

**Meeting of the
Pharmacy and Therapeutics Committee
March 30, 2006
Minutes**

Members Present:

Randy Axelrod, M.D., Chair
Mark Szalwinski, R. Ph., Vice Chair
Avtar Dhillon, M.D.
James Reinhard, M.D.
Gill Abernathy, M.S., R.Ph.
Renita Warren, Pharm.D.
Mark Oley, R.Ph.
Mariann Johnson, M.D.
Roy Beveridge, M.D.
Rachel M. Selby-Penczak, M.D.
Sue Cantrell, M.D.
Arthur Garson, M.D.

Guests:

65 representatives from pharmaceutical companies, providers, advocates, associations, etc.
Akshay V. Davé, M.D., Ophthalmology Consultant

DMAS Staff:

Patrick Finnerty, Agency Director
Cynthia B. Jones, Chief Deputy Director
Cheryl Roberts, Deputy Director of Programs and Operations
Scott Crawford, Deputy Director of Administration and Finance
Bryan Tomlinson, Director, Division of Health Care Services
Reatha Kay, Counsel to the Board, Office of the Attorney General
Rachel Cain, Pharm.D, Clinical Pharmacist
Keith Hayashi, R.Ph., Clinical Pharmacist
Katina Goodwyn, Pharmacy Contract Manager

First Health Staff:

David Adams, Pharm.D, Rebate Support
Debbie Moody, R.Ph, Clinical Manager
Donna Johnson, R.Ph, Clinical Manager
Justin Lester, Pharm.D, M.B.A., Rebate Support

A quorum was present

WELCOME AND INTRODUCTIONS FROM PATRICK FINNERTY, DMAS DIRECTOR

Mr. Finnerty welcomed everyone to the meeting and expressed his appreciation for the Committee's continued service to the Pharmacy & Therapeutics (P&T) Committee. He stated that the Committee has done a wonderful job and the success of the program was testimony of that work. He shared regrets from the new Secretary of Health and Human Resources, Marilyn Tavenner, that she could not attend the meeting today. Unfortunately, she had a number of other commitments, one of which is that the General Assembly is still in session. She sent her thoughts of appreciation to the Committee for all of their service and stated that she will attend a future meeting to meet all of the members.

Mr. Finnerty presented an update on Virginia Medicaid pharmacy issues that have occurred since the last meeting. At the last meeting, a discussion on erectile dysfunction drugs was deferred because the Commonwealth was considering whether or not it would continue coverage of those drugs. Subsequently, new legislation discontinued federal matching funds for erectile dysfunction drugs. Virginia followed suit and ended coverage of these products to treat erectile dysfunction on January 1, 2006. Virginia does continue to cover Revatio for patients with pulmonary arterial hypertension. There were some inquiries when coverage for these drugs was terminated; however, overall it was a smooth process.

Next, Mr. Finnerty reviewed the changes due to the implementation of Medicare Part D. Medicare Part D affects around 900,000 Virginians who are Medicare beneficiaries, of which 100,000 of them are low-income seniors that are also eligible for Medicaid (dual eligibles). Those dual eligibles were automatically enrolled in a Medicare Part D prescription drug plan. Mr. Finnerty noted that compared to implementation issues experienced in other states, Virginia's transition went relatively well. He attributes this to the amount of work Virginia did in advance of implementation including ensuring that the data sent to the Centers for Medicare and Medicaid Services (CMS) was accurate; working collaboratively with Becky Snead and the Virginia Pharmacists Association; and temporarily providing

coverage for drugs while transition issues existed. The Commonwealth paid for dual eligible recipients' prescriptions from February 1st to March 8th while the federal government offered matching funds to the states. During this time, the Department paid approximately \$5.5 million in prescription drug costs for dual eligibles enrolled in Part D, which will eventually be reimbursed by the federal government.

The Department continues to see some issues with Medicare Part D and expects Part D to reduce drug spend in PDL classes by about 55%. (*Correction: Total drug spend is expected to decline by 55% and PDL drug spend by over 65%*) Dr. Axelrod asked what percent of the population the reduction in PDL drug spend represented. Mr. Finnerty stated the Virginia Medicaid enrollment includes approximately 700,000 recipients; therefore, this reduction is based on about one-seventh of the total population.

Finally, Mr. Finnerty discussed the recent Federal Medicaid reform, known as the Deficit Reduction Act (DRA). The DRA was passed by Congress and signed by the President. It includes a number of mandatory changes in state Medicaid pharmacy programs. The following changes will effect how every state manages their pharmacy programs:

- Establishes a new Federal Upper Limit at 250% of Average Manufacturer Price (AMP) for multi-source drugs
- There are provisions for increased transparency by requiring monthly AMP reporting by manufacturers on all multi-source drugs
- States will have to submit annual reports on payment rates for all Medicaid covered drugs as well as dispensing fees for rebate purposes
- Manufacturers' best price will include all Federal Drug Administration (FDA) New Drug Applications (NDA)

The Department is beginning its efforts to meet their requirements for Federal Medicaid Reform.

In conclusion, Mr. Finnerty reiterated his appreciation for the Committee's attendance and their important work.

COMMENTS AND WELCOME FROM DR. RANDY AXELROD, CHAIRMAN

Dr. Axelrod also welcomed the Committee. He reiterated the issues experienced with the implementation of Medicare Part D and noted that he has been involved with Medicare Part D at Wellpoint. He noted that there has been significant impact on the Commonwealth. A recent report states that currently 41% of eligible Virginians have yet to enroll for Medicare Part D and still have no drug coverage. This rate is between 44-46% nationally. There is an expectation that between May 1st and May 15th, there will be a rapid increase in enrollment as those eligible may believe that they have to make a decision and enroll.

Mr. Szalwinski asked Mr. Finnerty about the amount of clawback paid to the federal government compared to the quoted percent reduction in total and PDL- specific drug spend. Mr. Finnerty responded that originally the estimated clawback for fiscal year 2007 was \$38 million more for dual eligibles than if DMAS would have continued to cover this group. The primary reason for this was that the baseline for the clawback was fiscal year 2003, when savings generated by the PDL program and other cost saving pharmacy programs implemented by DMAS over the past two years would not be considered. The clawback calculation is based on fiscal year 2003 per capita drug cost trended forward to fiscal year 2006. Virginia Medicaid's real pharmacy trend line for the past two years has been at 3%, largely due to the savings of the PDL program, whereas the federal government was trending it at about 15% per year. Virginia Medicaid did not get credit for a lot of the work on pharmacy cost savings initiatives. In the past two weeks, CMS has recalculated the clawback amount for states and is reducing Virginia's amount by about \$16 million. In fiscal year 2007, it will cost Virginia Medicaid an additional \$21 million to assist in providing pharmacy coverage to dual eligibles.

When the Governor set his budget for this year, he had to allocate \$37 million to pay for this program instead of those funds being spent in other programs, such as physician reimbursement. Dr. Axelrod asked about states' efforts to oppose the clawback amounts. Mr. Finnerty stated that a couple of states, led by Texas, were pursuing a recently filed lawsuit.

In response to a question from the Committee, Mr. Finnerty stated that although there have been adjustments to the clawback; it is still trended forward with fiscal year 2003 as the baseline. The trend line is now less than it was previously although, problems with the calculation in the first year will continue in future years.

Dr. Axelrod reviewed the agenda and described the presentation process for speakers. Dr. Axelrod noted that the Committee would spend some time focusing on long acting narcotics to review previous decisions by the Committee. He noted that an Ophthalmology consultant invited by the Committee was present and the order of the agenda may be altered.

ACCEPTANCE OF MINUTES FROM OCTOBER 31, 2005 MEETING

Dr. Axelrod asked if there were any changes, modifications or corrections to the minutes from the October 31, 2005 meeting. None were noted and upon request of the Chairman, the Committee voted on a motion and a second to approve the minutes of the October 31, 2005 meetings as written. The Committee voted unanimously to approve the minutes as drafted.

Dr. Axelrod asked that all of the ophthalmic classes be reviewed first.

REVIEW OF CURRENT PHASE I AND PROPOSED NEW OPHTHALMIC CLASSES

Joseph E. Iuorno, M.D., Assistant Clinical Professor, Residency Program Director, Department of Ophthalmology, Virginia Commonwealth University (VCU) Health System discussed the Ophthalmic Prostaglandin Agonist - Lumigan[®] and the Alpha-2 Adrenergic Glaucoma Agent - Alphagan P[®]

Dr. Iuorno noted that he is a physician who uses Alphagan P[®] for its properties. Alphagan P[®] has a different preservative property, Puritc, which decreases sensitivity and toxicity. He believes that because of this, the patient is more compliant with their prescription and has a better response to the therapy.

Dr. Iuorno stated that he is the Director for the residency program at VCU and Assistant Clinical Professor. He mostly sees indigent patients in the medical assistance program. He uses Alphagan P[®] a lot as therapy for glaucoma. Lumigan[®], in Dr. Iuorno's opinion, is the most effective prostaglandin. It decreases pressure better (up to 1.3 mg Hg) compared to other prostaglandins. It is a once a day dosage. It uses different receptors than other similar products.

Dr. Iuorno disclosed that he has no financial incentive from drug manufacturers. He is here today for his patients and uses both of these drugs for his patients.

Dr. Axelrod asked Dr. Iuorno if he finds in his practice that Lumigan[®] is more efficacious than other prostaglandin agonists? Dr. Iuorno responded that in his practice he wants to reduce the pressure in the eye as much as possible and that he believes that the biggest component in treatment is to reduce pressure, which Lumigan[®] provides. Dr. Iuorno stated that drug compliance is the only way to achieve this.

Laura Kososki, M.D., Medical Affairs Manager, ISTA Pharmaceuticals discussed the Beta Blockers used for Glaucoma - Istalol[®] and the Ophthalmic Anti-Inflammatory - Xibrom[®]

Istalol[®] is a once daily, non-blurring beta-blocker that decreases intraocular pressure. It does not cause transient blurred vision like other timolol preparations. Istalol[®] is also a good adjunct to prostaglandin.

Xibrom[®] works as an anti-inflammatory (NSAID). It is used for postoperative pain. It is dosed twice a day. Dr. Kososki noted an increase in compliance rates.

Dr. Garson asked about the mathematical definition of “cost effective” as stated in the presentation related to Istalol[®]. Dr. Kososki stated that by their calculations Istalol[®] is a less expensive agent for a second line agent compared to Alphagan P[®] and prostaglandin if used first line. This is their methodology used in stating that Istalol[®] is more cost effective than other branded medications.

Dr. Garson asked that all speakers refrain from using the term “cost effectiveness” unless it can be defined in terms of costs per quality-adjusted life.

Richard G. Fiscella, RPh, MPH, Clinical Professor, University of Illinois at Chicago discussed the Ophthalmic Quinolone - Gatifloxacin (Zymar[®]) and the Ophthalmic Antihistamine - Epiostat[®]

Ophthalmic antibiotics are used to prevent or treat non-vision threatening and vision threatening conditions. The advantages of fourth generation fluoroquinolones (G-FQ's), gatifloxacin (Zymar[®]) and moxifloxacin (Vigamox[®]) include better gram-positive activity than older Fluoroquinolones (FQ). They also have excellent gram-negative coverage, and improved activity against anaerobes, Mycobacterium, and Nocardia. Ophthalmic antibiotics are often approved by the FDA for the treatment of bacterial conjunctivitis; however, using the fourth G-FQ's for the treatment of bacterial conjunctivitis is often inappropriate. Gatifloxacin should be prescribed for treating bacterial keratitis and surgical prophylaxis. Gatifloxacin is well tolerated and has a near neutral pH range (6). It has excellent solubility and achieves peak ocular tissue concentrations occur within 15-30 minutes. Ciprofloxacin (pH 4.5) may precipitate in the eye when used frequently in bacterial keratitis. Oxifloxacin has been associated with some slowing of epithelialization and wound healing. Gatifloxacin has better ocular tolerability than moxifloxacin. Human corneal toxicity has been reported with moxifloxacin by slowing epithelial healing. Increased resistance has been reported in the older generation fluoroquinolones, especially to P. aeruginosa, Staphylococcus species, Streptococci, and anaerobes. Zymar[®] has less risk of contamination since it contains the preservative benzalkonium chloride (BAK). BAK provides coverage against not only bacteria, but also other common ocular pathogens including acanthamoeba and fungi. Vigamox[®] contains no preservative; it is the first multi-dosed product FDA approved without a preservative. Zymar[®] is also cost effective; a 5 ml bottle costs the same as Vigamox[®] in a 3 ml bottle.

Allergic conjunctivitis is estimated at prevalence from 5% to 25% of the population. Epiostat[®] has multi-action and comprehensive treatment with the following features: proven MCS; prevents histamine release; very potent H1-antagonist; fast relief of itching and control of vascular leakage; H2-receptor antagonist; and sustained decrease in pro-inflammatory mediators. Epiostat[®] is the only product to be identified to block H2-receptor affinity (possible benefit in reducing hyperemia and eyelid swelling). It has a Neutral pH, soothing upon instillation, rapid action (relief in 3 minutes and sustained duration for up to 12 hours).

Mr. Fiscella stated that he receives compensation equally from Allergen, Merck and Pfizer. In addition, he is on the speakers' list for each company.

Comments from Ophthalmology Consultant, Dr. Akshay V. Davé

Dr. Davé is board certified in Ophthalmology. He has been in private practice for 8 years. He has approximately 10,000 total patient visits each year and completes approximately 1,500 cases each year.

His practice is a cross spectrum of populations including cosmetic patients as well as Medicare and Medicaid patients. He does not have financial obligations to manufacturers; over the past eight years, he has accepted approximately \$1,000 in total focus group fees and various honorariums. These payments have been evenly split among the major pharmaceutical companies with ophthalmic products. Dr. Davé stated that his interest in attending this meeting was to maximize patient care while maintaining fiscal accountability. In his opinion, if the PDL had no branded preferred medications available other than a prostaglandin analog, it would be slightly sub-optimal, but acceptable. He suggested that at least one prostaglandin should be preferred.

Dr. Davé's opinions regarding the ophthalmic classes are noted below:

Alpha-2 Adrenergic Agents - Glaucoma

Alpha-2 agonists are third line or later therapy with below average efficacy and tolerability.

Dr. Axelrod asked the Committee if they had any questions. With no questions, Dr. Axelrod thanked the Ophthalmology consultant for his comments.

Beta Blockers - Glaucoma

Beta blockers are first and second line therapies with average efficacy and below average tolerability.

Dr. Axelrod asked for a decision concerning all of the ophthalmic classes.

Carbonic Anhydrase Inhibitors-Glaucoma

Topical Carbonic Anhydrase Inhibitors are third line or later therapies with below average efficacy but above average tolerability.

Prostaglandin Agonists - Ophthalmic

Prostaglandins are first and second line therapies with above average efficacy and tolerability. All of the products are similar. It is important to have one brand drug available in this class. He stated that Lumigan[®] is slightly less tolerated than the other two medications; although any of the three would be an excellent choice if the Committee picked only one.

Ophthalmic Antihistamines

This is a "nice to have" class it is not a "have to have" class. This potential new class is not as necessary as the quinolones and anti-inflammatories.

Ophthalmic Quinolones

This is a "must-have" class of medications. If these drugs were just available in generic form, it would be acceptable; ideally, at least one of the new quinolones, either Moxiflox or Gatiflox, would be preferred.

Ophthalmic Anti-inflammatory Agents

It would "nice" to have at least some of the generics as preferred. To have the class approved, in general, would be great as well.

Ophthalmic Mast Cell Stabilizers

This is a 'nice to have' class but it is not a 'have to have' class. This potential new class is not as necessary as the quinolones and anti-inflammatories

Mr. Szalwinski motioned that all of the ophthalmic classes on the table be considered PDL eligible. Mr. Oley seconded the motion. Dr. Axelrod asked if there was any further discussion regarding any of the ophthalmic subclasses. There was no discussion. The Committee voted unanimously to consider all ophthalmic classes reviewed as PDL eligible.

REVIEW OF NEW DRUG IN PDL PHASE I~ Xopenex® HFA

Richard L. Bennett M.D., Pediatrician, reviewed the new drug dosage form of the Beta Adrenergic ~ Xopenex® HFA from phase 1

Dr. Bennett is local pediatrician practicing in the inner city. Sepracor is reimbursing Dr. Bennett for his time away from the office. Dr. Bennett reviewed a study from *The Journal of Allergy and Clinical Immunology*, "(S) - Albuterol Activates Pro-Constrictory and Pro-Inflammatory Pathways in Human Bronchial Smooth Muscle Cells". The study concluded that Xopenex® is as effective as albuterol in treatment but because of the isomer, it has fewer side effects than albuterol. Dr. Bennett noted that in his population of children this is a strong advantage. The HFA allows for convenient use of the product when transitioning out of the hospital.

Ms. Abernathy asked if the difference in side effects with Xopenex® exists when there is dose equivalency with albuterol. Dr. Bennett stated that the first dose response is similar and there is the same efficacy from days 1-28 and days 28-56. Although the efficacy is similar, the side effects are different in their effect on potassium, sodium and glucose.

Ms. Abernathy asked what percentages of the population have significant side effects. Dr. Bennett noted that he does not have the percentage available but because his population is so young, compliance becomes a real concern if the patient or the parent will not use the product due to the side effects.

Mark Oley reviewed Xopenex® HFA – Short-acting Beta Adrenergic

Xopenex® HFA is a hydrofluoroalkane (HFA) metered-dose inhaler for the treatment or prevention of bronchospasm in adults, adolescents and children 4 years of age and older with reversible obstructive airway disease. It has been FDA approved since March 12, 2005 but has recently been made available on the market. This product is now available in this dosage form. It has been available since March 25, 1999 in a nebulizer form.

Mr. Oley motioned that Xopenex® HFA be PDL eligible. Mr. Szalwinski seconded the motion. The Committee voted unanimously to consider Xopenex® HFA as PDL eligible.

PHASE II PDL ANNUAL REVIEW

Charlie Kelly PharmD, CDE, Regional Scientific Manager for Takeda Pharmaceuticals America discussed the Thiazolidinedione-Oral Antidiabetics - Actos® and ActosPlus®

Dr. Kelly reviewed three main studies published since March 2005. They are as follows:

1. Head to head on lipids and glycemic control between Actos® and Avandia® (Head to Head)
2. Conversion trial from Avandia® to Actos® with stable statin background therapy (Complement)
3. Evidence-Based Outcomes Cardiovascular trial; the first for a glitazone (PROACTIVE)

Pioglitazone/metformin (Actoplus Met®) was released on August 29, 2005 by Takeda Pharmaceuticals. Dr. Kelly reviewed the recent double blind, placebo-controlled studies that evaluated the effects of rosiglitazone and pioglitazone on blood lipids in patients with type 2 diabetes mellitus. In this study, the authors concluded that pioglitazone showed a more beneficial treatment effect on blood lipids when compared with studies of rosiglitazone. The outcomes of a recent head-to-head study comparing pioglitazone to rosiglitazone, suggest the former was found to be superior to rosiglitazone for its effects

on lipids. Triglyceride levels were reduced by 51.9 +/- 7.8 mg/dl with pioglitazone, but were increased by 13.1 +/- 7.8 mg/dl with rosiglitazone ($p < 0.001$ between treatments). Additionally, the increase in HDL cholesterol was greater (5.2 +/- 0.5 vs. 2.4 +/- 0.5 mg/dl; $p < 0.001$) and the increase in LDL cholesterol was less (12.3 +/- 1.6 vs. 21.3 +/- 1.6 mg/dl; $p < 0.001$) for pioglitazone compared with rosiglitazone, respectively. LDL particle concentration was reduced with pioglitazone and increased with rosiglitazone ($p < 0.001$). LDL particle size increased more with pioglitazone ($p = 0.005$). Compliance with once a day Actoplus Met[®] is believed to be an advantage.

Ms. Abernathy asked about congestive heart failure as a side effect of Actos[®] and the studies reviewed. Dr. Kelly noted the side effects of fluid retention and edema are well documented in this class and applies to all of the products. An increase in congestive heart failure and hospitalization was seen in the study but people did not die because of congestive heart failure. Congestive heart failure leading to hospitalization and death was no different between placebo and Actos[®]. The actual hospitalizations for congestive heart failure increased due to Actos[®] but the overall number of hospitalizations were reduced.

Vanessa Land, Pharm. D., Regional Medical Scientist for GlaxoSmithKline discussed the Thiazolidinedione-Oral Antidiabetic - Avandaryl[®]

Avandaryl[®] is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of rosiglitazone and sulfonylurea, who are not adequately controlled on a sulfonylurea alone, or for those patients who have initially responded to rosiglitazone alone and require additional glycemic control. In a 24-week placebo-controlled study, rosiglitazone plus submaximal therapeutic doses of glimepiride, compared to up-titrated glimepiride, significantly reduced HbA1c and FPG. The most commonly reported adverse events in both groups included hypoglycemia, nasopharyngitis, and peripheral edema. The RESULT (Rosiglitazone Early vs. Sulfonylurea Titration) trial was a 2-year randomized, double-blind, active-controlled study, significantly more patients treated with rosiglitazone 4 or 8 mg/day plus glipizide reached a target HbA1c of $< 7\%$ at the last observation in the study compared to those treated with placebo plus up-titrated glipizide. Glycemic control was maintained in patients who received Rosiglitazone plus glipizide over the 2-year treatment period. Edema and hypoglycemia were reported more frequently in patients who received rosiglitazone plus glipizide. In addition, this trial demonstrated that combination therapy of Avandia 4 or 8 mg/day and an SU (glipizide) has potential to reduce health service utilization and cost of care in type 2 diabetes if compared to progressive titration of an SU (glipizide). Avandaryl[®] has a convenient once a day dosing which is believed to improve compliance.

Mark Oley reviewed the Second Generation Sulfonylureas

There has been no significant change in the class over the past year for the single agents. Combination agents were covered later. All of the second-generation sulfonylureas are FDA approved for treatment of Type 2 diabetes mellitus in patients whose hyperglycemia cannot be controlled by diet and exercise alone.

Mark Oley reviewed Alpha-Glucosidase

There are no significant changes in the class over the past year.

Mark Oley reviewed the Biguanide Combination Products

There are no significant changes in the class over the past year. Most products single and combination are now generic. Metaglip[®] is the latest agent to have a first time generic entering the market. There are currently four biguanide combination products available in the United States. All contain metformin - two in combination with a second generation sulfonylurea (glyburide or glipizide) and two in combination with a thiazolidinedione – TZDs (rosiglitazone or Pioglitazone). The combination products with a thiazolidinedione are discussed in the TZDs drug review. Glucovance[®] and Metaglip[®] are indicated for initial and secondary treatment of type 2 diabetes. Metformin works primarily by reducing hepatic glucose production. It also enhances insulin-stimulated glucose transport in muscle. Metformin

is considered a first-line therapy for adults with Type 2 diabetes. FDA approval of metformin contains a black box warning for causing lactic acidosis.

Mark Oley reviewed Meglitinides

There are no significant changes in the class over the past year.

Mark Oley reviewed Thiazolidinediones (TZDs)

Many new studies were released over the past year related to this class and several new combination products were made available. The new combination products include: Takeda Pharmaceuticals released Pioglitazone/metformin (Actoplus Met®) in August 2005 which is available in tablets (15 mg/500 mg, 15 mg/850 mg with dosing once – twice daily) and GlaxoSmithKline released Rosiglitazone/glimepiride (Avandaryl®) in November 2005 (4 mg/1 mg; 4 mg/2 mg; 4 mg/4 mg with dosing once daily). There are currently two thiazolidinediones (TZDs), rosiglitazone and pioglitazone, available in the United States. Both of these agents are available in combination with metformin. Rosiglitazone is also available in combination with glimepiride. The single TZD agents should be considered therapeutic alternatives based on their indications and adverse event profiles. However, a recent study, showed pioglitazone to be superior to rosiglitazone based on its effects on lipid profiles. Both TZDs have an approved FDA indication as an adjunct to diet and exercise to lower blood glucose concentrations in patients with type 2 diabetes mellitus for patients already stable on the agents and doses available in combination or for patients who have had inadequate response with either agent alone.

Both TZDs can be used alone or in combination with metformin, sulfonylureas, or insulin. The issues concerning effects on lipids remain debated in patients with type 2 diabetes mellitus. A recent study reported that TZDs prevent restenosis after coronary artery stenting, thus implying that TZDs may diminish the risk of the development of atherosclerotic disease. The risk-to-benefit ratio of TZDs remains undefined in the population as a whole.

The adverse events of both agents that occur with greater frequency compared to patients treated with placebo are fluid retention and edema. TZDs are not recommended for use in patients with NYHA Class III and IV heart failure. If a TZD is prescribed for a patient with heart failure (NYHA Class II), therapy should be initiated at the lowest possible dose and the patient should be monitored closely for weight gain, edema, or signs and symptoms of congestive heart failure exacerbation. Cases of congestive heart failure have been reported in patients both with and without previously known heart disease. Lactic acidosis is a life-threatening adverse effect of metformin. In January 2006, the manufacturer and the FDA notified health care professionals of reports of new onset and worsening diabetic macular edema for patients receiving rosiglitazone. In the majority of these cases, the patients also reported concurrent peripheral edema. In some cases, the macular edema resolved or improved following discontinuation of therapy and in one case, macular edema resolved after dose reduction. Until further research is accomplished, it should be assumed that both rosiglitazone and pioglitazone might share the possibility for these reported events.

Mr. Oley motioned that the diabetic agents reviewed be PDL eligible.

Mr. Szalwinski seconded the motion.

The Committee voted unanimously to consider all diabetic agents reviewed as PDL eligible.

Mark Oley reviewed Leukotriene Modifiers

Zileuton (Zyflo®) 600mg tablet has returned to the market this year, it is a leukotriene inhibitor. It has no advantage over the leukotriene modifiers. It has to be dosed 4 times a day and has some significant drug-to-drug interactions with propranolol, theophylline and warfarin. The FDA issued a warning letter on November 9, 2005 stating that the MOA sheet is false or misleading in that it presents efficacy claims for Zyflo®, but fails to communicate any risks associated with its use and fails to present the approved

indication. Thus, the MOA sheet misbrands the drug in violation of Sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) & 321(n). The MOA sheet raises public health and safety concerns through its complete omission of risk information for Zylflo by suggesting that Zylflo is safer than has been demonstrated. Zylflo is contraindicated in patients with active liver disease or transaminase elevations greater than or equal to three times the upper limit of normal (>3xULN). The warnings section of the package insert states that Zylflo[®] is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus.

Mr. Oley motioned that the Leukotriene Modifiers agents be PDL eligible.

Mr. Szalwinski seconded the motion.

The Committee voted unanimously to consider Leukotriene Modifiers agents as PDL eligible.

Mark Oley reviewed Non-Steroidal Anti-Inflammatory Drugs (NSAID)

There are no real changes in the class over the past year. Mobic[®] will be going generic within the next year.

Mr. Oley motioned that the NSAIDs be PDL eligible. Mr. Szalwinski seconded the motion.

The Committee voted unanimously to consider NSAIDs as PDL eligible.

Yvette Johnson-Threat, M.D. discussed the Serotonin Receptor Agonist - Relpax[®]

Dr. Johnson-Threat noted that she is not representing a manufacturer. She is here as an internist with a large female population and many of her patients are on Medicaid. One of the common conditions she treats is migraine headaches. She has had great success in treating my patients with Relpax[®]. It is effective with relief often seen within 30-40 minutes after taking a dose. She notes that she has found that patients do not have to take a second dose of the medication because the first dose is effective. This finding is more than anecdotal. The June 2005 *Journal of Managed Care Pharmacy* includes a study in which it compared triptans using the number needed to treat and doses needed to treat as measured endpoints. Relpax[®] had the lowest number of patients that needed to be treated in order to have 100 patients achieve clinical benefit. It also had the lowest doses needed to treat, meaning that patients need to use fewer doses to benefit. In turn, this means that Relpax[®] can be beneficial in terms of cost. Her analysis referenced in the Mullins analysis. Dr. Johnson-Threat asked the Committee to consider the addition of this highly efficacious and cost-effective drug to the formulary so that more patients can gain relief from this debilitating condition.

Russell C. Bowes III, Ph.D., Scientific Affairs Liaison, Ortho-McNeil Janssen Scientific Affairs, LLC discussed the Serotonin Receptor Agonist - Axert[®]

Mr. Bowes reviewed the non-responder data from Oct; 21(10):1603-10. Diener HC, Gendolla A, Gebert I, Beneke M. The focus was to evaluate Almotriptan use in migraine patients who respond poorly to oral sumatriptan. This study was a double-blind, randomized, placebo-controlled study in patients with a history of a previous poor response or no response to sumatriptan 50 mg. The non responders were randomized to receive either placebo or Axert[®] 12.5 mg for attack number two. 47.5% of those taking Axert[®] 12.5 and 23.2 % of those taking placebo experienced pain relief.

He reviewed the efficacy of almotriptan 12.5 mg in achieving migraine-related composite pain free interval as the endpoints.

Mr. Bowes reviewed the findings from Headache. 2005 Jul-Aug; 45(7):874-82. Ferrari M, Roon K, Lipton R et al. This meta-analysis of 53 trials concluded that Oral triptans (serotonin 5-HT_{1B/1D} agonists) are effective in acute migraine treatment. It also concluded that Safety profile of Axert[®], when compared to other triptans (based on this Meta-analysis) showed that Axert[®] is as well tolerated as all of the other serotonin receptor agonists. All of these products were found to be safe and effective

Cost effectiveness data from Lofland and Nash 2005 Citations: from The Lancet 2001; 358:1668-1675. Lofland JH, Nash DB. In this review, they compared the Oral serotonin receptor agonists for cost effectiveness. He noted that according to this review, Axert® and Maxalt® were the most cost effective products.

Mark Oley reviewed Serotonin Receptor Agonists (Triptans)

There are no real changes in the class over the past year.

Mr. Oley motioned that the Serotonin Receptor Agonists be PDL eligible.

Mr. Szalwinski seconded the motion.

The Committee voted unanimously to consider Serotonin Receptor Agonists as PDL eligible.

Mark Oley reviewed Oral Antifungal for Onychomycosis

There are no significant changes in the class over the past year.

Mr. Oley motioned that Oral Antifungal for Onychomycosis be PDL eligible.

Mr. Szalwinski seconded the motion.

The Committee voted unanimously to consider Oral Antifungal for Onychomycosis as PDL eligible.

Eric Zwick, PharmD, MBA Scientific Manager, Managed Care, Procter and Gamble discussed the Bone Ossification Suppression Agent - Actonel® (Risedronate)

Actonel® (35 mg once a week) and Actonel® (5 mg daily) are indicated for the treatment and prevention of osteoporosis in postmenopausal women. Actonel® is also indicated for the treatment and prevention of glucocorticoid-induced osteoporosis. With fracture as the primary outcome, Actonel® is the only agent that has shown full skeletal protection with prospective data showing significant fracture reductions at the spine, hip and non-vertebral sites including clavicle, humerus, wrist, pelvis, hip and leg. Fosamax® has only proven significant data at the spine and hip.

Studies in osteoporotic populations have shown that once patients fracture, 1 in 5 will fracture again within one year. Therefore, an agent is needed that works quickly. Actonel® is the only agent prospectively proven to rapidly reduce radiographic vertebral fractures up to 65% at 1 year. Actonel® has proven fracture reductions as early as 6 months at the spine and composite non-vertebral sites (clavicle, humerus, wrist, hip, pelvis and lower leg).

Actonel® is the only agent who has been prospectively studied using hip fracture as the primary endpoint in greater than 9,000 patients (NEJM). According to the Actonel® Safety Profile, Actonel® was specifically designed to minimize GI side effects associated with bisphosphonates. It was particularly important to Procter & Gamble Pharmaceuticals that Actonel® be evaluated in a group of patients with active GI diseases in phase III trials. Results demonstrated that there were no differences in GI adverse events between Actonel® treated and placebo groups. The FACT trial is a one year head to head study between Fosamax® and Actonel® with the primary endpoint being change in bone mineral density (BMD). The question is why was fracture not a secondary endpoint (fractures were only reported as adverse events) and why did clinical fractures increase in the alendronate group. Recent studies published in *The American Journal of Managed Care* and *The Journal of Managed Care Pharmacy* using a large managed care database looked at head to head comparisons of Actonel® and Fosamax® with regard to early fracture protection and GI events. In this real world research, Actonel® showed rapid 59% non-vertebral fracture protection vs. Fosamax® at one year and 45% less GI events in the first few months of treatment resulting in significant cost reductions.

Christina Israel, PharmD, FCCP, BCPS, Regional Manager, Primary Care Scientific Field Operations for Roche discussed the Bone Ossification Suppression Agent ~ Boniva® (ibandronate sodium)

Ibandronate is approved for the prevention and treatment of osteoporosis in postmenopausal women. The 150 mg once monthly is the first FDA-approved monthly treatment for any disease. Ibandronate has demonstrated efficacy, including robust fracture reduction, Rapid, significant increases in BMD that with continued increases at two years. Professional and regulatory organizations agree that fracture is the relevant endpoint in clinical trials for osteoporosis medications.

MOBILE TRIAL-Monthly Oral Boniva in LadiEs this was a non-inferiority study comparing IBN 150 mg once monthly with the approved dose of 2.5 mg daily. Lumbar spine BMD at 1 year was the primary efficacy endpoint. Methodology mirrored that used by other bisphosphonates (BPs) to obtain FDA approval of their less frequent dosing regimens (i.e. once weekly). At 1 year, IBN 150 mg once monthly produced substantial increases in lumbar spine BMD (4.85%) and proved to be non-inferior to the daily regimen.¹ Furthermore, the monthly regimen produced significantly greater increases in BMD at the lumbar spine, total hip and trochanter than the daily regimen.

IBN once monthly was well tolerated with a safety profile similar to that of 2.5 mg daily. There was no difference in the incidence of upper GI AEs between daily and monthly groups. Lumbar spine BMD continued to increase during the second year; a 6.6% gain over baseline was observed with 150 mg monthly vs. a 5.0% gain with 2.5 mg daily. Two-year data confirmed the efficacy and safety results seen at 1 year.

One of the key challenges in treating osteoporosis, as recognized by the Surgeon General in his report on Bone Health and Osteoporosis is patient adherence to their medications. While the advent of weekly BPs has improved adherence somewhat over that of daily regimens, adherence remains suboptimal. Noting findings from Cramer et al, Current Medical Research and Opinion 2005, the review of women who had been newly prescribed a once weekly or a once daily bisphosphonate, the majority of patients discontinued BP therapy within 1 year.

A longitudinal database study of patients receiving BP prescriptions from retail pharmacies reviewed adequate adherence. Only about 45% of patients receiving weekly medication achieved the adequate adherence threshold. The consequences of poor adherence to osteoporosis therapy are increased fracture and hospitalization rates, and higher medical costs. The Surgeon General's Report on Bone Health and Osteoporosis recommends simplifying osteoporosis treatment regimens as one strategy to improve adherence and recognizes the potential of improved adherence to positively impact clinical outcomes. BALTO I TRIAL, an open label crossover design study, women were randomized to treatment with oral IBN 150 mg once monthly or 70 mg oral weekly alendronate for 12 weeks. Patients then crossed over to treatment with the other study drug for 12 weeks. Patients indicating a preference preferred oral IBN once monthly to oral weekly alendronate. The BALTO study participants who preferred the once-monthly regimen indicated that it would be easier to follow the regimen over the long-term and that this regimen fit their lifestyles better. Simon JA et al, in The Female Patient 2005, a national cross-sectional survey of women's dosing regimen preferences in women receiving weekly bisphosphonate therapy for the treatment of osteoporosis showed that 63% expressed a preference for once monthly over once-weekly therapy.

Ms. Abernathy asked if Boniva was now available in IV form. Dr. Israel replied, yes, Boniva is now available in IV form. Ms. Abernathy asked if the Committee was reviewing both the IV and oral agents. Dr. Axelrod stated that both forms were being considered by the Committee. (*Correction: IV medications are not included on the PDL*)

Mark Oley reviewed the Bisphosphonates for Osteoporosis

There are no significant changes in the class over the past year.

Mr. Oley motioned that the Bisphosphonates for Osteoporosis be PDL eligible.

Mr. Szalwinski seconded the motion.

The Committee voted unanimously to consider Bisphosphonates for Osteoporosis as PDL eligible.

Mark Oley reviewed the Second Generation Cephalosporins

There are no real changes in the class over the past year.

Mr. Oley motioned that the Second Generation Cephalosporins be PDL eligible.

Mr. Szalwinski seconded the motion.

The Committee voted unanimously to consider Second Generation Cephalosporins as PDL eligible.

Mark Oley reviewed the Third Generation Cephalosporins

There are no significant changes in the class over the past year.

Mr. Oley motioned that the Third Generation Cephalosporins be PDL eligible.

Mr. Szalwinski seconded the motion.

The Committee voted unanimously to consider Third Generation Cephalosporins as PDL eligible.

Mark Szalwinski reviewed the Second Generation Quinolones – Systemic

The only real change in the class over the past year is the addition of Proquin XR[®]. It is a new extended release 500 mg tablet of ciprofloxacin hydrochloride, available for oral administration, and approved only for treatment of uncomplicated urinary tract infections (UTIs). The manufacturer, Depomed, has utilized its proprietary Gastric Retention[™] (GR[™]) technology to design Proquin XR[®] for preferential absorption in the upper intestine decreasing the incidence of gastrointestinal adverse events, including nausea and diarrhea. In a randomized, double-blind, Phase III clinical trial of 1,037 patients with uncomplicated UTIs, Proquin XR[®] eradicated the bacteria most commonly responsible for causing UTIs as compared to twice-daily Cipro[®]. Everything else within the class remains the same.

Mr. Szalwinski motioned that the Second Generation Quinolones be PDL eligible.

Mr. Oley seconded the motion.

The Committee voted unanimously to consider the Second Generation Quinolones as PDL eligible.

Dean Drosnes, M.D., Medical Science Specialist for Schering-Plough discussed Third Generation Quinolones - Avelox[®] (moxifloxacin)

Avelox[®] has a new indication for skin and skin structure infections (cSSSI) in adults caused by methicillin-susceptible Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae or Enterobacter cloacae.

It is available IV and PO. It allows a continuation of therapy from hospital to the community.

In recent studies, no participants developed hypoglycemia and hyperglycemia.

Bill Furlough, M.D., Infectious Disease Consultant, for Oscient Pharmaceuticals discussed the Third Generation Quinolone - Factive[®] (gemifloxacin)

Dr. Furlough is an infectious disease consultant in Arlington, Virginia. He speaks for many manufacturers concerning antibacterial agents. Factive[®] is a drug that has been well tolerated and shown to be effective in many at-risk patients including those who could have been hospitalized but were not due to the potency of the drug. It is indicated in Community-Acquired Pneumonia and P.aeruginosa. What distinguishes Factive[®] from other fluoroquinolones is that it has a lower MIC.

One issue in the community is how to compare all of the fluoroquinolones. One way is to compare the area under the curve (AUC) ratios with each other. It has been discovered by physicians that many of the newer quinolones can eliminate the organism with one dose of the product. Once one dose is given and re-culture it is noted that the microorganisms have been eradicated. This drug is very effective with fewer side effects. Dr. Furlough stated that he uses it in high-risk patients.

Patricia Colaizzi Cosler, Pharm.D., Ortho-McNeil Janssen Scientific Affairs, LLC discussed the Third Generation Quinolone - Levofloxacin[®] (levofloxacin)

Levofloxacin, the active enantiomer of ofloxacin is a synthetic, broad-spectrum, bactericidal antimicrobial with an antibacterial spectrum that covers a wide variety of gram-positive, gram-negative, and atypical pathogens. The plasma concentration and extent of exposure (AUC) after equal-dose oral or intravenous administration are similar. It has been available in Japan and South Korea since 1993 and in the US since December 1996, with more than 300 million patients treated worldwide. Levofloxacin is approved for eleven indications in the U.S.

Levofloxacin is the first fluoroquinolone approved for multi-drug resistant *S. pneumoniae* (MDRSP) and a short duration regimen of 5 days for the treatment of community-acquired pneumonia (CAP).

Levofloxacin was the first fluoroquinolone indicated for typical and atypical pathogens commonly associated with CAP. Recent indications include: Short-course 750 mg once daily for 5 days in acute bacterial sinusitis (ABS); Short-course 750 mg once daily for 5 days in CAP increases compliances CAP due to MDRSP; and Inhalation Anthrax (post exposure).

Potential benefits of short-course, high dose therapy with levofloxacin 750 mg include cost-savings that result from more rapid IV-to-PO switching and thus potentially reduced length of hospital stay. The incidence of drug-related adverse reactions in patients during Phase 3 clinical trials conducted in North America was very low. There have been no issues with hypoglycemia seen with levofloxacin.

Seventy-five percent of the hospitals in Virginia have levofloxacin on their formulary. This is a good agent for continuation of care.

Mark Szalwinski reviewed Third Generation Quinolones

The speakers have covered the changes in this drug class over the past year already. Avelox[®] has a new indication. The other issue is the FDA watch, which was issued for gatifloxacin (Tequin[®]), with warnings on February 15, 2006. Bristol Myers Squibb (BMS) issued a Dear Healthcare Professional (DHCP) letter to U.S. physicians announcing an update to the U.S. labeling for Tequin[®] (gatifloxacin) tablets and injection. The update includes labeling changes to strengthen the existing WARNING on hypoglycemia and hyperglycemia and adds a contraindication for use in diabetic patients. Serious reports of hypoglycemia and hyperglycemia continue to occur in patients both with and without a history of diabetes. These events can occur throughout the course of Tequin therapy. The labeling has also been updated to identify other risk factors for developing hypoglycemia and hyperglycemia, (i.e., older age, abnormal kidney function, and other blood glucose altering medications being used at the same time) while taking Tequin (gatifloxacin), and includes a recommendation for close medical monitoring.

Mr. Szalwinski motioned that the Third Generation Quinolones be PDL eligible. Mr. Oley seconded the motion.

The Committee voted unanimously to consider Third Generation Quinolones as PDL eligible.

Mark Szalwinski reviewed Macrolides

There are no significant changes in the class over the past year.

Mr. Szalwinski motioned that the Macrolides be PDL eligible. Mr. Oley seconded the motion.

The Committee voted unanimously to consider Macrolides as PDL eligible.

Cathy Kittrell, PA-C, Medical Science Liaison for McNeil Specialty Pharmaceuticals discussed the Antihyperkinesia Agent - Concerta[®]

An estimated 4 million patients were diagnosed with attention deficit hyperactivity disorder (ADHD) in the United States in 2002. The diagnosis of ADHD is typically made using criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). The DSM-IV contains very specific guidelines for determining ADHD. The behaviors must appear early in life and continue for at least 6 months. In children, the behaviors must be more severe and occur more frequently than in peers of the same age. Above all, the behaviors must create a real handicap in at least two areas of a person's life, such as school, home, work, or social settings.

With the development of a medication called OROS[®] MPH Concerta[®], patients with ADHD have a useful alternative to older stimulant medications. Concerta[®] is unique compared to other ADHD medications, as it offers 12-hour control of symptoms. The product's innovative OROS[®] technology helps distinguish itself from other extended-release psychostimulants by delivering MPH in a continuously ascending profile throughout the day, without increased risk for side effects, food effects, or concern over operating machinery or vehicles. This advanced system was designed to help a child maintain focus without in-school and after-school dosing. Additionally, the once-daily dosing of Concerta[®] can improve adherence and decrease the potential for mid-day wear-off effects or rebound because the controlled drug release results in lasting clinical efficacy through 12 hours.

The safety and efficacy of Concerta[®] for the treatment of ADHD is well established. Concerta[®] was also shown to significantly improve driving performance of adolescent boys with ADHD by minimizing driving errors (Cox 2004a; Cox 2004b; Cox 2005). The American Academy of Child and Adolescent Psychiatry's Practice Parameter for the Use of Stimulant Medications in the Treatment of Children, Adolescents, and Adults identifies Concerta[®] as being less prone to abuse and diversion than IR MPH tablets. Since the medication is administered once a day in the morning and does not necessitate the need for multiple doses during the day, it could not be easily given away or sold. Additionally, MPH is difficult to extract if the tablet is crushed. The osmotically released, timed drug-delivery system of Concerta[®] produces an ascending drug plasma profile that provides effective clinical efficacy throughout 12 hours with once-a-day administration. This distinct method of drug delivery for the treatment of patients with ADHD warrants evaluation of this drug for formulary placement by any organization's Pharmacy and Therapeutics Committee.

Andrine R. Swensen, MS, PhD, Outcomes Liaison Consultant for Eli Lilly and Company discussed the Antihyperkinesia Agent - Strattera[®]

Strattera[®] is a non-stimulant, non-controlled ADHD medication for children, adolescents, and adults. Strattera[®] offers continuous efficacy and has been proven effective in both hyperactive/impulsive and inattentive symptoms of ADHD. Strattera[®] has a proven safety and tolerability profile in children, adolescents, and adults. Strattera[®] has no appreciable abuse potential. Study data showed no pattern of diversion. Consequently, Strattera[®] can be prescribed without the specific concerns and inconveniences associated with Schedule II stimulants. The lack of abuse potential makes Strattera[®] an ideal ADHD treatment in patients with a history of substance abuse.

Strattera[®] can be prescribed safely in patients with comorbid Tourette's syndrome, chronic motor tic or anxiety disorders. Strattera[®] has also been studied in pediatric patients with ADHD and comorbid depression and in patients with comorbid anxiety; Strattera[®] appeared to be safe and effective in treating ADHD in these populations.

Pooled analyses of short-term placebo-controlled trials of Strattera[®] in children and adolescents revealed a greater risk of suicidal ideation early during treatment in those receiving Strattera[®] [0.4% (5/1357 patients)]. There have been two reported cases of markedly elevated hepatic enzymes and bilirubin, in the

absence of other obvious explanatory factors, out of more than two million patients during the first two years of post- marketing experience.

Mark Szalwinski reviewed Antihyperkinesis/CNS Stimulants

The drugs in class are comparable. There is a lot of press concerning this class. Atomoxetine (Strattera[®]) revised their labeling to include a boxed warning and additional warning statements regarding an increased risk of suicidal thinking in children and adolescents being treated with this drug. This was seen during the trial but not in post marketing data, which is very important to remember.

The rest of the products in the classes have had their issues, which have mostly been covered. Adderall XR[®], a new indication from Shire Pharmaceuticals Group, announced today that the US Food and Drug Administration (FDA) have approved this drug as a once-daily treatment for adolescents aged 13 to 17 ADHD. Since October 2001, Adderall XR has been approved in the U.S. for treatment in children aged 6 to 12 years and since August 2004 in adults 18 years and older. Focalin XR, an extended release version of Dexamethylphenidate (Focalin), is now available. With Concerta[®] and related products, the FDA has reported two possible safety concerns with the methylphenidate drug products. They are psychiatric adverse events (visual hallucinations, suicidal ideation, psychotic behavior, as well as aggression or violent behavior) and cardiovascular adverse events (chest pain). These concerns were generated from the analysis of post marketing reports. The present labeling warns that some of these conditions could be contraindicated with these products, but does not list the medications as a causative factor. The FDA expects to conclude the gathering of data and submitting this to the appropriate Committee in early 2006. Labeling changes are expected to result from this review. This has created a large number of comments. The FDA stated that they intend to review other stimulant products approved for ADHD including amphetamine products and atomoxetine.

Mr. Szalwinski motioned that the Antihyperkinesis/CNS Stimulants be PDL eligible. Mr. Oley seconded the motion. The Committee voted unanimously to consider Antihyperkinesis/CNS Stimulants as PDL eligible.

Long Acting Narcotics

Dr. Axelrod noted the previous Committee discussions regarding the long acting narcotics class, its criteria and the related edits. When reviewing this class previously, Dr. Beveridge provided a lot of information related to narcotics in the treatment of oncology patients. In addition, both Mark Oley and Mark Szalwinski have provided information on the guidelines for long acting narcotics from the Board of Pharmacy. Dr. Axelrod stated that the Committee needed to review what has happened with the class since it was implemented on the PDL and the status. Some of the guidelines for this PDL class are working well but some need the Committee's input and refinement. Dr. Axelrod noted that many states have innovative approaches to controlling the use of narcotics, such as registering all narcotics prescriptions using a physician-specific, secured numbered pad in New York State.

Mark Oley commented that the Board of Pharmacy is now requiring reporting from each pharmacy every fifteen days on the utilization of all controlled substances (schedules II, III and IV). This was implemented with in the past 30s day throughout the Commonwealth of Virginia. This information will be used to identify issues with habitual abuse across all pharmacies. This information is reported by the pharmacists processing these prescriptions. Dr. Sue Cantrell noted that the new Board of Pharmacy initiative would help with cases in Southwest Virginia where patients are "doctor-shopping" in border states and having the prescriptions filled in Virginia. Dr. Cantrell states that in Southwest Virginia there has been a shift from the abuse of Oxycontin to other narcotics.

Mr. Finnerty provided an update with respect to the current management of the long acting narcotics drug class. Mr. Finnerty stated that he would like to bring two issues to the attention of the Committee for discussion related to this class: 1) clarification of the intent of the Committee on the expiration date of the “Automatic Prior Authorizations” (APA) and 2) ensuring that the dispensing of narcotics is controlled as it related to the use of default prescriber identification numbers.

In meetings prior to the implementation of the long acting narcotics drug class, the Committee recommended that initially recipients who were stabilized on these medications and/or had certain diagnoses (i.e., oncology) be exempt from prior authorization requirements for these drugs; however, the specific length of time for this exemption was not established. The Department is concerned that this may not have been implemented as the Committee intended. Currently, no expiration date is set.

With the implementation of long acting narcotics on the PDL in January 2005, more than 7,000 “automatic” prior authorizations were granted to recipients who were stabilized on these drugs and/or had certain diagnoses. The “automatic” prior authorization allows an override of both the clinical and PDL requirements; therefore, providing full access to these medications at the physician’s request without clinical review.

New claims for long acting narcotics require the attempt of two short acting narcotics (within 6 calendar months prior to the claim) unless required for specific diagnoses. There are potentially two prior authorizations required for new claims – a clinical prior authorization (requiring two short acting narcotics) and the PDL prior authorization for non-preferred drug. All new prior authorizations have a duration of one year similar to other PDL classes.

Approximately 395 recipients are still producing claims for long acting narcotics claims under the automatic prior authorization based on data from February 2006. An analysis of these claims shows that at least 50 of these recipients have a oncology-related diagnosis. Further review will be needed to confirm all diagnoses among this group.

Mr. Finnerty stated that the Department also found that approximately 12% of these prescriptions (long acting narcotics APA) were filled (83 recipients of the remaining 395) was using default prescriber identification numbers by the pharmacy providers. The default prescriber ID is a number allowed by the Department, in limited instances, when the prescribing provider identification number is not available or one is not established. By using this number, the prescriber associated with the claim is unidentifiable.

DMAS noted that of particular concern are default prescriber identification numbers being used by pharmacy providers with prescriptions for controlled substances. In calendar year 2005, 17% (271,000) of all claims for controlled substances were processed using default prescriber identification numbers.

DMAS clarified that Virginia Medicaid utilizes a Medicaid-assigned identification number rather than the DEA number. The DEA number is only available on the written prescription; it is not captured on the DMAS adjudication system.

DMAS did have a broader issue with default prescriber ID numbers some time ago. With the assistance of the Virginia Pharmacists Association, on two different occasions (the most recent was February 15, 2006) there were major initiatives to reduce the use of default prescriber ID numbers. Prior to the implementation of the PDL default prescriber identification utilization was 20%-30% of all pharmacy claims. The utilization decreased with previous DMAS initiatives; however, they have eventually increased each time.

Dr. Axelrod and Mark Oley asked if there was any particular pattern among the use of the default prescriber ID number. The response was that this number is being used among various types of pharmacy providers, i.e., retail, long term care, etc.

Dr. Axelrod asked if the default prescriber ID number was a DMAS problem, a general pharmacy problem or both. Mark Oley replied the pharmacies are simply using the default ID number to process claims as quickly as possible. Dr. Axelrod asked if that was the right approach. Mark Oley replied, no, the numbers should be accessible so that the pharmacy provider may use them appropriately. DMAS clarified the Medicaid identification numbers are easily accessible via their web site, by requesting a compact disc with the information, or calling the First Health Services Clinical Call Center.

Mark Oley asked that DMAS research further the pharmacy locations and types that are utilizing the default prescriber ID numbers most to target those who abuse it. Dr. Axelrod questioned the feasibility of applying fines for those who habitually use the default prescriber ID numbers.

Mark Oley and Mark Szalwinski suggested that in many cases the default prescriber ID number are not being used illegitimately; however, they are used in claims processing for payment in manner that is noncompliant with DMAS' data requirements. Mark Szalwinski suggested if these numbers were not allowed it would force the pharmacy providers to use the correct numbers. This may create administrative/ customer service issues; however, it would address the multiple issues.

Mr. Finnerty suggested that DMAS staff collect additional information on this topic and discuss with members of the Committee and possibly Scottie Russell (Board of Pharmacy) and the Virginia Pharmacists Association to address the issues with the default prescriber ID numbers.

Mark Oley suggested that this was more of an administrative problem than a legal problem because the DEA number should be available on the actual written prescription. The Committee stated that it would be good to talk to the offending pharmacies to identify in what instances these default numbers are being used.

Dr. Garson stated that this was a major issue that does need to be addressed.

Gill Abernathy asked about the process is for medical residents. DMAS staff stated that this process was recently changed. Previously, there was just one default number for all residents throughout the State and now residents' prescriber ID numbers are tied to the facility to which they are affiliated.

Mark Szalwinski suggested that DMAS use DEA numbers rather than Medicaid-specific identification numbers. Mr. Finnerty replied that with the impending implementation of the National Provider Identification (NPI) number in May 2007 it would not be feasible to address the use of the DEA number. The implementation of the NPI should address many of these issues.

Dr. Axelrod summarized that the Committee would like more information from DMAS on the specifics of the use of the default prescriber ID numbers, particularly as it relates to narcotics. Dr. Axelrod asked that DMAS address these issues internally to the extent possible with available mechanisms.

Dr. Axelrod asked the Committee if they would like to address the remaining recipients who do not have an oncology diagnosis but continue to have the lifetime prior authorization available for long acting narcotics. Mr. Finnerty stated that the Department's recommendation was to terminate the lifetime prior authorizations for long acting narcotics on June 30, 2006 and have those recipients apply for new prior authorizations. Mr. Finnerty also asked that the Committee consider an authorization length of no longer than six months rather than one year as these are controlled substances.

Dr. Axelrod asked for the Committee's thoughts on terminating the lifetime PAs and modifying the PA length to six months. Mark Szalwinski asked if the prior authorization was attached to the patient and not the prescription. It is attached is to a patient with new prior authorization requests. The recommendation includes having those with the lifetime prior authorization to follow the same guidelines as the new PAs.

Dr. Beveridge stated that all patients with a lifetime PA, even those with oncology diagnoses, should be required to get a new prior authorization. Mark Oley asked how long it takes to process a prior authorization. DMAS stated that prior authorization requests are processed within minutes (less than 3 minutes) by the First Health Clinical Call Center by a physician or his/her staff.

A motion was made to eliminate the lifetime prior authorization for LAN and provide notification of the change. The motion was seconded. The Committee voted unanimously to eliminate the lifetime APA for LAN.

Mark Szalwinski stated that this would make the management of the long acting narcotics class similar to the other PDL classes.

A motion was made to change the length of the PA for LAN from one year to six months. The motion was seconded. The Committee voted unanimously to change the length of the PA for LAN from a year to six months.

Mark Szalwinski reviewed Long Acting Narcotics

FDA is investigating reports of death and other serious side effects from overdoses of fentanyl in patients using fentanyl transdermal (skin) patches for pain control. Deaths and overdoses have occurred in patients using both the brand name product, Duragesic[®] and the generic product. The FDA issued a public health advisory to alert patients and their caregivers and health care professionals of the potential hazards. In June 2005, the Duragesic[®] product label was updated to add new safety information in several areas of labeling, and a "Dear Healthcare Professional" letter about these changes was issued by the manufacturer.

On June 7, 2005, a Federal Appeals court ruled that Purdue Pharma had deliberately misled the government to win patent protection for its powerful painkiller OxyContin[®], invalidating its existing patents. This ruling has opened the door for generic manufacturers to produce generic formulations of all strengths of OxyContin[®].

All long-acting opiate categories are available in a generic formulation. Kadian[®] and Avinza[®] are two long-acting opiates not currently available generically.

Hydromorphone Extended Release (Palladone[®]) was removed from the market in July 2005 because of potential for severe side effects if taken with alcohol.

In October 2005, the FDA strengthened the warning that patients should not consume alcohol while taking Avinza[®]. Additionally, patients must not use prescription or non-prescription medications containing alcohol while on Avinza[®] therapy.

REVIEW OF NEW DRUG CLASSES FOR PDL ELIGIBILITY

Herpes Antivirals

Dr. Peter Wilbanks, OB/GYN, Virginia Women's Center/ GlaxoSmithKline discussed the Herpes Antiviral Agent - Valtrex[®]

Herpes has become very come one in four people in the US are infected. This is today the 2nd most prevalent sexually transmitted disease in the United states. The target of this group of people is to help

identify that they have the disease and identify how to reduce outbreaks and reduce spreading the disease.

Valtrex[®] is indicated for the episodic and suppressive treatment of recurrent genital herpes, the reduction in the risk of transmission of genital herpes in heterosexual adults when used as suppressive therapy in combination with safer sex practices, the treatment of initial genital herpes, the treatment of herpes zoster, and the treatment of cold sores in immunocompetent adults. Valtrex[®] is also indicated for the suppression of genital herpes in HIV-infected patients. It is the only product shown to stop the spread of the disease. Safe sex with condoms does not stop the spread of the disease.

Paula Pearson, Pharm. D, Regional Medical Scientist for GlaxoSmithKline discussed the Herpes Antiviral Agent - Valtrex[®]

Valtrex[®] (valacyclovir hydrochloride) is the hydrochloride salt of the L-valyl ester antiviral drug acyclovir. The addition of L-valyl ester to acyclovir results in 3-5 times higher bioavailability with Valtrex[®] than with acyclovir. Due to this improved bioavailability, Valtrex[®] provides higher antiviral serum concentrations and less frequent dosing than acyclovir. Valtrex[®] is indicated for the episodic and suppressive treatment of recurrent genital herpes, the reduction in the risk of transmission of genital herpes in heterosexual adults when used as suppressive therapy in combination with safer sex practices, the treatment of initial genital herpes, the treatment of herpes zoster, and the treatment of cold sores in immunocompetent adults. Valtrex[®] is approved for the treatment of first episode genital herpes at a dose of 1 g BID for 10 days. In a large, randomized, double-blind clinical trial, Valtrex[®] 1 g BID for 10 days and acyclovir 200 mg five times daily for 10 days were equally effective in reducing the duration of viral shedding, time to complete cessation of pain and promoting the complete healing of lesions in patients with initial genital herpes infections. Valtrex[®] is the only oral antiviral approved for the treatment of recurrent episodes of genital herpes with a three-day treatment regimen (500 mg BID for three days). A randomized, double-blind, multicenter trial showed that three and five-day courses of therapy with Valtrex[®] 500 mg BID for the episodic treatment of genital herpes infections are equivalent in terms of median time to lesion healing, median duration of pain, median length of episode and proportion of patients with aborted (non-progressing) lesions.

Valtrex[®] is the only antiviral approved for the reduction in the risk of heterosexual transmission of genital herpes in immunocompetent adults when used as suppressive therapy in combination with safer sex practices. Valtrex[®] has a favorable safety profile for all indications. In immunocompetent adults, side effects with Valtrex include nausea, headache, vomiting, abdominal pain, and dizziness. For HIV-infected patients receiving suppressive therapy with Valtrex[®], side effects included headache, fatigue and rash.

Mark Szalwinski reviewed the Herpes Antiviral Agents

There are currently three antiherpes agents available in the United States as indicated above. All three agents are recommended by the CDC for the treatment of genital herpes simplex infections (acute and suppressive therapy). Acyclovir is effective in treating initial or recurrent herpes simplex virus, herpes zoster, and varicella zoster virus infections. While prophylaxis of herpes-type infections and cytomegalovirus (CMV) infections in immunocompromised patients has been effective, only marginal responsiveness is documented in the treatment of CMV disease with acyclovir. Epstein-Barr virus is not sensitive to acyclovir and clinical infections do not respond to acyclovir.

Valacyclovir is rapidly converted to acyclovir following oral administration. Its significantly greater oral bioavailability results in plasma acyclovir levels comparable to those seen with intravenous acyclovir. In addition, fewer daily doses are required with valacyclovir. Valacyclovir may be of particular interest in the prevention of opportunistic cytomegalovirus (CMV) disease. Among bone marrow transplant patients, recipients of renal allografts, and patients with advanced HIV disease, intravenous acyclovir (500 mg/m² 3 times a day) has been effective in reducing the rate of CMV infection. With the serum

acyclovir concentrations achievable with oral valacyclovir, the need for intravenous therapy may be minimized, and fewer oral doses may be required.

Famciclovir is a prodrug of penciclovir. Penciclovir has shown potent antiviral activity against herpes simplex types 1 and 2 and varicella-zoster virus. However, its oral bioavailability is low, about 1.5% in animal studies. Esters of 6-deoxypenciclovir were investigated related to enhanced absorption of the active drug. Famciclovir was chosen for oral delivery of penciclovir due primarily to its stability in human duodenal contents—penciclovir has been shown to be well-absorbed when given as famciclovir, with famciclovir being converted to penciclovir in intestinal and liver tissues.

Acyclovir and famciclovir have comparable efficacy for treatment of recurrent herpes simplex infections in HIV-infected patients. When administered within 72 hours of first vesicle formation, famciclovir and acyclovir provided similar efficacy in the treatment of localized herpes zoster in immunocompromised patients. Famciclovir provided similar efficacy to acyclovir in the treatment of ophthalmic herpes zoster. Valacyclovir hydrochloride 1 gram 3 times daily for 1 week and famciclovir 500 mg 3 times daily for 1 week were equally safe and efficacious in treating herpes zoster in patients over 50 years of age who presented within 72 hours of rash onset. Oral valacyclovir prophylaxis significantly increased time to development of cytomegalovirus (CMV) viremia in seropositive heart transplant patients to 119 days (n=14) versus 19 days with acyclovir (n=13) in double-blind randomized trials. A randomized trial in patients with first episodes of genital herpes found valacyclovir to be as effective as acyclovir. Another trial found famciclovir to be comparable to acyclovir; in addition, valacyclovir and famciclovir require less frequent dosing. Comparative studies of valacyclovir or famciclovir with acyclovir have been conducted. The results of these studies suggest that valacyclovir and famciclovir are comparable to acyclovir in clinical outcome. Adverse Events Contraindications, warnings, adverse drug events, and drug interactions are similar for all antiherpes virus agents and are considered class effects. Most adverse events associated with these agents are mild. The most common adverse effects are headache, dizziness, and nausea. It is a Pregnancy Category B

Mark Szalwinski reviewed the Influenza Antiviral Agents

There are currently four influenza antiviral agents available in the United States. They are divided into two categories, adamantanes (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir). Amantadine, rimantadine, and oseltamivir are administered orally. Amantadine and rimantadine are available in tablet and syrup formulations, and oseltamivir is available in capsule and oral suspension formulations. Zanamivir is available as a dry powder inhalation. Amantadine oral dosage formulations and rimantadine tablets are available generically.

All four agents are FDA approved for the treatment of influenza in adults. Amantadine and oseltamivir are approved for the treatment of influenza in children ages one year and older; zanamivir is approved for the treatment of influenza in children ages seven years and older. Although rimantadine is not FDA approved for treatment of influenza in pediatric patients, it is used off-label in children. Amantadine, rimantadine and oseltamivir are FDA approved for influenza prophylaxis in both adults and children. Zanamivir is not FDA approved for influenza prophylaxis. Amantadine and rimantadine are chemically related antiviral drugs with activity against influenza A viruses. They block the uncoating of influenza A virus preventing penetration of virus into host. Neuraminidase inhibitors exert activity against both influenza A and B. Influenza virus neuraminidase is inhibited by altering virus particle aggregation and release.

Hypersensitivity to any of these products is a contraindication to their use. The most common adverse events of the antivirals are gastrointestinal (GI) and central nervous system (CNS) related. Although both adamantanes can cause these side effects, the incidence is higher with Amantadine. GI side effects include nausea, vomiting, diarrhea, and anorexia. CNS side effects include dizziness, insomnia, lightheadedness, nervousness, and anxiety. Both neuraminidase inhibitors also cause GI side effects

including nausea, vomiting, and diarrhea. Food may improve tolerability with oseltamivir. Zanamivir has been shown to cause bronchospasms. Therefore, it is not recommended for use in patients with underlying airway disease such as asthma and COPD. If zanamivir is used in this population, a fast-acting bronchodilator must be available. Should bronchospasm or decline in respiratory function develop, zanamivir should be discontinued. Zanamivir powder contains lactose; therefore, appropriate precautions should be taken in patients with lactose intolerance.

Dosage recommendations vary by age groups. Amantadine, rimantadine, and oseltamivir should be dose adjusted for renal impairment. Rimantadine should be dose adjusted for severe hepatic impairment. All four agents are in pregnancy category C.

The major distinguishing factor among the agents is their antiviral activity. The activity of adamantanes is limited to influenza A whereas the neuraminidase inhibitors have activity against both influenza A and B. This is very important if known influenza B strains are circulating within the community. During outbreaks of influenza B, neuraminidase inhibitors are treatments of choice over the adamantanes. All of these agents appear to be equally efficacious against influenza A, although neuraminidase inhibitors have not been directly compared with the adamantanes. Although most clinical studies related to these agents have been in young, healthy populations, there have been studies among nursing home populations as a component of influenza outbreak-control programs aimed at limiting the spread of influenza within chronic care institutions. Data is very limited on the efficacy or effectiveness of any of the antiviral drugs in preventing complications from influenza in high-risk populations or in preventing influenza among severely immunocompromised persons.

For any of these agents to be effective, they MUST be initiated within 48 hours of onset of influenza symptoms. This can be a drawback if patients do not seek proper medical care in a timely fashion or the illness is left undiagnosed at onset. These agents only reduce duration of illness by approximately one day and may also reduce severity of some symptoms. Tolerability of these agents can be difficult to assess since GI and CNS side effects encountered, can also be signs and symptoms of influenza. Drug resistance can develop with the adamantanes; therefore, their duration of therapy should be as short as possible. Duration of therapy for the neuraminidase inhibitors is five days.

Historically, influenza has caused global pandemics leading to severe illness, complications, and death. Influenza, or the “flu”, that is commonly experienced, is the seasonal flu. The Centers for Disease Control (CDC) defines this condition as “a contagious respiratory illness caused by influenza viruses”. The primary goal of therapy associated with influenza is prevention. Influenza vaccination is first line therapy in preventing the flu. The role of the antiviral drugs is as adjunctive therapy to vaccination.

COMMENTS FROM OFFICE OF THE ATTORNEY GENERAL

Ms. Reatha Kay from the Attorney General’s office stated that under the Virginia Freedom of Information Act (FOIA), specifically Virginia Code section 2.2-3711, a public body such as the P&T Committee, may go into a closed session for any of the 33 reasons listed in that statute. The discussion of manufacturer and wholesaler prices is not one of the 33 reasons listed.

She stated the Attorney General strongly supports the principles of open government embodied by the FOIA and believes in the opportunity of the Commonwealth’s citizens to witness the operation of government to the fullest extent.

Federal Law 42 U.S.C. 1396r-8(b)(3)(D) requires such pricing information to be kept confidential. On this point, federal law supersedes the Virginia FOIA. Since the P&T Committee must discuss this pricing information as part of its duties, pursuant to federal law a confidential meeting must occur for the consideration of this pricing information she cautioned only this confidential information should be discussed.

Mark Szalwinski made a motion for the P&T Committee to resume the meeting in another room to discuss this confidential information regarding prices charged by the manufacturers and wholesalers of the drug classes discussed at this P&T Committee meeting. This confidential meeting is authorized by Federal Law at 42 U.S.C. § 1396r-8(b) (3) (D) that requires this information to be kept confidential.

This motion was seconded and unanimously approved by the Committee.

The meeting adjourned to an executive session.

The Committee returned to the room, a motion was made to resume the meeting.

The motion was seconded and unanimously approved by the Committee.

Mr. Szalwinski noted that Dr. Axelrod would not return for the remainder of the meeting.

He asked for a motion for preferred products in the new drug classes.

Mark Oley motioned that based on a review of new drug classes the preferred Herpes Antivirals are:

ACYCLOVIR TABLET
VALTREX
ACYCLOVIR SUSP
FAMVIR

A motion was made to accept the products as read by Mark Oley.
This motion was seconded and unanimously approved by the Committee.

Mark Oley motioned that based on a review of new drug classes the preferred Ophthalmic Antihistamines are:

ZADITOR
PATANOL
ELESTAT
OPTIVAR

A motion was made to accept the products as read by Mark Oley.
This motion was seconded and unanimously approved by the Committee.

Mark Oley motioned that based on a review of new drug classes the preferred Ophthalmic Quinolones are:

VIGAMOX
OFLOXACIN DROPS
CIPROFLOXACIN HCL DROPS
ZYMAR
QUIXIN

A motion was made to accept the products as read by Mark Oley.
This motion was seconded and unanimously approved by the Committee.

Mark Oley motioned that based on a review of new drug classes the preferred Ophthalmic Anti-Inflammatory Agents are:

FLURBIPROFEN SODIUM

VOLTAREN DROPS
ACULAR
ACULAR LS
NEVANAC
XIBROM

A motion was made to accept the products as read by Mark Oley.
This motion was seconded and unanimously approved by the Committee.

Mark Oley motioned that based on a review of new drug classes the preferred Influenza Antiviral Agents are:

AMANTADINE HCL SYRUP
RIMANTADINE HCL
AMANTADINE HCL CAPSULE
RELENZA
TAMIFLU SUSP
TAMIFLU CAPSULE

A motion was made to accept the products as read by Mark Oley.
This motion was seconded and unanimously approved by the Committee.

Mark Oley motioned that based on a review of new drug classes the preferred Ophthalmic Mast Cell Stabilizers are:

CROMOLYN SODIUM OPHTHALMIC
ALOCRIL
ALOMIDE
ALAMAST

A motion was made to accept the products as read by Mark Oley.
This motion was seconded and unanimously approved by the Committee.

Mark Oley motioned that based on the annual review for Phase II, no changes will be made to the preferred status of drugs in the following classes:

BONE OSSIFICATION SUPPRESSION AGENTS
ANTIHYPERKINESIS
THIRD GENERATION CEPHALOSPORINS
CARBONIC ANHYDRASE INHIBITORS-GLAUCOMA
LEUKOTRIENE MODIFIERS
MEGLITINIDES- ORAL ANTIDIABETICS
ALPHA-GLUCOSIDASE INHIBITORS-ORAL ANTIDIABETIC
THIAZOLIDINEDIONES-ORAL AND COMBINATION ANTIDIABETIC
PROSTAGLANDIN AGONISTS-OPHTHALMIC
QUINOLONES -SYSTEMIC
MACROLIDES-PEDIATRICS
MACROLIDES –ADULT
ANALGESIC – NSAIDS
NARCOTICS: LONG ACTING
BETA BLOCKERS- GLAUCOMA
ALPHA-2 ADRENERGIC AGENTS- GLAUCOMA
SEROTONIN RECEPTOR AGONISTS
ONYCHOMYCOSIS ANTIFUNGALS
SECOND GENERATION CEPHALOSPORINS

A motion was made to accept the products as read by Mark Oley.
This motion was seconded and unanimously approved by the Committee.

Mark Oley motioned that based on the annual review for Phase II, the preferred Second Generation Sulfonylureas are:

GLIPIZIDE
GLYBURIDE
GLYBURIDE MICRONIZED
GLIPIZIDE ER
GLIMEPIRIDE

A motion was made to accept the products as read by Mark Oley.
This motion was seconded and unanimously approved by the Committee.

Mark Oley motioned that based on the annual review for Phase II, the preferred Thiazolidinedione-Metformin Combination Agents are:

AVANDAMET
ACTOPLUS MET

A motion was made to accept the products as read by Mark Oley.
This motion was seconded and unanimously approved by the Committee.

Mark Oley motioned that based on the annual review for Phase II, the preferred Hypoglycemics, Biguanide Type Agents are:

METFORMIN
METFORMIN ER
GLIPIZIDE/METFORMIN
GLYBURIDE/METFORMIN

A motion was made to accept the products as read by Mark Oley.
This motion was seconded and unanimously approved by the Committee.

Mark Oley motioned that based on the new drug reviewed from the Beta Adrenergic class (PDL Phase I), XOPENEX HFA was recommended as a preferred product.

A motion was made to accept the products as read by Mark Oley.
This motion was seconded and unanimously approved by the Committee.

CRITERIA DISCUSSIONS FOR PHASE II PDL DRUG CLASSES

The Committee reviewed the current criteria for drugs in PDL Phase II during the discussion on LAN, at that time one change to the LAN criteria was approved.

The next meeting of the P&T Committee will be scheduled for early June 2006.

The meeting was adjourned.