Mississippi Division of Medicaid
Drug Utilization Review (DUR) Board
Minutes of the November 15, 2007 Meeting

Members Attending: Billy Brown, PharmD.; Randy Calvert, R.Ph., Laura Gray, M.D.; Frank Marascalco, R.Ph., Chair; Andrea Phillips, M.D.; Lee Voulters, M.D.; Wallace Strickland

Members Absent: Roy Arnold, R.Ph.; Harold Blakely, R.Ph.; John Wallace, M.D.

Also Present:
DOM Staff: Judith Clark, R.Ph., DOM Pharmacy Bureau Director; Paige Clayton, PharmD, DOM DUR Coordinator; Carlis Faler, DOM Program Integrity Director

HID Staff: Dennis Smith, R.Ph., Project Manager; Ashleigh Holeman, PharmD; Kathleen Burns, R.N.

Call to Order:
Frank Marascalco, Chairman of the Board, called the meeting to order at 2:10 p.m.

Dr. Clayton asked that the Board proceed with business not requiring a vote while awaiting arrival of enough members to constitute a quorum.

Updates:
Cost Management Analysis
Mr. Smith began by presenting reports reflecting several months of data. Antipsychotic agents continued to lead the top 15 therapeutic classes by total cost of claims throughout the five month period reported. The top drugs based on number of claims were led by hydrocodone-acetaminophen and followed by Zyrtec. Dr. Holeman added that the top 200 national ranking for each drug has been added to the report for reference. This report also designates by an asterisk those products classified as preferred on the preferred drug list. These additions were made to facilitate the understanding of the number of claims for these top medications. The top drugs based on total claims cost were led by Singulair® in April 2007. At this time, Mr. Smith and Dr. Holeman reviewed the findings of the analysis of Singulair® utilization that was presented during the previous DUR Board meeting. Of 4,500 patients not having a diagnosis of either asthma or allergic rhinitis, the majority were found to have had a non-specific upper respiratory diagnosis. The report further found that from May 2006 to May 2007, approximately 62 percent of patients receiving Singulair® had an asthma diagnosis, while approximately 65 percent of patients who received Singulair® had an allergic rhinitis diagnosis. According to this information, there did not appear to be gross over utilization of Singulair®. The Board agreed with these findings. Dr. Holeman continued with the top 25 drugs based on total claims cost by pointing out the remaining four months was led by Risperdal®.

Old Business:

Due to the lack of a quorum at the September 20, 2007 meeting, Mr. Smith briefly summarized several reports that were presented during the meeting.

Potential Misuse of ADHD Agents

The first of these reports was a review of the utilization of stimulants indicated for the treatment of ADHD. Although the study findings did not indicate extensive over-prescription of these agents among adults, a retrospective DUR criterion was recommended to identify adult patients who may be using these medications inappropriately. After discussion, Mr. Strickland made a motion to approve the criterion and Dr. Phillips offered a second. The motion was unanimously approved.

Inappropriate Use of Antibiotics

Mr. Smith next introduced the report which focused on the possible negative impact of the over-prescription of antibiotics to very young children. He reiterated that the Board had reached a consensus during the September meeting to not address this issue from a retrospective DUR perspective at this time.

HIV Criteria Report

Dr. Holeman presented a synopsis of the retrospective DUR activity that has resulted from the DUR Board's approval in May of a large group of criteria focusing on the encouragement of appropriate antiretroviral therapy. A focused inquiry into the severity of the exceptions generated in May and June revealed that there is not a significant drug therapy problem in HIV patients enrolled in Mississippi Medicaid. Dr. Holeman continued that since the appropriate use of HIV medications is imperative for each patient, retrospective DUR criteria will continue to be used to assist physicians in providing effective treatment for their HIV patients.

New Business:

Alprazolam and Lorazepam Utilization

Due to a high number of claims for alprazolam and lorazepam and at the request of the board during the September meeting, Mr. Smith presented a review of the utilization of these agents. Due to their anxiolytic effects, these medications tend to have a very high abuse potential. The results of this review were somewhat surprising in that the highest utilization occurred among beneficiaries in the 30 to 59 age range. Utilization was also determined in the long-term care population and found that there were a relatively small number of claims in this group. It was noted that while Medicare Part D provides the majority of drug coverage for dually-eligible patients, coverage of generic benzodiazepines such as alprazolam and lorazepam falls through to Medicaid. The board members recommended further study of this utilization by HID with the removal of the one time fills for all groups. Dr. Voulters also requested that HID review chronic users such as those with two or more refills. Dr. Gray suggested that HID identify patients on concurrent SSRI therapy. Mr. Strickland pointed out that, with the new wavier program allowing patients to receive long term care at home from a relative, this data might be skewed. It was suggested that HID include plan number and category of eligibility when the reports are re-run. Dr Voulters also requested that HID look at the long-acting benzodiazepines focusing on the LTC and elderly groups. Dr. Phillips continued with a

request to add diazepam to the review as she is seeing it used more frequently in her practice with patients requesting refills from other physicians. Carlis Faler, Program Integrity Director, added that it may be helpful for these reports to also reflect gender.

Hydrocodone Utilization

Hydrocodone remains consistently one of the top five drugs based on the number of claims. This has generated a concern with the DUR Board as to how Medicaid can address this over -utilization with its beneficiaries. While high rates of hydrocodone use are cause for concern both at the state and national level, it is difficult to identify the complexity of the problem as Medicaid has set a monthly dispensing limit of 62, or two doses per day per running 31 days. It was noted that in some cases, beneficiaries are paying cash for the remainder of the prescription. Medicaid is working with the State Pharmacy Board to gain access to available data on cash purchases by Medicaid beneficiaries. This is expected to add valuable input into the possible abuse of these products and other medications of interest. Dr. Voulters requested an age analysis be generated as was done on the benzodiazepines. In addition, he further requested that other medications with abuse potential have the same detailed reports run. Dr. Gray requested that HID continue to review carisoprodol and run a comparison on all three of these medications with their age, diagnosis and long term utilization. She also suggested that HID report on the effectiveness of the carisoprodol Medicaid Prescribing Update, or "one-pager" that was previously approved by the DUR Board.

Impact of Quinine Removal on Utilization of Gabapentin and Lyrica®

Dr. Holeman presented a review of the impact of FDA action in removing quinine products from the market. On December 11, 2006, the FDA ordered all manufacturers to stop marketing unapproved products containing quinine. Currently, Qualaquin® is the only FDA approved product that contains quinine. Quinine is approved for the treatment of malaria but is often used off-label for leg cramps. Because of the drug's risks, FDA believes that it should not be used to prevent and treat leg cramps. At the request of the DUR Board, utilization data was gathered by HID on the continued use of quinine after the FDA mandate. The searches performed by HID were for utilization of quinine, gabapentin and Lyrica® and attempted to identify trends based on the date that firms had to cease marketing quinine, February 13, 2007. While some increase was noted in utilization of gabapentin and Lyrica®, it was not as large as expected. HID generated a second chart reflecting the use of Requip® and Mirapex ® which are indicated for restless leg syndrome and concluded that physicians are possibly utilizing these medications in place of quinine products. The data presented was interpreted to indicate that appropriate therapy has generally been implemented by treating physicians in the wake of the change in the marketplace.

Duplicate Utilization of Risperdal Consta® and Oral Atypical Antipsychotic Agents

Mr. Smith next presented a review of the utilization of Risperdal Consta®, a long-acting atypical antipsychotic injection approved for the treatment of schizophrenia. This agent is well-suited for patients for whom medication compliance is a challenge. According to the FDA-approved prescribing information, tolerability to oral Risperdal® should be established prior to initiating therapy with Risperdal Consta®. The labeling also stated

that oral risperidone or another antipsychotic medication should be given with the first injection of Risperdal Consta®, continued for three weeks, then discontinued to ensure that effective therapeutic plasma concentrations are reached and maintained prior to the main release phase of risperidone from the injection site. Mr. Smith continued by presenting findings of searches made by HID of the utilization from 1/1/2007 through 09/21/2007. The beneficiaries identified in these searches were intersected to determine those with utilization of Risperdal Consta® and one or more oral atypical antipsychotic agents. Beneficiaries with claims totaling less than 32 days of treatment with an oral agent were excluded from the study. The search resulted in 191 beneficiaries who received long-acting injectable risperidone and oral atypical antipsychotic therapy during the time period searched. According to this analysis, over 50 percent of the beneficiaries on Risperdal Consta® received greater than 31days of treatment with an oral atypical antipsychotic during the reviewed time. These findings indicate that many beneficiaries are receiving duplicate atypical antipsychotic treatment in addition to Risperdal Consta®. As a result, a retrospective DUR criterion was recommended to alert prescribers to the appropriate prescribing guidelines for this product. HID will bring such a criteria before the DUR Board at the next meeting for review and approval.

Approval of Minutes

Dr. Phillips voiced the need to be excused and requested that voting on appropriate matters take place due to the fact that when she left there would no longer be a quorum. The minutes of the previous two DUR board meetings on May 19, 2007 and September 20, 2007 were approved with a motion by Mr. Strickland and a second from Dr. Phillips. All members voted in favor of the motion.

Fourth Quarter Criteria Recommendations

In order to allow for voting on retrospective criteria recommendations, Mr. Smith presented the following criteria to the Board for approval.

- Elidel or Protopic/ Therapeutic Appropriateness - The topical calcineurin inhibitor, Elidel (pimecrolimus) or Protopic (tacrolimus), is indicated as second-line therapy for the short-term, non-continuous chronic treatment of mild to moderate atopic dermatitis in patients who are unresponsive or intolerant to other agents. Rare cases of malignancy (i.e., skin cancer and lymphoma) have been reported in patients treated with topical pimecrolimus. Application should be limited to the areas affected with atopic dermatitis.
- Protopic or Elidel / Age Appropriateness - The topical calcineurin inhibitors, Protopic (tacrolimus) and Elidel (pimecrolimus), are not recommended for use in children less than 2 years of age. The long-term safety and effects of these agents on the developing immune system are unknown.
- Protopic 0.1% / Age Appropriateness - The use of Protopic 0.1% ointment (topical tacrolimus) is not recommended in children less than 15 years of age. The 0.03% tacrolimus ointment is approved for use in children ages 2 to 15. Application should be limited to areas affected with atopic dermatitis. If signs and symptoms have not resolved within 6 weeks patient should be re-examined to confirm diagnosis.

- Elidel or Protopic/ Immunocompromised Patients - Elidel (topical pimecrolimus) or Protopic (topical tacrolimus) should not be used in immunocompromised adults and children. These patients are at risk for increased systemic exposure and adverse effects of pimecrolimus or tacrolimus.
- Topical Immunomodulators / Therapeutic Duplication - Therapeutic duplication of topical immunomodulator agents may be occurring.
- Tizanidine / Ciprofloxacin - Concurrent use of tizanidine and ciprofloxacin, a potent CYP 1A2 inhibitor, is contraindicated. Co-administration of these agents has been shown to cause significant increases in the AUC and Cmax of tizanidine resulting in hypotension, excessive sedation, and psychomotor impairment.
- Tizanidine / Fluvoxamine - Concurrent use of tizanidine and fluvoxamine, a potent CYP 1A2 inhibitor, is contraindicated. Significant alterations of pharmacokinetic parameters of tizanidine, including AUC, t1/2, Cmax, increased oral bioavailability and decreased plasma clearance, have been observed with concomitant fluvoxamine administration. Coadministration of these agents has resulted in profound hypotension, bradycardia and excessive drowsiness.
- Pioglitazone / Therapeutic Appropriateness - Pioglitazone-containing products (Actos/ActoPlusMet/Duetact) may increase the risk of fractures in female patients. Analysis of clinical trial data revealed an increased incidence of fractures in female patients taking long-term pioglitazone therapy as compared to females taking a comparator (placebo or active). Consider the risk of fractures when initiating or treating female, type 2 diabetic patients with pioglitazone.
- Rosiglitazone or pioglitazone/ Congestive Heart Failure & Fluid Retention – Rosiglitazone or pioglitazone-containing products may cause or exacerbate congestive heart failure. Their use is contraindicated in patients with NYHA class 3 or 4 heart failure and not recommended in patients with symptomatic heart failure. Patients should be observed for signs and symptoms of heart failure (rapid weight gain, dyspnea, and /or edema). If heart failure develops initiate appropriate therapy and consider alternative antidiabetic therapy.
- Codeine / Pregnancy - Nursing infants may be at an increased risk of morphine overdose if their mothers are taking codeine-containing products and are ultra-rapid metabolizers of codeine. If codeine use is necessary in the nursing mothers prescribe the lowest effective dose for the shortest amount of time. Inform mothers receiving codeine of the potential risks and signs of morphine overdose in themselves and their infants.
- Stimulants / Therapeutic Duplication - Therapeutic duplication of stimulants may be occurring (methylphenidate, dexmethylphenidate, amphetamine mixtures, methamphetamine, dextroamphetamine, lisdexamfetamine).
- Immediate Release Stimulants / Drug Abuse / Negating Agents - The patient has a diagnosis of substance use disorder (SUD) and is receiving immediate-release stimulant medication. Treatment recommendations for patients with the dual diagnosis of ADHD and SUD suggest that ADHD be treated with non-stimulant agents, extended-release stimulants or transdermal stimulant formulations to reduce the potential for misuse, abuse and/or diversion.

- Amphetamines / History of Drug Abuse - Amphetamines are contraindicated in patients with a history of drug abuse. Chronic, abusive use can lead to tolerance, extreme psychological dependence, and severe social disability.
- Stimulants / Arrhythmias & Cardiac Conditions - Stimulant products generally should not be used in children or adolescents with known structural cardiac abnormalities, cardiomyopathy, serious rhythm abnormalities or other serious cardiac problems. Sudden death has been reported in association with CNS stimulant treatment at usual doses in this population. All patients treated with stimulant medications should have a careful history (including family history of sudden death or ventricular arrhythmia) and physical exam to assess presence of cardiac disease.
- Stimulants /Bipolar Disorder - Particular care should be taken when using stimulants to treat ADHD patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder, and such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.
- Selzentry / Nonadherence - A review of the patient's prescription refill history suggests that the patient may not be taking the drug in the manner it was prescribed. Non-adherence to antiretroviral therapy may result in insufficient drug plasma levels and partial suppression of viral load leading to the development of resistance, HIV progression, and increased mortality.
- Selzentry /Therapeutic Appropriateness - Selzentry (maraviroc) is FDA approved to be used in combination with other antiretroviral agents to treat adult patients infected with only CCR5-tropic HIV-1 detectable virus, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. There is insufficient data to recommend monotherapy with this agent.
- Selzentry /Cardiovascular Events - Selzentry (maraviroc) should be used with caution in patients at increased risk for cardiovascular events. In clinical studies, more cardiovascular events, including myocardial ischemia and/or infarction, were observed in patients who received maraviroc as compared to placebo (1.3% vs. 0%).
- Selzentry /Liver Impairment - Selzentry (maraviroc) has been linked to hepatotoxicity that may be preceded by a systemic allergic reaction (e.g., pruritic rash, eosinophilia, or elevated IgE). Discontinuation of maraviroc should be considered in any patient with signs and symptoms of hepatitis, or with increased liver transaminases combined with rash or other systemic symptoms. Caution is advised if maraviroc is used in patients with pre-existing liver dysfunction or who are co-infected with hepatitis B or C.
- Selzentry / High Dose - The recommended dose of Selzentry (maraviroc) for patients receiving concomitant therapy with NRTIs, tipranavir/ritonavir, nevirapine, and other drugs that are not strong CYP3A inhibitors or CYP3A inducers is 300 mg twice daily.
- Selzentry / High Dose - Selzentry (maraviroc) is metabolized by the CYP3A isoenzyme and patients receiving concomitant therapy with protease inhibitors

(except tipranavir/ritonavir), delavirdine, ketoconazole, itraconazole, clarithromycin, or other strong CYP3A inhibitors (e.g., nefazodone and telithromycin) should receive a reduced dose of 150 mg of maraviroc twice daily.

- Selzentry / Low Dose - Selzentry (maraviroc) is metabolized by the CYP3A isoenzyme and patients receiving concomitant treatment with CYP3A inducers (e.g., efavirenz, rifampin, carbamazepine, phenobarbital, and phenytoin), without a strong inhibitor, should receive a dose of 600 mg of maraviroc twice daily.
- Selzentry / Renal Impairment - Selzentry (maraviroc) should be used with caution in patients with renal impairment, particularly in those with concurrent use of a CYP3A inhibitor and a CrCl < 50 mg/mL. Approximately 25% of maraviroc is renally eliminated and impairment may lead to increased drug concentrations and risk of dose-related adverse effects (e.g., dizziness and postural hypotension). Patients should be monitored for adverse effects.
- Selzentry / Hypotension - Selzentry (maraviroc) should be used with caution in patients with a history of postural hypotension or who are on concomitant medication known to lower blood pressure. The frequency of postural hypotension is increased at higher than recommended doses of maraviroc.
- Selzentry /Therapeutic Appropriateness - Selzentry (maraviroc) should only be used in combination with other antiretroviral agents in adult treatment-experienced patients infected with CCR5-tropic HIV-1 detectable virus, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. The agent is not active against CXCR4-tropic and dual-tropic viruses. Tropism testing and treatment history should guide use of maraviroc.
- Viracept / Therapeutic Appropriateness - Viracept (nelfinavir) has been found to contain the process-related impurity ethyl methanesulfonate (EMS), a potential human carcinogen. The FDA states that pediatric patients stable on nelfinavir therapy may continue therapy due to a favorable benefit-risk ratio. Pediatric patients who need to begin HIV treatment should not start on a regimen containing nelfinavir until further notice.
- Viracept / Therapeutic Appropriateness - Viracept (nelfinavir) has been found to contain the process-related impurity ethyl methanesulfonate (EMS), a potential human carcinogen. The FDA has recommended that pregnant patients currently receiving nelfinavir be switched to an alternative agent if possible and that those needing to begin HIV treatment not be offered nelfinavir until further notice. Pregnant women with no alternative treatment options may continue to receive nelfinavir because the benefit-risk ratio remains favorable.
- Haloperidol / Therapeutic Appropriateness - Higher doses and intravenous administration of haloperidol appear to be associated with an increased risk of QT prolongation, torsades de pointes and even sudden death. Particular caution is advised when prescribing haloperidol to patients with predisposing factors (e.g., cardiac abnormalities, hypothyroidism and electrolyte imbalance) that could cause an even greater risk of these serious adverse effects.
- Haloperidol / Over utilization - Haloperidol may be over-utilized. The recommended maximum dose is 100 mg per day. Exceeding this dose may enhance the risk of adverse effects (e.g., QT prolongation, torsades de pointes, extrapyramidal symptoms, seizures, and hypertension).

- Fentora / Therapeutic Appropriateness - Fentora (buccal fentanyl) is only approved for the treatment of breakthrough pain in patients with cancer who are already receiving and are tolerant to opioid therapy. Buccal fentanyl must not be used in opioid non-tolerant patients. The improper selection of patients, incorrect dosing and improper product substitution may result in a fatal overdose with this agent.
- Quetiapine / Substance Abuse - Seroquel (quetiapine) should be prescribed with caution to patients with a history of substance abuse. The agent has sedative and anxiolytic properties and may be misused by some patients. Closely observe patients for signs of misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior). Inappropriate use of quetiapine may put patients at risk for arrhythmias, hypotension, weight gain, and diabetes.

Mr. Marascalco continued with a vote on the criteria presented by HID. Dr. Phillips made a motion to approve the criteria presented with the exceptions of the pioglitazone/therapeutic appropriateness criteria and the pioglitazone/congestive heart failure and fluid retention criteria. Dr. Gray seconded the motion and all voted in favor.

Appropriate Antibiotic Use

Dr. Holeman presented a review of the appropriate utilization of antibiotics by Medicaid prescribers. Antimicrobial resistance among pathogens has become a common clinical problem and the association of resistance with the use of antimicrobial drugs has been documented in both inpatient and outpatient settings. This seems to have been given credence by the spread of organisms, such as MRSA, all essentially untreatable with routinely available antibiotics. Dr. Holeman continued by stating that decreasing the inappropriate use of antimicrobials has been listed as a primary solution to address the threat that antimicrobial resistance poses. To help combat the risk, HID presented and recommended the use of a Medicaid Prescribing Information Update, or "one-pager", which outlines the importance of appropriate treatment of upper respiratory tract infections and of prudent prescribing of antibiotics. HID recommends distribution of this document to prescribers by the Academic Detailing Staff and availability from the Division of Medicaid's website. After discussion of this approach, the Board's consensus was to support the distribution of this information as recommended.

Dr. Holeman then addressed the use of Zyvox®. At present, this antibiotic is non-preferred and subject to manual prior authorization review. Several recent studies have shown that outpatient use of Zyvox® may lower costs and prevent or shorten hospitalizations. Dr. Brown asked about the turn-around time of the prior authorization process. Mr. Smith answered that DOM requires that requests be processed within 24 hours, although most are responded to in less time. After discussion, the clear consensus of the DUR Board was to recommend no change to the present status of this product, continuing to require prior authorization approval, while encouraging appropriate use of this product.

Other

Dr. Gray suggested that HID analyze the utilization trends of Provigil® for the next Board meeting.

Boxed Warnings Update
Mr. Smith presented black box warnings, other warnings, and labeling changes issued by the FDA concerning the following:

Avandia (rosiglitazone)
FDA informed healthcare professionals of a potential safety issue related to Avandia (rosiglitazone). An on-going analysis of safety data for the treatment of type 2 diabetes mellitus using Avandia showed differing rates of ischemic cardiovascular events including heart attack or heart-related adverse events, some fatal, relative to other drugs used to treat diabetes mellitus. The clinical studies reviewed to date vary with respect to their populations, treatment regimens, and length of follow-up. Based on these data, the risk of ischemic cardiovascular events due to Avandia remain unclear. Prescribers should continue to carefully make individualized treatment decisions for patients with diabetes mellitus.

Exjade (deferasirox) Tablets For Oral Suspension
Novartis and FDA notified healthcare professionals of changes to the WARNINGS and ADVERSE REACTIONS sections of the product labeling for Exjade, a drug used to treat chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older. Cases of acute renal failure, some with a fatal outcome, have been reported following the post marketing use of Exjade. Most of the fatalities occurred in patients with multiple co-morbidities and who were in advanced stages of their hematological disorders. Additionally, there were post marketing reports of cytopenias, including agranulocytosis, neutropenia and thrombocytopenia in patients treated with Exjade where some of the patients died. The relationship of these episodes to treatment with Exjade is uncertain. Most of these patients had preexisting hematologic disorders that are frequently associated with bone marrow failure. Further, cases of leukocytoclastic vasculitis, urticaria, and hypersensitivity reactions (including anaphylaxis and angioedema) were reported. Healthcare professionals should monitor serum creatinine in patients who are at increased risk of complications, having preexisting renal conditions, are elderly, have co-morbid conditions, or are receiving medicinal products that depress renal function. Blood counts should also be monitored regularly and treatment should be interrupted in patients who develop unexplained cytopenia.

Propofol (marketed as Diprivan and generic products)
FDA informed healthcare professionals about several clusters of patients who experienced chills, fever, and body aches shortly after receiving propofol for sedation or general anesthesia. Multiple vials and several lots of propofol used in patients who experienced these symptoms were tested and there was no evidence that the propofol vials or prefilled syringes used were contaminated with bacteria or endotoxins. Propofol is an intravenous sedative-hypnotic agent for use in the induction and maintenance of anesthesia or sedation. To minimize the potential for bacterial contamination, propofol

vials and prefilled syringes should be used within six hours of opening and one vial should be used for one patient only. Patients who develop fever, chills, body aches or other symptoms of acute febrile reactions shortly after receiving propofol should be evaluated for bacterial sepsis. Healthcare professionals who administer propofol for sedation or general anesthesia should carefully follow the recommendations for handling and use in the product's full prescribing information.

Rocephin (ceftriaxone sodium) for Injection
Roche and FDA informed healthcare professionals of revisions to the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections of the prescribing information for Rocephin for Injection. The revisions are based on new information that describes the potential risk associated with concomitant use of Rocephin with calcium or calcium containing solutions or products. Cases of fatal reactions with calcium-ceftriaxone precipitates in the lungs and kidneys in both term and premature neonates were reported. Hyperbilirubinemic neonates, especially prematures, should not be treated with Rocephin. The drug must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines. Additionally, calcium-containing solutions or products must not be administered within 48-hours of the last administration of ceftriaxone.

Use of CellCept (mycophenolate mofetil) associated with increased pregnancy loss and congenital malformations
Roche and FDA notified healthcare providers that use of CellCept (mycophenolate mofetil) is associated with increased risk of first trimester pregnancy loss and increased risk of congenital malformations, especially external ear and facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney.
Based on postmarketing data from the United States National Transplantation Pregnancy Registry and additional postmarketing data collected in women exposed to systemic mycophenolate mofetil during pregnancy, the pregnancy category for CellCept has been changed from Category C (risk of fetal harm cannot be ruled out) to Category D (positive evidence of fetal risk). Labeling changes include the following sections: BOXED WARNING, WARNINGS/Pregnancy and Pregnancy Exposure Prevention, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Postmarketing Experience.

Within one week of beginning CellCept therapy, women of childbearing potential should have a negative serum or urine pregnancy test. In addition, women of childbearing potential (including pubertal girls and peri-menopausal woman) taking CellCept must receive contraceptive counseling and use effective contraception. Healthcare professionals and patients should be aware that CellCept reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness. See the Dear Healthcare Professional Letter for additional recommendations for women of childbearing potential.

Provigil (modafinil) Tablets- WARNINGS Added To Prescribing Information Regarding Serious Rash And Hypersensitivity Reactions, And Psychiatric Symptoms

FDA and Cephalon notified healthcare professionals of Warnings added to prescribing information for Provigil (modafinil). Provigil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder. The revised prescribing information updates safety information to include warnings regarding serious rash, including Stevens-Johnson Syndrome (SJS) and hypersensitivity reactions, and psychiatric symptoms. Rare cases of serious or life-threatening rash, including Toxic Epidermal Necrolysis, and Drug Rash with Eosinophilia and Systemic Symptoms have been reported in adults and children in worldwide postmarketing experience. Angioedema and multi-organ hypersensitivity reactions have also been reported in postmarketing experience.

Physicians should instruct their patients to immediately discontinue the use of Provigil and contact them if a rash or other hypersensitivity reaction occurs. Healthcare professionals and consumers should also be aware that Provigil is not approved for use in pediatric patients for any indication. In addition, psychiatric adverse experiences (including anxiety, mania, hallucinations, and suicidal ideation) have been reported in patients treated with Provigil. Caution should be exercised when Provigil is given to patients with a history of psychosis, depression, or mania.

Additional labeling revisions were made to the CLINICAL PHARMACOLOGY, PRECAUTIONS, and PATIENT PACKAGE INSERT sections.

Byetta (exenatide) and postmarketing reports of acute pancreatitis

FDA has reviewed 30 postmarketing reports of acute pancreatitis in patients taking Byetta (exenatide), a drug used to treat adults with type 2 diabetes. An association between Byetta and acute pancreatitis is suspected in some of these cases. Amylin Pharmaceuticals, Inc. has agreed to include information about acute pancreatitis in the PRECAUTIONS section of the product label.

Healthcare professionals should be alert to the signs and symptoms of acute pancreatitis and instruct patients taking Byetta to seek prompt medical care if they experience unexplained, persistent, severe abdominal pain which may or may not be accompanied by vomiting. If pancreatitis is suspected, Byetta should be discontinued. If pancreatitis is confirmed, Byetta should not be restarted unless an alternative etiology is identified.

Early Communication Issued Regarding Atrial Fibrillation With Oral And Intravenous Bisphosphonates

FDA issued an early communication about the ongoing review of new safety data regarding the association of atrial fibrillation with the use of bisphosphonates. Bisphosphonates are a class of drugs used primarily to increase bone mass and reduce the risk for fracture in patients with osteoporosis, slow bone turnover in patients with Paget's

disease of the bone, treat bone metastases, and lower elevated levels of blood calcium in patients with cancer.

FDA reviewed spontaneous postmarketing reports of atrial fibrillation reported in association with oral and intravenous bisphosphonates and did not identify a population of bisphosphonate users at increased risk of atrial fibrillation. In addition, as part of the data review for the recent approval of once-yearly Reclast for the treatment of postmenopausal osteoporosis, FDA evaluated the possible association between atrial fibrillation and the use of Reclast. Most cases of atrial fibrillation occurred more than a month after drug infusion. Also, in a subset of patients monitored by electrocardiogram up to the 11th day following infusion, there was no significant difference in the prevalence of atrial fibrillation between patients who received Reclast and patients who received placebo.

Upon initial review, it is unclear how these data on serious atrial fibrillation should be interpreted. Therefore, FDA does not believe that healthcare providers or patients should change either their prescribing practices or their use of bisphosphonates at this time.

Haloperidol Marketed As Haldol, Haldol Decanoate, And Haldol Lactate Get New Warnings And Revised Prescription Information

Johnson and Johnson and FDA informed healthcare professionals that the WARNINGS section of the prescribing information for haloperidol has been revised to include a new Cardiovascular subsection regarding cases of sudden death, QT prolongation and Torsades de Pointes(TdP) in patients treated with haloperidol, especially when given intravenously, or at doses higher than recommended. Although injectable haloperidol is only approved by the FDA for intramuscular injection, there is considerable evidence that the intravenous administration of haloperidol is a relatively common off-label clinical practice.

There are at least 28 case reports of QT prolongation and TdP, some with fatal outcome in the context of off-label intravenous haloperidol.

Healthcare professionals should consider this new risk information when making individual treatment decisions for their patients.

Fentora (fentanyl buccal tablet) and the occurrence of serious adverse events, including deaths as a result of improper patient selection, improper dosing, and/or improper product substitution

Cephalon issued two Dear Healthcare Professional Letters to inform prescribers and other healthcare providers of important safety information regarding Fentora. Fentora is indicated only for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Serious adverse events, including deaths, have occurred in patients treated with Fentora. These deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients), improper dosing, and/or improper product substitution. The healthcare professional letters provide key points regarding appropriate patient selection

and proper dosing and administration of Fentora to reduce the risk of respiratory depression.

Next Meeting Information:
Mr. Marascalco reminded the Board of the next meeting scheduled for February 21, 2008.

Mr. Marascalco called for a motion of adjournment at 4:10 p.m. Mr. Strickland made the motion, which was seconded by Dr. Gray. All voted in favor of the motion to adjourn.

Respectfully Submitted:
Health Information Designs