PIPELINE PREVIEW: 2016-2017

A SUMMARY OF THE PHARMACEUTICAL PIPELINE

María M. Lowe, Pharm.D., BCPS

patientslikeme

Health Data & Drug Information Clinical Specialist
Non-biased overview of the pipeline: **Not an all inclusive review of the pipeline**

This CPE program **will** include discussion of non-FDA approved (off-label) medication use

**Maria Lowe, Pharm.D., BCPS** declares that she has **no** financial relationships with commercial interests. However, her employer, PatientsLikeMe, has received funding from a variety of sources including the following:

Accorda  
Actelion  
Aetna  
Alexion  
AstraZeneca  
Avanir Pharmaceuticals  
Biogen Idec  
Boehringer Ingelheim  
Bristol-Meyer Squibb  
Bupa  
Celgene  
Computer Sciences Corporation  
CoPatient  
Curelator  
Denali Therapeutics  
EMD Serono  
Genentech  
inVentiv Health  
Janssen Pharmaceuticals  
Merck  
Novartis  
Pathway Genomics  
Patient Power  
inVentiv Health  
Janssen Pharmaceuticals  
Merck  
Novartis  
Pathway Genomics  
Patient Power  
inVentiv Health  
Janssen Pharmaceuticals  
Merck  
Novartis  
Pathway Genomics  
Patient Power  
inVentiv Health  
Janssen Pharmaceuticals  
Merck  
Novartis  
Pathway Genomics  
Patient Power  
inVentiv Health  
Janssen Pharmaceuticals  
Merck  
Novartis  
Pathway Genomics  
Patient Power  
inVentiv Health  
Janssen Pharmaceuticals  
Merck  
Novartis  
Pathway Genomics  
Patient Power  
inVentiv Health  
Janssen Pharmaceuticals  
Merck  
Novartis  
Pathway Genomics  
Patient Power  
inVentiv Health  
Janssen Pharmaceuticals  
Merck  
Novartis  
Pathway Genomics  
Patient Power  
inVentiv Health  
Janssen Pharmaceuticals  
Merck  
Novartis  
Pathway Genomics  
Patient Power  
inVentiv Health  
Janssen Pharmaceuticals  
Merck  
Novartis  
Pathway Genomics  
Patient Power  
inVentiv Health  
Janssen Pharmaceuticals  
Merck  
Novartis  
Pathway Genomics  
Patient Power  
inVentiv Health  
Janssen Pharmaceuticals  
Merck  
Novartis  
Pathway Genomics  
Patient Power  
inVentiv Health  
Janssen Pharmaceuticals  
Merck  
Novartis  
Pathway Genomics  
Patient Power  
inVentiv Health  
Janssen Pharmaceuticals  
Merck  
Novartis  
Pathway Genomics  
Patient Power  
inVentiv Health  
Janssen Pharmaceuticals  
Merck  
Novartis  
Pathway Genomics  
Patient Power
OBJECTIVES

BY THE END OF THIS PRESENTATION YOU WILL BE ABLE TO:

1. Describe recent trends in the FDA approval process

2. Compare and contrast emerging pipeline agents with currently available therapeutic options

3. Summarize the generic availability of commonly used agents over the next two years
## TOP AREAS OF CLINICAL DEVELOPMENT

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Number of Agents in Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticancer</td>
<td>4,176</td>
</tr>
<tr>
<td>Biotechnology</td>
<td>4,051</td>
</tr>
<tr>
<td>Neurological</td>
<td>2,513</td>
</tr>
<tr>
<td>Anti-infective</td>
<td>2,221</td>
</tr>
<tr>
<td>Reformulations</td>
<td>2,080</td>
</tr>
<tr>
<td>Alimentary/metabolic</td>
<td>1,999</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>1,499</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>950</td>
</tr>
<tr>
<td>Immunological</td>
<td>869</td>
</tr>
<tr>
<td>Respiratory</td>
<td>855</td>
</tr>
</tbody>
</table>

~50% of drugs in development are injectable formulations

~34% of drugs in development are oral formulations

PIPELINE TRENDS
USE OF FDA SPECIAL PROGRAMS FOR NMEs APPROVED

NME: New molecular entity
TRENDS OF 2016


Images available from:
What were some trends in the pipeline that you observed over the last year?

What are the therapeutic categories you feel have the potential for the greatest impact?
ONCOLOGY

PIPELINE TRENDS

Fast-paced area of development: represents approximately 30% of drugs in development

- 2016 has been somewhat slower than recent years
- Last year was a big year for multiple myeloma treatments
- Accelerated approvals: watch for confirmatory trials

Large price tags remain an issue: keep an eye on survival benefit compared to other treatments

- Value of these agents may not always be clear

Immuno-oncology remains a significant area of focus

- Competition is ramping up in lung cancer
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Anticipated Generic Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloxi® (palonosetron)</td>
<td>9/2018</td>
</tr>
<tr>
<td>Emend® (fosaprepitant injection)</td>
<td>3/2019</td>
</tr>
<tr>
<td>Faslodex® (fulvestrant)</td>
<td>3/2019</td>
</tr>
<tr>
<td>Sutent® (sunitinib)</td>
<td>2/2021</td>
</tr>
<tr>
<td>Tarceva® (erlotinib)</td>
<td>5/2021</td>
</tr>
<tr>
<td>Revlimid® (lenalidomide)</td>
<td>3/2022</td>
</tr>
<tr>
<td>Alimta® (pemetrexed)</td>
<td>5/2022</td>
</tr>
</tbody>
</table>

Please note: for the purposes of this table, proprietary names are utilized to distinguish patent expiration of the branded product.
ONCOLOGY
AGENTS IN DEVELOPMENT: OVARIAN CANCER

Rucaparib
- Oral, twice-daily inhibitor of poly-ADP ribose polymerase-1 (PARP-1)
- Seeking approval for the monotherapy treatment of advanced BRCA+ ovarian cancer after at least two prior treatments
  - ORR 54% (95% CI: 43.8-63.5)
  - Duration of response 9.2 months (95% CI: 6.6-11.7 months)
- FDA decision expected 2/23/2017

Also in development
- Niraparib - NDA submitted 11/1/2016

NDA: new drug application, ORR: objective response rate
ONCOLOGY
AGENTS IN DEVELOPMENT: LUNG CANCER

Brigatinib

- Oral, once-daily inhibitor of ALK and EGFR
- Seeking approval for the treatment of metastatic ALK+ NSLC who have progressed on Xalkori® (crizotinib)
- Phase II ALTA trial:
  - ORR 54%; median PFS 12.9 months
  - Intracranial ORR 67% in patients with measurable brain metastases
- Phase 3 ALTA 1L trial ongoing
  - Brigatinib vs. crizotinib in patients with locally advanced or metastatic ALK+ NSCLC with no prior ALK inhibitor therapy
- FDA decision expected 4/29/2017

ALK: anaplastic lymphoma kinase, EGFR: epidermal growth factor receptor, NSCLC: non-small cell lung cancer, ORR: objective response rate, PFS: progression-free survival
ONCOLOGY
AGENTS IN DEVELOPMENT: BREAST CANCER

Ribociclib [LEE011]
- Oral, once-daily inhibitor of cyclin-dependent kinase 4 and 6 (CDK4 & CDK6)
- Seeking approval in conjunction with letrozole as a first-line treatment of postmenopausal women with HR+/HER2- advanced or metastatic breast cancer
- Phase III MONALEESA-2 trial:
  - Ribociclib plus letrozole ↓ the risk of progression or death by 44% (HR = 0.556, 95% CI: 0.429-0.720; P = 0.00000329) vs. letrozole alone
  - FDA decision expected in the first half of 2017

HER2: human epidermal growth factor receptor 2, HR: hormone receptor
**IMMUNOLOGY**

**PIPELINE TRENDS**

**Significant area of focus within pipeline:** potential for a number of new product approvals in the first half of 2017

**Biosimilars:** more products are being approved, but what now?

- Delay in FDA guidance related to interchangeability
- Confusion over when agents will hit the market once approved
- Possible hesitation to prescribe
- Unclear cost-saving potential
### IMMUNOLOGY

#### AGENTS IN DEVELOPMENT

<table>
<thead>
<tr>
<th>Agent Name</th>
<th>Details</th>
<th>Phase of Development</th>
<th>Also in Development For</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brodalumab</td>
<td>Targets IL-17R</td>
<td>Seeking approval for the treatment of psoriasis</td>
<td>Psoriatic arthritis, RA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDA decision expected by <strong>11/16/2016</strong></td>
<td></td>
</tr>
<tr>
<td>Baricitinib (oral)</td>
<td>JAK1/JAK2 inhibitor</td>
<td>Seeking approval for the treatment of moderately-to-severely active RA</td>
<td>Atopic dermatitis, SLE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDA decision expected by <strong>1/19/2017</strong></td>
<td></td>
</tr>
<tr>
<td>Dupilumab</td>
<td>Targets IL-4R alpha</td>
<td>Seeking approval for the treatment of inadequately controlled moderate-to-severe atopic dermatitis</td>
<td>Also in development for the treatment of allergic asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDA decision expected by <strong>3/29/2017</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Please note:** all agents are administered subcutaneously unless otherwise indicated

IL: interleukin, JAK: janus kinase, SLE: systemic lupus erythematosus, RA: rheumatoid arthritis
### IMMUNOLOGY

#### AGENTS IN DEVELOPMENT

<table>
<thead>
<tr>
<th>Agent Name</th>
<th>Details</th>
<th>Phase of Development</th>
<th>Also in Development For</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirukumab</td>
<td>Targets IL-6</td>
<td>Seeking approval for the treatment of moderately-to-severely active RA</td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BLA submitted 9/2016</td>
<td></td>
</tr>
<tr>
<td>Sarilumab</td>
<td>Targets IL-6R</td>
<td>Seeking approval for the treatment of RA</td>
<td>Non-infectious uveitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10/2016 FDA declined approval</td>
<td></td>
</tr>
<tr>
<td>Benralizumab</td>
<td>Targets IL-5Ra</td>
<td>Phase III studies for severe asthma</td>
<td>COPD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BLA Filing is expected before end of 2016</td>
<td></td>
</tr>
</tbody>
</table>

*Please note:* all agents are administered subcutaneously unless otherwise indicated.
Lipid lowering and anticoagulant markets are getting crowded: a number of significant approvals in last 18 months

- First antidote for newer oral anticoagulants: Praxbind® (idarucizumab)
- Generic rosuvastatin

PCSK-9 inhibitors are here: now what?

- Focus on cost and place in therapy – pay for performance
- Awaiting outcomes data
- More competition in the lipid-lowering pipeline is yet to come but not from bococizumab
# CARDIOVASCULAR

## GENERIC PIPELINE

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Anticipated Generic Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azor® (olmesartan/amlodipine)</td>
<td>10/2016</td>
</tr>
<tr>
<td>Benicar® (olmesartan)</td>
<td>10/2016(^a)</td>
</tr>
<tr>
<td>Zetia® (ezetimibe)</td>
<td>12/2016</td>
</tr>
<tr>
<td>Aggrenox® (aspirin/dipyridamole)</td>
<td>1/2017</td>
</tr>
<tr>
<td>Vytorin® (ezetimibe/simvastatin)</td>
<td>4/2017</td>
</tr>
<tr>
<td>Adcirca® (tadalafil)</td>
<td>11/2017</td>
</tr>
</tbody>
</table>

**Please note:** for the purposes of this table, proprietary names are utilized to distinguish patent expiration of the branded product

\(^a\): also includes estimated generic entry of combination with hydrochlorothiazide
Bempedoic acid [ETC-1002]

- Oral, inhibitor of ATP-citrate lyase
- In development for the treatment of hyperlipidemia
- Phase II trials:
  - ↓ LDL 32-43% in patients with diabetes
  - ↓ LDL 27-32% in patients with history of statin intolerance
  - ↓ LDL 43-48% in combination with Zetia® (ezetimibe)
  - ↓ LDL 22% when added to atorvastatin 10 mg
- Phase III trials underway
  - Plans for development in fixed-dose combination with ezetimibe

ATP: adenosine triphosphate, LDL: low density lipoprotein
Andexanet alfa (AndexXa®)

- Modified version of Factor Xa which can sequester direct inhibitors
  - Allows native Factor Xa to restore hemostasis
- In development for use as antidote to betrixaban, Xarelto® (rivaroxaban), Eliquis® (apixaban), enoxaparin, and Savaysa® (edoxaban)
- FDA declined approval 8/17/2016

Also in development

- Ciraparantag [PER977] – Phase III
Development across existing classes: focus on new combinations and formulations

- Adlyxin® (lixisenatide) & Jentadueto XR® (linagliptin/metformin ER) approved
- Showdown to become first GLP/insulin combination product

Recent increase in insulin options: effort to make insulin faster and more convenient

- Basaglar® (insulin glargine): expected launch 12/2016

Safety remains an issue with these agents:

- Ongoing safety concerns related to DPP-4 inhibitors and SGLT2 products
- Cardiovascular risk reduction with Victoza® (liraglutide) and Jardiance® (empagliflozin)

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Anticipated Generic Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lantus® (insulin glargine)</td>
<td>2nd Half 2016(^a)</td>
</tr>
<tr>
<td>Januvia® (sitagliptin)</td>
<td>7/2022</td>
</tr>
<tr>
<td>Janumet® (sitagliptin/metformin)</td>
<td>4/2026</td>
</tr>
<tr>
<td>Onglyza® (saxagliptin)</td>
<td>11/2028</td>
</tr>
</tbody>
</table>

Please note: for the purposes of this table, proprietary names are utilized to distinguish patent expiration of the branded product.

\(^a\): date when biosimilar/follow-on biologic entry will be allowed, will not be a standard generic.
Sotagliflozin

• Oral, once daily dual sodium glucose co-transporter 1 and 2 inhibitor (SGLT-1 and SGLT-2)
  • SGLT-1 affects glucose absorption in the GI tract
  • SGLT-2 affects glucose absorption in the

• Phase III inTandem1 trial in type 1 diabetes:
  • Average A1C ↓ 0.35%-0.41% (p<0.001)
  • May potentially reduce meal time insulin needs

• Phase III studies in type 2 diabetes are expected to begin later in 2016
# ENDOCRINE

## AGENTS IN DEVELOPMENT: TYPE 2 DIABETES

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent Name</th>
<th>Phase of Development</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 Agonists</td>
<td>Semaglutide</td>
<td>Phase III</td>
<td>SC; Once-weekly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Also in Phase III as oral formulation</td>
<td>Oral formulation: once-daily</td>
</tr>
<tr>
<td></td>
<td>ITCA 650 (exenatide DUROS)</td>
<td>Phase III – NDA expected before end of 2016</td>
<td>SC; Once- or twice-yearly</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Evogliptin</td>
<td>Phase III</td>
<td>Oral, once-daily</td>
</tr>
<tr>
<td></td>
<td>Gosogliptin</td>
<td>Phase III</td>
<td>Oral, once-daily</td>
</tr>
<tr>
<td></td>
<td>Retagliptin</td>
<td>Phase III</td>
<td>Oral, once-daily</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>Bexagliflozin</td>
<td>Phase III</td>
<td>Oral, once-daily</td>
</tr>
<tr>
<td></td>
<td>Ertugliflozin</td>
<td>Phase III – NDA expected before end of 2016</td>
<td>Oral, once-daily</td>
</tr>
</tbody>
</table>

## ENDOCRINE
### AGENTS IN DEVELOPMENT: INSULIN

<table>
<thead>
<tr>
<th>Agent Name</th>
<th>Phase of Development</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin peglispro</td>
<td>Development terminated</td>
<td>Basal</td>
</tr>
<tr>
<td>Faster acting insulin aspart (NN1218)</td>
<td>NDA submitted</td>
<td>Mealtime</td>
</tr>
<tr>
<td><strong>MK-1293</strong></td>
<td>NDA submitted</td>
<td>Basal</td>
</tr>
<tr>
<td><em>Follow-on biologic insulin glargine</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esysta Bluetooth Insulin Pen</td>
<td>Application submitted</td>
<td>Varies</td>
</tr>
<tr>
<td>Buccal insulin spray (Oral-lyn™)</td>
<td>Phase III</td>
<td>Mealtime</td>
</tr>
<tr>
<td><strong>BioChaperone® Lispro</strong></td>
<td>Phase III planned for 2016</td>
<td>Mealtime</td>
</tr>
<tr>
<td><em>In development as U100 and U200</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral insulin capsule (ORMD-0801)</td>
<td>Phase II</td>
<td>Basal</td>
</tr>
<tr>
<td>Oral insulin (Insulin Tregopil)</td>
<td>Phase I</td>
<td>Mealtime</td>
</tr>
</tbody>
</table>

*NDAs: new drug application*
## ENDOCRINE

### AGENTS IN DEVELOPMENT: COMBINATION PRODUCTS

<table>
<thead>
<tr>
<th>Agent Name</th>
<th>Phase of Development</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saxagliptin/dapagliflozin</td>
<td>10/2015: FDA declined approval</td>
<td>Once-daily</td>
</tr>
<tr>
<td>Ertugliflozin/sitagliptin</td>
<td>Phase III</td>
<td>Once-daily</td>
</tr>
<tr>
<td>Ertugliflozin/metformin</td>
<td>Phase III</td>
<td>Once-daily</td>
</tr>
<tr>
<td>Lixisenatide/insulin glargine (iGlarLixi, LixiLan)</td>
<td>FDA decision expected in 11/2016</td>
<td>Once-daily</td>
</tr>
<tr>
<td>Liraglutide/insulin degludec (Xultophy)</td>
<td>FDA decision expected in 12/2016</td>
<td>Once-daily</td>
</tr>
</tbody>
</table>
CENTRAL NERVOUS SYSTEM
PIPELINE TRENDS

**Multiple sclerosis:** potential treatment for primary progressive disease

**Migraine therapy:** calcitonin gene related peptides for migraine prevention
  - Significant competition to become the first

**Pain management:** emphasis remains on abuse-deterring opioids
  - FDA guidance released: Abuse Deterrent Opioids Evaluation and Labeling
  - Priority for new FDA commissioner – outlined a plan for tackling the opioid epidemic
# CENTRAL NERVOUS SYSTEM

## GENERIC PIPELINE

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Anticipated Generic Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seroquel XR® (quetiapine ER)</td>
<td>11/2016</td>
</tr>
<tr>
<td>Relpax® (eletriptan hydrobromide)</td>
<td>12/2016</td>
</tr>
<tr>
<td>Azilect® (rasagiline mesylate)</td>
<td>2/2017</td>
</tr>
<tr>
<td>Pristiq® (desvenlafaxine)</td>
<td>3/2017</td>
</tr>
<tr>
<td>Strattera® (atomoxetine)</td>
<td>5/2017</td>
</tr>
<tr>
<td>Copaxone® (glatiramer acetate)</td>
<td>First half of 2018&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Treximet® (sumatriptan/naproxen)</td>
<td>2/2018</td>
</tr>
</tbody>
</table>

Please note: for the purposes of this table, proprietary names are utilized to distinguish patent expiration of the branded product

<sup>a</sup>: launch date is dependent upon pending patent litigation

ER: extended release
**CENTRAL NERVOUS SYSTEM**
AGENTS IN DEVELOPMENT: MIGRAINE PREVENTION

**Calcitonin gene-related peptides (CGRP)**
- Block activity of CGRP to minimize the vasodilation and neuroinflammation that leads to migraines
- First preventative therapy specific to migraines

<table>
<thead>
<tr>
<th>Phase III</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erenumab [AMG334]</td>
<td>TEV-48125</td>
</tr>
<tr>
<td>ALD403</td>
<td>MK-8031</td>
</tr>
<tr>
<td>Galcanezumab [LY2951742]</td>
<td></td>
</tr>
</tbody>
</table>

- Acute treatment of migraine
  - Ubrogepant [MK-1602] – Phase III
CENTRAL NERVOUS SYSTEM
AGENTS IN DEVELOPMENT: MULTIPLE SCLEROSIS

**Ocrelizumab (Ocrevus™)**
- IV, humanized MAB that targets CD-20+ B cells
- Seeking approval for the treatment of relapsing MS and PPMS
- **OPERA I** and **OPERA II** Phase III studies in RRMS:
  - ↓ **ARR by ~50%** vs. interferon beta-1a (Rebif®)
- **ORATORIO** Phase III study in PPMS:
  - ↓ **risk of progression of disability by 24%** vs. placebo
- FDA decision expected **12/28/2016**

ARR: annualized relapse rate, IV: intravenous, MAB: monoclonal antibody, MS: multiple sclerosis
PPMS: primary progressive multiple sclerosis, RRMS: relapsing remitting multiple sclerosis
Sphingosine-1 phosphate receptor modulators

- **Ponesimod**
  - Phase III **OPTIMUM** trial initiated 2015 – head-to-head vs Aubagio® (teriflunomide)
    - Also in Phase II for psoriasis and graft-versus-host disease

- **Ozanimod**
  - Phase III trials for MS
    - Also in Phase III for ulcerative colitis and Phase II for Crohn’s disease

- **Siponimod**
  - Phase III **EXPAND** trial for SPMS
    - ↓ risk of progression of disability by 21% vs. placebo

---

MS: multiple sclerosis, SPMS: secondary progressive multiple sclerosis
CENTRAL NERVOUS SYSTEM
AGENTS IN DEVELOPMENT: ABUSE-DETERRING OPIOIDS

Guidance issued in 2015:

- “The FDA is encouraging manufacturers to develop abuse-deterrent drugs that work correctly when taken as prescribed, but, for example, may be formulated in such a way that deters misuse and abuse”
  [http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm440713.htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm440713.htm)

Abuse-deterrent strategies

- Use of physical and chemical barriers to chewing or crushing
- Use of a sequestered opioid antagonist that is released upon manipulation of the product to neutralize the addictive chemicals
- Ingredients to promote aversion upon misuse
- Delivery systems for non-oral delivery
- Use of chemical entities such as a prodrug
## CENTRAL NERVOUS SYSTEM

### AGENTS IN DEVELOPMENT: ABUSE-DETERRING OPIOIDS

<table>
<thead>
<tr>
<th>Opioid Component</th>
<th>Available Products</th>
<th>Agents In Development</th>
</tr>
</thead>
</table>
| **Hydrocodone**  | • Hysingla ER® (hydrocodone bitartrate)  
                 | • Zohydro ER® (hydrocodone bitartrate)  | • AVERSION hydrocodone/APAP (AVERSION H/A)  
                 |                 | • Apadaz™ (benzhydrocodone hydrochloride and acetaminophen)  
                 |                 | • ER hydrocodone/APAP [MNK-155]  
                 |                 | • IR hydrocodone/APAP [TV-46763]  
                 |                 | • DETERx ER hydrocodone [CEP-33237] |
| **Morphine**     | • Emebda® (morphine sulfate and naltrexone hydrochloride)  | • Arymo® (ER morphine) |

APAP: acetaminophen, ER: extended release, IR: immediate release
### CENTRAL NERVOUS SYSTEM

**AGENTS IN DEVELOPMENT: ABUSE-DETERRING OPIOIDS**

<table>
<thead>
<tr>
<th>Opioid Component</th>
<th>Available Products</th>
<th>Agents In Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone</td>
<td>• Exalgo® (hydromorphone HCl ER)</td>
<td>• Hydromorphone/naloxone [PRC-062]</td>
</tr>
</tbody>
</table>
| Oxycodone        | • Oxydo® (oxycodone HCl IR)  
                  | • Oxycontin® (oxycodone HCl ER)  
                  | • Xtampza ER® (oxycodone ER)  
                  | • Targiniq ER ® (oxycodone and naloxone) | • Oxycodone/naltrexone ER [ALO-02]  
                  | • Avridi® (IR oxycodone)  
                  | • Remoxy® (oxycodone ER)  
                  | • SequestOx® (oxycodone/naltrexone) |
| Oxymorphone      | • Opana ER® (oxymorphone HCl ER) | • N/A |

ER: extended release, HCl: hydrochloride, IR: immediate release
Hepatitis C DAA market growth: will it slow soon?
- Market has grown quickly and dramatically
- Discontinued production of older agents
- Recent approval of Epclusa® (sofosbuvir and velpatasvir) and Zepatier® (elbasvir and grazoprevir)

Slow progress in the anti-infectives pipeline: few new products despite efforts to encourage development
- Safety update regarding fluoroquinolones
## INFECTIOUS DISEASES
### GENERIC PIPELINE

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Anticipated Generic Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaletra® (lopinavir/ritonavir)</td>
<td>12/2016</td>
</tr>
<tr>
<td>Norvir® (ritonavir)</td>
<td>12/2016</td>
</tr>
<tr>
<td>Prezista® (darunavir)</td>
<td>11/2017</td>
</tr>
<tr>
<td>Sustiva® (efavirenz)</td>
<td>12/2017</td>
</tr>
<tr>
<td>Reyataz® (atazanavir)</td>
<td>12/2017</td>
</tr>
<tr>
<td>Truvada® (emtricitabine/tenofovir)</td>
<td>12/2017</td>
</tr>
<tr>
<td>Viread® (tenofovir)</td>
<td>12/2017</td>
</tr>
<tr>
<td>Atripla® (efavirenz/emtricitabine/tenofovir)</td>
<td>8/2018</td>
</tr>
</tbody>
</table>

Please note: for the purposes of this table, proprietary names are utilized to distinguish patent expiration of the branded product.
## Infectious Diseases

### Agents in Development: Hepatitis C

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Details</th>
<th>Dosing and Duration</th>
<th>Regulatory Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>velpatasvir + sofosbuvir + voxilaprevir</td>
<td>NS5A inhibitor, NS5B polymerase inhibitor, &amp; NS3/4A protease inhibitor</td>
<td>Once daily for 6-12 weeks</td>
<td>Phase III</td>
</tr>
<tr>
<td>glecaprevir + pibrentasvir</td>
<td>NS3/4 protease inhibitor &amp; NS5A inhibitor</td>
<td>Once daily for 8-12 weeks</td>
<td>Phase III</td>
</tr>
<tr>
<td>grazoprevir + elbasvir* + MK-3682</td>
<td>NS3/4A protease inhibitor, NS5A inhibitor &amp; NS5B polymerase inhibitor</td>
<td>Once daily for 8 weeks</td>
<td>Phase II</td>
</tr>
<tr>
<td>odelasvir + AL-335 + simeprevir</td>
<td>NS5A inhibitor, NS5B polymerase inhibitor, &amp; NS3/4A protease inhibitor</td>
<td>Once daily for 6-8 weeks</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

*also in development with MK-8408, an enhanced version of elbasvir*
2015 National Action Plan for Combating Antibiotic-resistant Bacteria: sets forth the goal of accelerating the research and development of new antibiotics and/or related products

Agents in development include:

- Meropenem-vaborbactam (Carbavance®)
- Delafloxacin
- Eravacycline
- Solithromycin
- Plazomycin
- Fusidic acid (Taksta™)
- Omadacycline
- Iclaprim
- Lefamulin

https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf
Nonalcoholic steatohepatitis (NASH)

- Goal of treatment is to prevent advanced fibrosis, cirrhosis, and hepatocellular carcinoma
- Clinical trials may use surrogate endpoint: impact on steatohepatitis and impact on fibrosis progression
- Highly competitive area of development

<table>
<thead>
<tr>
<th>Phase III</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elafibranor</td>
<td>Simtuzumab</td>
</tr>
<tr>
<td>Ocalvia® (obeticholic acid)</td>
<td>Cenicriviroc</td>
</tr>
<tr>
<td>Aramchol</td>
<td>Emricasan</td>
</tr>
<tr>
<td>Oltipraz [PMK-N01Gl1]</td>
<td>GS-4997</td>
</tr>
</tbody>
</table>
What were some trends in the pipeline that you observed over the last year?

What are the therapeutic categories you feel have the potential for the greatest impact?
Oncology and immunology: expect these pipelines to continue to move quickly

Diabetes treatment space is getting crowded: keep an eye on insulin products and new combinations

Lots of excitement in the CNS pipeline: specifically with migraine prevention

HCV development continues: next round of products might further shorten treatment, but is the end in sight?
REFERENCES


Questions?