Meeting of the
Pharmacy and Therapeutics Committee
August 12, 2003
Minutes
Final

Members Present:
Randy Axelrod, M.D., Chair
Eleanor S. (Sue) Cantrell, M.D. (via phone)
Mariann Johnson, M.D.
Mark Oley, R.Ph.
Mark Szalwinski, R.Ph
Christine Tully, M.D.
Renita Warren, PharmD

Absent:
Roy Beveridge, M.D.
Avtar Dhillon, M.D.
Arthur Garson, Jr., M.D.
James Reinhard, M.D.

No quorum was present

Guests:
Jane Woods, Secretary of Health and Human Services
56 representatives from pharmaceutical companies, providers, advocates, associations, etc.

DMAS Staff:
Cynthia Jones, Chief Deputy Director
Cheryl Roberts, Deputy Director of Programs and Operations
Paige Fitzgerald, Counsel to the Board, Office of the Attorney General
Adrienne Fegans, Program Administration Specialist
Kim Piner, Counsel to the Board, Office of the Attorney General
Bryan Tomlinson, Director, Division Health Care Services
Absent: Patrick Finnerty, Agency Director

First Health Staff:
Ed Borovatz, Vice President of Pharmacy Benefit Services
Frank Shelp, MD, Medical Director
Donna Johnson, RPh, VA Clinical Account Manager
David Adams, PharmD, Rebate Support
Carol Perkins, PharmD, Clinical Support

Welcome and Introductions

Chairman Axelrod welcomed everyone to the meeting. He stated that there was not a quorum of Committee members present. Therefore, no votes could be taken. Chairman Axelrod explained that the Committee would proceed with the presentations and discussion of therapeutic class material. He said that the Committee would vote on this material at the next meeting on September 3, 2003.

Chief Deputy Director Cynthia Jones stated that in response to comments from the previous meeting, microphones were added so that everyone could hear the presentations and discussions. She further explained that due to the logistics that surround each meeting, DMAS wished to continue to hold each meeting in the DMAS boardroom.

Ms. Jones said that DMAS had received several questions concerning the prior authorization process. She stated that they are currently working on the specifications of that process and will put the preliminary process on the internet before the next meeting. There will also be a Preferred Drug List (PDL) Implementation Committee that will be reviewing the prior authorization process as well as adjudication.

Ms. Jones stated that the agenda would be the same for each meeting. Most of the items will be placeholders. There will always be a welcome from Pat Finnerty or Ms. Jones. The minutes of the previous meeting will always be presented. There will always be the opportunity for the public to make clinical presentations on the scientific material for the drug classes on each agenda. Lastly, there will always be a confidential meeting. These placeholder items will be on each agenda but may not necessarily be part of every meeting.

Acceptance of Minutes from June 18th meeting

Chairman Axelrod asked the Committee if they had any corrections, additions or deletions to the minutes of the July 30th meeting. No corrections were noted. The vote to accept the minutes will be taken at the September 3rd meeting.

Comments from the Chairperson

Chairman Axelrod asked that the presenters abide by the two basic rules as requested at the last meeting:

1. All presentations must be clinical in nature and based on scientific material. No anecdotal accounts are to be given.
2. All presentations must be limited to three to five minutes in length.

At the end of the presentations for each therapeutic class, Vice Chairman, Mark Szalwinski will make a brief summary presentation on each class.

Drug Class Discussions

Selective COX-2 Inhibitors and NSAIDs

Public Comments (Note: The copies of the handouts presented to the Committee are included at the end of the minutes):

1. Scott Schafer, Specialty Sales Force, Boehringer/Ingelheim.
   Mr. Schafer stated that Mobic® (meloxicam) is indicated for the relief of the signs and symptoms of osteoarthritis (OA). Mobic® deserves consideration for the PDL based on the following:
   a. Mobic® provides excellent management of the signs and symptoms of OA and provides efficacy comparable to established NSAID therapy.
   b. Convenient once-daily dosing.
   c. Low incidence of gastrointestinal(GI) adverse events

   In conclusion, Mr. Schafer stated that Mobic® would be a valuable addition to the PDL and a less expensive option to the COX-2 inhibitors.

2. Allan I. Goldberg, M.D., Executive Medical Director, Mid-Atlantic Region, Merck & Co., Inc.
   Dr. Goldberg stated that the GI tract toxicity of NSAIDs is well described. The COX-2 inhibitors have a lower incidence of GI toxicity. Dr. Goldberg cited the VIGOR study that compared Vioxx® (rofecoxib) with naproxen in approximately 8100 patients with OA. Overall, there was a 54% reduction in the primary end point of symptomatic ulcers and GI perforations, obstructions and bleeds. Another important finding of the study was the higher incidence of cardiovascular events observed with Vioxx® compared to naproxen. This difference could be due to the antiplatelet effect of naproxen or possibly a prothrombotic effect of Vioxx®. Therefore, it is very important that aspirin be given to those patients with cardiovascular disease while taking Vioxx®.

   Chairman Axelrod asked if there was any age distribution observations noted with these cardiovascular events with regards to mortality. Dr. Goldberg replied that no age distribution

was noted in the study. But the observations were considered significant and were therefore added to the product labeling.

Vice Chairman Szalwinski asked what was the longest time period of any trials with COX-2 inhibitors. Dr. Goldberg stated that the VIGOR trial was the longest with a duration of ten and a half months.

Chairman Axelrod asked if there was any age correlation with the incidence of non-myocardial events. Dr. Goldberg replied that an analysis had been performed that showed that the risk of adverse events does rise with increased age.

Mr. Oley asked if there is a differentiation in the class with regards to cardiovascular events with the inclusion of aspirin. Dr. Goldberg stated that it is difficult to evaluate across the class because the NSAIDs vary in antiplatelet activity.

3. Charles H. Bonner, M.D., Richmond based practicing physician, certified in Physical Medicine and Rehabilitation.
   Note: Chairman Axelrod asked all non-pharmaceutical presenters to declare if any particular drug company in this class sponsors them with research or otherwise. Dr. Bonner replied that he is not sponsored by any group.

   Dr. Bonner treats a lot of patients with muscloskeletal problems. He supports the inclusion of COX-2 inhibitors in PDL. Dr. Bonner described the mechanism of action of the COX-2 inhibitors. Because COX-2 inhibitors interact with only the cyclooxygenase-2 prostaglandins, they effectively treat pain and inflammation, but don't interfere with the clotting mechanisms or the gastric lining. Therefore, they are much safer than aspirin or other NSAIDs. Dr. Bonner stated that COX-2 inhibitors have become the standard of care for patients with osteoarthritis and rheumatoid arthritis. He stated that they are safe, effective and easy to dose. Most COX-2 inhibitors are dosed once or twice daily. They are recommended in patients with comorbid conditions who should not take conventional anti-inflammatory medications.

   Mr. Oley asked Dr. Bonner if he preferred one COX-2 in particular. Dr. Bonner replied that he prefers Bextra®. He believes it is a little more effective. He sometimes uses Celebrex® in certain patients. And he rarely uses Vioxx® because it is associated with edema in the lower extremities.

4. Laurie Cooksey, Pharm.D., VCU Healthsystems.
   Dr. Cooksey did not attend the meeting to make her presentation.

Presentation by Vice Chairman Mark Szalwinski

Dr. Szalwinski opened his discussion by describing the mechanisms of action for both the NSAIDs and COX-2 inhibitors. NSAIDs inhibit both COX-1 and COX-2 prostaglandins. Whereas, COX-2 inhibitors target only the COX-2 prostaglandins. COX-1 is the enzyme responsible for GI adverse effects as well as antiplatelet activity. The COX-2 enzyme is responsible for anti-inflammatory and analgesic effects. Therefore, COX-2 inhibitors claim to have comparable anti-inflammatory and analgesic effects to the NSAIDs but without the adverse effects. Dr. Szalwinski noted that Celebrex® has the largest number of indications, including the indication for familial adenomatous polyposis (FAP). Neither Vioxx® nor Bextra® have the indication for FAP. Contraindications are

hypersensitivity and allergy as well as advanced renal disease, hepatic insufficiency, hypertension and cardiac disease for all COX-2 inhibitors. There are variances in the half-lives of the COX-2 inhibitors, which explains why they are dosed differently. Dr. Szalwinski noted some additional points of interest concerning COX-2 inhibitors. In the treatment of dysmenorrhea, COX-2 inhibitors are generally not indicated unless risk factors are present. NSAIDs are equally effective and the adverse GI effects generally only appear with long term treatment. Dr. Szalwinski reiterated the fact that COX-2 inhibitors are not recommended in patients with cardiovascular risk factors. In summary, COX-2 inhibitors may be considered over NSAIDs for the treatment of arthritis in patients with known risk factors for ulceration or bleeding particularly in the elderly. However, whether one COX-2 offers an advantage over another is yet to be determined. Dr. Szalwinski urged that caution be used with these agents.

HMG CoA Reductase Inhibitors (Statins)

Public Comments (Note: The copies of the handouts presented to the Committee are included at the end of the minutes):

1. Joseph Green, Pharm.D., Medical Science Manager, Bristol-Myers Squibb.
   Dr. Green stated that based on the safety and efficacy of Pravachol® (pravastatin) he recommends that it be considered for addition to the PDL. Dr. Green said that to determine efficacy of the statins, one must consider the LDL lowering ability as well as the reduction in coronary events. He stated that pravastatin 40mg daily lowers LDL by 34%, lowers triglycerides by 24% and increases HDL by 12%. Pravachol® has been studied in over 20,000 patients. Dr. Green cited three major studies, West of Scotland Coronary Prevention, CARE and LIPID. Based on these studies, Pravachol® has a wide range of FDA approved indications. Pravachol® has one of the best safety profiles of all the statins. Less that one- percent of Pravachol®'s metabolism occurs in the cytochrome P450 unlike the other statins. Therefore, Pravachol® has fewer drug interactions than the others do. Also, Pravachol® is only 50% protein bound and as a result has lower interaction potential with highly protein bound drugs such as warfarin. Lastly, Pravachol® can be used in combination with other agents such as niacin and fibrates without increased risk of myopathy.

2. Dr. Andrea Zuckerman, Regional Medical Research Specialist Cardiovascular Medical Team, Pfizer Pharmaceuticals.

   Dr. Zuckerman stated that Lipitor® (atorvastatin) has demonstrated superior lipid lowering efficacy at helping patients achieve their LDL and non-LDL goals. It can lower LDL up to 61% and triglycerides up to 37%. Furthermore, Lipitor® has an excellent safety profile across the dosage range of 10 to 80 mg. Studies show that the incidence of adverse events is comparable to placebo and to other statins. Lipitor® shows no obvious dose-response in clinical adverse events, including myopathy. Lipitor®'s significant benefit on morbidity and mortality in older patients, those with hypertension, diabetes or post myocardial infarction (MI) was shown in the the recently reported outcomes studies ASCOT, CARDS, MIRACL and GREACE. It can be used in a broad variety of patients since it lacks significant drug interactions with warfarin, protease inhibitors, amiodarone and verapamil. Lipitor® has also received FDA approval for use in pediatric patients above the age of ten.

3. Allan I. Goldberg, M.D., Executive Medical Director, Mid-Atlantic Region, Merck & Co., Inc.
   Dr. Goldberg discussed the Heart Protection Study that demonstrates the importance of lipid management. Patients in this study were randomized based on risk factors rather than lipid

levels. Based on the findings of this study, Mevacor® (simvastatin) 40mg should be the initial starting dose for patients with risk factors such as cardiovascular disease, peripheral vascular disease and diabetes. The study revealed that patients with these risk factors treated with simvastatin had significant reductions in mortality. In particular, patients with diabetes had nearly a 30% risk reduction. Dr. Goldberg noted that it is still critical to monitor patients for myopathy. The new product label indicates that there should be an additional step to evaluate liver function when the 80mg dose is anticipated.

4. Walter Malloy, M.D., VCU Healthsystems. Not sponsored by any pharmaceutical company. Dr. Malloy stated that for 19 years the medical community has known that lowering cholesterol will decrease the cardiovascular risk rate. He presented information showing the incidence of deaths related to cardiovascular (CV) disease in Virginia from 1991 to 1995. Dr. Malloy presented the findings of several studies showing the reduction in CV disease by lowering LDL for various statins. He also presented information showing the LDL reduction rates and the incidence of rhabdomyolysis for each statin. Dr. Malloy concluded that not all statins fit all people. He wants to have the ability to select the right drug for each of his patients.

   Dr. Tully commented that until a few years ago it was thought that higher cholesterol levels were important in older patients to preserve cognitive function. Therefore, most geriatricians did not prescribe statins to their older patients. However, the British Journal of Medicine reported that higher levels of cholesterol were not necessary to maintain cognitive function. With this change in the literature, geriatricians are reconsidering treating their patients for high cholesterol. Dr. Tully also noted that the high cost of the statins is another impediment to their use in the elderly. Chairman Axelrod commented that there is a generic statin on the market and more on the way, so pricing may be less of a concern in the future.

Chairman Axelrod reminded the Committee that there are a number of written presentation materials on each of the therapeutic classes being discussed that should be reviewed prior to voting at the next meeting.

Presentation by Vice Chairman Szalwinski

Dr. Szalwinski stated that lovastatin is the only statin currently available as generic. The patent expires on Zocor® in the next 2 to 3 years and it may become available as generic at that time. Dr. Szalwinski began his comparison of the statins by pointing out that pravastatin is the only one that is not metabolized by cytochrome P450 enzymes. Therefore, it has no significant drug interactions. Mevacor®, Zocor® and Lipitor® are all metabolized by the cytochrome P450 enzyme CYP3A4 and therefore are expected to have similar drug interactions. Lescol® and Crestor® are metabolized the CYP2C9 enzyme. Dr. Szalwinski pointed out that there have been numerous studies on all of the drugs and as a result there are lots of indications for each. Most trials show that the statins have similar adverse events. All produce elevated liver transaminase, which is usually, dose related. Although rare, hepatitis, myositis and rhabdomyolysis have been associated with all statins. Simvastatin and lovastatin have the most documented drug interactions. Atorvastatin is metabolized by the same pathway as simvastatin and lovastatin and while not documented as much, it may have similar drug interaction potential. Pravastatin and fluvastatin have a drug interaction safety advantage because of how they are metabolized. In summary, Dr. Szalwinski stated that all of the statins have been shown to be effective. He agreed with Dr. Malloy that the main issue is not which statin should be used, but that a statin must be used to reduce the risk of CV events.

Chairman Axelrod asked about the effectiveness of niacin. Dr. Szalwinski replied that niacin effectively lowers LDL and raises HDL levels significantly. It is very inexpensive and cost effective. However, it is associated with a side effect profile that often limits its use. Niacin must be titrated slowly and monitored carefully to maximize its effectiveness.

Dr. Tully requested that the Committee include at least one of the statins with a decreased drug interaction profile, especially one that has minimal interactions with Coumadin®.

Sedative Hypnotics

Public Comments - There were no oral presentations to the Committee for sedative hypnotics.

Presentation by Vice Chairman Mark Szalwinski
Dr. Szalwinski stated that for the last 30 years benzodiazepines have been the preferred drugs for the treatment of insomnia. They work nonselectively on two separate central receptor sites – omega-1 and omega-2. Omega-1 is responsible for the sedative action and omega-2 is responsible for memory and cognitive function. Both are located in different areas of the brain. They are classified into 3 groups based on half-life. The short half-life group includes Halcion®. The medium half-life group includes Restoril® and Prosom®. The long half-life group includes Dalmane® and Doral®. All of these agents are available generically. All are available as multi-source products and are relatively inexpensive. The newer benzodiazepine agents (Z-class) include zolpidem (Ambien®), zaleplon (Sonata®) and zopiclone (Estora®, which is not yet FDA approved). These agents have a hypnosedative action comparable to benzodiazepines but with a very short half-life. They selectively work on the omega-1 receptor site. This is the receptor site responsible for the sedative effects. Since these agents do not interact with the omega-2 receptor site, they do not impair memory or cognitive function, as do the benzodiazepines. They have the same precautions as the benzodiazepines in that they should be used for a limited time period even in chronic relapsing conditions. They are still being evaluated for the long-term management of insomnia. A meta-analysis performed by Wagner (Ann Pharmacotherapy) in 1998 concluded that these agents offer few significant advantages in terms of adverse events over the older benzodiazepines.

Beta Adrenergics

Public Comments (Note: The copies of the handouts presented to the Committee are included at the end of the minutes):

1. Scott Schafer, Specialty Sales Force, Boehringer/Ingelheim.
   Mr. Schafer stated that COPD is major cause of morbidity and mortality throughout the world and the fourth leading cause of death in the United States. Almost 16 million Americans have COPD and the incidence is increasing each year. The treatment of COPD is very different from that of asthma. The goals of effective management of COPD with beta agonists are to prevent disease progression, relieve symptoms, improve exercise tolerance and health status, and prevent and treat complications and exacerbations. Mr. Schafer referred to clinical and pharmacoeconomic trials that show that Combivent® (ipratropium/albuterol) provides COPD patients with total lung coverage. It provides two separate and distinct modes of action, which provide symptom control and rapid relief. Combivent® provides greater efficacy and lung function than either ipratropium bromide or albuterol sulfate alone. There is no greater increase in side effects with the use of Combivent® than by using either agent alone.

Additionally, five medical societies and the World Health Organization endorse the use of combination therapy with ipratropium and albuterol in the treatment of COPD. Currently, Combivent® is the number one prescribed agent for the treatment of COPD. Because of its mode of action, it should not be classified strictly as a beta agonist. It should be in a class unto itself. There is no generic equivalent. Just as COPD is different than asthma, Combivent® should be distinguished from the beta agonists.

2. Richard Thompson, Senior Regional Medical Specialist, GlaxoSmithKline.
Mr. Thompson discussed the molecular structural differences between salmeterol and albuterol. These differences explain the longer duration of action and the greater smooth muscle effects of salmeterol. Salmeterol is also more selective for the noncardiac beta-receptor (beta-2) than is albuterol. Mr. Thompson stated that all of the clinical trials that he cited were sponsored by Glaxo but were designed to meet FDA standards and are all published in peer-reviewed journals. The trials show that salmeterol has a much longer duration of action than albuterol. One significant finding shows that there is some residual salmeterol remaining the patients in the morning. The levels never return to baseline as they do with albuterol. This is an important finding in that this is often the most problematic time for patients. The long acting properties of salmeterol also help to prevent nighttime asthma events. In addition to its bronchodilation properties, salmeterol has also been shown to exert a greater inhibition of histamine and leukotrienes (important agents in the inflammatory process) than albuterol.

   Lastly, Mr. Thompson stated that salmeterol is comparable to the other beta agonists in terms of side effects.

   Dr. Szalwiski asked about the availability of the metered dose inhaler of Serevent®. Mr. Thompson said that due to the Montreal Protocol requiring the elimination of fluorocarbons from all aerosol products, the metered dose formulation of Serevent® is being discontinued. It will only be available in the dry powder diskus formulation. GlaxoSmithKline is having trouble stabilizing the HFA formulation. Therefore, it is not yet available. However, the combination product of Advair®(salmeterol/fluticasone) is available in the HFA formulation.

3. Dean Handley, Ph.D., MBA, Senior Executive Director of Medical Communications, Sepracor, Inc.
Dr. Handley discussed the properties and benefits of Xopenex® (levalbuterol). Levalbuterol is the R-isomer of albuterol. Albuterol sulfate is a racemic mixture of the R and S-isomers. The S-isomer produces side effects that are very similar to the disease it is treating. The removal of the S-isomer from the racemic mixture produces a more effective bronchodilator. It has a longer duration of action and therefore can be used less frequently. This leads to better compliance and reduced hospitalizations. Requiring a prior authorization of levalbuterol jeopardizes access to this rescue medication. Levalbuterol is not interchangeable with albuterol either chemically or therapeutically.

4. Barry Tucker, Pharm.D., Regional Medical & Scientific Affairs Liaison, Schering-Plough.
Dr. Tucker stated that Norvartis sponsored most of the clinical trials involving Foradil® (formoterol). He said that the effective maintenance of asthma and COPD is the most critical point as it helps to keep patients out of the hospital. According to the COPD Guidelines, long acting beta agonists should be added to a patient's therapy at the point of moderate COPD. Dr. Tucker reported that over 100,000 deaths occur each year from COPD. Two-thirds of people with COPD are currently undiagnosed. If there is effective treatment available, why are more people not being treated? Dr. Tucker said that generally most of the treatments are

for maintenance. Since many patients do not experience immediate relief of COPD symptoms they do not take their medication. However, this is not the case with asthmatics. They get an immediate response when treating their acute symptoms. Foradil® has a rapid onset of five minutes, which has been shown to be statistically significant compared to salmeterol.

Presentation by Vice Chairman Mark Szalwinski

Dr. Szalwinski divided his discussion of beta agonists into 3 groups - long-acting beta agonists, short-acting beta agonist inhalers and short-acting beta agonist nebulizers.

1. Long-acting beta agonists include salmeterol and formoterol. There are no significant differences in these agents. They both have the same mechanism of delivery – inhaled dry powder. They have the same precaution and side effect profiles. They are only available as brand name products.

2. Short-acting beta agonist inhalers include Proventil®, Ventolin®, Alupent® and Maxair®. There is not a lot of controversy among these agents. They are moving towards HFA

   formulations. They all have the same efficacy and side effect profiles. And they are all used as rescue medication in the treatment of acute exacerbations of asthma.

3. Short-acting beta agonist nebulizers include Xopenex® (levalbuterol), Proventil® (albuterol), Accu-Neb (preservative-free albuterol) and Alupent (metopreterenol). This group is more controversial. Albuterol is available generically and is inexpensive. Whereas, Xopenex® (levalbuterol) is a brand name medication and is very expensive. Dr. Szalwinski cited an editorial from the Journal of Allergy and Clinical Immunology by Ahrens and Weinberger that gives a point by point argument to each Xopenex® claim. They state that the available data does not show that levalbuterol is any safer or effective than albuterol. They feel that Xopenex® increases the cost of asthma treatment with no added benefit.

Inhaled Corticosteroids

Public Comments (Note: The copies of the handouts presented to the Committee are included at the end of the minutes):

1. Richard Thompson, Senior regional Medical Scientist, GlaxoSmithKline.
   Mr. Thompson presented information about Flovent® (fluticasone), an inhaled corticosteroid used for the treatment of asthma. He presented the following key characteristics of Flovent®. First, Flovent® has high topical anti-inflammatory properties. The higher lipophilicity of fluticasone allows more drug to enter the lung tissue. Second, Flovent® has very selective glucocorticoid activity. Lastly, Flovent® has very low systemic bioavailability. Therefore, it does not have the systemic adverse effects that are associated with the older corticosteroids. Mr. Thompson cited clinical trials that compared fluticasone with two other inhaled corticosteroids. The first trial showed that fluticasone is more effective than budesonide for moderate to severe cases of asthma. The second trial that Mr. Thompson cited showed that fluticasone requires lower dosing than triamcinolone and this leads to a greater therapeutic effect with fluticasone.

   Mr. Thompson also presented information about Advair Diskus® (salmeterol/fluticasone). This combination product contains both a smooth muscle component (salmeterol) and an anti-

inflammatory component (fluticasone). Combining these two asthma medications leads to increased patient compliance and ultimately decreased hospitalizations.

2. Mark Francis, Aventis.
   Mr. Francis stated that Azmacort® (triamcinolone) is an orally inhaled corticosteroid used for the prophylactic treatment of asthma. It was introduced in the United States in 1982. The safety and effectiveness of Azmacort® are well documented. The inhaler has a built in spacer. The advantages of this device are that it improves deposition of the medication into the airways and it also compensates for poor patient inhalation technique.

Presentation by Vice Chairman Mark Szalwinski

Dr. Szalwinski stated that the inhaled corticosteroids are effective in treating the symptoms of asthma as well as the underlying disease process. There are five inhaled corticosteroids currently on the market – Qvar ® (beclomethasone), Pulmicort® (budesonide), AeroBid® (flunisolide), Flovent® (fluticasone) and Azmacort® (triamcinolone). They all have the same mechanism of action and all are effective. The mechanism of delivery differs in some of them. Dr. Szalwinski stated that all of these agents do a good job. The question is not which one to use, but how can we get asthmatics to use them more consistently and more effectively. The makers of Advair® would like for us to consider that adding a long acting symptomatic reliever along with a corticosteroid will lead to better compliance and outcomes.

Next Meeting

Chairman Axelrod reminded the Committee that the next meeting will be scheduled for September 3rd. The next meeting would begin with a brief discussion of the drugs reviewed today followed by a vote. Then another set of therapeutic classes will be presented and reviewed.

Adjournment

Chairman Axelrod adjourned the meeting at 4:15 p.m.