PCAB with an e-mail she had received from him the day before. She pointed out that their request for the postponement of the hearing was not accepted. The Chairman, PCAB explained that it was not acceptable for the PCAB to consider such a request a day prior to the actual hearing, particularly when all interested parties had been informed as far as way back on the 24 February 2006

and to aggravate matters, interested parties included foreigners who were already in Malta to attend the hearing on the next day.

Then, the PCAB called Dr Patricia Vella Bonanno to take the stand since she was indicated as being directly involved in establishing the equivalence ratios.

On cross-examination by the PCAB, Dr Vella Bonanno testified that the equivalence ratios emanated from different evidence taken from various studies and published data by independent bodies. Ms Vella Bonanno claimed that at that time the evidence available indicated the use of lower doses of statins. However, according to current literature, higher doses of statins were now being recommended. The witness declared that the same ratios used in the previous tender were re-confirmed for this tender.

Dr Vella Bonanno said that there were no significant differences between different brands of statins and that these could be interchanged. Furthermore she claimed that, ideally, under normal circumstances, the department would not change from one drug to another but it had to be realised that they had to make the best use of a specific budget.

When, in reply to a specific question by the PCAB, Dr Vella Bonanno indicated Prof Mallia as being ultimately accountable for the efficacy ratio, the Chairman PCAB, taking full consideration of the fact that Prof Mallia was turning out to be a pivotal witness in this hearing, requested Ms Debattista to ask Prof Mallia to come as the Board needed to cross-examine him about the issue of the equivalence ratio.

On cross-examination by Dr Demarco, Prof Frederick F. Fenech said that statins were drugs which were prescribed for heart diseases and to control the level of cholesterol in the arteries by reducing the level of 'bad' cholesterols and increasing the 'good' cholesterols. He said that different statins had different chemical structures and properties, and that, like all drugs, affected persons differently as this depended on the individual's response. The witness said that at the moment the tendency was for practitioners to prescribe drugs that had higher levels of statins because they were more effective.

In reply to a specific question regarding the possibility of any danger when changing drugs from one brand to another, Prof Fenech said that he would not change if he were obtaining good results with a specific type of drug. However, Prof Fenech continued by stating that if a brand was changed the real effect would only be known when the new brand was actually used.

When Prof Fenech was asked to give his opinion about the efficacy ratios currently in place, the reply given was that he was of the opinion that they were all right.

On his part, in his testimony, Dr Michele Bortolini, a Novartis employee, made reference to a study under the heading '*Efficacy and Tolerability of Fluvastatin and Simvastatin in Hypercholesterolaemic Patients'* which was published in a reputable clinical journal in 1996 by Professors Schulte and Beil. He claimed that this was an important piece of evidence not only because it was provided by an independent group of investigators but also because it was the only study available where these two brands of drugs (Zocor and Lescol) were compared under the same conditions.

The efficacy and tolerability of simvastatin and fluvastatin were compared in a randomised, parallel-group study using marketed formulations of the drugs and identical encapsulation of tablets to ensure blindness. He said that it was proved that the 20 mg and 40 mg of Zocor were equivalent to 40 mg and 80mg of Lescol respectively in terms of 'bad' cholesterol (LDL Cholesterol) reduction and 'good' cholesterol increases. Thus, this study concluded that the dose equivalence ratio of the two drugs was 1:2 (Simvastatin and Fluvastatin).

When the PCAB referred Dr Bortolini to the article's 'Acknowledgements' wherein it was stated: '*We thank Astra GmbH, Wedel, Germany, for supporting this study with a grant*', the witness declared that years ago Astra GmbH was the distributor of Lescol Fluvastatin, however, he asserted that Novartis were not involved in the study. He said that, as far as he was aware, the study was independently analysed. Here, the PCAB asked Dr Vella Bonanno to state whether it was normal praxis to have similar acknowledgements in the studies they went through for establishing the efficacy and equivalence ratios and she said that they would not consider such study in their deliberations.

On cross-examination by Dr Mizzi, Dr Bortolini testified that he was not aware of any other head to head study regarding trials of the same drugs which was published after the Profs Schulte and Beil report. At this point Dr Mizzi referred the witness to a study entitled '*Effects of Fluvastatin Slow-Release (XL 80 mg) Versus Simvastatin (20 mg) on the Lipid Triad in Patients With Type 2 Diabetes*' which was published in November/December 2005 by Drs Maurizio Bevilacqua, Velella Righini, Massimo Barrella, Tarcisio Vago, and Enrica Chebat respectively**.** Dr Mizzi said that this study, which was conducted not so long ago, showed that the equivalence ratio between Fluvastatin and Simvastatin was 4:1. The witness admitted that he was aware of this publication; however, he said that this study was not conducted with blinded drugs.

Continuing his testimony, Dr Bortolini said that the tolerability profile of these drugs differed because the chemical structure and the physical properties of the molecules were different. He said that several publications indicated that risks of patients suffering from muscular complaints, which were rare side effects with statins, were seen more with Zocor and with Lescol.

On cross-examination by Dr Demarco, Dr Robert G Xuereb, Consultant Cardiologist at St Luke's Hospital (SLH), testified that all patients suffering from heart diseases were treated with statins and that most patients were on Fluvastatin. He explained that statins were used to reduce the risk of heart attacks and strokes by lowering the LDL Cholesterol and improving the HDL levels. Dr Xuereb said that many studies compared the Lescol XL 80 mg (Fluvastatin) with the Zocor 40 mg (Simvastatin) on efficacy. He said that both Fluvastatin and Simvastatin were very well tolerated but the side effects with the first were less. When choosing a statin he kept these three points in mind efficacy, outcome and tolerability.

Dr Xuereb testified that it was not good practice to change from one product to the other because they would need to monitor again the cholesterol level and any possible side effects. He said that they changed from Fluvastatin to Simvastatin only when patients were intolerant or when they did not respond well to Fluvastatin therapy. Furthermore, in reply to a specific question by the PCAB, Dr Xuereb said that he would prescribe two (2) tablets of Simvastatin 20 mg for a patient who was on Lescol

XL 80 mg because from his experience the Fluvastatin 80 mg was equivalent to Simvastatin 40 mg.

On taking the witness stand Profs Carmel Mallia, Chairman, Drug and Therapeutics Committee, apologised for his late arrival but he clarified that it was not possible for him to leave the hospital earlier.

Prof Mallia started his testimony by declaring that, except for the initial process relating to the establishing of the equivalence ratios, he had no direct involvement in the adjudication process of this tender.

Prof Mallia testified that, as a group, statins were very effective drugs and, overall, there were minor differences between products. He said that it was very difficult to compare the Simvastatin and the Fluvastatin in terms of efficacy and tolerability. However, he considered that the first was a more potent drug than the latter and that he had more patients who were more intolerant with Fluvastatin than with Simvastatin. The witness said that although the current trend was to use higher dosages of statins, he personally preferred to start with lower doses and then act according to the patients' response. Some studies showed that higher dosages were more efficacious but, similarly, other studies showed that they were more toxic as well. Prof Mallia said that cardiologists used higher dosages in order to reduce cholesterol at the lowest levels possible.

With regard to the equivalence ratios, Prof Mallia testified that the ratio of 4:1 (Fluvastatin: Simvastatin) was established in 2002 by the Lipid Sub-Committee wherein it was concluded that these drugs were deemed to be comparable in terms of equivalent reduction in LDL cholesterol. He said that this equivalence was based on scientific evidence and on conclusions of many different studies, called *meta-analysis*. The witness said that, in spite of the fact that there were diverging views on efficacy ratios, they were comfortable in arriving to the equivalence ratio of 4:1 because they felt that the evidence analysed was strong enough to be able to recommend that conclusion. Furthermore, he pointed out that the Drugs & Therapeutics Committee, the Lipid Sub-Committee and Prof Albert Fenech who was the Chairman of the Department of Cardiology and the most senior cardiologist on the island, reconfirmed these ratios.

During his testimony Prof Mallia made reference to a report entitled *HMG-CoA Reductase Inhibitors (Statins)* produced by Orgeon Health Resources Commission, which after performing a meta-analysis of several articles, studies, clinical trials the subcommittee concluded *"by consensus that all statins when compared at equivalent doses achieve a similar increase in HDL-c'* and under *Table 1- Equipotent doses of statins"* it was determined that, with respect to their LDL-c lowering abilities, Fluvastatin 40mg and Fluvastatin 80mg were equivalent to Simvastatin 10mg and Simvastatin 20 mg respectively.

Dr Demarco intervened and claimed that he had statements signed by fourteen (14) consultants/ specialists in Malta who all affirmed a different ratio of 1:2. The appellants' lawyer explained that all these consultants declared that they would prescribe two (2) tablets of Zocor 20mg for a patient who was on a Fluvastatin 80mg. Dr Demarco argued that the decision should have been based on what was done in

practice because ultimately it was the actual prescription that counted for the purpose of the financial implications.

Dr Mizzi stated that there was no sign anywhere that the Adjudication Board had acted incorrectly.

At this point the PCAB decided, in agreement with the parties concerned, to adjourn the sitting for Monday, 20 March 2005 at 12.30 hours because it was felt necessary to cross-examine Prof Albert Fenech as his name had been referred to 'in absentia' and it seemed that he was deemed to be an authoritative point of reference as regards the Adjudication Board, so much so that he was consulted on the equivalence ratios.

The PCAB did not give its consent to Dr Demarco's request for both parties to have the possibility to bring one further witness each as, all in all, at that stage, enough witnesses were summoned by both parties, and further witnesses were considered by this Board not to be in a position to provide additional substance to the proceedings of the said hearing.

When the hearing reconvened on the 24 March 2006, the Chairman, PCAB, made a brief introductionin order to refresh everyone's memory and, following this, summoned Prof Albert Fenech, Head of the Cardiology Department at St Luke's Hospital, to the witness stand in order for the latter to give his own interpretation on the equivalence ratios.

Prof Fenech testified that that he was only contacted to give his opinion on the equivalence ratios. He pointed out that he was not contacted about clinical relevance, clinical practice and the choice of drugs.

On cross-examination by Dr Demarco, Prof Fenech confirmed that there were different studies in terms of different ratios vis-à-vis fluvastatin and simvastatin. He explained that these were based on achieving a target level of LDL and what dosage would achieve that target compared to the others. As regards the two drugs under consideration, more dosages of fluvastatin were needed to achieve the same target. However, he emphasised that in clinical practice they did not look at LDL level because recent studies showed that they needed to lower LDL at the lowest level possible, which could only be achieved by the use of the highest dose of statin available. Prof Fenech said that currently they had to use Lescol as a first line drug because they had no choice. The witness said that statins were used not only to lower the lipids but also to reduce inflammation in the arteries.

On cross-examination by Dr Mizzi, Prof Fenech confirmed that, in terms of equivalence, the ratio was 4:1 but as a physician he gave the highest dosage possible. Also he confirmed that the highest dose of Lescol on the market was 80 mg and that of Simvastatin was 40 mg.

In reply to a specific question by Ms Debattista, Prof Fenech confirmed that the equivalence ratios that he agreed with in October 2005 were the established equivalence ratios and that he considered that Fluvastatin 80 mg was equivalent to Simvastatin 20 mg.

During his testimony, Prof Fenech said that the 1998 protocol was now outdated and that it was no longer an agreed protocol because things have changed. He said that clinical practice made dosage equivalence irrelevant because they needed to treat heart patients with the highest dose of statins. Prof Fenech said that even though the equivalence was 4:1, if he were to shift a patient who was on Lescol 80 mg to Simvastatin he would prescribe a Zocor 40 mg tablet or two (2) tablets of Zocor 20 mg because they had to give patients the strongest possible medication. He said that the equivalence for him was an academic exercise because what they did in practice was different.

Prof Mallia intervened to explain that the equivalence was established after taking into consideration the evidence and conclusions of several trials, called meta-analysis and also the advice of Prof Albert Fenech. With regard to the issue as to whether this tender was addressing the current clinical needs as Prof Fenech was stating, Prof Mallia pointed out that the original protocol for the use of statins, which was established in 1998, had not been changed even though they attempted to do so in 2002. So, he argued that they were in a very difficult situation where they were trying to provide first class medicines with something which was outdated.

Ms Debattista emphasised that the GPS was working on the currently approved protocol. Also, she pointed out that although cardiologists were prescribing the higher dose statins, there was still a higher consumption of the lower dose statins. Ms Debattista said that during 2005 the consumption of statins was as follows: Fluvastatin 20 mg - 686,000, Fluvastatin 40 mg - 848,000, Fluvastatin 80 mg - just over 2m, Simvastatin 10 mg - just over 1m and Atorvastatin 20 mg - 130,000.

The Director GPS concluded by stating that it had to be acknowledged that they needed to adjudicate on certain parameters. She contended that the equivalence ratio used was the correct one. Ms Debattista said that they were recommending different dosage strengths of statins in order to cater for as many of their patients as possible within the agreed protocol.

In his concluding remarks Dr Demarco said that from Prof Fenech's testimony it resulted that, in practice, the dosage equivalence ratio of 4:1 was irrelevant. He said that the Head of the Cardiology Department, without hesitation, testified that if he were to shift a patient from Fluvastatin 80mg to Simvastatin he would prescribe Zocor 40 mg or two (2) tablets of Zocor 20 mg. As a consequence, the tender award was not made to the most economically advantageous offer because the cost of Fluvastatin 80 mg (Lm5.79/pack) would be much cheaper than two (2) packs of Zocor 20 mg (Lm5.42/pack x2 = Lm10.84). The appellants' lawyer contended that tenders should be awarded not on academic exercises but on practical reality. He claimed that the decision to award this offer to Merck Sharp & Dohme Interpharma was going to adversely affect public expenditure heavily.

On his part, Dr Mizzi said that on the basis of Prof Fenech's testimony, the appellants seemed to accept that, according to scientific findings, the ratio of the dosage equivalence was established at 4:1. He contended that when Prof Fenech said that if he had a patient who was on Lescol 80 mg he would shift him to Zocor 40 mg, he did not say this because the two dosages of drugs were equivalent in terms of efficacy but because as a cardiologist he preferred to give patients higher dosage/ more powerful drugs. Dr Mizzi said that the fundamental flaw in Novartis' argument was written in

one sentence in their submission wherein it was specified that '*The efficacy of fluvastatin 80mg is more comparable to that of Zocor® 40mg.*'

Finally, he emphasised that there had not been any shred of evidence that the procedure was faulty or incorrect. He maintained that the decision was fair because the Zocor 20 mg was equivalent to Lescol 80 mg and that these were the parameters that had to be taken into considerations from a financial point of view.

At this stage, the public hearing was brought to a close and the PCAB proceeded with its deliberations before reaching its decision.

This Board,

- having noted that the appellants, in terms of their reasoned 'letter of objection' dated 30th January 2006, and also through their verbal submission presented during the public hearings held on 15th and 24th March respectively, had objected to the decision taken by the General Contracts Committee communicated to them that the tender submitted by them was not accepted;

- having noted that the appellants' legal adviser's claim that his client's offer was rejected on the basis of an incorrect technical evaluation when Zocor 20mg was compared to Fluvastatin 80mg when the latter should have been compared to Zocor 40mg;

- having noted the evidence given by the Director GPS who explained that the Adjudicating Board's decision was based on the cost effectiveness of the product and on the same official equivalence ratios that were used in the previous tender and which in their turn were based on the scientific data available and on the various international studies;

- having heard various medical experts give divergent and, apparently, somewhat conflicting opinions on the efficacy, outcome and tolerability of the two statins on offer;

- having heard Prof. Albert Fenech, Head of the Cardiology Department at St Luke's Hospital, confirm that in terms of equivalence, Lescol XL 80mg was equivalent to Zocor 20mg even though, as a physician, he would shift a patient from Lescol 80mg to Zocor 40mg because he considered that heart patients should have the strongest possible medication;

- having noted the appellants' legal adviser in winding up his case, did not insist on querying Zocor 20mg equivalence vis-à-vis Lescol 80mg but claimed that current clinical practice has made dosage equivalence irrelevant and physicians were nowadays prescribing highest possible dosage of statins;

- having noted that there do not appear to be reliable statistics covering the various uses of statin upon which one can base a comparative costings of the various brands on offer and that the only relatively reliable yardstick available is that of the dosage equivalence;

- having been satisfied that the Adjudicating Board had acted correctly throughout the evaluation process

reached the following conclusion:

1. The procedure adopted by the Evaluation Committee was in line with the Public Procurement Regulations;

2. Although there may be a valid logic behind which the appeal was raised there is an absence of statistics upon which one can make a costing exercise through which such logic can be proven. This board therefore concurs with the solution adopted by the Evaluation Committee to accept the correctness of basing the relative cost on the equivalence dosage as worked out by the Drugs and Therapeutics Committee.

Consequently, appellants' objection to the decision reached by the General Contracts Committee to award Item 3 of Tender CT 2383/04 Advert No. 193/2004 for the Supply of Statin Preparations is not upheld.

This board wishes to recommend that because there could well be an opportunity for savings in the expense of the purchase of certain medicines more pertinent statistics should be retained of the uses made of such medicines to enable proper costings excercises to be made out as needed.

Furthermore, in terms of the Public Contracts Regulations, 2005, this Board recommends that the deposit submitted by appellants in terms of regulation 83, should not be refunded.

Alfred R Triganza	**Anthony Pavia**	**Edwin Muscat**
Chairman	Member	Member

April 17, 2006