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By Lynne Peterson

SUMMARY

The attention-getters at the meeting were: Lithium, Corcept Therapeutics' mifepristone (RU-486), and Forest Labs memantine. ♦ Despite the weight gain issue, doctors are not abandoning Lilly's atypical antipsychotic Zyprexa. They are trying Bristol-Myers Squibb's Abilify, seem to like it and find it comparable to Zyprexa, but they noted some agitation associated with Abilify. ♦ Sources are not at all optimistic about the outlook for Merck's Substance P. ♦ Lilly's Strattera for ADHD has not impressed sources as superior to other ADHD drugs. ♦ The FDA is putting increased emphasis on dose responses and finding the best, not the highest, dose. The agency may start requiring longer term data for labeling, is unlikely to accept surrogate endpoints, and will continue to refuse to allow superiority claims.

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Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-8387 Fax 772-334-0856
www.trends-in-medicine.com

New Clinical Drug Evaluation Unit (NCDEU) Meeting

Boca Raton, FL
May 27-30, 2003

This annual psychopharmacology meeting is sponsored by the National Institute of Mental Health.

There are not many exciting agents on the near horizon, sources agreed. Asked what new drugs are expected in the next three to five years, a Merck official said, "There will be a couple of new drugs for depression and a couple for anxiety…I'm not optimistic that this will be true in schizophrenia or bipolar disorder….but we'll see drugs for anxiety and depression in two to five years." An NIMH (National Institute of Mental Health) official said, "We'll need collaboration between industry, government and academia…and I hope our discussion will allow more creative collaborations to get new molecules out there to think about."

The new director of NIMH said, "I wouldn't be surprised if we look back at this as the Dark Ages of psychopharmacology." He indicated NIH may consolidate some of its institutes, "The new NIH director thinks 27 institutes are too hard to manage…He wants to find a way to consolidate or to manage the various institutes in a consistent manner." However, he praised the new collaboration between government, industry and academia – the molecular libraries project.

The three agents that generated the mo st interest at the meeting were:

- **Lithium** as a neuroprotective for Alzheimer's disease. Abbott's Depakote (valproate) also is being tested for this indication, but the enthusiasm at the meeting was for lithium.

- **FOREST LABORATORIES' memantine**, to improve cognition in Alzheimer's Disease. An NIMH official said memantine also is being explored in depression, "We are in the middle of a proof-of-concept study with Forest on whether or not this shows anti-depressant activity." (For more information on this see the Trends-in-Medicine Quick Pulse: **Memantine, June 2003.)**

- **CORCEPT THERAPEUTICS' mifepristone (RU-486)** for severe depression. Mifeprestone is a cortisol receptor antagonists. A Phase IIb study of 30 psychotic patients treated as in-patients found an 18% response with low dose (50 mg) mifeprestone, and a 42% with a higher dose (600 or 1200 mg).

  There also was a change in psychotic symptoms (a reduction of 50%, from 63% down to 27%). A speaker called this the most exciting anti-depressant in development, "Five patients with psychotic depression treated with 600 mg Mifepristone for four days showed dramatic clinical improvements."

Mifepristone (RU-486)

Measurement	600 mg for 7 days	Placebo
Study 02: Existing Medications permitted		
BPRS	28 days: Equal to placebo 7 days: 22.6 ($p<.05$)	28 days: Equal to drug 7 days: 12.1
50% reduction in HAMD	28 days: 51.5	28 days: 51.4

A researcher asked, "Does it work? There is a signal that it does, and the ongoing study should say. We still have questions about whether treatment leaves a patient less likely to recur and the mechanism of action." He said once-a-week dosing was selected because once-every-four-days was thought too short. NIMH officials complained that there are not enough trials ongoing in obsessive-compulsive disorder (OCD), bipolar disorder, autism, or eating disorders such as anorexia. An official said NIMH is looking forward to the results of the 400-patient adolescent depression study, which just finished enrollment and the STAR-D study in treatment resistant depression, which has enrolled more than 2,000 patients.

Future neuropharmacology drug development will require thinking differently, speakers agreed. They predicted more focus on combination therapy and genomics. An NIMH official wondered, "How will industry deal with phenotypic differences and differences in efficacy associated with that when we currently have low-cost, low-tech phenotypic differences we can detect?…In many cases there are male/female differences, differences based on menopausal status or smoking status – yet those subgroups analyses are not routinely done. So how will we deal with more complex issues in the future?…If you genotype in trials, you might lower the placebo effect, and I'm not sure pharmas will do that…Industry has become very conservative, picking targets that they feel will work, and less likely to invest in high risk/high gain drugs." A Merck official responded, "In the long-run, pharmas will have to do that or they won't be successful…That is the wave of the future…It will happen and companies have to adapt to that world...and it will be great for patients." A researcher said, "I think part of the challenge is for pharmaceutical industry and NIMH to fund trials that evaluate combination treatments. If they do that, we might find an agent which is modestly effective as monotherapy but which is highly effective in combination…In my view, in mood and anxiety we need to move from doing efficacy trials and more quickly get into representative patient populations." A pharma official described current research in depression as "very exciting," adding, "A lot of biology is going on to understand how antidepressants work, the role of BDNF in depression, etc…I don't think depression is where schizophrenia was 30 years ago...maybe it's where Alzheimer's Disease was 10 years ago…As markers become available to determine responders from non-responders, you will find targets that will allow better treatment."

SCHIZOPHRENIA

Cognitive Impairment in Schizophrenia

There is an abundance of data showing substantial cognitive impairment in schizophrenia, and cognitive impairment is a predictor of poor outcome. While the atypical anti-psychotics have a positive impact on cognitive deficits in schizophrenia, experts said they don't do enough. Clozaril has been shown to have a beneficial effect on selected neuropsychological tests and actually enhances performance on a broad range of domains, leading to improvement in verbal but not visual memory. Visual memory may worsen with Clozaril. Risperdal and Zyprexa exhibit selective cognitive benefits. None of these drugs restores normal cognitive functions.

Thus, experts are searching for other adjunctive therapies for the treatment of cognitive impairment in schizophrenia. Among the agents being studied is **Pfizer's Aricept (donepezil)**. A six-week open label study of Aricept found the most profound effects were on manual dexterity and processing speed. There also were benefits reported on verbal and visual memory, suggesting this is a strategy that may lead to enhancement of cognitive function through modulation of the cholinergic system.

Schizo-affective Disorder

Currently, the FDA considers schizophrenia and schizo-affective disorder as two different conditions—because that's the way they are listed in diagnostic nomenclature (DSM-IV). An FDA official said, "If the community rises up and says they are the same disease, then we would listen, but that hasn't happened…Companies were taking advantage of labeling…They wanted to claim schizo-affective without doing those trials…Don't ask us to approve broad claims if there is no data to support that, if they really are different claims."

Suicide

Suicide is a major problem in schizophrenia. One in every 250 schizophrenics dies of suicide, 50% attempt suicide, and there is a 10% lifetime prevalence of suicide. An FDA review of Clozaril trial data found there was a reduction in suicidality, but not sufficient for labeling. The INTERSEPT trial is examining schizophrenia patients at high risk of suicide to see if either Clozaril or Zyprexa reduces their suicidality. This prospective, randomized, international, parallel-group study will last two years.

BRISTOL-MYERS SQUIBB'S Abilify (aripiprazole)

Doctors indicated they are trying Abilify and are fairly happy with the results, but most emphasized that Zyprexa is still number one – "because it works." The weight gain (*See Weight Gain section below*) with Zyprexa is a concern, but

repeatedly, doctors said treating the psychosis comes first, and Zyprexa is very good at doing that. Abilify is doing better out of the gate than Pfizer's Geodon (ziprasidone) did, but most sources were not yet impressed enough with it to prescribe it ahead of Zyprexa – yet. One expert said, "Abilify is very, very good. There is some agitation, but you just need to taper the other atypical after you start Abilify. Abilify is equivalent to Zyprexa, but I won't abandon Zyprexa, even if there were a black box on it. There are populations that will respond to each of the atypicals."

JOHNSON & JOHNSON'S Consta (long-acting risperidone)

There was surprisingly little discussion of this agent, which was a hot topic at last year's meeting. A J&J researcher would say only, "We are working on it with the FDA, but I can't make a time prediction."

In a EUFAMI (European Federation of Associations of Families of Mentally Ill People) survey of 441 compliant patients on antipsychotics found:

- 60% had significant weight gain.
- 91% reported side effects related to the atypical antipsychotic taken.
- 54% reported weight gain as the most significant side effect.

Typical weight loss medications have little impact on the weight gain associated with psychotropic drugs. Abbott Laboratories' Meridia (sibutramine), for example, is contraindicated in patients on an SSRI, Roche's Xenical (orlistat) has unpleasant side effects, and the side effects of Johnson & Johnson's Topamax (topiramate) include glaucoma and an impact on cognition. A researcher said, "Naltrexone warrants further evaluation. A study found it stopped or reversed weight gain, and all patients reported a dramatic decrease in food craving…Amantadine also warrants further study. It has a good safety profile, reasonable cost and low abuse potential. A small study found it slowed weight gain, with weight change strongly correlated to length of amantadine treatment…Weight management strategy is still best met with exercise and diet at the outset of treatment. Preventing weight gain at the start of treatment is a crucial step."

ALZHEIMER'S DISEASE

See the*Trends-in-Medicine* Quick Pulse report on **Memantine, June 2003,** for coverage of Forest Laboratories' memantine from NCDEU.

Psychosis and Agitation of Alzheimer's Disease

Psychiatric and behavioral disturbances are an important part of Alzheimer's Disease, but this has not been the focus of most drug development programs. In 2000, the FDA indicated it would be willing to accept psychosis of Alzheimer's Disease as a focus of a development program, but there would need to be: (a) two studies and (b) two primary outcomes, with both a measure of psychosis and a global or functional improvement measure.

Physicians have been prescribing atypical anti-psychotics off-label for this purpose, but the FDA recently put a warning in the label for these drugs about their use in dementia. An FDA official said, "Our point is that they haven't been shown to be effective in that population…We don't really know anything about the safety (in that population). Our intention is not to say they are manifestly unsafe…but in the context of a warning that there is a particular concern. We are saying, 'Look, we don't even know if they work for this, so think about it before you use them.'"

JOHNSON & JOHNSON/SHIRE'S Reminyl (galantamine)

This currently is dosed BID, but J&J is working on a QD version. PK studies have been completed, and a J&J official said this has moved to clinical trials. One unconfirmed report is that J&J has already filed an sNDA.

NOVARTIS'S Exelon (rivastigmine)

Exelon also is currently dosed BID, but Novartis is not believed to be working on a QD version. Rather, Novartis is working on a patch for delivery of Exelon. The PK studies for this have been done, but the patch has not yet moved into clinical trials.

Weight Gain with Psychotropic Drugs

	Clozaril	Risperdal	Zyprexa	Seroquel	Lithium	Depakote	SSRIs
Average weight gain	10 kg	8.3 kg over 2 years	6.26 kg after 1.15 years	0.42 kg over 6 months	5.9 kg mean gain	7.5 – 11.9 kg mean gain	Weight neutral: Prozac, Serzone Weight gain: mirtazapine Weight loss: Wellbutrin
Notes	4.2/year weight-associated deaths, but prevents 4.9/year suicides	Not dose-dependent, weight plateaued in adults but not kids at 10 weeks	Not dose related, trend toward plateau after first 39 weeks, higher BMI predictor of less long-term weight gain	Glycemic control and weight improved by adding Seroquel to Clozaril	Mean BMI increased from 23.8 to 26.8	Did not plateau	

In addition, a four year trial of Exelon in mild cognitive impairment (MCI) is almost completed. The results will be available in the next few months. The endpoint is delay in diagnosis of Alzheimer's. Investigators will be meeting in two months to look at the data, and it should start to leak then. This is a double-blind, placebo-controlled trial, with the endpoint of time to development of AD.

ANTIDEPRESSANTS

Some of the impediments cited to testing antidepressants with new mechanisms are:

- The high failure rate of trials – due to the high placebo response, lack of dose response curves, imperfect descriptive scales.
- Difficulty using surrogate markers.
- No biochemical or molecular animal surrogate markers.
- No genetic-based models.
- Limited chronic animal models.
- Limited understanding of biochemistry in animal tests.

A Merck official listed the following as the most promising agents in depression: *Substance P analogs, mifepristone, beta 3 agonists, CRFs, vasopressin receptor-1B subtype antagonists, melatonin, and AMPA receptor modulators.*

Substance P analogs

Researchers at the meeting were not optimistic about the outlook for Merck's Substance P program. One said, "Merck is continuing to talk about it, but I don't think it will succeed." Another commented, "It's taking too long. If it were working, it would be moving ahead faster. I doubt it is going to work." A third said, "Merck's been making a lot of noise about markets and imaging – because the efficacy data is just not there. I don't think Substance P will work." A fourth said, "Substance P just doesn't look impressive."

Merck is working hard on understanding Substance P better. The company has been doing PET imaging to determine appropriate dosing. A Merck official discussed the Substance P analog L-759274, which Merck currently has in Phase III trials for melancholia (depression). It reportedly hasn't shown a dose response curve, but a Phase II trial led researchers to conclude that it may have antidepressant properties. The Merck official said, "We deliberately kept the (Phase II) trial to six weeks…This degree of severity was new territory for us, and we were not sure what the traffic would bear. Certainly, there is a possibility that if we had continued the trial we might have seen more separation (of the curves). That is a reasonable question. This is essentially a toe in the water, proof of concept, for us, and it is showing potential. This compound may not be the one to go to war on, but the clinical impression was that the patients were doing a lot better."

- *Asked if Merck's Emend (aprepitant, MK-0869) can be used off-label for depression,* an official said, "We are in Phase III with that agent and charging ahead…That trial is still enrolling…We have a rather active, vigorous program that is moving ahead…This is our original Phase III in depression."
- *Asked why nausea is higher with the second Substance P compound,* an official said, "When we had an active comparator, it tended to be 50% less…I think the choice of design handicapped us…You need to remember that in CINV (chemotherapy induced nausea and vomiting), MK-0869 by itself is not the anti-emetic…It is adding it to dexamethasone that works…Emesis with standard therapy +MK-0869 is significantly less than with standard therapy +placebo…so there is something about MK-0869 that is probably working…to have this effect. To some extent that is perhaps independent of its solo effect, which is quite favorable in other Phase II trials…It would be rather expensive to use MK-0869 off-label for depression…That's not terribly practical…and the way this is dispensed is tightly controlled. The FDA was insistent on limiting use to CINV."

6-Week Trial of Substance P L-759274

Discontinuations	L-759274 n=62	Placebo n=66	p-value
All	38%	37%	N/A
Due to adverse events	8%	3%	N/A
Due to lack of efficacy	5%	6%	Nss
Decline in HAMD	Down ~10.5*	Down ~7.5	p=.009
MADRS improvement	Down ~11.0	Down ~7.5	p=.042
Hamilton-A improvement	Down ~6	Down ~9	N/A
Adverse events	65%	76%	Nss
Headache	15%	17%	Nss
Somnolence	2%	17%	p<.05
Nausea	7%	14%	Nss

* Nss

GLAXOSMITHKLINE'S Wellbutrin XL (buproprion extended release)

Doctors were not very excited about this once-a-day version of Wellbutrin, but they weren't negative either. One said, "It will help doctors think about Wellbutrin, and it will help patients take Wellbutrin. It is an adherence and convenience enhancer." A Wellbutrin XL researcher speculated, "Seizures associated with Wellbutrin could be related to the peak, and Wellbutrin XL maintains a patient on a higher steady state level, so it may have fewer seizures complications…And the once-a-day dosing could expand the use."

Lilly's Cymbalta (duloxetine)

There wasn't any news on this antidepressant, but doctors seemed fairly enthusiastic about it. One said, "It has the potential to be huge and to expand the market. I'm very excited about it."

Lilly's Symbiax (OFC)

Symbiax is under investigation for treatment resistant depression and bipolar disorder. In preclinical data, OFC showed synergy between its two components Zyprexa and Prozac, but an official said, "We've been exploring OFC in treatment resistant depression (TRD) with some frustration. The FDA wants you to beat each individual constituent as well as placebo. We hope if the current trial is positive that we can take it to the FDA in TRD."

Other interesting agents in development to treat depression that were mentioned include:

- **Mifepristone** in psychotic depression.
- **CRFs**. An NIMH official said, "These are interesting preclinically, and the clinical story is that there are abnormalities in the CRF system, not only in depression but in other forms of anxiety disorders. An initial study was stopped, likely due to side effects unrelated to the mechanism…A proof of concept study published with Johnson & Johnson's drug, R121919/NBI-30775, found a higher dose is better than a lower dose…A number of companies are focusing on this, and we await the emerging results, not only in depression but in other mood disorders." A pharma official said, "CRFs may work, but not in depression, which would be a shame but not a killer."
- **AMPA receptor modulators**. Organon has ampakines under investigation to treat neurodegenerative disease, schizophrenia (ORG-24448 in Phase II), and depression. An official said, "Ampakines represent a novel mechanism towards non-MAO-based therapies for depression. Animal data suggests that ampakines may have anti-depressant properties, but we need to confirm that. The speculation is that they modulate both glutanergic and serotonergic effects…ORG-24448 is in Phase II in schizophrenia, and that is our best hope."
- **NK1 antagonists**. An NIMH official said, "This is a story we are waiting to see…Merck has developed an NK1 receptor ligand for imaging studies…and Merck is collaborating with us in looking at whether the ligand will help determine if there are abnormalities in the NK1 receptor in patients with depression."
- **NMDA antagonists**. Addicts sometimes take ketamine, which they call "Special K" for the acute sense of euphoria it produces in low doses. However, a proof of concept study found that a single dose of ketamine in depressed patients could cause a substantial change in Hamilton (HDRS) score that lasted for days. A speaker said this study needs to be replicated but is very interesting.
- **AVENTIS'S M-100907**, which NIMH is testing with escitalopram (Forest Lab's Lexapro) in treatment resistant major depression (TRD).
- **Beta 3 agonists**.
- **Vasopressin receptor-1B subtype.**
- **Melatonin.**

ANTI-ANXIETY AGENTS

Interesting anti-anxiety agents include:

- Selective GABA-A agonists with less sedation, less addiction, less alcohol interaction.
- Selective metabotropic glutamate receptor antagonists.

PFIZER'S pregabalin

A Pfizer researcher said, pregabalin, a reuptake inhibitor of GABA, seems to work by binding to the $\alpha 2\delta$ subunit of the calcium channel, "I think that means that downstream, you get a decrease in the release of glutamate, substance P, norepinephrine, etc. There is no direct effect on GABA…There is no data on pregabalin in depression, and no trials going on in depression, but there have been more than five short-term studies in anxiety. We filed in Europe for pain and epilepsy in March 2003, and GAD will follow. We will file later in 2003 in the U.S. as well."

Questions have been raised about whether pregabalin causes somnolence, but sources did not see this as a problem.

Pregabalin may be useful in:

1. Epilepsy, as an add on.
2. Neuropathic pain.
3. GAD.

LILLY

Lilly has two anxiety medications in development, but an official said neither will be on the market before 2006 or 2007:

- **Lilly's LY-354740**, a rationally-designed, constrained analog of glutamate. A Lilly official said, "In four out of five animal tests, LY-354740 showed a positive effect on stress and anxiety…(but) there were some ambivalent results in the last test (a conflict test). This does not have the adverse events of benzodiazepines…There is no evidence that it impairs learning or new memory." In human tests in generalized anxiety disorder (GAD), LY-354740 was tested at 20 mg and 200 mg and showed a significant reduction in startle potentiation, indicating it may be an effective anxiolytic without sedation. There was no evidence of rebound after discontinuation.

➢ **LY-544344**. A U.K. trial found no effect on cognitive functioning (including memory processes and psychomotor performance) or sleep and no daytime sedation, no alcohol interaction, and no significant effects on car driving performance. In a large trial in mild-to-moderate GAD testing 100 mg BID and 200 mg BID, side effects were comparable to placebo but far less than lorazepam, which had an 8% discontinuation rate.

Results of U.K. Study of LY-544344 in GAD

Measurement	Placebo	LY-544344 100 mg BID	LY-544344 200 mg BID	Ativan (lorazepam)
Mean HAMA reduction from baseline	-7.58	-9.51	-9.01	-9.82
Somnolence	1.0%	1.5%	3.5%	20.9%
Headache	7.4%	2.5%	4.5%	7.5%
Nausea	5.4%	3.0%	5.5%	5.2%
Dizziness	1.5%	1.5%	1.5%	8.2%
Disrupted attention	1.0%	0.5%	1.5%	9.0%

ADHD

There were several posters on ADHD, but not much, if any, new data. Doctors were asked how the various ADHD therapies – Novartis's Ritalin (methylphenidate), Johnson & Johnson/Alza's Concerta (methylphenidate), Shire's Adderall (amphetamine), and Lilly's Strattera (atomoxetine), and their comments included:

- "There is more kick-start with Ritalin LA than with Concerta or Strattera."
- "If patients have a history of abuse or a potential for abuse, then Strattera moves up my list of options. If not, it moves down. The efficacy of Strattera is less in clinical trials than other agents. However, I'm already using it in adults."
- "Strattera has tolerance issues in kids."
- "Adderall XR (Shire) also will have an adult indication soon."

Cephalon's Provigil (modafinil) also is being tested in ADHD. A researcher said, "Stimulants are still No. 1, but this is good if there is an abuse potential, or for kids with ADHD without hyperactivity. I think it has more effect than Strattera. Provigil works through the histamine system, not dopamine, and it is non-scheduled. It's used a lot off-label for adults…Provigil is more tolerability in kids than in adults, and it is well-tolerated in adults…Clinical trials are planned." It appears that 300 mg QD is the optimal dose for ADHD, though a researcher said the dose may be able to be optimized further.

SUBSTANCE ABUSE

➢ In a Phase I study of 12 normal volunteers, GBR12909 was dosed at 25-50-75-100 mg QD for 11 days, followed by a washout, and then dose up titration. There was a good dose response curve. Blood pressure and heart rate increased for three days after dosing, causing an expert to conclude, "We need to watch the cardiovascular effect, looking at metabolites. But there was no QTc in worrisome ranges, which was seen at 150 mg in previous studies. We think we found the dose – 100 mg. Now, we are doing another study to look at metabolites and safety. That study is halfway done, and then there will be a Cocaine Interaction Study."

➢ NS2359 is a monoamine uptake inhibitor. Three Phase 1 safety studies of single and multiple doses have been completed.

➢ Amantadine has been studied before as an agonist, and most of data was negative. However, it did show reduced cocaine desire in subjects with high cocaine withdrawal syndromes, so a researcher said there may be promise for subgroups.

Drugs in Development by NIH for Substance Abuse

Phase I	Phase IIa	Phase III
GBR12909	Odansetron	Selegiline
NS2359	Modafinil	Disulfiram*
Modafinil		
Metyrapone	**Phase IIb**	
RPR-102681	Reserpine	
Aripiprazole	Cabergoline	
Quetiapine	Tiagabine	
Disulfiram	Baclofen	

*** Planned**

MISCELLANEOUS

Other interesting agents in development:

- **Riluzole (Aventis's Rilutek)** – which is approved for ALS (amyotrophic lateral sclerosis), may have neuroprotective properties as well. An open design study reportedly showed "a hint of some efficacy."
- **Felbamate (Wallace's Felbatol)** – which was described as an interesting anticonvulsant that has been shown to be helpful in highly treatment-resistant bipolar patients, maybe because of an effect on the glutamate system, but which has hepatotoxicity.
- **PDE4s.** Reportedly, clinical studies with these agents as adjunctive therapy in Alzheimer's Disease are getting underway.

- **MAP Kinase phosphatase inhibitors**.
- **PKC inhibitors** for mania and anxiety. A NIMH official said that a preliminary study suggests that tamoxifen (AstraZeneca's Nolvadex) has an anti-manic effect and that larger clinical studies with tamoxifen are underway.
- **GSK-3 inhibitors** for mood stabilization.
- **Neuropeptide Y (NPY)**. A speaker said, "This is a good target for anxiety, affective disorders and substance abuse. It's the most potent compound I've seen in these models. NPY_{1-36} is the most potent, then PYY and NPY_{2-36}, and the least potent is NPY_{13-36}…In depression, the studies have been inconsistent over the years…but NPY is an attractive target in anxiety, affective disorders and alcohol dependence."

ARCHEMIX'S ARC-18

This is an aptamer for use in CABG surgery that would compete with heparin or the Medicine Company's Angiomax (bivalirudin), but not with warfarin. First-in-man studies are due to begin in 2004.

With the exception of Eyetech's Macugen (pegaptanib, EYE001), Archemix got all of the rights to aptamers from Gilead (with no royalties due to Gilead). An Archemix official said, "Aptamers take best of antibodies and small molecules without the negatives." The key features of these aptamers are their:

- High affinity and selectivity.
- Long half life (several days when conjugated with polyethylene glycol).
- Low cost of goods (~$800/gram).
- Low toxicity.
- Administration options. It can be given IV, IM or subcutaneously – but not orally.
- No antibody formation.
- Storage at room temperature.

Among the other aptamer applications Archemix is exploring are:

- ➢ Anti-HIV-1 RT aptamer.
- ➢ An anti-PDGF-A or –B for ophthalmic diseases such as proliferative vitreoretinopathy (PVF).
- ➢ ARC-126 for glomuleronephropathy.

THE REGULATORY SITUATION

An official of NIMH noted that collaboration between government and industry in psychiatric drug development "is not where it is in other areas, like oncology." In an effort to improve interaction between NIMH and the FDA, a joint meeting will be held in April 2004 to consider new approaches to drug development and new ways to assess cognition (imaging, etc.).

One of the problems in psych drug research is the lack of valid animal models. An expert said, "Inclusion of non-verbal measure of working memory would allow analogous animal models for drug development."

Agreeing on standard tests for neurocognition would also be helpful to drug development. The MATRICS task force is currently assessing candidate tests. In September 2003 there will be a panel of experts who will rate the qualities of the most promising candidate tests...and then the committee will select the top one or two tests per domain for an initial psychometric validation study. The MATRICS neuro-cognition committee chose seven cognitive factors for the NIMH cognitive battery, and they are mostly independent, with only mild correlation to each other.

Cognitive Domain	Related to Functional Outcome
Working memory	Yes
Attention/vigilance	Yes
Verbal memory and learning	Yes
Visual memory and learning	Yes
Reasoning and problem solving	Yes
Speed of processing	Maybe
Social cognition	Maybe

An expert said the FDA may not view performance on cognitive measures alone as sufficient evidence of patient improvement for drug approval but researchers are reluctant to set the bar too high by requiring a change in functional outcome because that is likely to lead to trial failure. The answer, he said, may be to develop proxy measures of outcome, which is what the MATRICS team is wrestling with now.

FDA officials discussed some of the agency's current concerns in this field, including:

➢ **The need to show a dose response.** One official said, "Often, it is the case that we don't have good dose response information with psych drugs…With the exception of HIV…you need to show a dose response…As a division, we will be asking for more dose response information in the future in applications – not necessarily in every single incidence, but it *is something we have not paid enough attention to, and we will be looking at this much more closely in the future." Other comments made about this issue include:*

- "It is the exception not to show a dose response."
- "When the study endpoint or adverse event is delayed, persistent or irreversible (i.e., treatment of depression), titration and simultaneous assessment of response is usually not possible, and a parallel dose response study is usually needed."

- "Typically in psych development, there are flexible range studies without fixed doses…and that makes it difficult if not impossible to determine the dose response and makes it difficult to write coherent labeling."
- "Because trials cannot identify an effective dose, they may pose safety problems…Specifically adequate safety experience must be obtained at the highest dose."
- "In flexible dosing, it is difficult to know how physicians themselves know when to stop titration…You may say patients not responding are pushed to the highest dose…(but) I'm concerned that patients may be pushed to the upper end of the range when a lower dose may be as effective."
- "Flexible dose studies are not useful in characterizing the dose/concentration response curve, especially in psychiatry."

➢ **Dose does matter.** Several drugs have been approved at one dose, but the preferred dose turned out to be much, much lower. An FDA official said, "There is still a perception that sponsors focus on higher doses for a 'win.'"

Dose-related changes in labels: 1980-1999

Specialty	% of NMEs with dose changes in the label
Neuropharmacology	27%
Cardiology	19%
Oncology	19%
Antiviral/anti-infective	25%

➢ **Superiority claims.** An official said, "Some divisions of FDA – not ours -- have approved superiority/comparative claims in labeling…because of (1) inadequate characterization of the dose-response for most psychotropics, (2) lack of information on what are equivalent doses, and (3) lack of information on multiple fixed doses of the NME and the comparator. This would take a big trial, and that generally is cost-prohibitive." Another official said, "What the FDA is concerned about is celebrating findings not worth celebrating, such as focusing on parts of a syndrome that respond the same way other parts respond. If you have differential efficacy, then there is a reason to celebrate...If you can show certain symptoms are non-specific (e.g., pain, fever), if we understood psychoses and could show that same psychosis is there in other areas, then there would be a reason to celebrate…I don't think we are anywhere close to that. Psychosis in schizophrenia doesn't even seem to have the same phenomenology…So we have a lot phenomenology and not a lot of understanding."

➢ **Maintenance data.** An official said, "To date, we have not generally required maintenance data prior to approval…(but) there is tremendous pressure to make this done prior to approval. Currently, it is routinely required as a Phase IV commitment…but we are interested in obtaining this data prior to approval."

➢ **Longer term data needed for labeling.** An official said, "We believe it is the open label phase that determines the duration of effects...and many studies we see have a relatively short open label (8-10 weeks vs. 68 weeks of drug)…We think six months is a reasonable period of time…In fact, our labeling currently, when it speaks about duration, usually has a statement based on the randomized phase that the drug has been shown to be effective up to 52 weeks...I think that is probably misleading because the duration of effect is learned from the open label portion of the trial, and it is difficult to know in a randomized phase the effect with dropouts and relapses along the way…I think label claims currently are potentially misleading…and we will be looking at that very closely in the near future."

➢ **Accelerated approval.**

➢ **Use of surrogate endpoints.** Drugs to treat cancer, hypertension and cholesterol have been approved on surrogate endpoints, which are useful where the clinical benefit is likely to be well in the future or where the implication of the effect on the surrogate is great because there is no other therapy. However, an FDA official said, "There has to be a big payoff…Surrogate endpoints are not likely to be accepted where clinical effects are easily measured, for example in epilepsy, depression, and psychosis."

Surrogates generally decrease the duration and size of studies, but a correlate is not a surrogate and validation of a surrogate requires that the effect of the intervention on the surrogate endpoint accurately predicts the effect on the clinical outcome. An FDA official said, "With a surrogate, a change in a very sensitive measure may not translate into a clinically meaningful effect."

➢ **Cognitive impairment.** Currently, schizophrenia is viewed by the FDA as a single clinical target, and new anti-psychotics are approved for "the treatment of schizophrenia." Cognitive deficits are acknowledged as one aspect of the schizophrenia syndrome but are not teased apart as a distinct target, and they are not even a part of the DSM-IV criteria for diagnosing schizophrenia.

➢ **Pseudospecificity.** The FDA considers a drug claim to be pseudospecific if it is found to be artificially narrow. For example, a claim might be ruled pseudospecific if it focused on a (a) subgroup/subset within an ill population, (b) particular aspect of an illness (e.g., a symptom), or (c) one model of a non-specific symptom. An official said, "The judgment of pseudospecificity would be based on lack of empirical evidence to support such a narrow focus…Pseudospecific

claims serve only promotional purposes, implying an advantage over other drugs in the class regarding that subgroup/symptom…Our preliminary judgment of pseudospecificity is subject to being disproved and can be overcome if a sponsor shows:

- Their drug is superior to other drugs in the class regarding that subgroup/symptom.
- Their drug is only effective in that particular subgroup or symptom.

Examples of a pseudospecific claim:

- Antidepressant only in women.
- Hallucinations in schizophrenia.
- Dental pain.

The FDA's position is that, until proven otherwise, a narrow claim is pseudospecific, and the burden is on the sponsors to provide evidence to overturn that. An official offered these examples:

- If a company wanted to study a drug for depression but only in women, we would consider that pseudospecific.
- If a company wanted to develop a drug only for hallucinations in schizophrenia, we would want it to study the drug across all the spectrum of schizophrenia symptoms.
- If a claim is for a non-specific symptom like dental pain and would celebrate that finding, we would say it is too broad. Study the drug in all pain models."

Questions the FDA asks when evaluating a pseudospecific claim include:

1. *What is the phenomenology and the course?* Are the cognitive deficits distinguished from other aspects of the illness? An official said, "Cognitive impairment probably is a separate domain. There is some thinking that cognitive impairment may predate the onset of diagnosis."
2. *What do experts think?* An official said, "Most experts do feel that cognitive impairment is a distinct aspect of illness, though it is not yet recognized in DSM-IV."
3. *What is the evidence to show a differential response?* It is important to show that some drugs are more effective than others.
4. *What is the mechanism?* If the mechanism of cognitive impairment were understood, that would help in understanding the treatment, but the mechanism is not yet understood.
5. *Does the cognitive impairment in schizophrenia look the same as cognitive deficits in other illnesses such as Huntington's Chorea or Alzheimer's Disease?* An official said, "My sense…is that while there are some similarities, there are important differences…So, right now, we would be inclined to limit cognitive impairment to schizophrenia and not consider it non-specific."
6. *Is the more narrow claim symptom-specific or non-specific?* Pain and fever are non-specific.

In implementing a development program for cognitive impairment in schizophrenia, the FDA advised sponsors to:

- Define cognitive impairment – is it one domain or multiple domains?
- Consider the variability in the profile and severity of deficits across patients.
- Look at the pattern of deficits over time -- overall for schizophrenia and for individual patients. An official said, "I've heard that cognitive impairment occurs early, often because of the onset of illness and then remains relatively stable over the course of the illness…but what happens with individual patients?"
- Decide what populations should be studied. Is it a problem in all schizophrenic patients or a subgroup. An official said, "My sense is that the general view is that it affects all schizophrenia patients and is not a subgroup, if it were a subgroup, you would need criteria to select the patients."
- Identify the phase of the illness to be studied – acute, residual, prodromal (if it can be detected prodromally).
- Consider the status of other schizophrenia symptoms. Would some level of positive symptoms need to be under control first?

IM formulations of atypical anti-psychotics have their own issues. An FDA official said, "The assumption is that IM formulations are treating the schizophrenic syndrome…The February 2004 advisory panel considered ziprasidone (Pfizer's Geodon) for agitation and Zyprexa IM for agitation in schizophrenia, bipolar mania and dementia…The committee endorsed the new claims but only as a specific symptom for each specific syndrome studied…They chose not to label this non-specific. The FDA could have gone either way – specific or non-specific , so we went with the panel…In retrospect, it occurs to me that we might have asked for a comparison of the IM to the oral to support the claims. We didn't do that…We are not unhappy with the decision not to do that...but logically we should have done that."