Iowa Medicaid Pharmaceutical and Therapeutics Committee
Minutes

Date: November 13, 2008

Chair: Susan Purcell, R.Ph.

Time: 8:40 a.m. to 4:45 p.m.

Location: Capitol Room 116, Des Moines, Iowa

Committee Members Present: Bruce Alexander, R.Ph., Pharm.D., BCPP; Matthew Osterhaus, R.Ph; Carole A. Frier, D.O.; Priscilla Ruhe, M.D.; Susan Purcell, R.Ph, CGP; Hayley L. Harvey, DDS, MS; Dallas Sanders, PA-C; Mary Larew, M.D.; and Charles Wadle, D.O.

Iowa DHS Staff Present: Susan Parker, Pharm.D., Pharmacy Consultant; and Brad Horn, Assistant Attorney General.

Iowa Medicaid Enterprise (IME) Staff Present: Tim Clifford, M.D.; John Grotton, R.Ph.; Sandy Pranger, R.Ph.; Erin Halverson, R.Ph.; and Melissa Biddle.

Chairperson Sue Purcell called the meeting to order.

I. Sue Purcell asked that each committee member, DHS staff, and IME staff introduce themselves to the public. (Hayley Harvey was not present then, as she arrived at 9:24). The September 11, 2008 open session minutes were reviewed. Mary Larew made the motion to approve the minutes. Bruce Alexander seconded the motion. The motion passed with no objections.

II. Legislative Report – Diabetic Review: The committee reviewed the draft of the letter regarding the diabetic PDL class that will be sent to the legislature by December 15th. They requested that the last sentence of the document, outlining P&T recommendations, be rewritten as follows: "Pharmaceuticals alone will not adequately treat diabetes; the non-pharmacological aspects of treatment, such as exercise, nutrition, and education must be promoted as well. The committee supports examination, improvement, and refinement of these modalities." Matt Osterhaus also claimed to have found a couple grammatical errors. Carole Frier motioned to accept these changes, Chuck Wadle seconded, and the motion passed with no objections.

III. PDL (Dr. Clifford): Manufacturer negotiations are going well. More information was provided in the confidential session.

IV. PA Criteria/Pro-DUR Edits (Susan Parker): The November 6th letter from the DUR commission contained the recommendations from their meeting on November 5th. They recommended placing a quantity limit of 5 per 30 days on Glucagen, and voted to add prior authorization criteria for Vusion Ointment and revise current prior authorization criteria for

Growth Hormones, Zyvox, Serotonin 5-HT1-Receptor Agonists, and Extended Release Formulations. They also voted to implement a quarterly narcotic utilization report.

V. Drug Rebate Issues: All manufacturers are currently in good standing.

VI. The public speakers were:

SPEAKER	SUBJECT
Pinakin Attawala from Schering-Plough	Vytorin
Mike Barger from Adel Family Practice	FlexPen, Novolog, and Levemir
Rich Wonderman from AstraZeneca	Atypical Antipsychotics
Jamie Street from AstraZeneca	Atypical Antipsychotics
Susan Abraham from Boehringer-Ingelheim	Mirapex
Jim Rothroffy from Boehringer-Ingelheim	Mirapex
Larry Carter from Jazz Pharmaceuticals	Luvox CR
Jason Ficks from Taro Pharmaceuticals	Ovide
Will Joseph from Bristol-Myers Squibb	Reyataz
Nancy Martin from Biogen Idec	Avonex
Jane Feldman from Sanofi-Aventis	Lantus
Diana Noller from Sanofi-Aventis	Lantus
Niddi Yaucher from Novartis	Tekturna and Tekturna HCT
Linda Burkett from Novo Nordisk	Norditropin
Renea Bradley from Novo Nordisk	Levemir, NovoLog, and FlexPen
Pamela Rodgers from Astellas Pharma	Vesicare and Protopic
Keva Kole from Shire Pharmaceuticals	Vyvanse
Andrea Hawkinson from Amylin	Byetta
Karen Loihl from Iowa Psychiatric Society	Mental Health Drugs on the PDL
Steve Helmke from Takeda	Actos
Wayne Cancro from Wyeth	Pristiq
Nanacy Bell from Pfizer	Lyrica
Felecia Williams from Merck	Januvia
Jeff Knappen from Allergan	Combigan
James Wilson from GlaxoSmithKline	Requip XL
Peggy Iverson from IA Alpha-1 Support Group	Prolastin and Alpha-1 Drugs

At 10:42, motion to go to closed session was made by Matt Osterhaus and seconded by Chuck Wadle. The motion passed with unanimous approval. Open session resumed at 12:51 pm.

VII. PDL Discussion and Deliberation (Dr. Clifford): In the Alzheimer's class it was recommended that the current preferred drugs, the Aricept's and Exelon's, remain preferred and that the generic galantamine be non-preferred, taking into account the financial issues previously discussed in closed session. In the Androgen category, the next recommended change is a changing of places between the Androgels and Testim. Looking at the utilization report there's been increasing demand for the Androgel products, so Androgel, Androgel Pump, and Androderm will now all the preferred and Testim non-preferred. It

was also recommended that Xopenex Nebulizer be changed to non-preferred for financial reasons. In the Anticoagulants category, it was recommended to make Innohep non-preferred. In the anticonvulsants, it was recommended to make Depakote non-preferred, as there is a new SMAC price on its generic divalproex sodium. All patients with Seizure Disorder will be grandfathered. Also, the new version of valproic acid, Stavzor, will be non-preferred. Keppra XR, which was talked about in the financial session, can be brought on as preferred. There's also a brand-generic switch as oxcarbazepine is now more cost effective than the brand Trileptal. Carol Frier moved to accept these recommendations, Chuck Wadle seconded, and the motion passed with no objections. In the ARB/CCB category, it was recommended to change Azor to preferred. In the Beta Blockers, it was recommended to change Coreg to non-preferred as the generic is now less expensive. In the Cholesterol Fibric Acid Derivatives, it was recommended to make Fenoglide non-preferred in order to continue with the current contract with Tricor. In the Statin high potency category, the manufacturers have negotiated for a 2-drug class, so one of the brands, Vytorin, has to become non-preferred. In the Statin low potency category, the pricing on pravastatin has changed so now all strengths can become preferred. In the Diabetic Insulin category, it was recommended to change Lantus, Humalog, Humulin R, Humulin N, Humalog 75/25, and Humulin 70/30 to preferred. Lantus Injection Solostar and Lantus Opticlick would be preferred with conditions. Dallas Sanders asked that the DUR Commission re-evaluate the prior authorization criteria for the insulin category, specifically in reference to Januvia and Byetta prescriptions. The P&T committee will also review this topic further at their March meeting. Carol Frier motioned to accept these recommendations, Matt Osterhaus seconded, and the motion passed with no objections. In the diuretics, the generic version of Inspra, eplerenone, is recommended to be non-preferred. In the GI inflammatory bowel agents category, Lialda was recommended to become preferred. In the GI miscellaneous category, it was recommended to make Relistor non-preferred as it is very expensive and has the potential for misuse. In the growth hormone category, it was recommended to keep Norditropin Cartridge and Norditropin Nordiflex Pen non-preferred, and to change Tev-Tropin to non-preferred after reviewing the utilization data on the marketshare report. Priscilla Ruhe motioned to accept these recommendations, Mary Larew seconded, and it passed unanimously. In the influenza agents category this year's batch of vaccines would all be preferred for adults. In the Triptans, it was recommended to change Maxalt (plain tablets only) to non-preferred because of their cost. In the Migraine combination class, it was recommended to change Treximet to preferred on a trial basis. It will be re-evaluated in 2009. In the narcotics, Zamicet Solution was recommended to remain non-preferred to keep utilization with the generics. In the Opthalmic Quinolones, it was recommended to change Ciloxan to preferred and Quixin to non-preferred. Zymar and I-Quix were both recommended to be non-preferred and placed in the new Opthalmic Quinolones Fourth Generation category. Matt Osterhaus motioned to accept these recommendations, Dallas Sanders seconded, and the motion passed unanimously. Matt Osterhaus also motioned for Mirapex to remain preferred until its generic comes out on the market. That was seconded by Dr. Mary Larew, and passed with no objections. In the phosphate binders, it was recommended to keep the class as it is and make Renvela non-preferred. In the rheumatoid arthritis biological category, it was recommended to add Humira Pen Kit Starter as preferred with conditions, and recommend a one-time fill so that patients are not receiving a starter kit every time they fill prescriptions. In the Sedative Hypnotics Non Benzodiazepines, it was

recommended to change brand names Ambien CR and Lunesta to non-preferred, as the generic Zolpidem has been able to hold down the class by itself in other states. Also, the Sonata generic, Zaleplon, is expected to be reduced in price in the coming year, and could then be changed to preferred as well. With these changes, this category will have major savings potential for the State. Sue Purcell motioned to accept these recommendations, Chuck Wadle seconded, and the motion passed with only Matt Osterhaus opposing (see next paragraph).

VIII. Reports: Dr. Clifford reviewed reports comparing permethrin and Ovide users in 2008 to attempt to address the resistance issue. Out of 3788 members profiled, only 100 would have failed on both permethrin products to qualify for Ovide. Some members may also have had a pre-existing prior authorization approval, or the pharmacies may have used the one-time override option. The data does not support the failure theory, or there would be more instances of qualification. Matt Osterhaus thinks the data is misleading, maybe altered by the new improved school nurse practices. As a pharmacist, he believes failure is more common than outlined on paper. Another chart outlined pediculicide usage from 2004 through 2008. Prescription totals have gone down even though there are 337,000 eligible members this year compared to 305,000 in 2004. From a cost point of view, the pricing on the permethrin products has dropped down over time, and they've created a large difference between their price and that of Ovide, even including the proposed supplemental rebate offer. There were other charts illustrating Triptan users (who did not have hypertension) who were also taking some sort of migraine prophylactic drug. 32.2% of Triptan users had also taken a high efficacy prophylactic sometime in 2008, and 32.3% had taken a lower efficacy prophylactic in 2008. However, the percentages went down when the criteria was narrowed to concurrent use, to 27.6% and 21.5% respectively.

IX. RDL Discussion and Deliberation (Antidepressants): The committee reviewed prepared comparison charts between drugs in this category. If a drug meets either of the legislative criteria, that drug would become preferred. In addition, first line therapy and financial reasoning would be optimal. Dr. Clifford asked the committee to refer to the class reviews, hand-outs, and also the drug class review on second-generation antidepressants by the Oregon Evidence-Based Practice Center that a number of Medicaid programs use. They did a very good review that just became final in October. In the SSRI class review, there was a chart that compared the various indications for each drug. It is also important to establish which drugs have evidence (randomized controlled trials versus placebo and/or comparator drugs, and meta-analyses) to support their usage. The drugs that have an indication for Major Depressive Disorder are: fluoxetine, sertraline, paroxetine, citalopram, escitalopram, bupropion, mirtazepine, and nefazadone. The only drug that doesn't have that indication is fluvoxamine. In addition to the drugs that have the indication for Obsessive Compulsive Disorder, one could also make a strong case for including citalopram and Lexapro based on the evidence. In addition to the drugs that have the indication for Panic Disorder, most experts would also consider fluvoxamine to have good evidence. There's also good evidence on sertraline for General Anxiety Disorder in addition to the indicated drugs. For Social Anxiety Disorder, there is good evidence on Lexapro in addition to the indicated drugs as well. With Seasonal Affective Disorder, bupropion has the indication, but there's good evidence with fluoxetine and sertraline too. With the Pre-menstrual Dysphoric Disorder, in addition to the drugs that have the indications, there's good evidence on the

venlafaxine, although it's not a SSRI. The committee then examined the adverse drug reaction table, manufactured for the indications that were usually most common, in most cases except fluvoxamine, in studies for Major Depressive Disorder. All the side effects are listed, admittedly with a fair bit of variability, in drug pairings. Citalopram was paired with escitalopram, fluvoxamine with fluvoxamine cr, paroxetine with paroxetine er, paroxetine with paroxetine mesylate, venlafaxine with desvenlafaxine, bupropion with Wellbutrin SR/XL, venlafaxine with venlafaxine er, and Seroquel with Seroquel XR. Of course, these are not actually comparative studies, merely a comparison of known side effects as compared to placebo. Citalopram and Lexapro are evenly split in terms of which has the most side effects. In terms of major differences (defined as greater than or equal to 10 percentage points), for headache Lexapro was at 24% and Citalopram 0%, and for dry mouth Citalopram was at 20% and Lexapro 6.5%. With fluvoxamine and Luvox CR, fluvoxamine has more side effects 33% of the time, Luvox CR had more 47% of the time, and they both had the same amount 20% of the time. Comparing major differences in individual side effects, Luvox CR had at least a 10% higher incidence of: headache, somnolence, insomnia, anorexia, diarrhea, nausea, and asthenia. Paroxetine and Paxil CR were almost evenly split as to having the higher percentage of side effects, and there were no major differences. Paroxetine and Pexeva were also comparable to each other; however, more nausea was reported on Pexeva. With venlafaxine and Pristiq, venlafaxine was higher 45% of the time, Pristiq was higher 39% of the time, and they were both equal 16% of the time. The only major difference was a higher incidence of nausea with Pristiq. With bupropion and Wellbutrin SR/XL, bupropion was higher 47% of the time, Wellbutrin SR/XL was higher 38% of the time, and they were equal 15% of the time. The only major difference was a higher incidence of tremor with bupropion. With venlafaxine and Effexor XR, venlafaxine was higher 45% of the time, Effexor XR 38% of the time, and they were equal 17% of the time, with no major differences at all. Seroquel and Seroquel XR were almost evenly split as to having the higher percentage of side effects, and there were no major differences on any given side effect. Dr Clifford also made another chart, using Oregon Evidence-Based Practice Center compiled data to compare the 6 most frequently reported side effects in head-to head randomized controlled trials: diarrhea, dizziness, headache, insomnia, nausea, and somnolence. He took each drug's average side effect rate for each of those categories and added them together, then made an average of the averages. Sorted in order from most side effects to least, they are: duloxetine 28.2%, nefazodone 21.0%, fluvoxamine 19.4%, venlafaxine 16.9%, bupropion 14.6%, sertraline 13.3%, fluoxetine 13.2%, paroxetine 11.9%, citalopram 10.8%, mirtazepine 9.5%, and escitalopram 6.5%. Fluvoxamine had the highest incidence of diarrhea, and mirtazepine the lowest. Duloxetine had the highest incidence of dizziness, and paroxetine the lowest. Nefazadone had the highest incidence of headache, and paroxetine the lowest. Fluvoxamine had the highest incidence of insomnia, and citalopram and escitalopram the lowest. Duloxetine had the highest incidence of nausea, and mirtazepine the lowest. Duloxetine also had the highest incidence of somnolence, and escitalopram the lowest. Dr. Clifford then reviewed more findings that came directly from the Oregon Evidence-Based Practice Center's Second Generation Antidepressants Drug Class Review report from October 2008. The report can be viewed in their entirety at www.ohsu.edu/ohsuedu/research/policycenter/DERP. This review project was extremely thorough, with very rigorous criteria. They examined all aspects of the studies. They did their own meta-analyses of studies. They took a look at

Major Depressive Disorder in adults, and also looked back to previous studies/reviews (such as by AHRQ) others had done before them that had concluded there were no significant differences between all the second-generation antidepressant drugs. Oregon updated the studies by looking at any of the new head-to-head trials that have since been published. Their overall impression is that "it appears very unlikely that this new evidence would have led to changes in the statistical results". Dr. Clifford would like to focus on the single-source brand names, drugs that would go from a recommended or non-recommended status onto the PDL: Lexapro, Effexor XR, Prestiq, Luvox, etc. There's some moderate evidence that Lexapro is more effective than citalopram for Major Depressive Disorder. There are some studies out there that show a higher response rate and higher remission rates with Lexapro (Lepola et al.2003, Moore et al. 2005, Yevtushenko et al. 2007). However, there are also studies that show no difference. However, there aren't any showing citalopram as superior. Oregon HSU also did some meta-analyses of the data. In the first one, there was a significant difference in response with Lexapro being superior, with the number it needed to treat being 12 in terms of response. There was a second meta-analysis looking at the effect size of the response, and that was larger for Lexapro as well. That was statistically significant, but the reviewers questioned whether it was clinically significant. In terms of the rating scales, for the most part, they went with the HAM-D or MADRS scales. In direct head-to-head studies, there's good data showing that Lexapro is not better than fluoxetine, and also that it's not better than paroxetine at 8 weeks. However, Lexapro was better after being on the drug for 6 months. There's also data out there showing that Lexapro is no better than sertraline. There are 3 studies that show that duloxetine is not better than Lexapro, and that there's a significantly higher discontinuation rate, presumably due to side effects. There have also been head-to-head studies looking at Lexapro versus bupropion, which found no significant difference. Taking a look at some of the other indications, where there's more limited data available, there is some data showing Lexapro is better than paroxetine for Generalized Anxiety Disorder. There is data showing that Lexapro is no different than paroxetine in treating Obsessive Compulsive Disorder. For Panic Disorder, there are studies showing Lexapro no different than citalopram. For Social Anxiety Disorder, studies show that Lexapro is no different than paroxetine. In summing up Lexapro, there is solid data favoring Lexapro over citalopram, but compared to the other SSRI's there's a lot of back and forth. Lexapro is not superior to all other SSRIs in terms of safety or efficacy but it probably is superior to citalopram in MDD efficacy. Dr. Clifford reminded the committee of their past discussion regarding the Star-D trial. After people had already taken an initial SSRI, this trial showed that there's not really any big difference in terms of what would be an optimal second agent. There's still enough good evidence to consider reacting favorably to Lexapro. In terms of side effects, it also appears to be more tolerable overall. Dr. Clifford believes that Lexapro does offer something substantial that would meet the first legislative criteria in terms of the therapeutic benefit profile, at least with respect to citalopram. In terms of side effect profile, it holds up pretty well, though that is probably moot as it would already meet criteria one to be preferred on the PDL. The manufacturer has been very good to the State over the years, so Iowa Medicaid weighs this also in the drug's favor and endorses keeping Lexapro preferred. Dr. Clifford commented that the Luvox CR versus fluvoxamine issue was adequately addressed earlier in the open session. There are no direct head-to-head studies that would encourage the State to favor one over the other at this point in time, though any new evidence will be examined as it

appears. Head-to-head studies between venlafaxine er (Effexor XR) and citalopram found no difference. Venlafaxine er has also been compared to Lexapro. In one study there was no difference in terms of response or remission. However, the patients on Lexapro responded faster, and there was significantly more nausea, sweating, and constipation with venlafaxine users. On the second study there was no significant difference in terms of outcome, but again there was significantly more nausea with the venlafaxine er. There have been ten venlafaxine versus fluoxetine studies. Eight of them showed no significant difference, and two favored venlafaxine er. Oregon (OHSU) also did a meta-analysis on the studies to take a look at the weighted effect, and they concluded there was no difference between them. Venlafaxine has also been compared to fluoxetine with no difference noted. Venlafaxine has been compared to sertraline. 1 of the 3 trials favored Effexor XR, and the other 2 showed no difference. Outside Major Depression, there are also some head-to-head studies for Panic Disorder, with venlafaxine er against paroxetine. The 2 studies had mixed results: the European study showed no difference, and the U.S. study showed venlafaxine was better (but they pointed out there was a big flaw with the study and they were comparing high dose venlafaxine to a medium dose of paroxetine). In PTSD, there was a study of venlafaxine er versus sertraline that found no difference. In Social Anxiety Disorder, there was a venlafaxine versus paroxetine study, and there was no difference there either. So there isn't a substantial amount of data that would favor venlafaxine over SSRI's as a class, but there is some data that implies there might be a slightly more potent positive effect with venlafaxine compared to the average SSRI drug. However, the drug is also less tolerable and causes more discontinuations that the average SSRI agent. The venlafaxine manufacturer was fairly fastidious in avoiding studies comparing the xr product to the short-acting product, but there certainly are some advantages with the long-acting form of the venlafaxine. Effexor XR is not the issue here (especially as the generic will be coming out shortly), but rather what to do with Pristiq. There is no head-to-head data that would really make a strong case to consider it over the Effexor right now. Again, this will need to be re-evaluated in the future as more data becomes available. There's really good data arguing to prefer venlafaxine, and even enough to make a case for the Effexor XR as being a valuable addition. It appears appropriate to draw the line on Pristiq, though, with the information available right now. The Star-D trial was again referenced because of what it says about the relative potency of SSRI and SNRI antidepressant drugs. Because of the side effect profile of the SSRI's as a class, it is important to have some non-SSRI second-generation anti-depressants on the PDL. Dr. Wadle asked if people who are stable on a medication would be required to change as a result of the committee decisions. Dr. Clifford said that if there was any drug that is currently recommended or non-recommended that was changed to non-preferred as a result of this meeting, then all of those users would be grandfathered. In a number of the head-to-head studies, there were some significant differences in tolerability and discontinuations. Venlafaxine had more nausea and vomiting than the SSRI's. Sertraline had more diarrhea than other SSRI's and more sexual dysfunction than some of the other SSRI's, though not all of them. Paroxetine had significantly more sweating, sexual dysfunction, and drowsiness than other SSRI's. Bupropion had a significantly lower degree of sexual dysfunction than some SSRI's, and a modest effect on decrease in weight. Mirtazapine was significant for causing weight gain. Venlafaxine's, again, have a significantly higher discontinuation rate than the SSRI's. In the UK, the second generation anti-depressant drug that has the highest fatal toxicity rate is venlafaxine. MAO Inhibitors

will be moved from recommended to preferred with conditions, with hard edits in place on the POS system to look for contra-indicated drugs. Dr. Frier asked if others had done this with mental health drugs, and Bruce Alexander replied that the VA had tightened up criteria on some of them. Chuck Wadle pointed out that on the last report there were four psychotropic drugs in the top five by cost, so they are very costly to the State. He said there were some other private payers that also had them in their top drugs reports. The committee decided to send a copy of this discussion and their recommendations to the DUR Mental Health Workgroup to be discussed further at their December 12th meeting before PDL implementation. Any discrepancies would be returned to the P&T committee. However, if the subcommittee agrees with the recommendations, the PDL could be updated without re-visitation by the P&T committee, as their next meeting is not until March.

X. RDL Individual Drug Recommendations and Voting (Antidepressants): It was recommended to change Nardil, Emsam, and Parnate from recommended to preferred with conditions, and to add a clinical prior authorization requirement for MAO Inhibitors to include a POS edit to look for contra-indicated drugs. Existing members using these drugs would be grandfathered. It was recommended to change Lexapro from recommended to preferred and accept the DUR Commission recommendation to split Lexapro 20mg tablets to achieve a 10mg dose and to split Lexapro 10mg tablets to achieve a 5mg dose. It was recommended to change Luvox CR 100mg and 150mg from non-recommended to non-preferred. It was recommended to change Paxil Susp 10mg/5mg from recommended to preferred. It was recommended to change Pexeva from non-recommended to non-preferred. It was recommended to change Pristiq 50mg and 100mg from non-recommended to non-preferred. It was recommended to change Cymbalta from non-recommended to preferred. It was recommended to change Maprotiline from recommended to preferred. It was recommended to change Wellbutrin XL from recommended to preferred. It was recommended to change Effexor XR from non-recommended to preferred. It was recommended to change Amoxapine from recommended to preferred. It was recommended to change Tofranil-PM from non-recommended to preferred. Finally, it was recommended to change Vivactil and Surmontil from recommended to preferred. Chuck Wadle motioned to accept these recommendations with a caveat that it be reviewed by the DUR sub-committee for input. The P&T committee would revisit any concerns or disparities at the March meeting. Dallas Sanders seconded, and the motion passed unanimously.

XI. RDL Discussion and Deliberation (Antipsychotics): There is very little to be deliberated in this category that would result in any change at all, in terms of how the PDL is actually working currently. Before talking about status changes, the committee reviewed how things looked currently in the Atypical category. Right now, the brand version of Risperdal is preferred over the generic. The other related versions of Risperdal, including Invega, are non-recommended. Abilify and Zyprexa are non-recommended. Seroquel is recommended, but not the XR version. Geodon is recommended. Clozapine and Fazaclo are preferred. The Typicals weren't mentioned, as no changes would really occur there. There is sufficient evidence to indicate that in refractory patients with schizophrenia that clozapine is a more effective antipsychotic compared both to typical and atypical antipsychotics. However, it's pretty clear, with the studies and meta-analyses that have come out, upon examining the efficacy of the atypicals, there is very little data that would support any of the other atypicals except for clozapine being superior to the others. There might be some case for

Zyprexa (olanzapine) in terms of outcomes in some studies, but there are no outcomes that hold up universally across all studies. This revelation is made worse by the fact that one could fairly compare them to most of the Typicals as well. The real issue on which to focus in the Atypicals then is their tolerabilities as they probably vary more substantially in side effect profiles than in therapeutic benefits. Other groups and state Medicaid mental health directors have already taken a look at the CATIE trial, and they were not reluctant to issue a recommendation stating that it is not unreasonable to have an atypical PDL. However, good selection and pairing of Atypicals is fundamental in a potential PDL, because access to drugs that might be substantially different in side effect profiles than the other atypicals is especially important. In this framework, it is important at the very least to have preferred at least one drug from each of the following pairs: risperidone/paliperidone, olanzapine/quetipaine, ziprasidone/aripiprazole and clozapine. This category is complicated, especially after what's occurred with schizophrenia with the various bi-polar indications. The CATIE trial, the OHSU drug class review and the GHS atypical class review were referenced as data sources. Dr. Clifford doesn't believe there are any significant findings to support superiority or inferiority of any one atypical drug over the others. But there is enough variation in the side effect profiles that a good representation of products are needed on the PDL. In reviewing the therapeutic benefits of all the atypical antipsychotics it became very readily apparent that Risperdal, Seroquel, Geodon, Zyprexa, Abilify and clozapine readily met the first and/or second legislative criteria. However, Dr. Clifford thought Invega (paliperidone) was problematic and might be worth some discussion. Bruce Alexander had previously referenced a 2008 Pharmacotherapy Journal (Marino and Caballero) article reviewing the treatment of schizophrenia with Invega. Once they were able to figure out what constituted a comparative dose, they determined there was similar efficacy between Invega (6-12mg per day) and Risperdal (4-6mg per day). The authors refer to one brief double-blind comparison study, but that was against Seroquel and not Risperdal. Consequently, there is data out there showing that Invega was significantly better at improving one of the outcomes, in looking at the PANSS scores, than Seroquel. Even if this head-to-head data was not against Risperdal, it still provides some type of benchmark against other products in the class. Because there wasn't a direct comparison between Risperdal and Invega, the authors rearranged the data in order to do a virtual comparison. They took several placebo controlled trials on schizophrenia with Risperdal and tried to line up doses to figure out what the results would have been. This is certainly not ideal, but what they found across the various studies was that the Invega had similar effectiveness to the Risperdal at what would prove to be equivalent doses. Chuck Wadle asked if there was a cost difference between the two. He's concerned about people that would probably have used Risperdal switching to Invega, particularly in non-schizophrenic cases. Bruce Alexander echoed his concern. Dr. Clifford admitted that this was a difficult decision looking at the data available. He suggested that the committee might want to rely more heavily on input from the Mental Health Subcommittee before making a final decision one way or the other on this particular drug. The manufacturer of Invega has made a very substantial offer to the State (although there is still a price difference), and there is perhaps a real legitimate argument if committee members feel it brings enough substantial improvement in efficacy and/or tolerability to become preferred. From the open session comments and questions, it is clear that there is no head to head data presently that supports Invega being more effective or safer than Risperdal. Sue Purcell asked if this topic could be

skipped over until the Mental Heath Workgroup had a chance to discuss it. Dr. Clifford said that he would prefer that the committee voted their prerogative, and if the sub-committee reaches a different conclusion the P&T decision would not be implemented without further discussion. Bruce Alexander commented that if they were taking a strictly formulary approach to this category, clozapine would definitely be on it with no argument. Otherwise, differences in therapeutic profiles are minimal. Looking at adverse effects (and metabolic syndrome is one that's getting most of the attention these days), one comes down to ziprasidone versus aripiprazole, which are referred to as metabolic neutral. If there's not a therapeutic difference between those two drugs, that leaves risperidone and paliperidone. If it costs a lot more, and it's not better, then it doesn't belong on the formulary. That leaves the issue of quetiapine and the XR version, which is a toss-up clinically and financially. There is no good head to head data here either, as reiterated during the open comment session, so it would be reasonable to prefer only the Seroquel and keep users in line for the generic in several years. Dr. Clifford said that for the purposes of a vote and what gets forwarded to the Workgroup, it would be best to ignore the financial aspect and base the decision purely on clinical analysis of efficacy and side effects.As had been noted with the antidepressants, the drugs with dissolvable version were allowed to represent their originator drug side effect profile data.

XII. RDL Individual Drug Recommendations and Voting (Antipsychotics): It was recommended to change Invega from non-recommended to preferred. However, as stated in the previous paragraph, the committee chose to refer this drug to the Mental Health Workgroup prior to implementing a PDL status change. It was recommended to change Risperdal from recommended to preferred. It was recommended to change Risperdal M-Tab from non-recommended to non-preferred. It was recommended to change Risperdal Consta from non-recommended to preferred. It was recommended to change Seroquel from recommended to preferred. It was recommended to change Seroquel XR 200mg, 300mg, and 400mg from non-recommended to non-preferred with conditions and keep the clinical prior authorization requirement. It was recommended to change Zyprexa from non-recommended to preferred. It was recommended to change Zyprexa Zydis from non-recommended to non-preferred. It was recommended to change Abilify from non-recommended to preferred. It was recommended to change Abilify Discmelt from non-recommended to non-preferred. It was recommended to change Geodon from recommended to preferred. Lastly, it was recommended to change Moban from non-recommended to preferred. Chuck Wadle motioned to accept these recommendations (with the exception of Invega) with a grandfather clause for existing users. Bruce Alexander seconded, and the motion passed with no objections.

XIII. RDL Discussion and Deliberation (Stimulants): We used the OHSU drug review, the GHS drug class review and several Cochrane reviews as references. Focusing on the nine most frequent side effects in looking at the PI's, the drugs were sorted by rank order of least number of highest side effect rate categories. Focalin had none, and neither did Metadate CD. Ritalin LA, Concerta, and Focalin XR were the highest once. Daytrana, Strattera, and Adderall XR were the highest twice. Vyvanse was the highest four times. The next chart looked at it from another direction, sorting by lowest total side effects across nine categories. Ritalin LA had 4, Concerta 23, Focalin 30, Metadate CD 33, Focalin XR 63, Daytrana 64, Strattera 71, Adderall XR 76, and Vyvanse 107. There was no single stimulant

that scored at least 10% higher on a side effect than all the others, but there were three incidences where a drug scored 10% higher than any other stimulants. Strattera had abdominal pain as a side effect 18% of the time, while Ritalin LA and Daytrana both had 0%. Vyvanse has appetite loss as a side effect 39% of the time, while Focalin had 6% and Ritalin LA and Concerta had 2%. Vyvanse had insomnia as a side effect 19% of the time, while Focalin, Focalin XR, and Strattera all had 0%. The following information came from the Oregon Evidenced-Based Center report on stimulants in children. There's a lot of data out there comparing the short-acting versions with the extended-release. Comparing the short-acting methylphenidate versus the long-acting versions in children, they were unable to identify significant differences in symptom improvement. There were some studies that had conflicting results, where the short-acting methylphenidate showed less efficacy at times than the Concerta version. However, this mainly occurred when there was a beneficial difference favoring Concerta in open label studies, not double-blind studies. So if one insisted on a higher level of evidence, there's no substantial difference. There is very little head-to-head data on the short-acting versus long-acting drugs, but what is available doesn't favor the long-acting versions. There is some data comparing long-acting to long-acting versions of drugs. From several small crossover studies, there's some data showing that Ritalin LA was superior to Concerta, but again that was just on some of the efficacy measures on the outcomes, not all of them. Oregon didn't think these were the best studies, and only rated them as fair. There was also some limited evidence showing that Metadate CD was superior to Concerta, but it was strange in the sense that it was only better in the morning. Both drugs were the same in the afternoon, and Concerta was better in the evening. Thus, it's really difficult to prefer one long-acting version over another because of such a mixed bag of results. There are various studies out there comparing short-acting to short-acting versions. Evidence clearly shows that there's no substantial difference between the Dextroamphetamines and the short-acting methylphenidates. There are several trials out there that show that Adderall is superior to methylphenidate, but again it's fairly limited evidence. It's not clear superiority. There were some studies that compared short-acting dextroamphetamine to Adderall, but Oregon felt the studies were fairly poor. There was also another arm of that study that compared long-acting dextroamphetamine to the short-acting dextroamphetamine, and at least in the afternoon the long-acting version was better. They thought that compliance was worse in having to take the multiple short-acting tablets. The data was so insubstantial on comparisons of Focalin to other drugs that Oregon didn't feel they could say anything about it. One particular study of Vyvanse compared to Adderall XR, which concentrated particularly on the SCAMP DS scores, found that it was comparable to Adderall XR. There were a couple of studies comparing Strattera to the short-acting methylphenidate (no difference in efficacy) and to Adderall XR, which was found to be superior to Strattera on most efficacy measures. There really isn't much in the way of good evidence from head-to-head studies comparing side effects in children. When short-acting methylphenidates were compared to long-acting methylphenidates, there was no evidence of any difference in adverse events. When different versions of long-acting methylphenidate were compared to each other, there was no difference in the head-to-head trials. When dextroamphetmine was compared to short-acting methylphenidate, there was some limited evidence suggesting weight loss was worse with dextroamphetamine than methylphenidate. When Adderall was compared to short-acting methyphenidate, the BID dosing on Adderall led to significantly higher rates of loss of appetite and sleeping problems

compared to methylphenidate. When short-acting dextroamphetamines were compared to long-acting dextroamphetamines or to Adderall, temporarily there was greater weight loss with Adderall and the long-acting dextroamphetamine, but it didn't hold up over time. Strattera had significantly more vomiting and somnolence that short-acting methylphenidate and Adderall XR, but the short-acting methylphenidate caused more abnormal thinking. When Vyvanse was compared to Adderall XR, there were no significant differences in side effects. So even though Vyvanse's side effects look bad on the table based on placebo trials, in head-to-head trials it doesn't hold up as being significantly different. In terms of long-term safety issues, obviously there aren't any direct head-to-head trials comparing long term side effect rates, so everything is based on observational studies. When short-acting dextroamphetamines were compared to methylphenidates, they came up with mixed findings in regards to effects on height in children. In one case there was no difference to what happened to height over a six year period. In another one of the observational studies, dextroamphetamine had a stronger effect in decreasing growth across a two year period. When short-acting methylphenidate was compared to un-medicated control groups, no significant differences were found. Strattera only had transient effects on height, and they didn't hold up over time. In comparing short-acting dextroamphetamines to methylphenidate for effects on weight, the studies consistently show that dextroamphetamine had a stronger effect at suppressing weight in the first two years. However, over time, the two drugs became comparable and neither had a strong effect, regardless. There were some non-direct comparative studies on Concerta and Strattera, and neither of them seemed to have any substantial weight suppression effect long-term. In uncontrolled studies of Strattera, the worst thing that could be said was that its effect on weight was comparable to methylphenidate, but again probably mostly transient. For looking at ticks, seizures, and cardiovascular events, there's no comparative data out there at all. Going back and pooling the original placebo studies, Oregon doesn't feel that there's any data that really supports stimulants as causing ticks. Chuck Wadle inquired if there was any info on modafinil, since it was listed as preferred on the draft PDL. Dr. Clifford replied that if manufacturers of the drug used existing data comparing modafinil to placebo to seek an indication for ADHD, then it would get it. However, in terms of efficacy to the existing products, there's nothing to say it's superior, or that it brings anything new to the table. That said, there is definite off-label use of modafinil for ADHD. Dr. Clifford reiterated that the primary aim of the meeting, in terms of dealing with the parameters laid out by the legislature, was to concentrate first on the drugs that have something very chemically similar and establishing how they would be treated on the PDL. Dr. Frier asked for clarification on how these drugs would be treated when not being used for mental health, such as for sleep apnea and MS. In terms of the law, the legislature is not talking about holding drugs down to just their indication. Instead, it wants the committee to take a look at the evidence of the drug. Sue Purcell commented that the committee has an opportunity to work with the psychiatric community now, and come up with some agreements. Dr. Clifford stressed that the committee first needed to address drugs thought very clinically similar: dissolvable versions, extended-release versions, pro-drugs, metabolites, and isomers. He believes there is a good legitimate reason to go after other drugs, but it's just a matter of timing. The drugs that have been presented were researched heavily before being brought to the committee to be addressed at this meeting. Matt Osterhaus asked if they could look at similar molecular products' structures: Metadate CD (non-recommended), Concerta (recommended), and

Ritalin LA (non-recommended). When brought onto the draft PDL, the Concerta was listed as preferred. He wondered if this was a financial decision. Dr Clifford reviewed the reasoning on the methylphenidates. He gave a clinical nod to the methylphenidate short-acting generics, but there was no good evidence to suggest anything else demonstrating a significant improvement over those. Then he looked at first line therapies, and possibly getting better compliance with long-acting versions, as well as CMS and supplemental rebates. The combination of these factors is why the generic methylphenidate cr, Focalin, Daytrana, and Concerta are all shown as preferred on the draft PDL.

XIV. RDL Individual Drug Recommendations and Voting (Stimulants): It was recommended to change all strengths of Vyvanse, Adderall, Focalin, Focalin XR, and Daytrana from recommended to preferred. It was recommended to change Metadate CD from non-recommended to non-preferred. It was recommended to change Concerta from recommended to preferred. It was recommended to change Ritalin LA from non-recommended to non-preferred. Methamphetamine hcl will be removed from the PDL because it is no longer being made, and dopram will also be removed because it is only to be used in a hospital setting. Finally, it was recommended to change Strattera and Provigil from non-recommended to preferred. Mary Larew motioned to accept these recommendations, Bruce Alexander seconded, and the motion passed unanimously.

XV. RDL Discussion and Deliberation (All Other Categories): The only recommended change was to make Novoseven RT Injection 1mg, 2mg, and 3mg recommended in the Antihemophilic Agents category. Bruce Alexander motioned to accept the recommendations for the remainder of the RDL categories, and Priscilla Ruhe seconded. The motion passed with no objections.

XVI. Antipsychotic Clarification: Susan Parker asked the committee to clarify the intent of their decision on atypical antipsychotics, did they want the member to just fail a preferred agent or did they intend the prior authorization criteria to be amended to include failure on the parent compound first. There are PA forms now for Seroquel XR and Luvox CR that require the member to fail on the parent compound first. Risperdal M-Tab, Zyprexa Zydis, Abilify Discmelt, and Invega will be added to this PA form with similar criteria. To receive a PA for Risperdal M-Tab, there would need to have been a failure on Risperdal, failure on Zyprexa for Zyprexa Zydis, Abilify for Abilify Discmelt, and risperidone for Invega.

The P&T committee will be emailed a copy of these minutes for approval so that they may be supplied to the Mental Health Workgroup prior to their December 12th meeting. A motion was made by Hayley Harvey to adjourn the meeting. Chuck Wadle seconded the motion. All in attendance approved. The meeting adjourned at 4:45 p.m. The next scheduled meeting will be March 12, 2009.