2009 Top 10
Unpartnered Cardiometabolic Projects

Michael C. Rice
Senior Consultant, Defined Health
**Defined Health** is a leading consultant to biopharmaceutical companies, working primarily in the space where business development meets clinical development.
The information in this presentation has been obtained from what are believed to be reliable sources and has been verified whenever possible. Nevertheless, we cannot guarantee the information contained herein as to accuracy or completeness.

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Thanks for making it up from Orlando!
AHA Scientific Sessions - Nov 14-18, 2009

“Hmmm. I wonder what I am missing in the late breaking sessions?”
Agenda

• CVM Top 10 Alumni, Where are they Now?

• Environment Driving This Year’s Selection Criteria:
  – CVD, Pharma’s largest market, built upon groundbreaking cardioprevention therapies is now a mature market.
  – Cardiovascular risk reduction is now the greatest medical bargain to improve patient outcomes with a SOC Generic.
  – Despite this satisfaction there remains significant unmet need; however, it is increasingly difficult to prove outcomes benefits of new prevention drugs in late-stage trials on top of this SOC Generic.
  – Legacy franchises are facing difficulty in persevering with current strategies focused on LCM and attempting to validate new surrogates.
  – The result is a changing of the guard in leading CVD franchises with legacy franchises transitioning to adjacent growth areas driven by type 2 Diabetes and Obesity.
  – Albeit, a heightened FDA scrutiny on cardiovascular safety has also changed the regulatory risk on developing diabetes and obesity drugs and future studies may necessitate CVD outcome studies to justify investment.

• Within this context, Defined Health has selected this year’s Cardiometabolic Top 10 unpartnered projects from a combined CVD and Metabolism pipeline.

• The 2009 CVD Top 10 Unpartnered Projects
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- The 2009 CVD Top 10 Unpartnered Projects
## CVD Top 10 Alumni: Where are they now? 2006

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</tr>
</tbody>
</table>

* 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…”
## Developmental Agent

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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

*Not presented in any particular order*
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<td>Dyslipidemia</td>
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<td>II</td>
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<td>Cardiac myosin activator</td>
<td>II</td>
<td>AHF / CHF</td>
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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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<tr>
<td>VT 111 (Viron Therapeutics Inc.)</td>
<td>Serine protease inhibitor</td>
<td>II</td>
<td>Reperfusion Injury</td>
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<td>MC 1 (Medicure Inc.)</td>
<td>Vitamin B6 metabolite</td>
<td>III</td>
<td>Myocardial Infarction</td>
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Alliance with Schering-Plough
- WW development and marketing
- Undisclosed terms

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<tr>
<td><strong>MLN1202</strong> <em>(Millennium Pharma)</em></td>
<td>CCR2 antagonist (mAB)</td>
<td>II</td>
<td>Atherosclerosis</td>
</tr>
<tr>
<td><strong>VIA-2291</strong> <em>(VIA Pharma)</em></td>
<td>5-lipoxygenase inhibitor</td>
<td>II</td>
<td>ACS</td>
</tr>
<tr>
<td><strong>QRX-431</strong> <em>(QuatRx Pharma)</em></td>
<td>Selective thyroid beta agonist</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td><strong>REG-1</strong> <em>(Regado Biosciences)</em></td>
<td>Aptamer-antidote pair to Factor IX</td>
<td>II</td>
<td></td>
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<tr>
<td><strong>PRT-054021</strong> <em>(Portola Pharma)</em></td>
<td>Factor Xa inhibitor</td>
<td>II</td>
<td>Thrombosis</td>
</tr>
<tr>
<td><strong>rNAPc2</strong> <em>(Nuvelo Pharma)</em></td>
<td>Factor VIIa/tissue factor inhibitor</td>
<td>II</td>
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Millennium was acquired by Takeda in April 2008 for $8.2bn

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MedTRACK, Company Press Releases

TA Partnering Meeting, November, 2009 - Pg. 11  © Defined Health, 2009
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<tr>
<td><strong>NX-CP105</strong> <em>(Neuronyx)</em></td>
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<tr>
<td><strong>FX-O6</strong> <em>(Fibrex Medical)</em></td>
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In August 2009, Ikaria acquired an exclusive worldwide license Under this agreement, Ikaria is responsible for preclinical and clinical development, and commercialization of FX 06. FIBREX will receive upfront and milestone payments, and royalties on net sales.
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In July 2009, Merck will pay Portola an initial fee of $US50 million. Portola is eligible to receive additional cash payments totaling up to $US420 million upon achievement of certain development, regulatory and commercialization milestones, as well as double-digit royalties on worldwide sales of betrixaban.
## CVD Top 10 Alumni: Where are they now? 2008

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<tr>
<td><strong>RVX-208</strong> Resverlogix Corp.</td>
<td>Small Molecule ApoA-I agonist</td>
<td>2</td>
<td>ACS/ Dyslipidemia</td>
</tr>
<tr>
<td><strong>Varespladib(A-002)</strong> Anthera Pharma</td>
<td>sPLA2 Inhibitor</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>MBX-8025</strong> (Metabolex)</td>
<td>selective PPAR-delta agonist</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>TRIA-662</strong> Cortria Corp.</td>
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<tr>
<td><strong>Eprotirome</strong> Karo Bio</td>
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<tr>
<td><strong>CD NP</strong> Nile Therapeutics</td>
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<tr>
<td><strong>Urocortin 2 (CRF2)</strong> Neurocrine Biosciences</td>
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<tr>
<td><strong>Mydicar</strong> Celladon Corp.</td>
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<tr>
<td><strong>BL-1040</strong> BioLineRx USA Inc.</td>
<td>Resorbable Polymer Hydrogel</td>
<td>2</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td><strong>ATI5923</strong> ARYx Therapeutics</td>
<td>VKOR inhibitor Anticoagulant</td>
<td>2</td>
<td>Thrombosis/AF</td>
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Ikaria Holdings Inc had agreed to pay $285 million for a license to develop and market its BL-1040 drug for heart attack patients.
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• The 2009 CVD Top 10 Unpartnered Projects
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 ($Bln), Total Industry and Cardiovascular Sector 2009 and 2014(E)**

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2014</th>
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<tbody>
<tr>
<td>Total Industry</td>
<td>647</td>
<td>751</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>93</td>
<td>81</td>
</tr>
<tr>
<td>Diabetes</td>
<td>27</td>
<td>39</td>
</tr>
<tr>
<td>Obesity</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
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.

EvaluatePharma, DH analysis
Major CVD growth drivers soon to 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.
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- The 2009 CVD Top 10 Unpartnered Projects
Cardioprevention is now the greatest medical bargain (SOC Generic):

Past Success in CVD Ignored the Impact of Therapeutic Substitution With SOC Generics.
Simvastatin (Zocor) Was First SOC Generic to Have a Major Impact, but Others are Imminent

Currently Marketed Blockbusters Under Threat From Emerging SOC Generics

EvaluatePharma, Defined Health analysis

© Defined Health, 2009
The Impact of a SOC Generic Has Already Hit Home for Pfizer

Figure 59: Cholesterol Market—New Rx Market Share and Total Market (Weekly Data)

JP Morgan Prescription Pad, 26 April 2009
Agenda

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DH Analysis
© Defined Health, 2009
Breakthrough therapies have improved outcomes, yet CVD remains the highest 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.
## Top 10 Most Expensive Medical Conditions in the US

<table>
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<th>Condition</th>
<th>Cost ($ billion)</th>
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<tbody>
<tr>
<td>Heart conditions</td>
<td>76</td>
</tr>
<tr>
<td>Trauma disorders</td>
<td>72</td>
</tr>
<tr>
<td>Cancer</td>
<td>70</td>
</tr>
<tr>
<td>Mental disorders including depression</td>
<td>56</td>
</tr>
<tr>
<td>Asthma and chronic obstructive pulmonary disease</td>
<td>54</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42</td>
</tr>
<tr>
<td>Diabetes</td>
<td>34</td>
</tr>
<tr>
<td>Osteoarthritis and other joint diseases</td>
<td>34</td>
</tr>
<tr>
<td>Back problems</td>
<td>32</td>
</tr>
<tr>
<td>Normal childbirth</td>
<td>32</td>
</tr>
</tbody>
</table>

Data from the Medical Expenditure Panel Survey, a detailed source of information on the health services used by Americans, the frequency with which they are used, the cost of those services, and how they are paid.

Leading CVD franchises have become gun shy in taking on expensive pivotal cardioprevention trials after experiencing numerous late-stage trial failures.

- Developing new CVD drugs for the broad market will be challenging:
  - In 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.
New Therapies: Victims of Success in Cardioprevention

• “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 products

Aggregate CVD Sales of Leading Pharma Companies by Product Age

Older products serve as cash cows as new products lag in market penetration.

Truly innovative products penetrating into a genericized preventative cardiovascular market.

Recent growth driven by mid-life products as fruits of 90s’ innovation and “fast followers” in a given drug class.

EvaluatePharma, DH analysis
Agenda

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• The 2009 CVD Top 10 Unpartnered Projects
CVD Franchises have attempted to maintain their current status with fast followers, LCM, FDCs.

"A strategy to reduce cardiovascular disease by more than 80%.
A single pill combining:

- A statin (10-mg atorvastatin or 40-mg simvastatin or lovastatin)
- Three BP-lowering drugs, at half-standard dose (thiazide, beta blocker, and ACE inhibitor)
- 0.8-mg folic acid
- 75-mg aspirin

The heart.org, Fuster, Topol, Krumholtz, Sackner-Berstein.
And Attempting to Validate New Surrogates Which Can Prove Catastrophically Risky: HDL

Defined Health’s 2006 – 2007 Insight Series: “HDL Therapeutics in the Wake of Torcetrapib”

Pfizer’s Statement on the End Of All Torcetrapib Clinical Trials

December 2, 2006 11:10 p.m. EST

$21 B
The debate surrounding the ENHANCE trial took a bit of a twist this past week when attention turned to the LDL-cholesterol hypothesis, with some experts arguing that lowering LDL cholesterol to prevent clinical events is an unsophisticated premise and that other factors beyond lowering LDL cholesterol are involved. Other reports openly questioned whether this latest evidence suggests it might not be important to reduce cholesterol levels.

"The idea that you're just going to lower LDL and people are going to get better that's too simplistic, much too simplistic," Dr Eric Topol (Scripps Translational Science Institute, La Jolla, CA) told the New York Times last week.

Experts say, however, that this is not the dismissal of decades of research, including numerous studies in the past few years adding evidence to the "lower is better" cholesterol hypothesis. With many of those trials, researchers used higher and higher doses of statins to drive down cholesterol levels, all with the intent of further reducing clinical events. Instead, some say that how cholesterol is lowered is as important as how much.

"The message for me is not that lowering LDL cholesterol doesn't work to prevent disease progression or to prevent clinical events," Dr Steven Nissen (Cleveland Clinic, OH) told heartwire. "The important thing to remember is how the cholesterol levels are lowered. Statins do a lot more than reduce LDL cholesterol. They also increase HDL cholesterol, decrease triglycerides, and decrease C-reactive protein levels. Ezetimibe doesn't do any of these things."
Together, the results available to date provide support for the concept that the use of statins to reduce LDL cholesterol to target levels with the subsequent addition of a drug to raise HDL cholesterol levels (niacin), rather than a drug to lower LDL cholesterol levels (ezetimibe), is a more effective treatment for patients at high cardiovascular risk.

“...this drug was introduced and became very popular without a large, well-designed study to look at whether it could reduce cardiovascular events,” said Dr. Steven Nissen, the chairman of cardiovascular medicine at the Cleveland Clinic.
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• The 2009 CVD Top 10 Unpartnered Projects
Result: Leading CVD franchises are exiting or transitioning to adjacent therapy areas.

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

EvaluatePharma, DH analysis.
Result: Merging of CV and Metabolic Silos

- CVD indications are multi-factorial, therapies cross over into:
  - Metabolics (dyslipidemia, diabetes),
  - Inflammation (endothelial dysfunction, vasculitis, reperfusion injury)
  - Hematology (thrombosis, TIA, stroke)
- Adjacent indications often offer growth opportunities to augment receding revenues in core business.
- Diabetes is a particularly similar indication characterized with patient population largely overlapping with CVD patients.
Leading CVD Franchises…
…the Changing of the Guard

WW Sales ($MM) of Top CVD Companies

- AstraZeneca
- Merck & Co
- Sanofi-Aventis
- Daiichi Sankyo
- Boehringer Ingelheim
- Pfizer
- Novartis
- Bayer AG
- Abbott Laboratories
- Servier
- Bristol-Myers Squibb

EvaluatePharma, DH analysis

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Diabetes
T2DM Market Composition

- In the US, there are ~21MM patients with T2DM. Among those, ~16MM are diagnosed and ~13.5MM are treated with OADs (oral anti-diabetic drugs), insulin, or both.
- Among the ~13.5MM treated T2DM patients, it is estimated that 1.5 M are treated with insulin only, with the remaining ~12MM patients are treated with OADs.
- A high level of unmet need remains, since only 36% of patients achieve their HbA1c goals (HbA1c is the most widely used marker to measure longer-term glycemic control).
- The total market for the diabetic category is estimated at $27B in 2009.

SG Cowen’s 2009 TA outlook; JP Morgan diabetes update; NIH National diabetes Information Clearing House (NDIC); DH analysis.
Diabetes and the Heart Disease are Closely Linked

- CVD is a major complication in diabetics and the leading cause of premature death among people with diabetes.
- Diabetes is associated with increase in classic CVD markers of endothelial dysfunction, prothrombic state and inflammation.

Cardio-metabolic Risk Factors
CVD complications Generates Greatest % Cost of Chronic Diabetes Management

- Much of the morbidity and cost of diabetes management is attributable to long-term, diabetes-related complications, particularly cardiovascular disease (CVD).

*Taken from Caro et al. (2002).*
Current Treatment Paradigm – A Wide Range of Therapeutic Choices

- Practitioners have more options in their armamentarium than ever before for T2DM (5 new classes of drugs have been approved in the last decade).
- Furthermore, there are several fixed dose combination (FDC) drugs, almost 30 different brands, generics and several types of insulin available to choose from.

**Schematic representation of approach to T2DM treatment**

1 OAD  2 (or 3) OADs  Insulin

*DH primary and secondary research.*
## Advantages vs. Disadvantages of Available Classes of Anti-Diabetic Agents

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Key Advantages</th>
<th>Key Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>• Extensive experience, low cost and high potency.</td>
<td>• Upper and/or lower GI side-effects in 10-15% of patients.</td>
</tr>
<tr>
<td></td>
<td>• Relatively benign, no hypoglycemia as monotherapy.</td>
<td>• Contraindicated in patients with renal insufficiency.</td>
</tr>
<tr>
<td></td>
<td>• Neutral on weight, favorable on lipids.</td>
<td>• Rare risk of lactic acidosis.</td>
</tr>
<tr>
<td>Secretagogues</td>
<td>• Extensive experience, low cost and high potency.</td>
<td>• Significant concerns regarding hypoglycemia and weight gain.</td>
</tr>
<tr>
<td>SFUs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretagogues</td>
<td>• Rapid reduction pf post-prandial hyperglycemia and potentially lesser risk of hypoglycemia.</td>
<td>• Modest potency and higher cost compared to SFUs.</td>
</tr>
<tr>
<td>Glinides</td>
<td></td>
<td>• Risk of hypoglycemia still higher than other OADs.</td>
</tr>
<tr>
<td>TZDs</td>
<td>• High potency and no hypoglycemia as monotherapy.</td>
<td>• Weight gain and edema.</td>
</tr>
<tr>
<td></td>
<td>• Reduction in triglycerides (Actos) and increase in HDL.</td>
<td>• Increased risk of congestive heart failure.</td>
</tr>
<tr>
<td></td>
<td>• Benefits demonstrated in large post-marketing studies.</td>
<td>• Increased risk of fractures in women.</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>• 2-4% weight loss.</td>
<td>• SC injection.</td>
</tr>
<tr>
<td></td>
<td>• Lack of severe hypoglycemia in combination with metformin.</td>
<td>• Nausea in significant number of patients.</td>
</tr>
<tr>
<td></td>
<td>• Potential for beta cell preservation.</td>
<td>• Potential safety concerns such as risk of pancreatitis &amp; cancer.</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>• Once a day oral and well tolerated.</td>
<td>• Modest efficacy.</td>
</tr>
<tr>
<td></td>
<td>• Weight neutral and no risk of hypoglycemia.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Potential for beta cell preservation</td>
<td></td>
</tr>
<tr>
<td>α-glucosidase</td>
<td>• No risk of hypoglycemia.</td>
<td>• Modest efficacy.</td>
</tr>
<tr>
<td>inhibitors</td>
<td>• Weight neutral.</td>
<td>• Potentially severe GI tolerability issues (bloating, diarrhea and cramps).</td>
</tr>
<tr>
<td>Insulin</td>
<td>• Potency</td>
<td>• SC injection.</td>
</tr>
<tr>
<td></td>
<td>• Safety.</td>
<td>• Requires regular monitoring and titration of dose.</td>
</tr>
<tr>
<td></td>
<td>• Benefits such as reduction in triglycerides and increase in HDL.</td>
<td>• Weight gain and risk of hypoglycemia.</td>
</tr>
</tbody>
</table>
Novel Anti-Diabetic Agents are Expected to Fit as Adjunct to Metformin and Insulin in Improving Glycemic Control Without Risk of Unwanted Side-Effects

- In the evolving T2DM treatment paradigm there continues to be a need for convenient to use agents with long-term efficacy in reducing HbA1c and additional cardio-metabolic risk factors with minimal side effects such as weight gain and hypoglycemia.
- Due to the nature of T2DM pathogenesis and progression, weight loss efficacy is an attractive value proposition for a novel anti-diabetic agent.
T2DM Treatment Trends Indicate Huge Gains for Newer Classes of Drugs in the Future

• Metformin and Insulin will remain anchors of T2DM therapy.
• However, over the coming years it is expected that there will be considerable shift among other drug classes in terms of patients and prescription share.
• DPP-IV inhibitors and GLP-1 analogues are expected to emerge as winners in the T2DM market.
• DPP-IV inhibitors are weight neutral and do not cause much hypoglycemia while GLP-1s have the added benefit of weight loss.

Figure 10: US T2D Therapy Usage as Share of Treated Patients

Source: JPMorgan estimates, Company data.

Note: 2006-2008 sales and script data by class and specialty has been charted out in the Appendix.
Obesity
The Numbers of Obese Adults and Children are Remarkably Large and Growing

Obesity Trends* Among U.S. Adults

(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)

1990

1998

2007

- A remarkable one-third of the US adult population (~75MM individuals) meet clinical definition of Obesity (BMI>30). Another one-third is overweight (BMI 25-30).
- Obesity rates continue to rise steadily in other developed and developing countries of the world.

*BMI = body mass index calculated in kg/m²


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Obesity: A Widespread Problem

Developed countries, including U.S. and Western Europe, and women, exhibit highest rates of Obesity, defined as body mass index (BMI) above 30

Figure 5: Prevalence of Adult Obesity by Sex and Country

Source: World Health Organization (WHO)
Obese Individuals are significantly at High-Risk for CV Mortality Due to Obesity Related Co-Morbidities

- Obesity related co-morbidities and CV mortality risk increase with increase in BMI.
- **Morbid Obesity** is commonly defined as BMI of 40 or more, or a BMI 35 or more with an Obesity related disease, such as uncontrolled T2DM, hypertension, dyslipidemia, or heart disease.

**Risk of cardiovascular mortality by Weight**

- **NHANES 1999-2004** reported that 4.8% of US adults are BMI >40 (~10MM individuals).
- **American Society of Metabolic and Bariatric Surgery (ASMBS)** estimates that ~15MM individuals in the US have a BMI >35 with multiple Obesity related co-morbidities or a BMI >35.

The Data Show That Even 5% Weight Loss Helps

- Studies have shown that losing as little as 5% of total body weight can significantly improve co-morbid disease markers.
- A 5% weight loss results in lower HbA1c (a key diabetic measure), lower blood pressure, lower LDL ("bad cholesterol") and total cholesterol and higher HDL, or "good cholesterol."
- A 5-10% weight loss can further improve these measures as well as lower triglyceride cholesterol levels and improve sleep apnea.
- These findings are the basis for current FDA drug development guidelines for Obesity which focus on a 5% weight loss.

**Figure 15: Improvement in Insulin Sensitivity in Type 2 Diabetics with Weight Loss (after 1 year)**

Source: Archives of Internal Medicine 1997, 147:1749

**Figure 13: Improvement in Plasma Lipids Associated with Weight Loss**


*Battle of the bulge JP Morgan report 2008.*
The Market Potential for a Weight Loss Drug is Huge, But So is the Risk

- The rapid adoption of phenfen prior to being taken off the market represents the huge potential for an efficacious Obesity drug.
- However, the withdrawal of Accomplia and fen-phen frame the high regulatory and safety risk.
- Several of the largest pharmaceutical companies in the world have discontinued Obesity programs due to such risk.

Total Worldwide Obesity Therapeutic Category Sales, 1986 - 2014

- Phentermine and Other Stimulants
- Cannabinoid antagonist
- Lipase inhibitor
- SNRI
- Other

Evaluate Pharma, DH Analysis
TA Partnering Meeting, November, 2009 - Pg. 53

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Agenda

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Diabetes and Obesity Drug Development: Framing the Risk

- Acceptance of adverse events in Pharma therapy

**Tolerance for Adverse Events**

- High
  - Diabetes
  - Cardio-prevent.
  - Metastatic Cancer
  - Neurodegenerative Disease
- Low
  - ED
  - OAB
  - Pain
  - Insomnia
  - Obesity?

**Increasing Morbidity - Imminent Mortality**
New FDA Guidelines Likely To Increase Development Timelines, Cost, And Postmarketing Requirements For New Diabetes Agents

- In December 2008, FDA provided updated guidance for the development of drugs and therapeutic biologics for the treatment of diabetes mellitus.
- Specifically, this guidance makes recommendations about how to demonstrate that a new antidiabetes therapy to treat type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk.
- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all Phase II and III trials…
Despite the Astounding Epidemiology, Obesity Has Been a Challenging Area for Drug Development

Clinical Development Risk
- Lack of predictability of the off-target CNS side effects from preclinical models (Accomplia).

Regulatory Risk
- FDA has a poor appetite for risk considering the risk/benefit ratio of treating Obesity.
- FDA may require additional safety studies over the 1 year efficacy trial.

Commercial Risk
- Less than optimal reimbursement.
- Lack of understanding of who is the target physician population.
- Payers have been reluctant to reimburse for treatment of Obesity in the past.

Post Marketing Safety Risk
- The phen-fen and Accomplia experience.
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Most late stage projects unavailable, remaining mid-stage are stalling, but early pipeline rich in science driven innovation

Clinical Development by Phase

[Bar chart showing clinical development phases with focus on preclinical, phase 1, phase 2, phase 3, pre-reg, and registered phases.]

IDdb, DH analysis
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 Evaluate Pharma and BioCentury lists

Adis R&D Insight, IDdb3, DH analysis

TA Partnering Meeting, November, 2009 - Pg. 60
CVD alliances needed, but deal making 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.
  - Historically, the anemic rate of transactions since 2000 indicates that available projects may be declining or potential partners are passing over opportunities.
The universe of investigational CVD agents was compiled from licensed databases and industry experience:

1. Create CVD + Met 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

   Combine, Remove Redundancies

   600 CVD + Met Agents in Active Clinical Development WW

2. Remove Unavailable Agents

   Evaluate Based on Selection Criteria

   Compare and Prioritize

   Invite Selected Companies

   1,100 CVD + Met Agents in Clinical Development WW
Projects sponsored by companies with substantial CVD development capabilities and marketing reach were deprioritized in the database.

1,100 CVD + Met Agents in Ph I to Registration WW

600 Active agents

315 optimistic projects

Top 22 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

1,100 CVD + Met Agents in Ph I to Registration WW

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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
Projects were then rated based on selection criteria indicating project attractiveness to a potential partner.

- 895 CVD Agents in Late Preclinical to Registration WW
- 600 available agents
- 315 optimistic projects
- Top 22 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

Intrinsic to Agent
- Unmet Needs
- Market Potential
- Novelty
- Precedents
- Clinical
- Competition
Biotech companies with early-stage (pre-IND to Phase I) assets are faced with the need to demonstrate proof-of-concept for their approach. In reality, the need is to go beyond proof-of-concept (demonstrating that the science is applicable to the disease) to prove that its approach provides a clinically and commercially relevant value proposition that makes the program attractive to potential partners.

To survive, biotech companies must embark on clinical programs that go beyond scientific proof-of-concept to demonstrate clinical and commercial “proof-of-relevance” to potential partners.
Projects then were compared among their peers based on company attributes and advertised availability.

- 895 CVD Agents in Late Preclinical to Registration WW
- 600 available agents
- 61 optimistic projects
- Top 22 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

Amongst Peers:
- Exclude Prior Top 10 unless clear progress achieved.
- Exclude DH current client target
- Company Management
- WW Availability
- “For out-license”

DH Analysis
TA Partnering Meeting, November, 2009 - Pg. 66
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Company sponsors of projects making the final list were invited and projects were tracked over the last several months.
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## 2009 Top 10 Unpartnered CVD Projects*

<table>
<thead>
<tr>
<th>Developmental Agent</th>
<th>MOA</th>
<th>Clinical Phase</th>
<th>Indications</th>
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</thead>
<tbody>
<tr>
<td><strong>Budiodarone</strong></td>
<td>Potassium Channel Antagonist</td>
<td>II</td>
<td>Atrial Fibrillation</td>
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<td><strong>Aryx</strong></td>
<td>ARYx Therapeutics</td>
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<td>IL-1 Beta Inhibitor</td>
<td>I</td>
<td>Type II Diabetes</td>
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<td><strong>Xoma</strong></td>
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</tr>
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<td><strong>ARRAY 403</strong></td>
<td>Glucokinase Stimulant</td>
<td>I</td>
<td>Type II Diabetes</td>
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<td>I</td>
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<td>Preclin</td>
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<td>Hypertension</td>
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* Not presented in any particular order

DH Analysis, Company Websites
TA Partnering Meeting, November, 2009 - Pg. 69
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Defined Health's Therapeutic Insight will be a featured track at these 2010 EBD conferences:

- **BIO-Europe Spring® 2010**  
  March 8–10, 2010  
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- **BIOPharm America® 2010**  
  September 15–17, 2010  
  Boston, MA