2008 Top 10
Unpartnered Cardiovascular Projects

Michael C. Rice
Senior Consultant, Defined Health
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Agenda

• CVD Top 10 Alumni, Where Are They Now?
• Environment Driving This Year’s Selection Criteria
  – CVD Commercial Trends
  – CVD Pipeline Inventory
  – Dealmaking Trends in CVD
• This Year’s Criteria and Process
• The 2008 CVD Top 10 Unpartnered Projects
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### Where Are They Now?
#### 2 Years ago, Top 10 Unpartnered CVD Projects

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**MedTRACK, Company Press Releases**

2 Years ago, Top 10 Unpartnered CVD Projects

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Acquired by Gilead Sciences for $2.5 Billion

“**Myogen represents a unique scientific and strategic fit with our company, bringing to Gilead a late-stage product candidate that addresses an area of significant unmet medical need…**”

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## Where Are They Now?

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Genzyme receives exclusive WW rights
- Moved to Phase III
- $325mm up front
- PP to $825mm in dev. and reg.
- MS: $50mm for approval for homozygous
- FH: $150mm for heterozygous FH
- $375mm total for first non-FH indication
- $250mm for a follow-on product
- $125mm in dev. funding from Isis

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**Alliance with Amgen**
- Advanced to Phase II
- Upfront $42MM cash and $33MM stock
- Milestones up to $600MM + Royalties

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Alliance with Schering-Plough
- WW development and marketing
- Undisclosed terms

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MedTRACK, Company Press Releases
TA Partnering Meeting, November, 2008 - Pg. 9

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## Where Are They Now?

### Last Year’s Top 10 Unpartnered CVD Projects

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<td>MLN1202 (Millennium Pharma)</td>
<td>2008</td>
<td>II</td>
<td>Atherosclerosis</td>
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<td>VIA-2291 (VIA Pharma)</td>
<td>2008</td>
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<td>ACS</td>
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<td>QRX-431 (QuatRx Pharma)</td>
<td>2008</td>
<td>II</td>
<td>Dyslipidemia</td>
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<td>2008</td>
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Protherics was acquired by BTG in Sept. 2008 for about £218mm ($419mm) in stock.
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Millennium was acquired by Takeda in April 2008 for $8.2bn
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CVD’s Tremendous Revenue Contribution

- CVD, exceeding $90B, is a big business and will continue to be a very critical component of the entire pharmaceutical industry.

**WW Sales ($MM), Total Industry and Cardiovascular Sector**

- **2008 Total Industry**: 502
- **2008 Cardiovascular**: 92
- **2014 Total Industry**: 610
- **2014 Cardiovascular**: 84

EvaluatePharma, DH analysis

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Breakthrough Therapies Have Improved Outcomes, Yet CVD Remains the Highest Area of Unmet Therapeutic Need

- AHA estimates over 70M Americans have a cardiovascular condition.
- Responsible for 700K deaths annually, CVD is the major cause of death in the US.
- Despite increased chance of survival of acute events, heart disease is still the leading cause of death for both women and men in the United States.
Staggering Increasing Costs of CVD

- Costs associated with CVD is estimated at over $400B.
- In 2007, heart disease alone is projected to cost more than $270B, including health care services, medications, and lost productivity.

AHA Heart Disease and Stroke Statistics
http://www.americanheart.org/presenter.jhtml?identifier=1200026

TA Partnering Meeting, November, 2008 - Pg. 15
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However, CVD is Already Declining in Revenue

- CVD is a shrinking market among the therapeutic areas in terms of share of contribution to the overall pharmaceutical market.
- Decline is largely driven by generic erosion of off-patent products.
Major CVD Growth Drivers Will Soon be Eroded by Generic Competition

- Antihyperlipidemics, ARBs and antiplatelets have driven growth.
- Genericization will greatly accelerate in 2011 when Lipitor (Pfizer) and Plavix (BMS, s-a) go off patent.
- In the next 3 years, almost the entire cardioprevention market will be genericized.

Total Worldwide CVD Therapeutic Category Sales, 1986 - 2013

- ACE inhibitors
- Angiotensin II antagonists
- Anti-coagulants
- Anti-hyperlipidaemics
- Beta blockers
- Calcium antagonists
- Cardiac therapy
- Cerebral & peripheral vasotherapeutics
- Diuretics
- Fibrinolytics
- Other anti-hypertensives
- Other cardiovasculars
- Platelet aggregation inhibitors

EvaluatePharma, DH analysis
TA Partnering Meeting, November, 2008 - Pg. 17
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Pending Deaths of Broad Labeled Cardioprevention Drugs

- Coreg (1995-2007)
- Norvase (1992-2007)
- Altace (1991-2008)
- Diovan (1998-2012)
- Plavix (1997-2011)
- Lipitor (1997-2011)
CVD Has Been Plagued With Expensive Late-Stage Trial Failures

• Expensive late-stage CVD trial failures have been far too frequent.
• Developing new CVD drugs for the broad market will be challenging:
  – Amidst the debate over the value of surrogate markers, outcomes data have become a prerequisite for FDA approval.
  – New agents must be tested on top of an increasingly effective SOC.
  – Since SOC therapy has already reduced hospitalization and mortality dramatically, trials to collect enough events and demonstrate significant improvement are becoming increasingly large and expensive.
  – Accordingly, the safety data collected from these large trials have increased the hurdles for new entrants in terms of toxicity.
• The rising efficacy bar and safety hurdle have decreased the predictability of Phase III success based on Phase II success.

DH analysis, company news releases, clinicaltrials.gov
Merck/Schering-Plough Pharmaceuticals Provides Results of the ENHANCE Trial

Merck/Schering-Plough Pharmaceuticals announced today the primary endpoint and other results of the ENHANCE (Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) trial. Merck/Schering-Plough has submitted an abstract on the ENHANCE trial for presentation at the American College of Cardiology meeting, which will be held in March 2008, and is awaiting notification of acceptance from the College.

Experts Speculate on Cordaptive Rejection

April 30, 2008 – While the FDA's "not-approvable" letter on Merck's Cordaptive (a combination of niacin plus the antiflushing agent laropiprant) might have come as a shock to many, some physicians say it was not so unexpected in the current regulatory climate.

While the reasons behind the rejection have not been made public, Merck is saying that it will continue to pursue approval, and most lipid experts contacted by heartwire were of the opinion that the FDA probably wants to see more safety data on the laropiprant part of the combination and that recent events such as the ezetimibe controversy may have made the agency particularly cautious on approving new drugs without extensive data.

A Changed Regulatory Environment?

Dr William Boden (Buffalo General Hospital, New York) told heartwire that he was not overly surprised that Cordaptive had been rejected, but he said many other people would be surprised. "It was widely anticipated that this drug would be approved. Many people felt it was almost certain. Merck has been running 'coming-soon' advertisements in the major medical journals. This will be a big setback for the company," Boden said. "But the FDA has become increasingly more vigilant recently about approving drugs before the full safety data have been evaluated. It is still burned about the Vioxx [rofecoxib, Merck] scandal. We don't know why the FDA rejected Cordaptive, but we can speculate that it was unconvinced that Merck had done its due diligence with regard to safety," he added.

Dr Allen Taylor (Walter Reed Army Medical Center, Washington, DC) has similar views. Noting that the FDA did originally accept the new drug application for Cordaptive, he points out that it is somewhat out of line for the agency to reject the application further down the line just because there is a lack of information. But he speculated that recent events may have made the FDA have second thoughts.

"The environment around laropiprant has changed in the past few months. There is much skepticism about surrogate markers at the moment, and a high-profile paper published recently in the New England Journal of Medicine [1] drew attention to the large numbers of drugs that have been withdrawn shortly after approval and suggested that drugs were being approved too hastily in the US. And the ezetimibe controversy has not helped. That drug was approved based on a surrogate end point without a real understanding of what it was doing, and it is being used far beyond the data. All these things are bound to color the way the FDA makes its decisions," Taylor said.

Dr Greg Brown (University of Washington School of Medicine, Seattle) commented to heartwire: "As I understand, in the current phase 3 studies of Cordaptive in combination with simvastatin, with or without ezetimibe, the combinations have shown additive and excellent effects on LDL-C, triglycerides, and HDL-C. And compliance with Cordaptive is significantly improved. However, the total number of phase 3 patients is in the several thousands, with most of those results published, at least in abstract form.

Others were unwilling to speculate too much, given the lack of information from the FDA and the company. Dr Scott Grundy (University of Texas Southwestern Medical Center, Dallas) commented to heartwire: "One might surmise that it had something to do with laropiprant, because the FDA has approved combinations of [extended-release] Niaspan (Abbott) with both simvastatin and lovastatin. I think it would not be wise for me to speculate further in the complete absence of any information on the niacin/laropiprant combination."

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Facts:

DH analysis, company news releases, clinicaltrials.gov

FDA delays decision on TriLipix, Abbott's new fenofibrate

October 23, 2008 | Michael O'Riordan

Bethesda, MD - The US Food and Drug Administration (FDA) needs more time to complete a review of TriLipix, Abbott Laboratories, the maker of the newer, patent-protected fenofibrate, announced Wednesday.

Abbott applied for FDA approval for use of the drug as monotherapy and in combination with statins. The FDA has not asked more data, according to Abbott, just more time, and the company expects a decision by the end of 2008.

TriCor, an older fenofibrate that Abbott hopes TriLipix will replace, has been a massive moneymaker for the company, breaking the $1 billion mark in sales in 2007. In the first nine months of 2008, worldwide sales are again nearing the $1 billion range.
“Over the past three decades, mortality rates for highly prevalent cardiovascular diseases, including acute coronary syndromes, heart failure, and sudden death, have continuously improved owing to the clear benefits of therapies proved to be efficacious in double-blind, randomized, controlled trials. With these mounting, cumulative successes, however, the marginal benefit of any proposed intervention decreases. Realistic limits, both operational and financial, to the size of study samples decrease the statistical power and the absolute treatment effect detectable in these trials.”

Joseph Loscalzo

New Replacements are Failing to Sustain Franchises with Aging Assets

Aggregate CVD Sales of Leading Pharma Companies by Product Age

- Truly innovative products penetrating into a genericized preventative cardiovascular market.
- Older products serve as cash cows as new products lag in market penetration.
- Recent growth driven by mid-life products as fruits of 90s’ innovation and “fast followers” in a given drug class.

EvaluatePharma, DH analysis
Lack of Innovative Replacements has Brought CVD Revenue Growth to a Grinding Halt

Although smaller in market size, Oncology is the clear growth leader fueled by high value biologicals.

CVD has yielded its historically double-digit growth as generic alternatives are increasingly available.

EvaluatePharma, DH analysis
The CVD Pipeline is Sparse Compared to That of Other TAs

- Although CVD is the largest pharmaceutical market, it accounts for only 5% of today’s clinical stage pipeline.

Clinical Development by Indication

- Oncology & Immunomodulators: 32%
- Cardiovascular: 5%
- Central Nervous System: 19%
- Dermatology: 1%
- Endocrine: 6%
- Gastro-Intestinal: 4%
- Genito-Urinary: 3%
- Musculoskeletal: 5%
- Various: 2%
- Respiratory: 6%
- Sensory Organs: 2%
- Systemic Anti-infectives: 12%

*Pipeline included 6,125 pipeline agents in Phase I clinical development to Registration.*

Adis R&D Insight, IDdb, DH analysis

TA Partnering Meeting, November, 2008 - Pg. 24

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Most Late-Stage Projects are Unavailable, but the Early Pipeline is Rich in Innovation

- Though development efforts are not in proportion to the CVD market size, there are numerous late-stage projects and an active early-stage effort.

Clinical Development by Phase

- Preclinical: 635
- Phase 1: 132
- Phase 2: 192
- Phase 3: 67
- Pre-registration: 18
- Registered: 8

IDdb, DH analysis

© Defined Health, 2008

TA Partnering Meeting, November, 2008 - Pg. 25
New CVD Inventory Sourced from Biotechs

- Approximately 50% of novel CVD agents entering the clinic are now originating from Biotechs.
- Many are available for licensing.

Proportion of CVD Pipeline By Originator

- DH has identified numerous small CVD R&D organizations*:
  - There are approximately 104 Biotechs involved in CVD development
  - There are 48 Specialty/Regional Pharma in the US, EU and Japan.

* Combining the EvaluatePharma and BioCentury lists
Alliances are Needed, but Dealmaking is Anemic

- Few deals despite opportunity and need to replace products losing patent protection.
  - The cardiovascular market is maturing, and much-needed commercial replacements must emerge soon for the sector to sustain its recent growth.
  - The anemic rate of transactions since 2000 indicates that available projects may be declining or potential partners are passing over opportunities.
  - Is risk intolerance forcing Pharma to shift resources away from CVD?

Deals on CVD Drugs in Clinical Stage Development (PI-Registered)
Transforming CVD: Three Potential Overlapping Strategies

(1) Bring an oncology-like development model into cardioprevention
- Initial launch for advanced/refractory disease or pharmacogenomically defined patient segments.
- Subsequent label expansion to earlier lines of therapy and broader patient segments with post-marketing studies.

(2) Focus on overt disease rather than risk factors
- High unmet need indications [CHF, PAD].
- Acute care - injectable biologicals.
- Medical options for indication predominantly managed by intervention.
- Delipidation, clot dissolution, antiarrhythmics.

(3) Adopt regenerative/reparative medicine approaches
- Cell therapies and therapeutic angiogenesis that repair damaged cardiac tissue and vasculature.
Transforming CVD: Oncology vs. CVD Markets

**Oncology**

- **Treatment of active disease**
  - Primary prevention non-existent, adjuvant being evaluated.
- **Poor SOC**
  - Evolving, poor to modest efficacy, significant toxicity.
- **Very high unmet need**
  - Advanced disease mostly incurable.
  - Harsh side effects from therapy.
- **New development is science driven**
  - New biologicals augmenting chemotherapy.
  - New drugs introduced in advanced and refractory disease.
- **Outcomes data often unnecessary**
  - Surrogate markers acceptable (RR, TTP, PFS), noninferiority.
- **Managed care providers rely on oncologist for drug choice**
  - Evolving SOC.
  - Generics presently unavailable for most high-value agents.

**Cardiovascular**

- **Preventative therapeutic area**
  - Therapy determined by existing surrogate risk factors.
- **Adequate SOC?**
  - Primary prevention: advanced and firmly established for risk reduction. High toxicity hurdle.
  - Secondary prevention: inadequate at preventing progression or treating active disease.
- **Less unmet needs for most CVD patients**
  - Although some indications untouched.
  - Poor SOC in treating acute episodes.
  - Symptomatic improvement often decreases outcomes.
- **Outcomes driven**
  - Survival and decreased hospitalization are key drivers.
- **Reimbursement regulated by managed care**
  - Standardized treatment algorithm.
  - Generic replacements available.
Transformation Opportunity: Increase Reward for Treating Overt Disease

Cost Distribution by Type of Service ($ billion)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Outpatient Office Visits</th>
<th>Hospital Stays</th>
<th>ER Visits</th>
<th>Prescribed Medicines</th>
<th>Home Health</th>
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<td>12.6</td>
<td>48.4</td>
<td>2.9</td>
<td>8.2</td>
<td>4.4</td>
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<tr>
<td>Hypertension</td>
<td>10.1</td>
<td>5.9</td>
<td>0.7</td>
<td>23.0</td>
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<td>5.4</td>
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<td>15.2</td>
<td>3.1</td>
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<tr>
<td>Hyperlipidemia</td>
<td>5.8</td>
<td>0.4</td>
<td>—</td>
<td>17.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Agenda

• CVD Top 10 Alumni, Where are They Now?
• Environment Driving This Year’s Selection Criteria
  – CVD Commercial Trends
  – CVD Pipeline Inventory
  – Dealmaking Trends in CVD
• This Year’s Criteria and Process
• The 2008 CVD Top 10 Unpartnered Projects
Defined Health Used the Following 5 Steps to Select the Top 10 Most Promising Compounds for Partnering:

- Create CVD Investigational Agent Database (Phase I to registered)
- Remove Unavailable Agents
- Evaluate Based on Selection Criteria
- Compare and Prioritize
- Invite Selected Companies

Clinical Development by Phase:

- Preclinical: 635
- Phase I: 132
- Phase II: 192
- Phase III: 67
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Windhover's Top 10 Licensable CVD Projects

IDdb, DH analysis
The Universe of Investigational CVD Agents was Compiled from Licensed Databases and Industry Experience

1. Create CVD Investigational Agent Database (Phase I to registered)
   - Wolter’s Kluwer Adis R&D Insight (3,938 Agents PI-Reg.)
   - Thomson’s IDdb3 (3,994 Agents PI-Reg.)
   - Defined Health & Windhover Ad-hoc Additions

2. Combine, Remove Redundancies
   - 2154 CVD Agents in Development WW

3. Verify classification
   - 895 CVD Agents in Active Clinical Development WW
   - 399 CVD Agents in late Preclinical to Registration WW
Projects Sponsored by Companies with Substantial CVD Development Capabilities and Marketing Reach were Deprioritized

- 895 CVD Agents in Late Preclinical to Registration WW
- 399 available agents
- 61 optimistic projects
- Top 20 CVD Projects selected
- Windhover’s CVD Top 10 Projects

Create CVD Investigational Agent Database (Phase I to registered)
Remove Unavailable Agents
Evaluate Based on Selection Criteria
Compare and Prioritize
Invite Selected Companies

Originator / Developer
- Large Pharma
- Specialty Franchise

895 CVD Agents in Late Preclinical to Registration WW

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- Windhover’s CVD Top 10 Projects

Reviwed CVD Programs By Indication

- Atherosclerosis: 41
- A. Fib: 12
- CHF: 40
- Dyslipidemia: 14
- MI: 30
- Hypertension: 60
- Vascular: 23
- ACS: 4
- Other: 22
- V. Fib: 14
- ADHF: 13
- Thrombosis: 88
- Restenosis: 11
- Reperfusion: 27

Projects Sponsored by Companies with Substantial CVD Development Capabilities and Marketing Reach were Deprioritized

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Projects Were Then Rated Based on Selection Criteria Indicating Project Attractiveness to a Potential Partner

- Projects were rated based on selection criteria.
- Selection criteria included:
  - Unmet Needs
  - Market Potential
  - Novelty
  - Precedents
  - Clinical
  - Competition

- Intrinsic to Agent

Create CVD Investigational Agent Database (Phase I to registered)
Remove Unavailable Agents
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Windhover's CVD Top 10 Projects
Projects Then Were Compared Among Peers Based on Company Attributes and Advertised Availability

- 895 CVD Agents in Late Preclinical to Registration WW
- 3999 available agents
- 61 optimistic projects
- Top 20 CVD Projects selected
- Windhover's CVD Top 10 Projects

Create CVD Investigational Agent Database (Phase I to registered)
Remove Unavailable Agents
Evaluate Based on Selection Criteria
Compare and Prioritize
Invite Selected Companies

Among Peers:
- Exclude Prior Top 10
- Exclude DH current client target
- Company Management
- WW Availability
- “For out-license”

895 CVD Agents in Late Preclinical to Registration WW
Company Sponsors of Projects Making the Final List were Invited and Projects Tracked Over the Last Several Months
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### 2008 Top 10 Unpartnered CVD Projects* 

<table>
<thead>
<tr>
<th>Developmental Agent</th>
<th>MOA</th>
<th>Clinical Phase</th>
<th>Indication</th>
</tr>
</thead>
</table>
| **RVX-208**  
*Resverlogix Corp.* | Small Molecule ApoA-I agonist | 2 | ACS/ Dyslipidemia |
| **Varespladib (A-002)**  
*Anthera Pharma* | sPLA$_2$ Inhibitor | 2 |
| **MBX-8025**  
*(Metabolex)* | Selective PPAR-delta agonist | 2 |
| **TRIA-662**  
*Cortria Corp.* | Nicotinic Acid analogue | 2 | Dyslipidemia |
| **Eprotirome**  
*Karo Bio* | Selective thyroid hormone receptor modulator | 2 |
| **CD NP**  
*Nile Therapeutics* | Selective NPR-B agonist | 2 | HF (Acute) |
| **Urocortin 2 (CRF2)**  
*Neurocrine Biosciences* | CRF2 receptor agonist | 2 |
| **Mydicar**  
*Celladon Corp.* | AAV1/SERCA2a | 2 | HF (Chronic) |
| **BL-1040**  
*BioLineRx USA Inc.* | Resorbable Polymer Hydrogel | 2 | Myocardial Infarction |
| **ATI5923**  
*ARYx Therapeutics* | VKOR inhibitor Anticoagulant | 2 | Thrombosis/AF |

* Not presented in any particular order
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