Eli Lilly & Company

Cymbalta

For The Treatment of Major Depressive Disorder

U.S. Strategic Pricing Study

Exploratory Qualitative Market Research
Conducted With Payers, Physicians, and Patients

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Study Objectives
PAYERS

- Identify specific contracting strategies currently employed with the antidepressant class; assess opinions regarding contracting strategies
- Identify economic obstacles which could possibly impede the addition of Cymbalta to formulary
- Determine currently formularies for antidepressants, restrictions, rationale of any management of SSRIs versus SNRIs, and recent changes to antidepressant formularies
- Explore assessment of current Cymbalta product profile
- Determine formulary status reaction with contracting at various price points

Study Objectives
PHYSICIANS

- Understand physicians' perceptions of cost and availability of currently marketed antidepressants
- Understand how physicians' perceptions of cost (as they define and think about cost) impact their prescribing behavior
- Identify key elements that shape physician perceptions of cost and availability
- Determine frequency and degree of influence of each such element
- Identify product attributes/ perceived benefits physicians feel justify cost premium

Study Objectives
PATIENTS

- Understand the context in which patients view cost and out of pocket expense (absolute dollars or incremental dollars over alternatives)
- Understand how patient cost affects behavior, both in terms of first prescription and subsequent refills
- Understand frequency and likelihood of pharmacy intervention
- Identify frequency of sample use prior to incurring out of pocket expense
- Understand role of out of pocket cost in making decision to fill either the first prescription or deciding to refill

Strategic Business Decisions The Research Study Will Support

- Findings from this qualitative study will support a determination of list price strategy and rebate strategy for Cymbalta.
- **Findings born out of this market research study need to be viewed and evaluated in the collective context of the totality of qualitative and quantitative studies undertaken to support price and rebate strategy determinations for Cymbalta.**

Methodology and Sample

Interviewee	Interview Type	Sub-Groups	# Interviewed
Payers	Individual Phone Interviews	Pharmacy Directors Medical Directors	21 2
Physicians	Focus Groups	Specialists (Psychiatrists) PCPs	24 23
Patients	1:1 Interviews	Females Males	19 3

I. PAYERS

Summary of Findings

Payer Sample Demographics

- Participants represent Lilly's Top Forty key, validated managed care customers
- Participants were screened for their active involvement in contracting negotiations and decisions
- Twenty-two (21) managed care organizations and two (2) pharmacy benefits management companies are represented

Plan Demographics
Pharmacy Benefit Design

- Three Tier N=14
- Closed, Two Tier N=3
- Open, Two Tier N=2
- Open, Flat Co-Pay N=2
- Closed, Flat Co-Pay N=1
- Four Tier (Tier 3=50% co-pay, Tier Four=Nonformulary) N=1

Managed Care Organizations' Approach To the Antidepressant Class

The Managed Care' View of Antidepressants

- Managed care organizations continue to view antidepressants as an important, yet very costly, therapeutic class.
- Antidepressants remain among the top five classes in terms of overall drug expenditure for all health plans surveyed.
- Most organizations maintain fairly open formularies because they understand the need for and importance of therapeutic options for this complex disease state as well as the highly individualized nature of patient' response.

How Antidepressants Are Reviewed

- Most managed care organizations (two-thirds) view and review the antidepressants as two distinct subgroups:
  - SSRIs
  - All Other Newer Agents (Non-TCAs, AKA "Atypicals")
  - However, one-third of health plans interviewed do view and review the antidepressants as one broad therapeutic class.

Recent Changes Within the Antidepressant Class

- Changes in market dynamics, new entries, and contracting opportunities are what spur non-annually scheduled reviews.
- The two most recent changes within the antidepressant class have been the introduction of generic Fluoxetine and the movement of Prozac to tier three/ nonformulary and the introduction of Paxil CR, which has been reviewed by half of the represented plans (only half of those chose to add the product to formulary.)
  - While the vast majority of plans have conducted a full class review of the antidepressants within the last year, some plans (6 of 23) have not reviewed the totality of the class within the last two years.

Anticipated Changes to the Antidepressant Class
No Actions Taken to Plan for Anticipated Events

- Most health plans know that both patent expirations and new product introductions are likely to occur in the antidepressant class over the next two years; however, they are not taking any actions in anticipation of these events.
  - Almost all know Lexapro will be introduced
  - Some, though less than half, are aware of Duloxetine, though Lilly's product is rarely identified by name
  - Most anticipate patent expirations for Paxil, Zoloft, and Celexa; all are uncertain when they will occur and acknowledge, unaided, that such changes in market dynamics could be significantly delayed by legal actions on the part of the respective manufacturers.

Anticipated Changes to the Antidepressant Class
No Actions Taken to Plan for Anticipated Events

- Health plans are not undertaking strategies to prepare for these changes in market dynamics; most are very focused on the current implications of generic Fluoxetine's entry and trends related to its uptake.
  - A few plans are currently exploring the feasibility of taking action (formulary changes, restrictions, academic detailing) to promote the use of generic Fluoxetine first line for all new starts.

An Overview of the Antidepressant Formulary

The Antidepressant Class: A High Degree of Coverage and Availability

- Health plans surveyed are not exerting a high degree of formulary control over the antidepressant class, with the exception of Remeron and Serzone.
- Effexor / XR is on formulary/ tier two among all plans surveyed.
  - Only one plan has any type of restriction specific to Effexor's utilization, limiting tier two coverage to psychiatrist' use only.
- The vast majority of plans have all three branded SSRIs discussed - Paxil, Zoloft, and Celexa - available on formulary/ tier two.

Current Antidepressant Formulary

- Among all antidepressants, Remeron, followed by Serzone, are the least available on formulary/ tier two.
  - **Half of those surveyed do not cover Remeron for lack of perceived clinical benefit**. Cost and low utilization were cited by a very small minority of plans as the rationale for nonformulary/ tier three status.
  - **Close to half of the participating health plans do not cover Serzone based on safety concerns**.

Current Antidepressant Formulary

- Of the twenty-three (23) organizations surveyed:
  - Four **(4) do not cover Celexa** because of exclusivity clauses/ potential loss of market share incentive rebates with other SSRI manufacturers.
  - Three **(3) do not cover Zoloft** because of contracting issues with Pfizer.
  - Two **(2) do not cover Paxil** because of a perceived lack of cost effectiveness (efficacy, side effects, cost).
  - **Paxil CR is nonformulary/tier three in over half (14 of 23).** Seven plans have not reviewed Paxil CR; five see the product as a patent gimmick without clinical merit; two do not currently have Paxil on formulary.
  - **Wellbutrin SR is nonformulary/tier three within two plans** because of inappropriate utilization for smoking cessation.

Restrictions on Antidepressants

- The majority of plans surveyed do not employ any restrictive action for the antidepressant class.
- The most common restriction on the antidepressants is a tablet splitting program. This restriction is implemented by seven of the twenty-three participating organizations (7 of 23).
  - Three plans institute quantity level restrictions for all antidepressants, also referred to as dose optimization, in which specific dosage strengths are not covered.
  - Three plans implement quantity limits of thirty per Rx.
  - Three require prior authorization of Wellbutrin SR for depression use only; one plan restricts Effexor/ XR and Wellbutrin SR, first line, to specialist' use only.

Early Reviews of Antidepressants

- Antidepressants, with the exception of the initial introduction of Prozac and the advent of the SSRI class, are rarely, if ever reviewed in a faster-than-normative time line.
- For some plans that time line is two to four months; however, for many organizations, the time line for formulary review is a minimum of six months.
- Anti-infectives, chemotherapy agents, MS drugs and HIV therapies are categories most likely to receive the fastest formulary reviews.

Early Reviews of Antidepressants

- Exceptions to this review timeline for antidepressants are rare and would include:
  - One plan reviewed Prozac Weekly within its first two months post-launch because its introduction prompted a re-assessment of the Lilly contract.
  - One plan reviewed Celexa in its first three months to take advantage of a compelling, early acceptance rebate incentive.
  - Future introductions of breakthrough products on the order of Prozac.

Formulary Status: Definitions for Nonformulary, Tier Three, Exclusion

- "Off-formulary" is defined by Pharmacy Directors as nonformulary or tier three.
- For three tier lives, a product that is not added to formulary is automatically placed on the third tier.
- For closed formulary lives, a product that is not added to formulary is automatically nonformulary, and available only through a medical exception approval process.
- Exclusions are products or therapeutic classes that are excluded from benefit design, meaning they are not available, not covered, and for which no medical exceptions are made.

The Antidepressants:
Utilization Monitoring,
Cost Drivers, and Other Key Concerns

How Cost and Utilization Are Monitored

- All managed care organizations monitor utilization within the antidepressant class on a routine basis.
  - Data can be cut numerous ways to reflect key information needs.
  - Plans do take in to account the weighted average of all doses per product in their utilization analysis.
- Standard metrics include:
  - Average paid ingredient cost, Average cost per Rx
  - Percentage growth, Percentage market share by product
  - Cost per Rx PMPM, Cost per Rx PMPY
  - Weighted average cost per day of therapy per 1,000 members.

Cost Drivers: Weighted Dose Distribution, QD/BID Dosing

- Most health plans are not *routinely* assessing whether or not the weighted dose distribution and/ or QD versus BID dosing are having a significant impact on net cost.
- Among plans that have examined this issue, a few different perspectives emerge:
  - This is a recognized issue and the plan has quantity level limits, quantity edits, and/ or tablet splitting restrictions to address it
  - Dose titration is viewed as a necessary component of some antidepressant therapy and the plan is not focused on it
  - There is an acknowledgement among a small number of plans of high dose utilization of Effexor (N=5) impacting net cost, but Effexor is not a high cost/ utilization driver, so no action is taken
  - Wellbutrin SR is cited for dose escalation and BID dosing (N=2), again, no action is being taken because it is not a cost driver.

Most Significant Concerns Regarding the Antidepressant Class *Cost, Compliance, and Outcomes*

- Cost, Compliance and Health Outcomes continue to dominate as the top three most significant concerns regarding the antidepressant class.
- Antidepressants remain in the top five most expensive drug expenditure categories among all organizations surveyed.
- Health plans remain uncertain as to the actual long term value of antidepressant therapy and fear that many, if not most, patients are not staying on medication long enough to achieve and sustain optimal therapeutic outcomes.

An Overview of Current Antidepressant Contracting

Current Contracts for the Antidepressant Class: What Managed Care Finds Most Appealing
Flat Access Rebates with Market Share Incentives

- Flat access rebates with market share incentives (often tiered incentives), are by far, the most preferred contract type; however, there are some organizations that prefer a flat access rebate without any market share incentives for the antidepressant class.
  - Pharmacy Directors emphasize that a rebate has to at least equal the loss of member co-payment dollars lost when a product is moved from tier three to tier two.

Current Contracts for the Antidepressant Class: What Managed Care Finds Most Appealing
Low List Price, Minimal Rebating

- All organizations prefer a low list price and minimal rebating versus a higher list price and moderate rebating:
  - Health plans prefer to have their money up front (time/ value/ $)
  - MCOs believe rebates send a negative message to physicians and members regarding the business relationship between MCOs and Pharma
  - Most do not like the administrative burden of monitoring any level of rebates.

Current Contracts for the Antidepressant Class: What Managed Care Finds Least Appealing
Bundling

- Any type of bundling agreement is viewed by all managed care decision makers as the least appealing contract type because it does not allow for individual clinical determinations for each given product.
  - Managed care views bundled agreements as a forced acceptance of products they may view as clinically inferior, overpriced relative to clinical value, or a "me-too."
- Contracts with particularly restrictive language are also very unappealing:
  - Terms that disallow for contract re-negotiation during the contract period
  - Requirements regarding co-payment ceilings for a given tier.

Current Contracts for the Antidepressant Class: What Managed Care Finds Least Appealing
Bundling

- While many plans find what they refer to as "preference" agreements (AKA as exclusivity contracts) acceptable, a few plans do not like and will not accept contracts with terms that specify that a product can only be one of two or one of three on formulary for a given class or designated product grouping.

An Overview of Current Contracts Within the Antidepressant Class *Pfizer and GSK*

- Most current contracts for the antidepressant class are access-driven with tiered market share incentives.
- Pfizer, and to a lesser degree GSK, continue to have a significant number of bundled contracts and typically require some level of exclusivity within the SSRI class. Some, though not many exclusivity contracts, (referred to by plans as preference agreements) do include Effexor/ XR and Wellbutrin in the formulary product mix.
  - Products are most often not identified specifically
  - Exclusivity for this class is typically defined as one of two or one of three in whatever basket the pharmaceutical company has specified (all branded SSRIs, SSRIs and Effexor, etc.)

An Overview of Current Contracts Within the Antidepressant Class
Wyeth-Ayerst

- Less was recalled, top of mind, regarding the specifics of Wyeth's contracts, in large part because Effexor represents far less drug expenditure for health plans than do the SSRIs.
- Those that could recall specifics state that Wyeth's contract for Effexor/ XR is access-driven, although it appears Effexor/ XR is sometimes bundled with Premarin products.

An Overview of Current Contracts Within the Antidepressant Class
Wyeth-Ayerst

- A few complain that Wyeth's contracts are overly complicated in their terms and language.
- A few indicate that Wyeth requires some level of preference (exclusivity) within the atypical antidepressants, e.g., one of X among Wellbutrin SR, Serzone, Remeron, and Effexor.
  - One Pharmacy Director states that Wyeth is most interested in blocking the availability of Wellbutrin SR and negotiates their contract to this end.

An Overview of Current Contracts Within the Antidepressant Class
Forest

- The phrase "simple and straightforward" was used by numerous participants to describe Forest's contracting.
- Forest was also commended for its willingness to edit the terms of a contract as needed.
- Forest's contracts are access-based (where the plan gets a standard % rebate) and unbundled.

Antidepressant Manufacturers Perceived As Most Aggressive Pricing and Contracting

- Among respondents who believe an antidepressant manufacturer does stand out as most aggressive in its approach to pricing and contracting, Forest is viewed by managed care as the company with the most aggressive approach to pricing and contracting; however, many managed care decision makers feel none of these companies are distinctive or unique in terms of their pricing and contracting strategies.
  - One Pharmacy Director praised both Lilly and SmithKline (in the past) for the most aggressive contracting efforts.

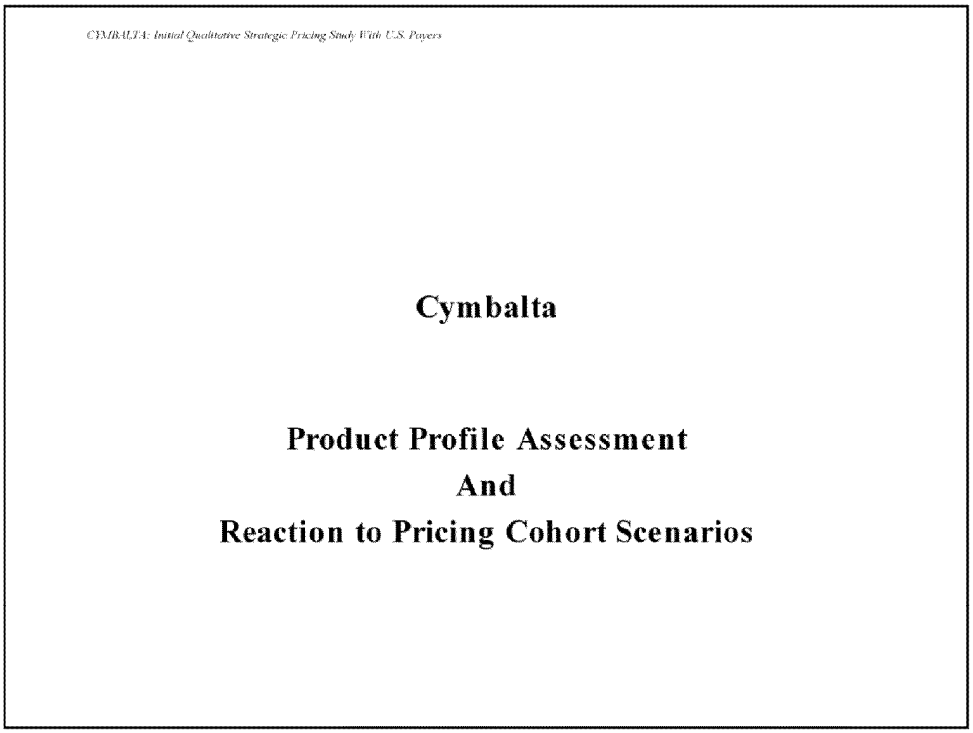
An Overview of Current Contracts Within the Antidepressant Class
Market Share Contracts

- Among plans represented, for market share contracts, the geography used to calculate market share is either the plan alone or against national performance. Plans appear comfortable without whatever geography (plan or national) is being used for their given contracts.

- Market share agreements can be calculated numerous ways.
  - Percent of market share of all SSRIs is the most common market basket for calculation, though the market basket could, and sometimes does, include other products, such as Effexor/ XR and Wellbutrin SR.
  - None of the contracts, among any of these plans, offer high dose protection for any antidepressants.

No Contract Impediments Exist To Hinder the Addition of Cymbalta

- None of the managed care organizations surveyed have any existing contract restrictions that would preclude the addition of Cymbalta to formulary.



Cymbalta Product Profile Assessment Overview
Methodology

- Participants were faxed a current, two-page Cymbalta product profile in advance of the interview and were asked not to read the information until so requested by the interviewer.
- After reviewing the profile during the telephone interview, participants were divided in to three cohort groups to explore reaction to formulary status with contracting at specific price points. Two set price points were provided for each group.
- If the respondent asserted that the product would not be added to formulary at either price point, participants were then asked, unaided, to determine where the product would need to be priced from a net price per day to be added to formulary.

Cymbalta Product Profile Assessment Overview
Price Cohorts

- Cohort Group I: N=8
  - Net Price **Premium to Effexor of 20%**
  - Net Price **Parity to Effexor**
- Cohort Group II: N=9
  - Net Price **Premium to SSRIs of 20%**
  - Net Price **Parity to SSRIs**
- Cohort Group III: N=6
  - Net Price **Parity to SSRIs**
  - Net Price **Discount to SSRIs of 20%**

Cymbalta Product Profile Assessment
Looks Interesting, Lacks Clear Differentiation

- Many participants began their assessment of Cymbalta with the phrase "looks interesting;" however, very, very few went on to ascertain clear areas of differentiation or superiority.
- None, at first blush, without the clarity and emphasis of marketing and positioning, believe Cymbalta offers clear clinical advantage over the SSRIs or Effexor.

Challenges or Limitations Posed By the Product Profile Selected for this Research Study

- The fact that Cymbalta was studied at 80 mg and will be introduced at 30 mg and 60 mg was a major issue for payers.
- For many participants, the lack of onset, efficacy, safety, and remission, data, at dosage strengths that will be marketed, clearly weakened the overall presentation of clinical information.

Challenges or Limitations Posed By the Product Profile Selected for this Research Study

- While some applaud the fact that a head-to-head study was undertaken, several managed care decision makers question why the comparator is Paxil, rather than Effexor, and *why* Paxil 20 mg, which they view as a less than effective dosage strength.

- Additionally, some wording in the profile appeared to mute the overall significance of the information for some participants:
  - Phrases such as "were 112% more likely to achieve remission" were challenged for their clinical merit and statistical significance.

Other Challenges or Limitations
Lack of Understanding of Depression With Physical Complaints

- Managed care decision makers continue to be challenged, unaided, in terms of their ability to understand the relevance, importance, and uniqueness of a product that reduces overall pain in validated somatic symptom and pain scales.
- As a result, four types of responses to this data are expressed by managed care:
  - A *Dismissal* of the information as unimportant
  - An *Assertion* is made that all antidepressants address associated somatic pain
  - *Concern* is expressed about potential cost and utilization as a pain medication
  - Somatic symptoms data is *Overlooked altogether* in the managed care' assessment of the product profile.

Key Product Comparators For Formulary Review
All Formulary Antidepressants and Effexor Specifically

- The vast majority of health plans (18 of 23) expect Cymbalta to be reviewed in relation to all formulary antidepressants - SSRIs and Atypicals.
  - The other five organizations anticipate the review focusing on clinical value in relation to only the Atypicals.
- Based upon its mechanism of action, the key product comparator will be Effexor.
- The introduction of Cymbalta will not prompt plans to view the SNRIs as a distinctive class.

Response to Pricing Scenarios

Cohort Group I: N=8
Cohort A: Net Price **Premium to Effexor of 20%**
Cohort B: Net Price **Parity to Effexor**

- None of the eight participants in this cohort group would expect Cymbalta to be added to formulary at any premium to Effexor.
- Without significant clinical superiority, which was not immediately evident to participants, none would expect Cymbalta to be added to formulary at net parity pricing to Effexor.
- Expectations for where Cymbalta would need to come in, from a net price per day, to be added to formulary, ranged from a 10% to a 40% net discount to Effexor; one Pharmacy Director indicated a 25% to 30% net discount to Celexa is needed.

Response to Pricing Scenarios

Cohort Group II: N=9
Cohort A: Net Price **Premium to SSRIs of 20%**
Cohort B: Net Price **Parity to SSRIs**

- None of the nine participants in this cohort group would expect Cymbalta to be added to formulary at any premium to the SSRIs.
- Four of nine definitively believe Cymbalta would be added at parity to the SSRIs. One additional respondent feels it would be added if parity priced to, specifically, Celexa.
- Among the other four respondents, expectations for where Cymbalta would need to come in, from a net price per day, to be added to formulary, ranged from15% to 20% less than a clinically equivalent SSRI, to $2 per day, to some degree of price advantage relative to the least expensive SSRI.

Response to Pricing Scenarios

Cohort Group III: N=6
Cohort A: Net Price **Parity to SSRIs**
Cohort B: Net Price **Discount to SSRIs of 20%**

- One of the six participants in this cohort group would expect Cymbalta to be added to formulary at parity to the SSRIs. One other sees the product being added if net cost is equivalent to that of Celexa, specifically.
- An additional two respondents feel Cymbalta would be added at a 20% net discount to the SSRIs.
- Among the other two respondents, neither believes Cymbalta will be added to formulary/ placed in tier two, regardless of cost. One feels that product has no clear clinical advantage in a saturated market; the other states that the P&T Committee views all SNRIs as second-line (tier three) relative to the SSRIs.

Response to Cymbalta's Clinical Profile And Pricing Scenarios In Summary - The "Whys" Behind Responses

- The focus among managed care organizations currently is to seek methods to improve compliance and long term outcomes in the treatment of depression, and, to lower cost in a class that is consistently in the top five of drug expenditures.
  - Among health many plans, there is a pervasive perception that a lot of money and medication is being thrown at this disease state with relatively poor compliance and questionable long term outcomes.
  - Some plans are also turning their attention to trying to promote, either through step therapy guidelines or academic detailing, the use of generic Fluoxetine first line.
- In short, little initial enthusiasm exists for products not viewed as different or innovative.

Response to Cymbalta's Clinical Profile And Pricing Scenarios In Summary - The "Whys" Behind Responses

- While they recognize the importance of individualized treatment and the need for therapeutic options for depression, health plans can be very cautionary in their initial assessments of new products, particularly if they cite inconsistencies or perceived holes in the presentation of clinical information.

- Without the strength of a marketing and message campaign, this particular Cymbalta product profile did not stand up very well, on its own merits, for managed care decision makers.
  - As stated earlier, a few aspects of the profile left managed care very unclear as to the product's clinical value in a market that is perceived as saturated and in need of only novel, inexpensive, or clearly differentiated new agents.

Response to Cymbalta's Clinical Profile And Pricing Scenarios In Conclusion

- While only five of twenty-three participants state that they expect formulary acceptance at parity pricing to the SSRIs, the fact remains that with a strong positioning campaign, a directed educational effort regarding physical symptoms, and answers to consistently raised clinical questions, the formulary acceptance outlook for Cymbalta can be far more favorable.

- It is important to reflect upon the fact that Effexor is on formulary in all of the plans surveyed and that no existing contracts would impede the addition of Cymbalta.

Verbatims

Verbatims
An Assessment of Cymbalta, Reaction to Pricing Scenarios

- *"These findings are hard to evaluate; the presentation of the data really leads to a lot of important questions, particularly about what happened at 80 mg and higher doses of this drug and what will occur if physicians are prescribing a 30 mg with a 60 mg. What kind of side effects are we likely to see? I also have no idea how large some of these studies are... I think the comparator will be Effexor, so it seems strange that the head-to-head was against Paxil, but our review will evaluate this product against our total formulary for depression. At any premium to the SSRIs this product will not get added, especially with all of our safety concerns with new products. Our typical script, without rebate, is $93.85 for Effexor, compared to $76.41 for Paxil. At parity with our most cost-effective SSRI, it's a may-add, but only if there is a clear safety or efficacy advantage over Effexor."*

Verbatims
An Assessment of Cymbalta, Reaction to Pricing Scenarios

- *"The data compared to Paxil is interesting and the the reduction of symptoms in two weeks, if born out, is impressive, particularly if this improves compliance. I would have hoped for better anxiety scores and the physical symptoms piece is interesting, something I have just learned about recently. I question why there are not studies against Effexor, makes me unsure who is their competition or if there's some data being withheld because it isn't favorable. I don't honestly see any clear differentiation, so I think it will come down to cost unless you have a compelling compliance story. Without a study against Effexor, I don't think we would add this. At a twenty percent premium to Effexor, I don't think anyone will add it. Even at parity, we won't add it. Effexor is well established and has significant market share here, and this doesn't look to serve a new niche. I'd say you'd have to come in at close to a fifteen percent discount to Effexor."*

Verbatims
An Assessment of Cymbalta, Reaction to Pricing Scenarios

- *"This drug looks pretty good on paper in terms of its efficacy. My major concern is why it was studied at 80 mg and will be introduced at 30 mg and 60 mg - what did they see at 80 and what are the clinical findings at these lower doses? Looks like they've compared apples to oranges, given the dosing in the trials is not what will be marketed. And what dose are the side effects based upon? Given the comparison to Paxil, this product will be looked at against all SSRIs, but so far, I can't see anything clinically that sets it apart. At parity with the SSRIs - and that's a broad spectrum of cost to us - I would not see any reason to add this. It will sit in tier three for some time. At a twenty percent discount to the SSRIs, we will take a closer look, and then it becomes a may-add, but this profile leaves too many questions to be able to ascertain the formulary outcome."*

Verbatims
An Assessment of Cymbalta, Reaction to Pricing Scenarios

- *"Initially, I would say this product looks good. I like that it's a balanced, dual reuptake inhibitor and the remission numbers are substantial, and the side effect profile looks pretty good. The comparison to Paxil is good, as is the incidence of sexual dysfunction. My concerns are that it may be perceived as a heavy dose product, it sounds like two to three times the average dose for an antidepressant - how do you titrate and are there HAMD scores for 30 mg use and 60 mg use? The P & T Committee will also question whether we will see off label use for pain. The potential use for pain really bothers me. At a twenty percent premium to Effexor this is clearly a tier three product. The market is over-priced now. At parity, things don't look any more promising. It's a crowded field, so you will have to build some incentive in for managed care, twenty five to thirty percent below Celexa and we'll be interested."*

Verbatims
An Assessment of Cymbalta, Reaction to Pricing Scenarios

- *"The emphasis on pain reduction is unique, but the expansion of the pain category worries me. We don't need another Neurontin, but if it is effective in pain and less expensive than a product like that, that's a good thing. The comparison to Paxil 20 mg is weak. That is not an effective strength and I think Paxil is one of the weaker drugs, clinically, in this category, so I am not sure the comparison affords them much. The remission rates look interesting but what does "112% more likely" really mean; that's very vague. The dry mouth and nausea are a bit of a concern. We'll look at this relative to all antidepressants on our formulary. Right now, the pain piece could have some promise for differentiation but also some fear regarding utilization. We'd also like to see a comparison to Fluoxetine 20 mg or Zoloft 100 mg. At parity with SSRIs, we'd place it in the third tier and see what psychiatrist' use looks like. At $2/day, we'll take a look at the six-month mark. Given that our push right now is to get doctors to prescribe generic Fluoxetine first line, this drug won't get a lot of attention until a fair amount of clinical experience is established."*

II. PHYSICIANS

Summary of Findings

Physician Sample Demographics

- Four major U.S. markets are represented in this qualitative strategic physician pricing research:
  - Atlanta
  - Philadelphia
  - Chicago
  - Los Angeles
- Focus groups were conducted with both Primary Care Physicians and Psychiatrists in each of the four markets.
- Physician research was fielded the week of June 24th - June 27th, 2002.

Physician Sample Demographics

- Primary Care Representation: N=23
  - Internal Medicine N=11
  - Family Practice N=11
  - General Practice N= 1
  - Six Primary Care Physicians from each of three markets, five from one market
- Psychiatrist Representation: N=24
  - Six Psychiatrists from each of four markets

Physician Criteria For Participation

- Primary Care Physicians and Psychiatrists
  - 1 - 30 years in practice
  - Age 30 to 65
  - >80% of time spent seeing patients in-office
  - Started or changed antidepressant therapy for >5 patients in last two weeks
  - No contract (advisory, clinical trial) with pharmaceutical manufacturers
  - No participation in antidepressant market research in past three months
  - Have seen two or more representatives within last month:
    - Forest, GSK, Lilly, Pfizer, Wyeth

Physician' Perceptions of Antidepressant' Availability

Antidepressants Are Viewed As Highly Available

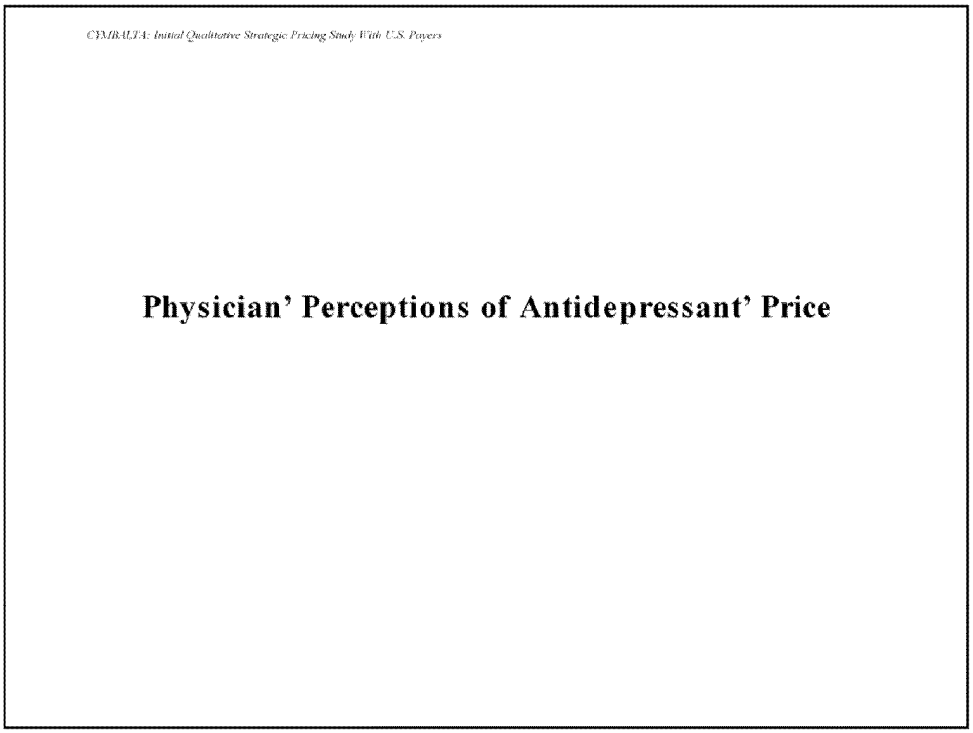
- Primary Care Physicians view the entire antidepressant class as one for which there is a very high degree of product availability, as contrasted to classes such as the PPIs, COX IIs, and statins.
- Among Psychiatrists, atypical antipsychotics and psychostimulants represent therapeutic classes that are perceived as posing less choice and more restrictions to utilization and availability.

Availability Is Not Driving Antidepressant Prescribing Decisions

- Physicians feel they cannot keep up with the ongoing, myriad of changes to each local health plan's formulary.
- As a result, physicians make clinical determinations as to the optimal treatment of depression and deal with formulary availability issues as they come up.

Availability Is Not Driving Antidepressant Prescribing Decisions

- If a particular product is not available on a particular formulary, given the very individualized nature of antidepressant response, physicians will lobby a managed care organization for approval.
  - They also combat availability issues by generously providing samples, particularly for new starts, and economically challenged patients (indigent, Medicaid, working poor, Medicare.)



Lack of Knowledge Regarding Antidepressant Cost

- Primary Care Physicians and Psychiatrists were unable to clearly identify relative price, relative availability, or speak to an understanding of list price.
- Price - actual and relative - are simply not on the radar screen of importance to physicians.

Lack of Knowledge Regarding Antidepressant Cost

- Both Primary Care Physicians and Psychiatrists lack knowledge of pharmaceutical product' cost and are uncomfortable even engaging in drug cost discussions because of their lack of expertise and information in this arena.
  - Price is not driving prescribing decisions for antidepressants.

How Physicians Define and Think About Antidepressant Cost
What The Patient Pays

- Physicians define and think about antidepressant cost, first and foremost, in terms of anecdotal payment information received from patients, often expressed as complaints about patients' out-of-pocket expense, "Do you know how much this drug cost me?" or, " My co-payment for this product was X and I usually only have to pay Y!"

Lack of Knowledge Regarding Antidepressant Cost
List Price and Most/Least Expensive Antidepressant

- Physicians' lack of price knowledge is no more evident than in two exercises they completed during each focus group.
- First, they were asked to define "list price."
- Then, physicians attempted, individually, to arrange four antidepressants in order from the most to the least expensive: Paxil, Zoloft, Celexa, Effexor XR.
- There was absolutely no consensus in response to either question, nor was there a high degree of comfort that their assertions were anything but mere guesswork.

Lack of Knowledge Regarding Antidepressant Cost
Definitions of List Price

- Physician' definitions of "list price" include the following:
  - Retail price
  - Average wholesale price
  - Wholesale price
  - Price a pharmacy pays for a drug
  - Price a patient pays out-of-pocket for a drug
  - Price per unit
  - Price per month supply
  - Sticker price
  - Manufacturer's price

Lack of Knowledge Regarding Antidepressant Cost
No Consensus in Perceptions of Most and Least Expensive Antidepressant

- Each of the four products - Paxil, Zoloft, Celexa and Effexor XR - is perceived by some segment of Primary Care Physicians and Psychiatrists as both the *most* and the *least* expensive antidepressant.
  - Effexor XR is viewed by a majority of PCPs as the most expensive antidepressant, followed by Paxil.
  - A majority view Celexa as the least expensive antidepressant, followed by an even split of responses between Paxil and Zoloft.
  - A majority of Psychiatrists also perceive Effexor XR to be the most expensive of these four products, followed by Zoloft.
  - Celexa is seen by a majority of Psychiatrists as the least expensive antidepressant, followed by Paxil.

Other Information Sources Regarding Antidepressant Availability and Price

- In addition to patients, who are the most influential and consistent source of cost and availability information for physicians, other sources of information include:
  - Pharmaceutical company representatives
  - Managed care organizations (formulary booklets/ cards)
  - Internet or PDA-based programs such as Eppocrates
  - Other on-line sources that convey information about local health plan' formularies.

How Price and Availability Perceptions Influence Physician' Prescribing of Antidepressants

Key Influencers That Shape Physicians Perceptions of Availability and Price
Cash-Payment and Co-Payment Patient Complaints

- While, in general, there is a perceived lack of hurdles to the availability and price of antidepressants, the most influential factors that shape physicians perceptions of availability and price, and, that in certain instances, can steer a physician to prescribe an alternative antidepressant are, in order of degree of influence:
  - #1: Cash-Paying Patient Complaints
  - #2: Co-Payment Patient Complaints
  - #3: Communication From Pharmacies Regarding Coverage Issues

Most Influential Elements That Shape Physicians Perceptions of Availability and Price
Cash-Payment Patient Complaints

- Complaints from the cash-paying patient are typically the most loudly voiced and most frequent complaints that shape physician' perceptions of availability and price.
  - This patient segment includes: Medicare and Medicaid recipients, the indigent, the working poor, the self-insured, and the affluent who have opted out of managed care.
  - Physicians will attempt to get approval for nonformulary medications for these patients, and if necessary, will seek alternative antidepressants, particularly for the less fortunate, indigent, and for Medicare patients on numerous medications who have a capped pharmacy benefit. However, physicians are very resistant to switching stabilized depressed patients.

Most Influential Elements That Shape Physicians Perceptions of Availability and Price
Co-Payment Patient Complaints

- Complaints from the co-payment patient are also frequent and strident.
  - This patient segment includes patients with HMO and PPO pharmacy benefit coverage.
  - These patients may complain that their co-payment amount has gone up, or, that the medication cost them more than what they have paid previously, or, that they paid more for this medication as compared to others drugs they take.
  - Physicians will attempt to get approval for nonformulary medications for these patients, and if necessary, will seek alternative antidepressants, though they may be less apt to jump through hurdles for chronic complainers who demonstrate an attitude of entitlement.

Most Influential Elements That Shape Physicians Perceptions of Availability and Price
Communication from Dispensing Pharmacies

- Communication from dispensing pharmacies, in the form of telephone calls and faxes, is the third most influence source of availability and price information.

- This communication is often referred to by treating physicians as a daily bombardment or onslaught of requests:
  - Product is not on formulary, dosage strength is restricted
  - Product requires an appeals or approval process by the HMO
  - Product was on the patient's formulary last month, but is no longer a covered benefit
  - Patient's co-payment for this product has gone up and the patient requests an alternative.

Most Influential Elements That Shape Physicians Perceptions of Availability and Price
Communication from Dispensing Pharmacies

- Because physicians believe that antidepressants are widely available, communication from pharmacies is a less impactful hurdle and influencer of prescribing decisions for *this* therapeutic class, as compared to others, such as the PPIs, Statins, Antibiotics, and COX IIs.

Most Influential Elements That Shape Physicians Perceptions of Availability and Price
Other Potential Influencers

- Participants were asked about the degree to which other influencers pose a hurdle and their relative degree of impact on prescribing decisions.
- While all physicians receive communication directly from managed care organizations, in the form of letters, academic detailing, and occasionally, physician report cards, this information is not impacting physician prescribing decisions relative to antidepressants.
- Information from pharmaceutical representatives regarding the availability and price of their product or competitive products is also not perceived as influential.

Celexa:
Initial Perceptions That Influenced Early Adoption

Celexa:
Early Adopters Swayed By Promotion Of Clinical Benefits

- Among Primary Care Physicians and Psychiatrists surveyed who were early adopters of Celexa, all shared a common trait of being highly influenced by Forest's positioning of clinical benefits relative to other SSRIs.
  - In particular, Forest's promotion of Celexa having fewer side effects was very compelling, specifically, *less sexual dysfunction*, *fewer drug-drug interactions*, and *better tolerated.*

Celexa:
Early Adopters Swayed By Promotion Of Clinical Benefits

- Knowledge that Celexa was already marketed in Europe and that significant clinical data was available also influenced early adopters.
- While several recall Celexa being touted as cheaper and more cost effective, few physicians indicate that price influenced their early prescribing of the product.

Future Antidepressant Market Entries:
Familiarity with, Perceptions of, and
Price Expectations for Duloxetine MDD and Lexapro

Familiarity with, Perceptions of, and Price Expectations for Cymbalta (Duloxetine MDD)

- Less than half of all participants are familiar with Duloxetine MDD:
  - Fourteen (14) of Twenty-Four (24) Psychiatrists
  - Three (3) of Twenty-Three (23) Primary Care Physicians
  - Of the four markets surveyed, physicians in Atlanta and Chicago were the most familiar with Cymbalta; physicians from Philadelphia and Los Angeles the least familiar.

Familiarity with, Perceptions of, and Price Expectations for Cymbalta (Duloxetine MDD)

- Among those who are familiar with Lilly's newest antidepressant, the following perceptions exist:
  - Dual mechanism of action
  - Serotonin plus norepinephrine reuptake inhibitor
  - Indication will be for the treatment of depression with pain.

Familiarity with, Perceptions of, and Price Expectations for Cymbalta (Duloxetine MDD)

- Sources of information about Cymbalta have almost exclusively been different forums of communication from Lilly.
- Physicians hope, but do not necessarily expect, Cymbalta will come to market at a lower cost as compared to Effexor XR, in an effort to garner early acceptance and overall market share.
- A few physicians, Psychiatrists in particular, commented that they would expect a new antidepressant marketed by Eli Lilly to be expensive.
- A select few indicate they would expect the product to be expensive given its dual mode of action.

Familiarity with, Perceptions of, and Price Expectations for Cymbalta (Duloxetine MDD)

- Physicians are doubtful Cymbalta can compete at any price premium to Effexor XR.
- They believe that only three factors could justify or warrant consideration of premium pricing relative to Effexor XR:
  - Faster onset of action
  - Efficacy at a lower dose relative to Effexor XR coupled with Greater ease of titration, or,
  - A significant decrease in rate and severity of withdrawal/ discontinuation syndrome.

Familiarity with, Perceptions of, and Price Expectations for Lexapro

- A far greater number of physicians are familiar with Lexapro, as compared to Cymbalta.
- Greater than half of all participants are familiar with Lexapro:
  - Eighteen (18) of Twenty-Four (24) Psychiatrists
  - Eleven (11) of Twenty-Three (23) Primary Care Physicians
  - Of the four markets surveyed, physicians in Atlanta, Philadelphia, and Chicago were the most familiar with Lexapro; physicians from Los Angeles the least familiar.
- Information regarding Lexapro has come from Forest' representatives and clinical literature.

Familiarity with, Perceptions of, and Price Expectations for Lexapro

- Among those who are familiar with S-Citalopram, the following perceptions exist:
  - Isomer of Celexa
  - More potent/ efficacious
  - Improved side effect profile - a "cleaner" Celexa.
- Physicians believe Forest will enter the market with a similar pricing strategy as was undertaken for Celexa and that Lexapro will come to market at a lower cost to Celexa and all other SSRIs.
  - Improved efficacy, less sexual dysfunction, and lack of discontinuation syndrome could each, potentially, warrant premium pricing of Celexa.

Physician' Perceptions of Product Attributes or Positioning That Justify Premium Pricing

Physicians Draw No Inferences About the Clinical Value of a Pharmaceutical Products Based Upon Price (More Expensive versus Less Expensive)

- Physicians were asked if a product were introduced with a significant premium in price, relative to competitors, would they draw any inferences regarding the efficacy, safety, or clinical benefit of the product based upon its cost.

- All concur that they would not draw any inferences about the clinical value of a product based upon its price.

Product Attributes That Justify A Premium Price Over Other Antidepressants

- Improvement in efficacy, faster onset of action, and reduction in side effects relative to other antidepressants, are the key attributes that most quickly surface in physicians' minds as justification for premium pricing.
  - A reduction in sexual dysfunction is the most compelling side effect justification for premium pricing.
  - Minimization of withdrawal syndrome is also seen as important.

III. PATIENTS

Summary of Findings

Patient Sample Demographics

- Patient research was fielded in the same four markets, during the same time frame, as the Physician research
- In-depth, one-on-one interviews were conducted with male and female patients in each of four markets (Atlanta, Philadelphia, Chicago, and Los Angeles)
- Patients surveyed have, collectively, taken most newer antidepressants in the past five years:
  - Prozac, Prozac Weekly, Paxil, Zoloft, Celexa, Wellbutrin, and Effexor
  - Each participant has taken at least two antidepressants in the past five years.

Patient Sample Demographics

- Total Patient Representation N=22
  - Atlanta N=4
    - 4 Females
  - Philadelphia N=7
    - 6 Females
    - 1 Male
  - Chicago N=6
    - 5 Females
    - 1 Male
  - Los Angeles N=5
    - 4 Females
    - 1 Male

Patient Criteria For Participation

- Patients with Depression
  - A ratio of 4 females to 1 male per city
  - Age 35 to 55
  - Diagnosis and treatment of depression by a PCP and/ or Psychiatrist
  - Prescribed and taken two different antidepressants within past five years and able, unaided, to identify products taken
  - No market research participation in last six months
  - No employment related to advertising, marketing, physicians' office, hospital, clinic, lab, pharmacy or HMO
  - HMO/ PPO pharmacy benefit coverage

A Note About Participant Patients

- For those who did not view the research live, it is important to put in to context the experience of depression among patients surveyed.
- All of the patients from this study exemplify how difficult it is to determine the "ideal" antidepressant for a given individual (optimal efficacy, coupled with minimal, tolerable side effects.)
- They also exemplify patients suffering from depression who are truly treatment seekers. Each continued to seek care, by visiting multiple physicians and trying multiple pharmaceutical products, in an effort to achieve healthier and more meaningful and productive lives.

The Context In Which Patients View Cost and Out-of-Pocket Expense

Absolute Dollars

Versus

Incremental Dollars Over Alternatives

The Context In Which Patients View Cost and Out-of-Pocket Expense
Absolute Dollars

- Patients with managed care coverage and a pharmacy benefit think about cost and out of pocket expense in terms of absolute dollars they pay for a medication in the form of a co-payment.
- Patients with a pharmacy benefit do not typically think about the cost of a medication - positively or negatively, particularly a chronic medication, which they view as essential to their health and well being, such as an antidepressant.
- Patients who take multiple medications for complex conditions an/ or co-morbidities think of cost in terms of *total, cumulative* absolute out of pocket dollars incurred on a monthly basis.

How Patient Cost Affects Behavior Both In Terms of First Prescription And Subsequent Refills

And

The Role of Out of Pocket Expense In Determinations to Fill Either First Prescription And Subsequent Refills

How Patient Cost Affects Behavior Both In Terms of First Prescription And Subsequent Refills

- All patients surveyed place great importance on their mental well being and its impact on their functionality and quality of life.
- As a result, patients are far more likely to fill both a first prescription and subsequent refills of an antidepressant they view as effective and relatively well-tolerated.

The Role of Out of Pocket Expense In Determinations to Fill Either First Prescription And Subsequent Refills

- Patients may delay the purchase of an initial prescription, or not fill it altogether, if the out of pocket cost is significantly greater than a typical co-payment and, if they view the product as non-essential or something they can do without.
- Among all patients surveyed, an effective antidepressant is viewed as an essential, a necessity.
- Patients will pay for any **antidepressant** they feel is providing a beneficial outcome - even if their co-payment for the product increased by twenty dollars per prescription (a typical differential between a two tier and a three tier co-payment.)

How Patient Cost Affects Behavior Both In Terms of First Prescription And Subsequent Refills

- Products for which an initial prescription and subsequent refills may not be filled because of cost, i.e., out of pocket expense - or where the patient might ask for a generic or lower cost alternative include:
  - Products taken on a PRN basis:
    - Migraine treatments, such as Imitrex
    - Topical Antifungals, such as Lamisil
    - Antivirals, such as Zovirax for Herpes
  - "Lifestyle" products:
    - Renova for mitigation of wrinkles
  - Acute treatments that are nonformulary or cost significantly more in terms of out of pocket expense than normally incurred
    - Antibiotics
    - Antihistamines

Frequency and Likelihood of Pharmacy Intervention

Frequency and Likelihood of Pharmacy Intervention
Fairly Frequent and Routine

- Most patients surveyed are routinely informed by a pharmacist or pharmacy technician when a lower cost alternative to the medication their physician prescribed is available.
- Patient response varies based upon their view of a specific medication and therapeutic class. Again, for patients who are stabilized on an antidepressant, particularly among patients that have tried two or more products, there is far less willingness to be switched to a lower cost brand or generic alternative.
- Patients frequently want to speak with their physician prior to accepting a cheaper alternative to the medication prescribed.

Frequency of Sample Use
Prior to Incurring Out of Pocket Expense

Frequency of Sample Use
Prior to Incurring Out of Pocket Expense
Frequent and Routine

- The majority of patients surveyed routinely receive samples prior to having to pay out of pocket when initially starting a medication.
- Most received samples of first and subsequent antidepressants prescribed for them, and a few patients continue to receive samples, periodically, as part of their ongoing treatment for depression.

Patient Willingness to Try a Generic Product;
Patient Willingness to Try a Generic Antidepressant

Patients Are Open to Trying A Generic Product But Would Not Switch If Stabilized On An Antidepressant

- Patients are willing to try a generic product and have frequently tried generic products in other therapeutic classes.
- However, patients who are stabilized on an antidepressant are not willing to be switched, at the pharmacy, to a generic **antidepressant**.

PAYER PARTICIPANTS

Managed Care Organizations
And
Pharmacy Benefits Management Companies

Participating Organizations

- *Altius Health Plans, UT*
- *AV-Med Health Plan, FL*
- *Blue Care Network, MI*
- *Blue Cross/Blue Shield of Kentucky, KY*
- *Blue Cross of California, CA*
- *CHA Health, KY*
- *Cigna Health Care, TX*
- *Coventry Health Care, TN*
- *Dean Health Plan, WI*

Participating Organizations

- *Excellus Blue Cross/Blue Shield, NY*
- *Group Health Cooperative of South Wisconsin, WI*
- *Henry Ford Medical Group, MI*
- *Intermountain Health Care, UT*
- *Kaiser Permanente, CA*
- *Medica, MN*
- *Med Impact, IN [PBM]*
- *Mid Atlantic Medical Services, Inc., MD*
- *Ochsner Health Plan, LA*

Participating Organizations

- *Oxford Health Plan, CT*
- *PacifiCare, CA [Rx Solutions - PBM]*
- *Penn State Geisinger Health Systems, PA*
- *Premera Blue Cross, WA*
- *United Health Care of Wisconsin, WI*