PHARMA'S FRONT-RUNNERS

Profiling a dozen agents on deck plus 203 products in the wings, MM&M's Pipeline 2012 sees a year of change. **Marc Iskowitz** reports

Welcome to *MM&M*'s Pipeline 2012, a guide to late-stage R&D and a tip sheet on what's generating the most buzz in drug development. Scrutinizing the new crop of front-runners, readers may ask themselves: Is the blockbuster still alive?

As pharma troops further into biotech territory, an area often characterized by smaller patient pools and more limited sales, maybe there should be a lesser threshold of commercial success.

Not so fast, says Ben Weintraub, PhD, director of research at Wolters Kluwer *in*Thought. Exhibit A, he says, is Vertex's drug for treating hepatitis C virus, Incivek. Since jumping from the pages of our Pipeline 2011 report to a May approval by the FDA, Incivek is well on its way to making history—reaching a billion dollars in sales by year's end would make it the fastest new product launch on record.

"The idea that the age of the blockbuster is over is definitely not true," Weintraub asserts. While Incivek is no Lipitor, it "still shows that a new drug can get taken up and used, change the standard of care, and make a lot of money."

Huge, chronic markets like diabetes or cardiovascular disease are no longer the only tickets to success. "Now, what you need to become a blockbuster," he says, "is a specialty drug, one that's expensive—to offset the smaller treatment population—but one that fills a significant unmet need."

Among potential blockbusters set to launch in the next few years, several are speciality drugs. In hepatitis C, we may see another one.

Drug developers are getting closer to an all-oral HCV regimen that eliminates the need for injected interferon. The first of these is expected to reach market in 2015. Until then, Boehringer Ingelheim's BI-201335 could make inroads on Incivek and Merck's Victrelis. On similar lines, some are looking for Biogen Idec's BG-12 to unseat Novartis' Gilenya as the preferred oral multiple sclerosis drug.

Among oral small molecules, Pfizer's tofacitinib and AstraZeneca/Rigel's fostamatinib have their sights set on challenging injected biologics in rheumatoid arthritis. There are also expectations that the novel oral anticoagulant Eliquis (Bristol-Myers Squibb/Pfizer) could be the third such agent approved and make a serious bid for cardiologists' Rx pads, although inexpensive warfarin could curb sales.

In addition to the infectious disease, neurology, rheumatology and cardiovascular sectors, this report dives into oncology, where the big story is the recent slate of personalized medicine approvals: BMS's Yervoy, Pfizer's Xalkori and Roche/Plexxikon's Zelboraf. In these pages you'll read about other biologics being developed for targeted lines of tumor treatment. Metabolic and orphan therapies, plus respiratory and women's health, are highlighted in the report, too.

Consistent with our methodology the last several years, top picks are based on consultation with Wolters Kluwer *in*Thought, Adis R&D Insight, GfK HealthCare and other experts. Each profile has a snapshot of safety and efficacy data vs. the standard of care and, where available, the estimated month of approval, plus a quick way to gauge the likelihood of an FDA OK called the *in*Thought Approvability Index (anything above 50% stands a good chance). Rounding out the report are analyst comments, revenue forecasts and lists of other key products. (For more extensive lists, go to mmm-online.com.)

THERAPEUTIC CATEGORIES:

Cardiovascular

PRODUCTS GENERATING BUZZ

Dalcetrapib Roche
Indication: Atherosclerosis (Phase III)
What the clinical trials found: In the Phase IIb Dal-vessel trial, dalcetrapib raised HDL cholesterol levels 31% vs. placebo without any of the off-target effects that troubled torcetrapib, an earlier CETP inhibitor that Pfizer pulled from testing due to a higher death rate. In the Dal-plaque trial, dalcetrapib beat placebo on some measures of plaque burden.
***in*Thought Approvability Index and Comment:** 53%. Raising HDL is a good thing, but CETP inhibition is risky. And Roche, while it has a lead on Merck's Phase III CETP inhibitor anacetrapib, may be at a disadvantage compared to its rival because it does not significantly lower LDL cholesterol. Anacetrapib does so while impacting HDL to a greater degree. Large-scale clinical outcomes trials, under way now, will determine whether the difference is meaningful. Estimated approval: October 2013 (Source: Wolters Kluwer *in*Thought).
Revenue forecast: If it works, huge.
What the analysts are saying: Physicians may view dalcetrapib as significant because it does two things, increases HDL and alters the morphology of plaque. Statins and fibrates will be left in the dust—we take them to improve LDL, but they don't do much for HDL, and fibrates can cause changes in blood sugar and are not good for patients with diabetes, who often have these other risk factors. The Dal-outcomes study will be the litmus test in terms of whether this agent has an impact in the CV world. *—Portia Gordon, VP, research & consulting, GfK HealthCare*

Eliquis (apixaban) Bristol-Myers Squibb/Pfizer
Indication: DVT; stroke prevention in Afib (Preregistration)
What the clinical trials found: In the Aristotle Phase III trial, apixaban showed a 21% reduction compared to warfarin in the primary endpoint of stroke or systemic embolism, an 11% reduction in mortality and a 31% reduction in major bleeding. Neither of the novel oral anticoagulants on the market—J&J/Bayer's Xarelto (rivaroxaban) nor Boehringer Ingelheim's Pradaxa (dabigatran)—can match it in overall mortality or safety.
***in*Thought Approvability Index and Comment:** 92%. Oral anticoagulant Eliquis looks set to be a blockbuster, despite two other novel oral anticoagulants already available. Estimated approval: March 2014 (Source: Wolters Kluwer *in*Thought).
Revenue forecast: $2 billion in 2015, says Sanford Bernstein's Tim Anderson; $4.2 billion in 2017, says Leerink Swann's Seamus Fernandez.
What the analysts are saying: With BI's Pradaxa and J&J/Bayer's Xarelto now approved in SPAF, the best Eliquis can be is third to this market. In order to get on formularies, Eliquis will need to show not only clinical superiority but be competitive in terms of price. To rise above Pradaxa, Xarelto and warfarin (and be compelling to payors), Eliquis needs to duplicate trial results as being better for stroke, bleeding and mortality in atrial fibrillation. Still, if physicians become comfortable using one of the other warfarin replacement agents and see good results, this could be a problem for Eliquis. Warfarin, available for pennies a day, will keep some share. *—Portia Gordon, VP, research & consulting, GfK HealthCare*

OTHER KEY PRODUCTS IN THE PIPELINE

Pivlaz Actelion
Cerebral vasospasm (Ph. III)

Imagify Acusphere
Vascular disorders diagnosis (Prereg.)

Gencaro ARCA
Heart failure (Prereg.)

Desmoteplase Bayer Schering
Stroke (Ph. III)

Generx Cardium Therapeutics
Myocardial ischaemia (Ph. III)

Stedivaze Clinical Data
Coronary disorders (Ph. III)

Edoxaban Daiichi Sankyo
SPAF (Ph. III)

Tafamidis FoldRx
Cardiomyopathies (Ph. III)

Apadenoson Forest
Coronary disorders (Ph. III)

Azimilide Forest
Ventricular arrhythmia (Ph. III)

Darapladib GlaxoSmithKline
Heart attack prevention

Flurpiridaz F-18 Lantheus
CAD diagnosis (Ph. III)

Cangrelor The Medicines Co.
Ischaemic heart disorders (Ph. III)

Anacetrapib Merck
Heart attack prevention (Ph. III)

Tredaptive (MK-0524A) Merck
Niacin controlled release/laropiprant Atherosclerosis (Ph. III)

MK-0524B Merck
Laropiprant/niacin/simvastatin Hyperlipidaemia (Ph. III)

MK-0653C Merck
Atorvastatin/ezetimibe Hypercholesterolaemia (Prereg.)

Vernakalant (MK-6621) Merck
Atrial fibrillation (Prereg.)

Vorapaxar (MK-5348; SCH530348) Merck *Thrombosis (Ph. III)*

LCZ 696 Novartis
Heart failure (Ph. III)

CorVue Pfizer
Cardiovascular disorders (Prereg.)

Betrixaban Portola
SPAF (Ph. II)

Stedicor Procter & Gamble
Ventricular arrhythmias (Ph. III)

Aleglitazar Roche
CV risk reduction (Ph. III)

Otamixaban Sanofi
ACS (Ph. III)

Semuloparin Sanofi
Thromboembolism (Ph. III)

REGN727(SAR236553) Sanofi/Regeneron
Hypercholesterolaemia (Ph. II/III)

Temusi Sanofi
Peripheral arterial disorders (Ph. III)

Defibrotide Sigma-Tau
VOD (Ph. III)

Azilsartan/chlortalidone Takeda
Hypertension (Ph. III)

Neucardin Zensun
Heart failure (Ph. III)

Infectious Disease

PRODUCTS GENERATING BUZZ

BI-201335 Boehringer Ingelheim
Indication: Hepatitis C (Phase III)
What the clinical trials found: In Phase IIb clinical trials, overall rates for sustained viral response (SVR, which is considered cure) reached 83% with this once-daily oral protease inhibitor, when the 240mg dose was taken with pegylated interferon and ribavirin. Safety and tolerability look good.
***in*Thought Approvability Index and Comment:** 58%. BI-201335 has early evidence of a good SVR in combination with interferon. Our model expects the first all-oral direct-acting antiviral regimens to enter the US market in late 2015. Once they do, we expect them to become standard of care. Estimated approval: October 2014 (Source: Wolters Kluwer *in*Thought).
***in*Thought revenue forecast:** $953 million in peak sales by 2018
What the analysts are saying: The most important thing for HCV therapy is improving efficacy, tolerability and safety, and this drug may help on all three fronts. Recently launched protease inhibitors were associated with significant issues in tolerability and drug-drug interactions. The BI drug also improves convenience with its once-daily dosing vs. the multiple doses of the current protease inhibitors. It's not the Holy Grail for hep. C—an all-oral therapy which is efficacious—because you still need to take interferon, but if it continues to prove tolerable and safe, this will be a very potent competitor. *—Will Leskin, SVP, research & consulting, GfK HealthCare*

Integrase Single-Tablet Regimen "Quad" (elvitegravir/FTC/TDF/cobicistat) Gilead
Indication: HIV (Preregistration)
What the clinical trials found: The once-daily Quad pill recently met its primary endpoint in terms of noninferiority vs. the standard of care (Atripla). A trial assessing Quad vs. a protease inhibitor (Reyataz) is due to report out soon.
***in*Thought Comment:** The fact that it has to have a "booster" (cobicistat) suggests to some doctors that the integrase inhibitor (elvitegravir) was not strong enough to stand on its own. But if it's effective, safe and tolerable, the Quad pill is going to do extremely well in the marketplace (Source: Wolters Kluwer *in*Thought).
Revenue forecast: $1.7 billion by 2018, says ISI Group's Mark Schoenebaum.
What the analysts are saying: Gilead's Quad pill brings four promising agents, including the first new integrase inhibitor since Merck's Isentress together with Truvada and boosting agent cobicistat—which may prove revolutionary in and of itself if it can beat current protease-inhibitor booster ritonavir (Norvir, Abbott) in tolerability and safety. The Quad would be the company's first completely proprietary one-pill regimen (Gilead's recently approved Complera product combines its drug Truvada with Janssen's Edurant). *—Will Leskin, SVP, research & consulting, GfK HealthCare*

OTHER KEY PRODUCTS IN THE PIPELINE

MEDI-3250 AstraZeneca
Influenza vaccine (Prereg.)

Numax AstraZeneca
Resp. syncytial virus inf. (Ph. III)

Daclatasvir (BMS-790052) Bristol-Myers Squibb
HCV, combo therapy (Ph. III)

Ceftolozane/tazobactam Cubist
Gram-negative infections (Ph. III)

Hepatitis B vaccine 1018-ISS conjugate Dynavax *(Ph. III)*

Eritoran (E5564) Eisai
Sepsis (Ph. III)

Cobicistat Gilead
HIV/AIDS (Ph. III)

Elvitegravir Gilead
HIV/AIDS (Ph. III)

Emtriva/Viread Gilead
Hepatitis B, combo therapy (Ph. III)

GSK 2321138A GSK
Flu virus vaccine, quadrivalent (Ph. III)

MenHibrix GSK
Meningococcal group C/Y infections (Prereg.)

GSK 2282512A GSK
Quadrivalent seasonal influenza virus vaccine (Ph. III)

H5N1 (pre-)pandemic influenza virus vaccine GSK *(Ph. III)*

Dolutegravir (1349572) GSK/ Shionogi *HIV/AIDS (Ph. III)*

1349572+abacavir+lamivudine GSK *HIV/AIDS (Ph. III)*

GSK 2321138A GSK
Flu virus vaccine, quadrivalent (Ph. III)

GSK 1437173A GSK
Varicella zoster vaccine (Ph. III)

Raxibacumab Human Genome Sciences *Anthrax (Ph. III)*

Doribax Johnson & Johnson
Nosocomial pneumonia (Prereg.)

TMC435 (simeprevir) Johnson & Johnson
Hepatitis C, combo therapy (Ph. III)

MK-3415A Merck
C. difficile inf. (Ph. III)

MK-7009 (vaniprevir) Merck
Hepatitis C, combo therapy (Ph. III)

V 212 Merck
Varicella-zoster vaccine (Ph. III)

V 503 Merck
HPV vaccine (Ph. III)

DTP-HepB-Polio-Hib vaccine Merck/sanofi pasteur *(Ph. III)*

Efavirenz/lamivudine/tenofovir disoproxil fumarate Mylan
HIV/AIDS (Ph. III)

Tobramycin dry-powder inhal. Novartis *CF-associated RTI (Ph. III)*

Alisporivir Novartis
HCV, combo therapy (Ph. III)

Moxifloxacin/dexamethasone Novartis *General infections (Ph. III)*

Fluad Novartis
Flu virus infections, elderly (Ph. III)

Optaflu Novartis
Flu vaccine, cell culture-derived (Ph. III)

Omadacycline Novartis
Skin and soft tissue inf. (Ph. III)

Prulifloxacin Optimer
Gram-negative infections (Ph. III)

Anidulafungin/voriconazole Pfizer
Aspergillosis (Ph. III)

Prevnar 13 Adult Pfizer
Prophylactic vaccine (Prereg.)

PSI-7977 Pharmasset
HCV, all-oral (Ph. III)

VX-222 Vertex
HCV, quad regimen (Ph. III)

Dalbavancin Vicuron
Skin & soft tissue infections (Ph. III)

Neurology

PRODUCTS GENERATING BUZZ

BG-12 Biogen Idec
Indication: Multiple sclerosis (Phase III)
What the clinical trials found: The Phase III CONFIRM data replicated the robust efficacy seen in the DEFINE trial, with BG-12 reducing relapse rates by 44% for the twice-a-day administration. CONFIRM, while not designed as a head-to-head, had a Copaxone arm, and Copaxone had a lower-than-expected 29% reduction in relapse rate. The interferons are generally in the 30-50% range.
***in*Thought Approvability Index and Comment:** 84%. BG-12 is likely to become the preferred oral agent for MS, beating out Novartis's Gilenya (fingolimod) on safety and ease of use. BG-12 is also likely to take market share from Biogen and Élan's Tysabri (natalizumab). We expect neither BG-12 nor Gilenya to significantly impact the current market for interferons or Copaxone, at least until the agents have several years on the market without major safety issues. Estimated approval: July 2012 (Source: Wolters Kluwer *in*Thought).
***in*Thought revenue forecast:** $2.1 billion in peak sales by 2018.
What the analysts are saying: BG-12 will be an important player, and the fact that it is looking better than Copaxone, which is the market leader and is a daily injection, bodes well for an oral product, even one that's not once-a-day. It's hitting on some unmet needs, including better safety and tolerability. Gilenya has had strong uptake, and we can expect BG-12, which doesn't have the monitoring issues of Gilenya, to have good uptake as well, especially if, down the road, it's placed in a first-line therapy position and challenges Copaxone. Biogen Idec already sells Avonex, the leading interferon product, and Tysabri, so its sales force has a solid reputation among neurologists. *—Louise Gillis, assoc. VP, research & consulting, GfK HealthCare*

Bapineuzumab Pfizer/Johnson & Johnson
Indication: Alzheimer's disease (Phase III)
What the clinical trials found: A Phase II study showed some signs of efficacy and higher risk of a form of brain swelling called vasogenic edema, at least in ApoE4 carriers. Radiographic data looking at bapineuzumab's effect on plaque were supportive of an effect but not overwhelmingly positive.
***in*Thought Approvability Index and Comment:** 33%. There is evidence that bapineuzumab, which targets A-beta amyloid plaque, slows the progression, but treatment prior to cognitive decline may be required for clinical benefit. Estimated approval: April 2014 (Source: Wolters Kluwer *in*Thought).
***in*Thought revenue forecast:** $4.4 billion in peak sales by 2018
What the analysts are saying: Clinicians are intrigued by this drug's mechanism of action in preventing amyloid plaques from forming, or reducing those formed. But the jury is still out as to whether it translates to the silver bullet the market is looking for: something that halts disease progression. *—Marite Talbergs, SVP, research & consulting, GfK HealthCare*

OTHER KEY PRODUCTS IN THE PIPELINE

Daclizumab Abbott
Multiple sclerosis (Ph. III)

TC-5214 AstraZeneca
Depression (Ph. III)

Gammagard S/D Baxter
Alzheimer's disease (Ph. III)

BIIB 017 Biogen Idec
Multiple sclerosis (Ph. III)

Buprenorphine transmucosal BioDelivery
Pain (Ph. III)

BMS-214778 Bristol-Myers Squibb
Circadian rhythm sleep disorders (Ph. III)

Bupivacaine CR Durect Corp.
Postoperative pain (Ph. III)

Fosphenytoin CyDex Pharma
Status epilepticus (Ph. III)

EMD 1195686 EMD Serono
Parkinson's disease (Ph. III)

Perampanel Eisai
Epilepsy (Ph. III)

LY20140023 Eli Lilly
Schizophrenia (Ph. III)

Solanezumab Eli Lilly
Alzheimer's disease (Ph. III)

Cariprazine Forest
Schizophrenia/bipolar (Ph. III)

F2695 Forest
MDD (Ph. III)

IPX066 GlaxoSmithKline
Parkinson's disease (Ph. III)

Etodolac-lidocaine patch IL Pharma
Pain (Ph. III)

Baclofen XR Impax Labs
Muscle spasticity (Ph. III)

Fentanyl sublingual Insys
Cancer pain (Prereg.)

IP 880 Iroko
Pain (Ph. III)

Diclofenac inj. Javelin
Pain (Prereg.)

Ereska Javelin
Pain (Ph. III)

Dexpramipexole Knopp
ALS (Ph. III)

Istradefylline Kyowa Hakko
Parkinson's dis. (Prereg.)

Carbamazepine IV Lundbeck
Epilepsy (Ph. III)

Dihydroergotamine inhalation Map Pharma
Migraine (Prereg.)

Carisoprodol SR Meda
Spasm (Ph. III)

Arcoxia Merck
Pain (Ph. III)

Bridion (sugammader) Merck
Neuromuscular blockade (Ph. III)

MK-4305 (suvorexant) Merck
Insomnia (Ph. III)

MK 3814 Merck
Parkinson's disease (Ph. III)

Indiplon Neurocrine Biosciences
Insomnia (Prereg.)

Sumatriptan transdermal NuPathe
Migraine (Prereg.)

Remoxy Pfizer
Pain, abuse-resistant (Prereg.)

Dimebon Pfizer
Alzheimer's, early stage (Ph. III)

Naltrexone/oxycodone Pfizer
Pain, abuse-resistant (Ph. III)

Ocrelizumab Roche/Genentech
Multiple sclerosis (Ph. III)

Lemtrada Sanofi
Multiple sclerosis (Ph. III)

Teriflunomide Sanofi
Multiple sclerosis (Pre-reg.)

Stedesa Sunovion
Epilespy (Ph. III)

Laquinimod Teva
Multiple sclerosis (Ph. III)

Oncology

PRODUCTS GENERATING BUZZ

Pertuzumab Roche
Indication: Breast cancer (Phase III)
What the clinical trials found: In the Phase II neoadjuvant (prior to surgery) Neosphere trial of 417 women with early-stage, HER2-positive breast cancer, pertuzumab/Herceptin/chemo significantly improved the rate of complete tumor disappearance (or pathological complete response) 45.8% vs. 29% for Herceptin/chemo. In a Phase III trial, the combo regimen met the primary endpoint of progression free survival (PFS), with no new safety signals observed.
***in*Thought Approvability Index and Comment:** 63%. Data suggest pertuzumab/Herceptin/chemo provides a more comprehensive blockade of HER signaling pathways than standard of care. Estimated approval: 2012 (Source: Wolters Kluwer *in*Thought).
Revenue forecast: 300 million Swiss francs ($328 million) in 2015, says Sanford Bernstein's Tim Anderson.
What the analysts are saying: This drug could potentially be used in early disease settings, where it was shown to more or less double the response rate. Pertuzumab's future depends on the scope of the increase in PFS vs. Herceptin/chemo, which we don't yet know, and then overall survival, a secondary endpoint. If approved, the HER2-targeted drug would be the first novel targeted agent sanctioned for use in combination with an existing targeted agent and chemo. But the potential increase in cost of therapy is something physicians fear, since Herceptin is already a very pricy therapy. It's also being trialed together with Roche's T-DM1, another HER2-targeted drug in the pipeline. *—Petra Maertens, director, oncology syndicated studies, GfK HealthCare*

Zaltrap (aflibercept) Regeneron/Sanofi
Indication: Metastatic colorectal cancer (Prereg.), metastatic prostate cancer (Phase III)
What the clincial trials found: In the Phase III Velour trial, adding aflibercept to a FOLFIRI regimen improved overall survival 18.3% vs. placebo (p=0.0032) and progression-free survival 24.2% vs. placebo (p=0.00007) in patients with metastatic colorectal cancer (mCRC) previously treated with oxaliplatin.
***in*Thought Approvability Index and Comment:** 64% (CRC). Zaltrap looks like a very interesting concept, one which may fill an unmet need for patients who have K-ras-mutation-positive mCRC. Look for a K-ras-mutation companion diagnostic to be developed. Estimated approval: 2012 (Source: Wolters Kluwer *in*Thought).
Revenue forecast: €238 million ($322.7 million) in 2015, says Sanford Bernstein's Tim Anderson.
What the analysts are saying: Zaltrap represents a completely new class of cancer drugs—the recombinant-fusion-protein. Data suggest it has potential in second line for mCRC, where the most commonly used drug, BMS/Lilly's Erbitux, should not be used in some patients (those whose tumors have a certain feature called a K-ras mutation). Zaltrap can be used regardless of patients' K-ras mutation status, opening up the possibility for a further targeted second-line therapy. This could be the first new CRC therapy in five years. Prostate cancer, the follow-up indication, is a more competitive area with four new drugs approved. *—Petra Maertens, director, oncology syndicated studies, GfK HealthCare*

OTHER KEY PRODUCTS IN THE PIPELINE

Ganitumab Amgen
Pancreatic cancer (Ph. III)

Trebananib (AMG 386) Amgen
Fallopian tube/ovarian cancer (Ph. III)

Zibotentan AstraZeneca
Prostate cancer (Ph. III)

Clodronic acid Bayer
Bone metastases (Prereg.)

Vargatef (BIBF 1120) Boehringer Ingelheim *Idiopathic pulmonary fibrosis/ovarian cancer (Ph. III)*

Brivanib alaninate Bristol-Myers Squibb *Liver cancer (Ph. III)*

Necitumumab Bristol-Myers Squibb/Eli Lilly *NSCL (Ph. III)*

Ramucirumab Bristol-Myers Squibb
Breast cancer/CRC (Ph. III)

Sapacitabine Daiichi Sankyo
AML (Ph. III)

Tivantinib Daiichi Sankyo
NSCL (Ph. III)

Lenvatinib (E 7080) Eisai
Thyroid cancer (Ph. III)

Ramucirumab Eli Lilly
Gastric cancer (Ph. III)

Enzastaurin Eli Lilly
Diffuse large B cell lymphoma/glioblastoma (Ph. III)

Dabrafenib (2118436) GSK
Malignant melanoma/NSCL (Ph. III)

Trametinib (1120212) GSK
Malignant melanoma (Ph. III)

MAGE-A3 (astuprotimut-R) GSK
Malignant melanoma (Ph. III)

Trabectedin J&J
Soft tissue sarcoma (Ph. III)

V 503 Merck
HPV vaccine (Ph. III)

Ridaforolimus (MK-8669) Merck
Sarcoma (Prereg.)

Midostaurin Novartis
AML (Ph. III)

Panobinostat Novartis
Multiple myeloma (Ph. III)

Axitinib Pfizer
Renal cancer (Prereg.)

Bosutinib (PF 05208763) Pfizer
CML (Ph. III)

Inotuzumab ozogamicin Pfizer
NHL (Ph. III)

GA101 (obinutuzumab) Roche
B cell lymphoma/CLL/NHL (Ph. III)

T-DM1 (trastuzumab emtansine) Roche *Breast cancer (Ph. III)*

Vismodegib Roche
Basal cell cancer (Prereg.)

Iniparib Sanofi
Breast/NSCL (Ph. III)

Ombrabulin Sanofi
Sarcoma (Ph. III)

Motesanib (AMG706) Takeda
NSCL (Ph. III)

TAK-700 (orteronel) Takeda
Prostate cancer (Ph. III)

Custirsen Teva
Prostate cancer (Ph. III)

Rheumatology

PRODUCTS GENERATING BUZZ

Tofacitinib Pfizer
Indication: Rheumatoid arthritis/plaque psoriasis (Phase III)
What the clinical trials found: Data from a Phase III trial testing tofacitinib vs. Abbott's self-injectable Humira support this oral drug's clinical potential: ACR20: 47%; ACR50: 28%. In response, Humira has claimed ACR20: 65%; ACR50: 52%. Safety appears comparable to that seen with approved RA biologics, although there was a doubling in the rate of infections in the long-term extension studies with the 10mg vs. 5mg dose and possible renal effects. With a broad range of immunosuppresive properties, tofacitinib is being studied in several autoimmune conditions in addition to RA, including ankylosing spondylitis, ulcerative colitis, psoriasis, psoriatic arthritis and organ transplant rejection.
***in*Thought Approvability Index and Comment:** 85% (RA). This JAK inhibitor's oral formulation hits an unmet need in RA. Due to adverse events, our research suggests the drug will be most often used after at least one tumor necrosis factor (TNF) inhibitor. Dosing advantages aside, it won't replace the TNF inhibitors, but it will push back use of other biologics. Estimated approval: 2H 2012 for RA, followed by other indications (Source: Wolters Kluwer *in*Thought).
***in*Thought revenue forecast:** $1.7 billion in peak sales by 2017
What the analysts are saying: The wave of Phase III reporting by Pfizer appears very positive with efficacy in line with current self-injectable treatments like Humira, with a possibly equal or somewhat better side effect profile. It looks like this will be the first oral treatment to market and an option that compares well against the current therapies. From that standpoint, it should do exceptionally well. *—Geoff Penney, VP, research and consulting, GfK HealthCare*

Fostamatinib (R788) AstraZeneca + Rigel
Indication: Rheumatoid arthritis (Phase III)
What the clinical trials found: In a three-month Phase II trial, this oral Syk inhibitor was shown to be safe but not effective in RA patients unresponsive to biologic agents. In a six-month Phase II study, it met a primary signs and symptoms efficacy endpoint with responder rates of ACR20: 67%; ACR50: 43%. In the Phase III program, two 12-month studies will test fostamatinib in patiens responding inadequately to disease-modifying antirheumatic drugs (DMARDs) including methotrexate, and a six-month study will assess fostamatinib in patients who have previously responded inadequately to anti-TNF therapy.
***in*Thought Approvability Index and Comment:** 55% (RA). A second oral kinase inhibitor behind tofacitinib, fostamatinib should take some of the $23-billion worldwide market for DMARDs. It may also expand the market on the back of the substantial number of patients who are candidates for biologics but don't use them because of injection fears. Estimated approval: 2014 (Source: Wolters Kluwer *in*Thought).
Revenue forecast: $1.3 billion in peak sales by 2017, says Collins Stewart's Salveen Richter
What the analysts are saying: The jury is still out. We are looking to early Phase III trials (which started at the beginning of 2011) to dispel the more disappointing findings seen in Phase II. But at that point, it does become an issue of second-to-market and what opportunities can AZ/Rigel exploit given Pfizer/tofacitinib's first-to-market status. Once-a-week, twice-a-week and once-a-month injection therapies will still hold appeal, particularly for physicians, despite the pressure from patients to try a needleless option. And research suggests the I.V. and self-injection therapies will continue to be cost competitive, especially given the heavy use of co-pay cards and other patient support programs, so there will be serious cost pressures on both these oral therapy brands when they reach market. *—Geoff Penney, VP, research and consulting, GfK HealthCare*

OTHER KEY PRODUCTS IN THE PIPELINE

Hydrocodone/paracetamol controlled release Abbott
Osteoarthritis (Prereg.)

Apremilast Celgene
Psoriasis (Ph. IIII)
Psoriatic arthritis (Ph. III)

LY2439821 (ixekizumab) Eli Lilly
Rheumatoid Arthritis (Ph. III)
Psoriasis (Ph. II)

Tabalumab (LY 2127399) Eli Lilly
Rheumatoid arthritis (Ph. III)
Lupus (Ph. III)

Linaclotide Forest
IBS (Prereg.)

Traficet-EN (1605786) GSK
Crohn's disease (Ph. III)

Lodotra Horizon/SkyePharma
Rheumatoid arthritis (Prereg.)

IP 880 Iroko
Osteoarthritis (Ph. III)

IP 889 Iroko
Osteoarthritis (Ph. III)

Arcoxia (etoricoxib/MK 663) Merck
Rheumatoid arthritis (Ph. III)
Ankylosing spondylitis (Ph. III)

MK-3222 Merck
Psoriasis (Ph. II/III)

Naproxcinod NicOx
Osteoarthritis (Prereg.)

Calcitonin oral (SMC 021) Novartis
Osteoarthritis (Ph. III)

Secukinumab (AIN-457) Novartis
Psoriasis (Ph. III)
Psoriatic arthritis (Ph. III)
Rheumatoid arthritis (Ph. III)

Sarilumab (REGN-88) Regeneron
Rheumatoid arthritis (Ph. III)
Ankylosing spondylitis (Ph. III)

Actemra (tocilizumab) Roche
Rheumatoid arthritis, subcutaneous form (Ph. III)

Vedolizumab (MLN0002) Takeda
Ulcerative colitis (Ph. III)
Crohn's (Ph. III)

VX-509 Vertex
Rheumatoid arthritis (Ph. II)

Other

PRODUCTS GENERATING BUZZ

METABOLIC

Bydureon (exenatide long-acting release) Amylin
Indication: Type 2 diabetes (Prereg.)
What the clinical trials found: In the DURATION-6 trial, Bydureon patients saw a reduction in A1C of 1.3 percentage points vs. 1.5 points for Novo Nordisk's Victoza. A tQT study showed Bydureon, even at high levels, did not prolong heart rhythms.
***in*Thought Approvability Index and Comment:** 88%. Following EU approval in June, US approval looks likely now that Amylin has answered FDA concerns. The question is, can Amylin, which is taking over the exenatide franchise from Eli Lilly, make the most of the opportunity? Novo's Victoza may be hard to beat. Estimated approval: January 2013 (Source: Wolters Kluwer *in*Thought).
***in*Thought Revenue forecast:** $1.8 billion in peak sales by 2018
What the analysts are saying: This once-a-week version of twice-daily Byetta has had a long regulatory review but may significantly expand the GLP-1 market. PCPs and endocrinologists seem to view this class as a way to impact weight and, presumably, other co-morbidities like blood pressure and cholesterol. Still, these products can get hemmed in commercially unless they can broaden beyond a mostly niche patient base, affluent people unable to control their weight. Issues will be the same as they are with any new drug in the metabolic space—cost and ensuring endos and PCPs are familiar with how to best use the product. *—Dave Jacobson, PhD, SVP, Roper global diabetes group, GfK HealthCare*

ORPHAN DISEASE

GALNS (BMN-110) BioMarin
Indication: MPS IVa, or Morquio A syndrome (Phase III)
What the clinical trials found: Phase I/II 36-week data were encouraging, and additional 24-week extension data showed a durable response. A Phase III trial began in February 2011, with data scheduled to report in late 2012.
***in*Thought Approvability Index and Comment:** 75%. This product, which has orphan drug exclusivity in the US and EU, looks like it serves an unmet need. BioMarin has done this three times before, and this could be their fourth orphan drug. Expected approval: September 2013 (Source: Wolters Kluwer *in*Thought).
***in*Thought Revenue forecast:** $272 million in peak sales by 2018
What the analysts are saying: The data for this drug look promising. Patients with MPS IVa who have been on GALNS for about two years are stable. But additional data, due out next year, are needed to help clarify the drug's prospects. Until then, it appears that GALNS is a niche product, but one with a lot of promise. It definitely meets a need; other than bone marrow transplant, there's nothing out there yet for MPS IVa. Patients—some 350,000 with the inherited genetic disorder—are looking for a silver bullet. *—Marite Talbergs, SVP, research & consulting, GfK HealthCare*

OTHER KEY PRODUCTS IN THE PIPELINE

METABOLIC

BI 10773 Boehringer Ingelheim/Eli Lilly *Type 2 diabetes (Ph. III)*

Dapagliflozin BMS/AZ
Type 2 diabetes (Prereg.)

Kombiglyze XR Bristol-Myers Squibb *Type 2 diabetes (Ph. III)*

Lorcaserin Eisai/Arena
Obesity (Prereg.)

Dulaglutide Eli Lilly
Type 2 diabetes (Ph. III)

Empagliflozin Eli Lilly
Type 2 diabetes (Ph. III)

LY 2963016 Eli Lilly
Type 2 diabetes (Ph. III)

Otelixizumab GlaxoSmithKline
Type 1 diabetes (Ph. III)

Syncria (albiglutide) GSK
Type 2 diabetes (Ph. III)

Canagliflozin J&J
Type 2 diabetes (Ph. III)

Afrezza MannKind
Insulin inhalation (Prereg.)

MK-3102 Merck
Type 2 diabetes (Ph. II/III)

Odanacatib MK-0822 Merck
Osteoporosis (Ph. III)

Insulin degludec Novo Nordisk
Type 1 diabetes (Prereg.)

Aleglitazar Roche
Type 2 diabetes (Ph. III)

Lixisenatide Sanofi
Type 2 diabetes (Ph. III)

Alogliptin Takeda
Type 2 diabetes (Prereg.)

TAK 875 Takeda
Type 2 diabetes (Ph. III)

Contrave Takeda/Orexigen
Obesity (Prereg.)

Qnexa Vivus
Obesity (Prereg.)

ORPHAN PRODUCTS

Metreleptin Amylin
Lipodystrophy (Prereg.)

Migalastat GSK
Fabry's disease (Ph. III)

Taliglucerase alfa Pfizer
Gaucher's disease (Prereg.)

Ataluren PTC Therapeutics
Cystic fibrosis (Ph. III)

Kalydeco (ivacaftor) Vertex
Cystic fibrosis (Prereg.)

RESPIRATORY

Olodaterol (BI-1744) Boehinger Ingelheim *COPD (Ph. III)*

Aclidinium bromide Forest
COPD (Prereg.)

Aclidinium/formoterol Forest
COPD (Ph. III)

Umeclidinium (573719) GSK
COPD (Ph. III)

Relovair (642444) GSK
Asthma (Ph. III)

Sinapultide J&J
Neonatal resp. distress synd. (Prereg.)

MK-7243 (SCH 697243) Merck
Allergy (Ph. III)

MK-3641 (SCH 039641) Merck
Allergy (Ph. III)

Glycopyrrolate inhalation (NVA 237) Novartis *COPD (Ph. III)*

Albuterol+Spiromax Teva
Asthma/COPD (Ph. III)

FP Spiromax Teva
Asthma (Ph. III)

WOMEN'S HEALTH

Elagolix Abbott
Endometriosis (Ph. II/III)

Prasterone vaginal Bayer
Vaginal atrophy (Ph. III)

LibiGel BioSante
Female sexual dysfunction (Ph. III)

Elonva Merck
Female infertility (Ph. III)

MK-8962 (SCH 900962) Merck
Fertility (Ph. III)

Aprela Pfizer
Menopausal symptoms (Ph. III)

Oporia Pfizer
Postmenopausal osteoporosis (Prereg.)

Viviant Pfizer
Postmenopausal osteoporosis (Prereg.)