Drug Pipeline and Trends Insights

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Senior Director, Pipeline and Trend Forecasting, Part D

Prescription Solutions
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Today’s Webinar Agenda
Providing You With Insights Into the Following. . .

Welcome & Introductions
– Jane Lutz, Senior Director, Consultant Relations

Presentation Topics
– Presenter, Brian Kolling, Pharm.D., Senior Director, Pipeline & Trend Forecasting
  ▪ Annual “State of the Pipeline”
  ▪ Top Developments for 2011
  ▪ Therapeutic Category Review
    ▪ 2011 Approvals
    ▪ On the Horizon
    ▪ Generics

Question and Answer Session
Brian Kolling, Pharm.D.

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Senior Director, Pipeline & Trend Forecasting, Part D

Brian Kolling is the Senior Director of Pipeline and Trend Forecasting for Part D at Prescription Solutions. He is responsible for forecasting the business impact of pipeline drugs on UnitedHealth Group Medicare Part D plans. He also provides consultative input on trend management and formulary strategies for the Part D pharmacy team.

Prior to joining Prescription Solutions, Dr. Kolling was the Chief Pharmacy Officer at UnitedHealth Pharmaceutical Solutions, where he directed the clinical pharmacy activities for the UnitedHealthcare commercial business. Dr. Kolling also spent several years at Express Scripts, where he established a pipeline practice and co-authored the Express Scripts Drug Trend Report.

Dr. Kolling received his Bachelor of Science and Doctor of Pharmacy degrees from the University of Minnesota.
Overall Pipeline Activity Declining

TOTAL NUMBER OF PIPELINE PRODUCTS

Source: Cowen and Company

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Pipeline by Disease State

Drugs in Development

- Cancer
- CNS
- Diabetes
- Infectious Disease
- Respiratory
- Cardiovascular
- Vaccines
- Arthritis

Legend:

- Preclinical
- Phase I
- Phase II
- Phase III
- NDA
Pipeline Comparison: 2011 to 2006

Source: Cowen & Co
R&D – Where Are We Headed?

- New drug approvals have not kept pace with R&D spend
- The “patent cliff” has resulted in fundamental changes to research on new drugs
- Higher barrier to entry means more investment, yet most money today is spent in Phase II or earlier, which has highest failure rate

Solutions?

- In-license pipeline products later in development and leave early development work to partner company
- Share development risk with a similar-size company
- Shift to “friendlier” market (i.e. specialty, emerging markets)
- Exit selected markets
Two Approaches to address lagging R&D

January 22, 2011

Federal Research Center Will Help Develop Medicines
By GARDINER HARRIS

The Obama administration has become so concerned about the slowing pace of new drugs coming out of the pharmaceutical industry that officials have decided to start a billion-dollar government drug development center to help create medicines.

February 1, 2011

New Chief Revises Goals and Spending for Pfizer
By DUFF WILSON

Pfizer, the drug maker, announced plans Tuesday to slash its research spending by as much as $2.9 billion in the next two years, including closing the English labs that invented Viagra.
### Drug Approvals in 2011 - YTD

#### New Molecular Entities

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tradjenta</td>
<td>BI/Lilly</td>
<td>Type 2 diabetes</td>
<td>May 2</td>
</tr>
<tr>
<td>Zytiga</td>
<td>J&amp;J</td>
<td>Metastatic prostate cancer</td>
<td>April 28</td>
</tr>
<tr>
<td>vandetanib</td>
<td>AstraZeneca</td>
<td>Advanced medullary thyroid cancer</td>
<td>April 6</td>
</tr>
<tr>
<td>Horizant</td>
<td>GSK</td>
<td>Restless legs syndrome</td>
<td>April 6</td>
</tr>
<tr>
<td>Yervoy</td>
<td>BMS</td>
<td>Malignant myeloma</td>
<td>March 25</td>
</tr>
<tr>
<td>Benlysta</td>
<td>GSK</td>
<td>Lupus</td>
<td>March 9</td>
</tr>
<tr>
<td>Daliresp</td>
<td>Forest</td>
<td>Add-on for severe COPD</td>
<td>March 1</td>
</tr>
<tr>
<td>Edarbi</td>
<td>Takeda</td>
<td>Hypertension</td>
<td>February 25</td>
</tr>
<tr>
<td>Viibyrd</td>
<td>Forest</td>
<td>Depression</td>
<td>January 21</td>
</tr>
<tr>
<td>Natroba</td>
<td>Parapro</td>
<td>Head lice</td>
<td>January 18</td>
</tr>
</tbody>
</table>
## First-Time Generics in 2011

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Generic</th>
<th>Annual sales (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vfend</td>
<td>Pfizer</td>
<td>February 15</td>
<td>$260 million</td>
</tr>
<tr>
<td>Xalatan</td>
<td>Pfizer</td>
<td>March 22</td>
<td>$626 million</td>
</tr>
<tr>
<td>Concerta</td>
<td>J&amp;J</td>
<td>May 1</td>
<td>$1.4 billion</td>
</tr>
<tr>
<td>Femara</td>
<td>Novartis</td>
<td>June 3</td>
<td>$669 million</td>
</tr>
<tr>
<td>Levaquin</td>
<td>J&amp;J</td>
<td>June 20</td>
<td>$1.5 billion</td>
</tr>
<tr>
<td>Uroxatral</td>
<td>Sanofi-aventis</td>
<td>July 18</td>
<td>$249 million</td>
</tr>
<tr>
<td>Zyprexa</td>
<td>Lilly</td>
<td>October 23</td>
<td>$2.5 billion</td>
</tr>
<tr>
<td>Caduet</td>
<td>Pfizer</td>
<td>November 30</td>
<td>$339 million</td>
</tr>
<tr>
<td>Lipitor</td>
<td>Pfizer</td>
<td>November 30</td>
<td>$5.3 billion</td>
</tr>
</tbody>
</table>
Generic Opportunity Still Significant

Annual Brand Sales Value for Products Losing Exclusivity

Source: FDA Orange Book, SEC Filings, IMS Health, USPTO, & BofA Merrill Lynch Global Research
Top Developments to Watch - 2011

1. Zyprexa and Lipitor generics
2. Approval and launch of telaprevir and/or boceprevir
3. The clinical development of vorapaxar
4. Additional Phase III results for tofacitinib
5. Approval and launch of BenLysta
Cardiovascular Pipeline – 2011 Approvals

Brilinta (ticagrelor) - AstraZeneca

- Reversible ADP receptor blocker
- Proposed indication: Acute coronary syndrome
- PDUFA: July 20

Xarelto (rivaroxaban) - Bayer/J&J

- First-in-class Factor Xa inhibitor
- Proposed indication: prophylaxis of DVT and PE in patients undergoing hip or knee replacement surgery
- CRL issued by FDA 5/09; assume PDUFA date Nov 2011
Cardiovascular Pipeline – On the Horizon

Eliquis (apixiban) – BMS/Pfizer

- Factor Xa inhibitor for stroke prevention in atrial fibrillation and VTE prevention and treatment
- AVERROES trial vs. aspirin stopped early due to clinical benefit seen with apixaban; ARISTOTLE study will compare Apixiban to warfarin and should report mid-2011
- NDA filing after ARISTOTLE results released

Edoxaban – Daiichi-Sankyo

- Factor Xa inhibitor for atrial fibrillation and VTE
- Phase III results vs. enoxaparin in VTE prevention were generally positive; results vs. warfarin in AF expected in 2012
- US filing strategy not disclosed
Cardiovascular Pipeline – On the Horizon

Lomitapide – *Aegerion*
- Oral MTP-I inhibitor for homozygous familial hypercholesterolemia
- MTP-I prevents assembly and limits release of lipoproteins
- LDL and TG reductions of 50%
- NDA filing by end of 2011; orphan drug status

AMR101 – *Amarin*
- Oral therapy for the treatment of elevated triglycerides and mixed dyslipidemia
- Single active ingredient (ethyl icosapentate)
- MARINE and ANCHOR trials show decrease in triglycerides with little impact on LDL
- NDA filing expected 3Q 2011
Cardiovascular Pipeline – On the Horizon

MK-0524A – Merck

- Niacin plus laropiprant (anti-flushing agent) for treatment of primary hypercholesterolemia
- MK-0524B adds simvastatin
- Refiling for MK-0524A expected in 2012; followed by 0524B filing

Dalcetrapib – Roche

- CETP inhibitor for the treatment of dyslipidemia
- Phase IIb/III plaque and endothelial data expected in 2011; Outcomes study may report interim data as well
- Path to approval is likely complicated, given past experience in class
- NDA filing in 2013
## Cardiovascular Pipeline

### Generics:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Generic launch</th>
<th>Additional info</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricor</td>
<td>Abbott</td>
<td>March 2011-July 2012</td>
<td>▪ Settlement; launch likely 7/1/12</td>
</tr>
<tr>
<td>Lipitor</td>
<td>Pfizer</td>
<td>November 2011</td>
<td>▪ Settlement</td>
</tr>
<tr>
<td>Avapro</td>
<td>BMS</td>
<td>March 2012</td>
<td></td>
</tr>
<tr>
<td>Plavix</td>
<td>BMS</td>
<td>May 2012</td>
<td></td>
</tr>
<tr>
<td>Atacand</td>
<td>AstraZeneca</td>
<td>December 2012</td>
<td></td>
</tr>
<tr>
<td>Diovan</td>
<td>Novartis</td>
<td>September 2012</td>
<td></td>
</tr>
<tr>
<td>Niaspan</td>
<td>Abbott</td>
<td>September 2013</td>
<td>▪ Settlement</td>
</tr>
<tr>
<td>Crestor</td>
<td>AstraZeneca</td>
<td>July 2016</td>
<td>▪ Recent court ruling could extend to 2018</td>
</tr>
</tbody>
</table>
CNS Pipeline – 2011 Approvals

Remoxy (oxycodone) – Pfizer
- Twice-daily formulation for treatment of chronic pain
- Contains ORADUR gel cap technology – less prone to abuse?
- PDUFA 6/23/11

Zelrix (sumatriptan) – Nupathe
- Transdermal sumatriptan for treatment of acute migraine
- Single-use patch; controlled delivery over 4 hours via iontophoresis
- PDUFA 8/29/11
CNS Pipeline – On the Horizon

Telcagepant (MK-0974) - *Merck*

- Oral calcitonin-gene related peptide (CGRP) receptor antagonist for treatment of acute migraine
- Central action may result in lower rate of CV effects
- On track for 2009 NDA filing until liver enzyme elevations emerged in Phase II trial migraine prevention trial; revised filing in 2011

Levadex (dihydroergotamine) – *MAP/Allergan*

- DHE via oral inhaler
- Sustained pain relief for up to 48 hours
- Fewer adverse effects when compared to injectable DHE
- Approval in 2012 targeted
CNS Pipeline – On the Horizon

Cariprazine (RGH-188) - *Forest*

- Atypical antipsychotic for treatment of schizophrenia and bipolar mania
- Mechanism similar to Abilify, but potential for improved safety profile
- Phase III results expected 2nd half 2011

**TC-5214 – Targacept/AstraZeneca**

- Nicotinic ion channel blocker for major depressive disorder
- Developed as adjunct to first-line antidepressants
- Phase III began 2H10; NDA filing in 2012
# CNS Pipeline

## Generics:

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<th>Generic launch</th>
<th>Additional info</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zyprexa</td>
<td>Lilly</td>
<td>October 2011</td>
<td></td>
</tr>
<tr>
<td>Lexapro</td>
<td>Forest</td>
<td>March 2012</td>
<td>▪ Multiple generics (3 plus auth)</td>
</tr>
<tr>
<td>Seroquel</td>
<td>AstraZeneca</td>
<td>March 2012</td>
<td></td>
</tr>
<tr>
<td>Provigil</td>
<td>Cephalon</td>
<td>April 2012</td>
<td>▪ Settlements</td>
</tr>
<tr>
<td>Geodon</td>
<td>Pfizer</td>
<td>September 2012</td>
<td>▪ Multiple generics possible</td>
</tr>
<tr>
<td>Lunesta</td>
<td>Sepracor</td>
<td>May 2014</td>
<td>▪ Settlements</td>
</tr>
<tr>
<td>Cymbalta</td>
<td>Lilly</td>
<td>July 2014</td>
<td>▪ Multiple generics possible</td>
</tr>
<tr>
<td>Abilify</td>
<td>BMS</td>
<td>April 2015</td>
<td></td>
</tr>
</tbody>
</table>
Respiratory Pipeline – 2011 Approvals

Arcapta (indacaterol) – *Novartis*

- Once-daily beta agonist inhaler developed as monotherapy for COPD and combination therapy for asthma
- FDA AdCom recommended approval of low-dose but felt high-dose was no more efficacious
- Combination with Asmanex and NVA237 (LAMA) to follow
- PDUFA: July 2011
Respiratory Pipeline – On the Horizon

Eklira (aclinidium) – Almirall/Forest

• Twice-daily muscarinic antagonist (LAMA) inhaler for COPD
• Monotherapy and combination inhaler with formoterol in development
• NDA for monotherapy expected in 2011

Glycopyrronium (NVA237) – Novartis

• Inhaled long-acting muscarinic antagonist for the treatment of COPD
• Early data suggest similar efficacy to Spiriva
• Combination inhaler with Arcapta in development
• Phase III results expected 2q11 with filing soon after
Respiratory Pipeline – On the Horizon

Relovair (fluticasone furoate/vilanterol) – GSK

- Once-daily inhaler for COPD and asthma
- Clinical trials suggest modest FEV1 improvements over Advair
- LABA onset of action within minutes
- Phase III results 2H11

GSK573719/vilanterol – Theravance/GSK
Spiriva/olodaterol – Boehringer Ingelheim
QVA149 – Novartis

- Combination LAMA/LABA inhalers for COPD
- All in Phase III or starting Phase III in 2011
Diabetes Pipeline – 2011 Approvals

Dapaglifozin - *BMS/Astra-Zeneca*

- Oral sodium glucose co-transporter-2 (SGLT-2) inhibitor – suppresses glucose re-absorption and increases glucose excretion
- Reductions in body weight and blood pressure seen in clinical trials
- Urinary tract and genital infections are primary side effect
- PDUFA: 10/28/11

Bydureon – exenatide once-weekly (*Amylin*)

- GLP-1 analog
- Recent DURATION-6 trial failed to demonstrated non-inferiority to Victoza (A1C reduction 1.3% for Bydureon, 1.5% for Victoza)
- CRL issued Oct 2010; FDA requested a thorough QTc study
Diabetes Pipeline – On the Horizon

Lixisenatide – *sanofi-aventis*

- Daily GLP-1 analogue
- Phase III top-line data vs. exenatide suggest non-inferiority but fewer hypoglycemic events
- NDA filing 2012

Degludec – *Novo Nordisk*

- Long-acting basal insulin
- Phase III data vs. Lantus indicate lower fasting glucose level with degludec, and a trend toward lower nocturnal hypoglycemia
- Phase III for Degludec/Victoza combo expected to begin in 2011
Dificid (fidaxomicin) – *Optimer/Cubist*

- Oral therapy for treatment of *C. difficile*-associated diarrhea
- New class of antibiotics called macrocycles
- Phase III: non-inferior to vancomycin in clinical cure rate, with significantly lower recurrence rate
- FDA AdCom voted 13-0 for approval; PDUFA May 30

Linaclotide – *Forest*

- Oral guanylate cyclase receptor agonist for chronic constipation and irritable bowel syndrome with constipation
- Acts locally in the gut; no systemic exposure
- Efficacy in abdominal pain may provide marketing advantage
- NDA expected 3Q 2011
### Additional Patent Expirations

#### Generics:

<table>
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<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Generic launch</th>
<th>Additional info</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avandia</td>
<td>GSK</td>
<td>March 2012</td>
<td>▪ Teva exclusive</td>
</tr>
<tr>
<td>Singulair</td>
<td>Merck</td>
<td>August 2012</td>
<td>▪ No exclusivity</td>
</tr>
<tr>
<td>Actos</td>
<td>Takeda</td>
<td>August 2012</td>
<td>▪ Settlement with multiple companies</td>
</tr>
<tr>
<td>Revatio</td>
<td>Pfizer</td>
<td>September 2012</td>
<td>▪ No exclusivity</td>
</tr>
<tr>
<td>Aciphex</td>
<td>Eisai/J&amp;J</td>
<td>May 2013</td>
<td></td>
</tr>
<tr>
<td>Nexium</td>
<td>AstraZeneca</td>
<td>April 2014</td>
<td></td>
</tr>
<tr>
<td>Actonel</td>
<td>Warner Chilcott</td>
<td>June 2014</td>
<td>▪ 35 mg only</td>
</tr>
</tbody>
</table>
Specialty Drugs – A Shifting Market

2010
LIPITOR
Cholesterol
PLAVIX
Anti-clotting
ADVAIL
Asthma
COPD
REMICADE
Arthritis
ENBREL
Arthritis
HUMIRA
Arthritis
AVASTIN
Cancer
RITUXAN
Cancer
DIOVAN
Hypertension
CRESTOR
Cholesterol

2014
AVASTIN
Cancer
HUMIRA
Arthritis
ENBREL
Arthritis
CRESTOR
Cholesterol
REMICADE
Arthritis
RITUXAN
Cancer
LANTUS
Diabetes
ADVAIL
Asthma
COPD
HERCEPTIN
Cancer
NOVOLOG
Diabetes

Source: Reuters 04/13/2010 http://www.reuters.com/article/idUSLDE63C0BC20100413
Specialty Drugs – Hepatitis C

Victrelis (bocepravir) – *Merck*
- Oral protease inhibitor (TID)
- Add to existing interferon/ribavirin therapy (24, 32, or 44 week courses used in Phase III)
- Priority review; FDA AdCom unanimously recommended approval; PDUFA in May 2011

Telaprevir – *Vertex*
- Oral protease inhibitor (TID)
- Add to existing interferon/ribavirin therapy (8 or 12 week courses used in Phase III)
- Priority review; FDA AdCom unanimously recommended approval; PDUFA 5/23/11
Specialty Drugs – Rheumatoid Arthritis

Tofacitinib – Pfizer

- Oral JAK1 and JAK3 inhibitor for the treatment of rheumatoid arthritis
- JAK inhibition suppresses multiple immune response pathways
- Renal, hepatic, and CV side effects may require monitoring
- Phase III results announced throughout 2011; filing later this year

Fostamatinib – AstraZeneca

- Oral SYK (spleen tyrosine kinase) inhibitor
- SYK inhibition blocks signaling of immune cells responsible for the destruction of cartilage and bone
- NDA filing in 2013
Specialty Drugs – Multiple Sclerosis

Laquinamod – Teva
- Oral, once-daily therapy
- “Unclear how it works exactly, but it does something good”
- First Phase III released in 2010; BRAVO trial vs. Avonex TBR in 2011

Teriflumomide – sanofi-aventis
- Oral, once-daily therapy
- Metabolite of leflunomide; teratogenicity is a concern
- First Phase III released in 2010; TERENE trial vs. Rebif TBR in 2011

BG-12 – BiogenIdec
- Oral, twice daily therapy
- Phase III DEFINE study suggests similar efficacy to Gilenya
- NDA filing possible late 2011/early 2012
Questions?

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