Repurposing, Translational Medicine and other Strategies for De-Risking CNS

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Defined Health

February 27, 2007
SAVE THE DATE APRIL 25 & 26, 2007
InterContinental The Barclay New York

THE NEW REALITIES OF FINANCING DRUG DEVELOPMENT: IMPLICATIONS FOR PHARMA AND BIOTECH M&A AND LICENSING RELATIONSHIPS

THE FUTURE OF CARDIOVASCULAR THERAPEUTICS: NEW MARKERS AND IMPLICATIONS FOR THE CARDIOVASCULAR SPACE

REPURPOSING, TRANSLATIONAL MEDICINE AND OTHER STRATEGIES FOR DE-RISKING CNS

THE EMERGING PRICING CHALLENGE: A HURDLE OR A DRIVER OF INNOVATION?

THE DERMATOLOGY ENIGMA: EXPLORING THE DISCONNECT BETWEEN UNMET NEEDS AND PHARMA INVESTMENT

GETTING PERSONAL AND GETTING PAST IT: BEYOND CANCER’S INDIVIDUALIZED THERAPIES TO "LESS IMPERSONAL" MEDICINE

MALE AND FEMALE SEXUAL DYSFUNCTION: ATTRACTIVE MARKETS; ELUSIVE TARGETS

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My Disclaimer

If I knew how to de-risk CNS, I would be sitting on a beach in Hawaii rather than in a conference room in New Jersey in February (with you lovely people).

This is an interactive, audience-participation-required exercise – putting our minds together to wrestle with this important issue.
Let’s Just Face It. CNS is a Risky Area.

- CNS has one of the highest pipeline attrition rates in the industry.
- In addition to a higher attrition rate, CNS drugs take longer (114 months) to develop than any other category.

Let’s Just Face It. CNS is a Risky Area.

CNS Has Historically Been One of the Therapeutic Areas Showing A Low Success Rate in the Clinic.

Figure 1 | Success rates from first-in-man to registration. The overall clinical success rate is 11%. However, if the analysis is carried out by therapeutic areas, big differences emerge. The data are from the ten biggest drug companies during 1991–2000. (The companies are AstraZeneca, Bristol-Myers Squibb, Eli Lilly, F. Hoffman-LaRoche, GlaxoWellcome, Johnson & Johnson, Novartis, Pfizer, Pharmacia, Schering-Plough and SmithKline Beecham; data were obtained by Datamonitor in the Pharmaceutical Benchmarking Study). CNS, central nervous system.
Let’s Just Face It. CNS is a Risky Area.

• And that failure is often late in development
  • CNS and oncology show the lowest rates of failure in Phase I (30-40%), but late-stage failure is high (50-60% Phase III).
  • This is in contrast to metabolic disease and urology, for example, where Phase I failure rates are high (50-60%), but late-stage failure rates are relatively low (30-40% Phase III).


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So, Why Go There?

• Significant unmet need remains

  -- Diagnosis and treatment rates remain astoundingly low for many CNS disorders, leaving plenty of untapped market potential (just some of which are illustrated below).
So, Why Go There?

- The market is **BIG** and has the potential to get a lot **BIGGER**.
  - CNS drugs (minus pain) account for 11 of the top 25 drugs on the US market.
  - US annual sales for these top 11 are in excess of $17 billion.
  - Neurology/psychiatry represents a $50+ billion therapeutic category WW (second only to cardiovascular disease) that is growing at 15% per year.
  - As the population ages, the number of patients with diseases of the CNS increases dramatically.
The Fundamental Questions?

• Is the risk associated with CNS unavoidable?

• Or are there ways in which we can meaningfully de-risk CNS?
De-Risking Checklist

- Safety
- Target
- Efficacy
- Commercial
What Does De-Risking CNS Really Mean?

• As a therapeutic category, CNS is made up of lots of different diseases, facing all kinds of risk. Do we apply the same de-risking strategy to all?
To Discuss De-Risking Strategies for CNS, How About a Different View?

- Alzheimer’s Disease
- Severe / Refractory Disease
- Parkinson’s Disease
- Multiple Sclerosis
- ALS
- Spinal Cord Injury
- Traumatic Brain Injury
- ADHD
- Sleep Disorders
- Migraine
- Depression / Anxiety
- Pain

Impact on Quality of Life vs Size of Patient Population

Illustrative
To Discuss De-Risking Strategies for CNS, How About a Different View?

Impact on Quality of Life

Size of Patient Population

Illustrative

Sleep Disorders  Pain
Migraine  Depression / Anxiety
ADHD

Alzheimer’s Disease
Epilepsy
Schizophrenia
Parkinson’s Disease
Multiple Sclerosis
ALS
Spinal Cord Injury
Traumatic Brain Injury
Some Observations

- Not to trivialize, but it is possible to argue with the degree of impact on quality of life for some of the CNS disorders which represent the largest patient populations. Safety has been the primary risk considered for drugs targeting these indications.

- Large patient populations
- Primary care dominated
- Standard of care reasonable
- Crowded markets
- “Me toos” & “Me betters”
- Growing generic competition

Impact on Quality of Life
Some Observations

• In the near future, the ability to advance standard of care and differentiate in these markets necessitates novelty, inherently pushing risk toward target and efficacy; unknown mechanisms also increase safety / side effect risk.

• Early pipeline of novel mechanisms

- Sleep Disorders
- Migraine
- Depression / Anxiety
- Pain
- ADHD

Impact on Quality of Life

+ Target risk
+ Efficacy risk
↑ Safety / side effect risk
Commercial risk
Some Observations

- For some CNS disorders, there is an undeniable impact on quality of life. In large, these markets are not well served (meaning currently available agents don’t work that well) which is why we have been focused on safety / side effects and commercial risk. Again, innovation in the pipeline will require that we also tackle target and efficacy risk.

**Impact on Quality of Life**

- Therapeutically, not well served
- Elusive disease biology

**Target risk**

- Efficacy risk
- Safety / side effect risk
- Commercial risk

**Size of Patient Population**

- Alzheimer’s Disease
- Epilepsy
- Schizophrenia
- Parkinson’s Disease
- Multiple Sclerosis
- ALS
- Spinal Cord Injury
- Traumatic Brain Injury
- ALS
The Focus, at the Earliest Stages, Has Been on Safety

- Historically, and out of necessity, we have used safety in animal and Phase I studies as a first screener in CNS disease (no matter what type) to determine which compounds to move forward in the clinic.
Why the Historical Focus on Safety in CNS?

- Because we can reasonably assess safety at an early stage of drug development (animal tox, Phase I).

- Because the science and tools to assess the therapeutic value of a target and potential efficacy of a specific compound are not predictive …

- But that is changing.

*Hurko, O. and Ryan J.L. NeuroRx Vol.2, No.4, 2005.*
What We Have Been Working With in CNS

- Animal models that have minimal predictive value.
  - It is safe to say that animal models are not identical to human disease. However, in no other therapeutic area is that more true than for diseases of the CNS, demonstrably the organ system most uniquely distinguishing humans from laboratory animals.
  - How can you really tell if a mouse is less depressed, psychotic, cognitively impaired or even in pain?
  - Transgenic models of AD show relatively little neurodegeneration, neuroinflammation, cognitive or behavioral impairment.
  - Even in diseases where there is a greater mechanistic understanding (e.g., MS), there are still significant disparities between the animal models used in discovery validation and the human diseases being targeted for treatment.

• “Messy” mechanisms.
  – The brain is complex; multiple transmitters and intersecting brain circuits are implicated in many CNS disorders.
  – CNS drugs may have multiple MOA’s / potential indications – and can vary in efficacy across the CNS targets with which they interact.

What We Have Been Working With in CNS

• Unpredictive predictors of clinical outcome.
  – There is a real lack of useful surrogate endpoints for CNS disorders, unlike some other disease areas (e.g., hypertension, infectious disease).
  – This means that making the right choice of targets and molecules for development is even more crucial.
What We Have Been Working With in CNS

- Highly subjective clinical endpoints.
  - For many CNS diseases, clinical endpoints are subjective, associated with patient, administrator and physician bias.
Addressing Safety Early Doesn’t Always Address Safety Late

• Some high profile late-stage CNS failures and stumbles due to safety issues
  – AN-1792 AD Vaccine (Elan/Wyeth)
  – Sparlon (ADHD, Cephalon)
  – Tysabri (MS, Elan/Biogen-Idec)
But We Still Keep Trying

- Safety
- Target
- Efficacy
- Commercial

De-Risking Strategy #1: Repurposing & Repositioning
De-Risking Strategy #1: Repurposing and Repositioning

• Repurposing
  – New indication for a product currently on the market somewhere in the world.

• Repositioning
  – New therapeutic focus / indication for a compound in development (e.g., Indevus’ pagoclone for anxiety repositioned for the treatment of stuttering).
Focus on Repurposing

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of safety (perhaps in a different patient population)</td>
<td>Not novel, not cool</td>
</tr>
<tr>
<td>Known MOA; eliminates NCE risk</td>
<td>Danger of cross-over sales from generics</td>
</tr>
<tr>
<td>“Quick to Clinic” potential</td>
<td>IP issues</td>
</tr>
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</table>
Repurposing in CNS … A Few Examples

• FP 0011 (Faust Pharmaceuticals); Phase II Parkinson’s
• Flurizan (Myriad); Phase III AD
• Doxepin low dose (Somaxon Pharmaceuticals); Phase II insomnia
• Fampridine-SR (Acorda Therapeutics); Phase III Multiple Sclerosis
Fampridine-SR: A Repurposing Success Story?

- In laboratory tests, the potassium channel blocker 4-aminopyridine (4-AP) has been shown to improve impulse conduction in nerve fibers with myelin damage.

- 4-AP has been used historically in the treatment of multiple sclerosis (MS) patients where it produces clinically important improvements; however, well-defined and controlled studies are warranted to assess the efficacy and safety of prolonged administration.

- 4-aminopyridine also has a history of use in much higher doses as a bird poison under the trade name Avitrol (Avitrol Corporation).

- Fampridine-SR (Acorda Therapeutics) is a sustained release formulation of 4-AP in Phase III for the treatment of MS.

Fampridine-SR: A Repurposing Success Story?

- On September 25, 2006, Acorda announced statistically significant results from the PIII study of Fampridine-SR for walking improvement in multiple sclerosis patients.
  - 34.8% of people taking Fampridine-SR experienced a consistent improvement in walking speed compared to 8.3% with placebo (p <0.001).
  - The effect was maintained throughout the 14-week treatment period. There was an average increase in walking speed over the treatment period compared to baseline of 25.2% for the responder group versus 4.7% for the placebo group (p < 0.001).
  - Statistically significant improvement in the 12-item MS walking scale for walking responders versus non-responders (p <0.001).
  - Increased response rate on the Timed 25-Foot Walk was seen across all 4 major types of MS.
  - Statistically significant increases in leg strength in subjects receiving Fampridine-SR compared to placebo.

- All of these data are consistent with results of previous Phase II study, MSF202.

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Fampridine-SR: A Repurposing Success Story?

ACORDA THERAPEUTICS as of 23-Feb-2007

De-Risking Strategy #2

- Safety
- Target
- Efficacy
- Commercial

Translational / Experimental Medicine
Translational / Experimental Medicine

• What is it, besides a buzzword?
  – Bridge between discovery research and drug development
  – Series of quick experiments designed to indicate whether or not a compound has clinical applicability
Translational / Experimental Medicine

- Addresses fundamental questions early in the process:
  - **Is the drug being given to the right patients?**
    - Patient identification / stratification biomarkers
    - Genetic studies / Pharmacogenomics
      - Can also lead to transgenic models and RNAi knockdown models
  - **Is the drug reaching the right target (with the appropriate degree of saturation and for the right duration)?**
    - Neuroimaging studies
  - **Is the drug working?**
    - Efficacy biomarkers (e.g., MRI-detected lesions in MS brain) – as opposed to validated surrogate markers
Could the ability to answer these questions have prevented the late-stage failure of …

- Sarizotan (Parkinson’s Disease Dyskinesia; Merck KGaA)
- NXY-059 (Ischemic Stroke; Renovis/AstraZeneca)
Did the ability to answer at least some of these questions prevent a late-stage failure of Aprepitant (Merck) for the treatment of depression?

MRK (Whitehouse Station, N.J.) found that its candidate oral NK-1 receptor antagonist, MRK 0869, was doing what it was supposed to do — it was getting into the brain and attaching to a target receptor. “Imaging gave us the definitive proof that we had the compound for the receptor,” said Mervyn Turner, senior vice president of worldwide licensing and external research.

The problem, according to Turner, was the target was obviously the wrong receptor for depression because it was having no observable beneficial effect. Armed with this insight, the pharma company did not have to waste time and money trying other compounds on the target.

“Merck’s PET imaging study with MRK 0869 probably cost about $25,000 to $35,000 a patient in a trial that would need to have 10 to 20 subjects. But the results enabled them to not waste any more money on other trials with that compound or variations of the compound,” Sorensen said.
Imaging as a Key Translational Medicine Tool for CNS

- As in other therapeutic areas (e.g., oncology, cardiovascular disease), imaging is becoming a key tool in the search for new CNS medicines.
- Advances in technology and the development of useful ligands are just beginning to contribute at the earliest stages to:
  - Target validation (receptor occupancy)
  - PK (regional distribution and rate of distribution in distinct brain regions), PD
  - Dosing
  - Efficacy markers & clinical endpoints
  - Product differentiation
Case Study: Imaging & AD

Is the drug being given to the right patients?

- Development of disease-modifying therapy for neurodegenerative disease is hampered by late diagnosis. For example, Alzheimer’s disease (AD) can be definitively diagnosed only on autopsy of brain tissue.

- A goal of translational medicine is the development of reliable diagnosis at the earliest point in the disease process to allow intervention with disease-modifying therapy at the earliest point in the disease process.

Alzheimer’s is Currently Confirmed only at Autopsy

Cortical atrophy  Enlarged ventricles

Adapted from Novartis presentation “Clinical Application of Imaging to Drug Development”

Case Study: Imaging & AD

Is the drug being given to the right patients?

- The value of neuroimaging to identify early signs of neuronal dysfunction was first demonstrated using resting glucose positron emission tomography (PET) in asymptomatic individuals carrying mutations for early-onset AD.
- This finding was later extended to individuals at high risk for the development of typical late-onset sporadic AD by virtue of their apolipoprotein E status and an affected first-degree relative.

Adapted from Novartis presentation “Clinical Application of Imaging to Drug Development”

Case Study: Imaging & AD

Is the drug reaching the right target (with the appropriate degree of saturation and for the appropriate duration)?

- Radiolabeled PET ligands can provide a quantifiable three-dimensional image of receptor occupancy in the brain. Receptor occupancy of an unlabeled drug of interest, administered at pharmacological doses, can be estimated by measuring displacement of the radiolabeled tracer.

The targeting tracer [11C]-PIB is being used in clinical studies to estimate the amount and location of B-amyloid in the brain as well as potentially the interaction of drugs with targets at these sites.


Adapted from Novartis presentation “Clinical Application of Imaging to Drug Development”
The potential utility of efficacy biomarkers is greatest for chronic disorders like AD for which there is a long delay before clinical improvement can be observed reliably even though the initial beneficial effects on the disease pathophysiology may have begun early in the course of drug treatment.

Adapted from Novartis presentation “Clinical Application of Imaging to Drug Development”

Case Study: Imaging & AD

- The Alzheimer’s Disease Neuroimaging Initiative (ADNI) is a $60 million, 5-year public-private partnership.
- The National Institute of Aging (NIA), National Institute of Biomedical Imaging and Bioengineering (NIBIB) and the FDA are working together with support from the following companies and organizations: Pfizer, Wyeth Research, Eli Lilly, Merck, GlaxoSmithKline, AstraZeneca, Novartis, Eisai, Elan Corporation, the Institute for the Study of Aging (ISOA), and the Alzheimer’s Association.

http://www.nih.gov

Goals:

- identify the best neuroimaging methods, brain physiological parameters, biological markers, clinical and cognitive information for following aging and disease progression over a 3 year period
- standardize methods of data collection
- develop a public reference dataset and repository of clinical material
- provide information for early identification of patients at risk, to permit early intervention
- assess ability to use neuroimaging parameters as a surrogate endpoint in MCI/AD trials
Neuroimaging: Challenges for Pharma & Biotech

• New method / probe development
  – Internal, outsourced, partnered?
  – IP issues
  – Capacity at academic PET centers

• New method / probe application
  – Standardized protocols
  – Robust (but sensitive) analysis methods
  – Identification of imaging endpoints that qualify as biomarkers and surrogate markers

FDA’s Critical Path Initiative: A Partner to Translational Medicine

- Critical path is NOT about the drug discovery process. Critical Path is concerned with the work needed to move a candidate all the way to a marketed product.
- Critical path is intended to integrate new science into the regulatory process.

http://www.fda.gov/oc/initiatives/criticalpath

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In Jan 2006, the FDA released a final guidance for Exploratory IND studies. As part of FDA’s “Critical Path Initiative,” this process is a new tool available to the industry that enables a faster, more cost-effective path to early clinical development.

**Phase 0: Exploratory IND Studies**

- Exploratory IND studies are intended to provide clinical information for a new drug candidate at a much earlier phase of drug development; intended to help to identify the best candidates for continued development and eliminate those lacking promise.
- These clinical trials occur very early in Phase 1, involve very limited human exposure, and have no therapeutic intent.
- Exploratory IND studies are conducted prior to the traditional dose escalation, safety, and tolerance studies and provide important information on pharmacokinetics (PK) and bioavailability of a candidate drug.
Phase 0: Oncology Is a First Mover

- Particularly for targeted agents.

<table>
<thead>
<tr>
<th>Current challenges in cancer-drug development</th>
<th>Phase 0 trials</th>
</tr>
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<tbody>
<tr>
<td>Suboptimal use of target assessment and imaging techniques in early-phase clinical trials</td>
<td>Biomarker development and assay qualification in human tissues before the initiation of the trial</td>
</tr>
<tr>
<td></td>
<td>The evaluation of imaging studies that provide functional and metabolic information about the effects of a drug on its target(s)</td>
</tr>
<tr>
<td></td>
<td>The integration of such assays and/or imaging studies in phase 0 trials to establish the mechanism of action in vivo in actual patient samples</td>
</tr>
<tr>
<td>Establishment of the maximum tolerated dose as a primary endpoint in trials with molecularly targeted agents</td>
<td>Evaluation of target modulation is a primary endpoint</td>
</tr>
<tr>
<td>Late-stage failures with low rates of anticancer drug approvals</td>
<td>Allow for the systematic de-prioritization of investigational agents that do not show expected biological effects</td>
</tr>
<tr>
<td>Long timelines for the development of promising agents</td>
<td>The early initiation of first-in-human, proof-of-concept trials that provide data to better inform and expedite subsequent clinical development should shorten drug-development timelines</td>
</tr>
<tr>
<td>Increasing number of complex trials that require substantial resources</td>
<td>Investing resources in early-phase trials that involve a small number of patients should help prioritize resource allocation for subsequent larger trials</td>
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Phase 0: Oncology Is a First Mover

- Particularly for targeted agents.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Phase 1 trials</th>
<th>Phase 0 trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>Establish the maximum tolerated dose</td>
<td>Target modulation or ability to image the target of interest</td>
</tr>
<tr>
<td>Dose escalation</td>
<td>Determine safety and toxicities</td>
<td>Achieve desired systemic exposure or target modulation, enabling dose selection for future studies</td>
</tr>
<tr>
<td>Preclinical biomarker studies</td>
<td>Not consistently performed before the trial</td>
<td>Required to have plasma drug (pharmacokinetic) and preclinical biomarker (pharmacodynamic) assay development and assay qualification before the initiation of the clinical trial</td>
</tr>
<tr>
<td>Biomarker assays</td>
<td>Not performed consistently, most phase 1 trials do not emphasize pharmacodynamic markers</td>
<td>Biomarker assays and/or imaging studies are integrated to establish the mechanism of action in actual patient samples</td>
</tr>
<tr>
<td>Number of patients</td>
<td>Usually &gt;20</td>
<td>10–15</td>
</tr>
<tr>
<td>Dosing</td>
<td>Multiple</td>
<td>Limited</td>
</tr>
<tr>
<td>Therapeutic benefit</td>
<td>None expected; however, tumour response is evaluated to enable continued dosing in case evidence of clinical benefit is found</td>
<td>None</td>
</tr>
<tr>
<td>Tumour biopsies</td>
<td>Optional</td>
<td>Serial tumour biopsies required to evaluate the effect of the drug on its target(s)</td>
</tr>
<tr>
<td>Pharmacokinetic/ pharmacodynamic analysis</td>
<td>Samples are usually batched and analysed at a later time</td>
<td>Real time</td>
</tr>
</tbody>
</table>
To De-Risk at an Early-Stage, Commercial Direction is Essential

• Bridging the science and the clinic is all well and good, but where is the bridge going?

• Matching drug potential to clinical circumstances, unmet needs and potential benefit to the patient requires early commercial input.

• What does the market need/want? Multiple disciplines should have say so into which compounds live and which die at the early stage.
As CNS faces a wealth of early-stage novel drug candidates:

- How do we address the risk associated as early as possible?
- How do we provide commercial input to make better go / no go decisions?
- How do we take advantage of existing (and progress development of new) technologies to assess internal and external opportunities, especially as partnering deals continue to move to earlier stages of development?

Nature Reviews Drug Discovery, Volume 3, August 2004, 711
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