Respiratory

With generics firms taking aim at high-flying blockbusters, Big Pharma stalwarts in the asthma and COPD market are pinning their hopes for the future on a flurry of innovative biotech-developed assets. **Noah Pines** charts the rarefied air of the respiratory space

As the legacy titans of the respiratory category start to totter, large companies are pinning their future hopes on innovative biotech-developed assets, patient-friendly delivery systems, and advancements in low incidence and rare breathing disorders.

Take respiratory market leader GlaxoSmithKline's Breo/Relvar and Anoro as examples. Developed by biotech partner Theravance, the COPD duo forms the backbone of GSK's aspiration to mitigate its reliance on the $8.8-billion Advair business, which accounts for nearly 20% of total sales. Advair, known as Seretide overseas, faces erosion due to branded competition and generic copycat threats.

Highlighting the urgency, US sales of drugs for respiratory ailments shrank 7% in the 12 months to November 2013, to $23.2 billion, according to figures from IMS Health, as major brands like Merck's Singulair succumbed to the aftereffects of patent expiry.

Despite its loss of patent protection, however, Advair has yet to be defenestrated by generic knockoffs due to its inhaler system—and may not encounter meaningful rivalry until 2016, according to Bernstein Research senior pharmaceuticals analyst Tim Anderson.

Adds Uwe Tigor, EVP and chief medical officer at ad agency Palio+Ignite, "Advair continues to succeed due to ingenious technology, the Diskus, which has not been eclipsed by a similarly patient-friendly inhaler. Most of the inhalers out there are not rated as friendly." The evidence: GSK boosted Advair US sales by 7% last year, giving the drug a 22% share of the market.

That the wind is still in Advair's sails is good news to GSK, particularly since Breo Ellipta's launch has underwhelmed the financial community. Approved last May for COPD, Breo Ellipta is a once-a-day inhalable treatment that combines fluticasone furoate, a corticosteroid, with a long-acting beta agonist (LABA) called vilanterol.

Sensing a slow lift-off in December, Morgan Stanley analysts cut Breo Ellipta's global sales forecast from $1.6 billion to $800 million in 2020. Anderson says its disappointing debut is likely due to payer headwinds since it may be seen as only adding incremental value.

For this reason, Anderson and other analysts' hopes have pivoted toward GSK's next potential respiratory blockbuster, Anoro Ellipta, approved in December and recently recommended by EMA as a once-daily treatment. Anoro is the first once-a-day COPD combination that marries an LABA drug with a long-acting muscarinic antagonist (LAMA). "GSK has high hopes for Breo," Anderson tells *MM&M*, "but most investor enthusiasm is focused on the Anoro."

GSK's British neighbor, AstraZeneca, also is girding itself for heated competition for its respiratory heavyweight, Symbicort, whose key patents recently expired in Europe. On the European front, regulators approved Teva's DuoResp Spiromax inhalation powder for asthma and COPD. And next year, Symbicort generics are set to hit the US.

As the COPD market becomes more crowded, other companies are seeking to differentiate by developing patient-centric support services to enhance adherence and facilitate reimbursement. "The biggest problem with most of these new entrants is that they are going to hit payer challenges," points out Tigor. Forest Labs launched the STRIDE program to educate patients on the usage of its Pressair multiple-dose dry powder inhaler technology (which is used to deliver COPD drugs Tudorza and Daliresp) and to help them negotiate the hurdles of insurance coverage and offer co-pay assistance.

"In STRIDE, we see the opportunity to provide a service to help patients get the highest possible benefit from our medicines," Marco Taglietti, Forest EVP, drug development & research, and its chief medical officer, tells *MM&M*.

TOP 50 RESPIRATORY PRODUCTS, 2013

Category leaders, ranked by US sales for the 12 months to Nov., and their full-year media spend

Rank	Product	Manufacturer	US sales $ (millions)	Vs. prior 12 months	TRx (millions)	Vs. prior 12 months	US DTC media $ (000s)	Vs. prior 12 months	US journal media $ (000s)	Vs. prior 12 months
1	**Advair Diskus**	GlaxoSmithKline	$5,106.9	7.0%	16.2	7.7%	$98,004.2	-12.5%	$0.0	N/A
2	**Spiriva Handihaler**	Boehringer Ingelheim	$2,997.0	11.0%	9.5	4.5%	$52,131.0	-42.1%	$1,187.0	>100.0%
3	**Symbicort**	AstraZeneca	$1,525.5	26.0%	6.0	2.8%	$104,526.6	21.1%	$630.0	37.0%
4	**ProAir HFA**	Teva	$1,188.5	10.0%	26.2	12.4%	$152.0	-31.1%	$1,906.0	-27.2%
5	**Nasonex**	Merck	$1,136.9	4.0%	7.9	3.7%	$24,955.5	-46.3%	$0.0	N/A
6	**Flovent HFA**	GlaxoSmithKline	$1,056.4	4.0%	5.9	2.8%	$0.0	N/A	$0.0	N/A
7	**Budesonide**	Generic	$1,041.9	9.0%	2.6	1.2%	$0.0	N/A	$0.0	N/A
8	**Xolair**	Genentech/Novartis	$815.1	19.0%	0.2	0.1%	$0.0	N/A	$878.0	72.2%
9	**Ventolin HFA**	GlaxoSmithKline	$750.0	7.0%	17.7	8.4%	$0.0	N/A	$0.0	N/A
10	**Combivent Respimat**	Boehringer Ingelheim	$501.5	>100.0%	1.7	0.8%	$0.7	N/A	$116.0	>100.0%
11	**Qvar**	Teva	$510.0	24.0%	3.5	1.7%	$30.3	81.4%	$749.0	52.5%
12	**Pulmozyme**	Genentech	$488.4	8.0%	0.1	0.1%	$0.0	N/A	$0.0	N/A
13	**Montelukast sod**	Generic	$488.1	>100.0%	29.4	13.9%	$0.0	N/A	$0.0	-100.0%
14	**Advair HFA**	GlaxoSmithKline	$403.8	14.0%	1.3	0.6%	$0.0	N/A	$0.0	N/A
15	**Combivent**	Boehringer Ingelheim	$490.5	-54.0%	1.9	0.9%	$0.0	N/A	$0.0	N/A
16	**Fluticasone Prop**	Generic	$394.1	-27.0%	37.2	17.6%	$0.0	N/A	$0.0	-100.0%
17	**Dulera**	Merck	$318.7	65.0%	1.4	0.7%	$43,146.3	-1.0%	$0.0	-100.0%
18	**Tobi**	Novartis	$331.4	2.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
19	**Levalbuterol HCl**	Generic	$279.3	>100.0%	1.1	0.5%	$0.0	N/A	$0.0	N/A
20	**Proventil HFA**	Merck	$244.2	20.0%	4.4	2.1%	$0.0	N/A	$0.0	N/A
21	**Pulmicort Respules**	AstraZeneca	$249.9	22.0%	0.5	0.2%	$0.0	N/A	$0.0	N/A
22	**Albuterol**	Generic	$220.0	22.0%	15.1	7.2%	$0.0	N/A	$0.0	N/A
23	**Asmanex Twisthaler**	Merck	$217.8	5.0%	1.2	0.6%	$0.0	N/A	$0.0	N/A
24	**Atrovent HFA**	Boehringer Ingelheim	$212.4	8.0%	0.8	0.4%	$0.0	N/A	$0.0	N/A
25	**Brovana**	Sunovion	$197.4	17.0%	0.3	0.2%	$0.0	N/A	$620.0	-40.2%
26	**Pulmicort Flexhaler**	AstraZeneca	$121.9	6.0%	0.7	0.3%	$0.0	N/A	$0.0	N/A
27	**Xopenex HFA**	Sunovion	$120.8	-13.0%	2.1	1.0%	$0.0	N/A	$0.0	N/A
28	**Perforomist**	Dey	$113.7	17.0%	0.2	0.1%	$0.0	N/A	$243.0	N/A
29	**Singulair**	Merck	$122.3	-97.0%	0.8	0.4%	$0.0	N/A	$0.0	N/A
30	**Albut Sulf/Ipratro**	Generic	$111.8	44.0%	4.3	0.0	$0.0	N/A	$0.0	N/A
31	**Daliresp**	Forest	$100.9	58.0%	0.5	0.2%	$0.0	N/A	$631.0	-100.0%
32	**Triamcinolone Actn**	Generic	$105.0	-10.0%	1.4	0.6%	$0.0	N/A	$0.0	N/A
33	**Veramyst**	GlaxoSmithKline	$96.4	-31.0%	0.8	0.4%	$0.0	N/A	$0.0	N/A
34	**Serevent Diskus**	GlaxoSmithKline	$78.6	-5.0%	0.3	0.2%	$0.0	N/A	$0.0	N/A
35	**Zyflo Cr**	Cornerstone	$70.5	34.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
36	**Ipratropium br**	Generic	$67.3	10.0%	2.9	1.4%	$0.0	N/A	$0.0	N/A
37	**Tudorza Pressair**	Forest	$67.3	N/A	0.3	0.1%	$221.5	N/A	$6,247.0	>100.0%
38	**Flovent Diskus**	GlaxoSmithKline	$64.9	15.0%	0.5	0.2%	$0.0	N/A	$0.0	N/A
39	**Tobi Podhaler**	Novartis	$51.3	N/A	N/A	N/A	$0.0	N/A	$0.0	N/A
40	**Revatio**	Pfizer	$63.2	-81.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
41	**Remodulin**	United Therapeutics	$57.2	9.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
42	**Foradil Aerolizer**	Merck	$53.7	-4.0%	0.2	0.1%	$0.0	N/A	$0.0	N/A
43	**Alvesco**	Sunovion	$54.6	2.0%	0.3	0.1%	$0.0	N/A	$0.0	N/A
44	**Rhinocort Aqua**	AstraZeneca	$50.9	-15.0%	0.3	0.2	$0.0	N/A	$0.0	N/A
45	**Curosurf**	Chiesi/Cornerstone	$44.9	11.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
46	**Xopenex**	Sunovion	$48.0	-87.0%	0.1	0.1	$0.0	N/A	$0.0	N/A
47	**Qnasl**	Teva	$37.7	>100.0%	0.4	0.2	$233.3	N/A	$325.0	65.1%
48	**Maxair Autohaler**	Graceway	$34.5	71.0%	0.1	0.1%	$0.0	N/A	$0.0	N/A
49	**Omnaris**	Sunovion	$31.9	-19.0%	0.3	0.1%	$0.0	N/A	$0.0	N/A
50	**Ephedrine Sulf**	Generic	$29.0	49.0%	N/A	N/A	$0.0	N/A	$0.0	N/A

Sources: Sales/TRx, IMS Health; DTC media spend, Nielsen; journals, Kantar Media.

CLINICAL CORNER

Drugs on the market do a decent job of controlling most cases of mild-to-moderate asthma. One of the next big disease targets for innovator firms in the respiratory area is the severe end of asthma and other chronic respiratory diseases.

Bernard Tisserand

According to experts interviewed by *MM&M*, companies are taking a targeted biologic approach to developing these drugs. Moreover, this is a Big Pharma—not biotech—phenomenon, points out Tim Anderson, the Bernstein Research analyst, and Bernard Tisserand, VP for respiratory clinical development, INC Research.

While not likely to mature into commercial titans like GlaxoSmithKline's Advair and AstraZeneca's Symbicort, these investigational agents are poised to address a major unmet medical need in small, high-risk patient groups. Take severe asthma for example, which impacts about 15 million people, representing 5%–10% of worldwide asthma sufferers. GSK, AZ and Roche are all are developing monoclonal antibodies designed to help this small but in-need patient subgroup.

GSK's mepolizumab, in Phase-III clinical trials, is furthest along. It's one of the few agents in the drugmaker's pipeline not being developed by Theravance, GSK's biotech partner which hatched COPD drugs Breo Ellipta and Anoro Ellipta. At press time, GSK said the investigational IL-5 antagonist had met the primary endpoint in its second Phase-III study, this one among patients with severe eosinophilic asthma, and that it plans to make global regulatory filings at the end of the year. Recently, GSK, along with the National Institute of Allergy and Infectious Diseases (NIAID), announced that mepolizumab is also being studied in patients with eosinophilic granulomatosis with polyangiitis (EGPA), a rare disease that can be life threatening.

Meanwhile, MedImmune, the biologics arm of AstraZeneca, initiated the Phase-III "Windward" trials for its IL-5 monoclonal antibody, benralizumab. The first Windward trial, dubbed CALIMA, was initiated in late 2013 to gauge benralizumab's ability to reduce exacerbations in patients with uncontrolled, severe asthma who have failed high-dose inhaled corticosteroids (ICS) combined with an LABA.

Not to be outdone, Roche presented Phase-IIb data on lebrikizumab, its novel IL-13 monoclonal antibody targeting a cytokine that contributes to airway inflammation and asthma disease process in a subset of patients. The biologic appears to be most effective in patients with high levels of periostin, a protein that indicates a certain type of asthma, according to data presented at the American Academy of Allergy, Asthma and Immunology (AAAAI) in San Diego.

This implies that Roche will take an individualized, biomarker-driven approach in identifying patients with high periostin levels. Similar to the GSK and AZ studies, patients enrolled in the studies were severe asthma sufferers receiving high dose ICS and asthma controller therapy. Lebrikizumab also is slated to be studied in idiopathic pulmonary fibrosis (IPF), another rare respiratory illness.

At the recent American Academy of Allergy, Asthma & Immunology (AAAAI) annual meeting, Boehringer Ingelheim—the largest privately held company in the respiratory space—presented data that it hopes will propel its $5-billion Spiriva (tiotropium) brand. Initial results from a Phase-III study show Spiriva to be effective across a variety of asthma severities, but the results were seen in heavily pre-treated patients with severe asthma. While questions swirl over whether candidates for Spiriva Respimat can be pre-identified by a specific phenotype, the study could support its addition as an add-on therapy to future asthma guidelines.

In cystic fibrosis (CF), Vertex still dominates the conversation and is fortifying Kalydeco's label. While it was initially indicated for patients with at least one copy of the G551D mutation, Kalydeco recently received the FDA nod for eight additional mutations, which swells the US eligible patient population by 150. With a sticker price of $300,000, that adds $45 million in potential new revenue.

Vertex is now awaiting regulatory decisions in other large markets. "Kalydeco is perpetually in the news with good reason. It's come to be a mainstay for a lot of affected people with some uncommon mutations," points out Leon Henderson, senior analyst at *in*Thought. He is anticipating an initial Phase-III readout from the TRAFFIC and TRANSPORT trials combining Kalydeco with VX-809. "Approval here increases the eligible population six- to seven-fold."

Meanwhile, in pulmonary arterial hypertension (PAH), category trailblazer Actelion recently received both US and EU approval for Opsumit (macitentan), a novel dual endothelin receptor antagonist and the first oral medicine in the category shown to delay disease progression and reduce the need for hospitalization. This is significant—initial PAH treatments developed over the past 10 years have only offered symptomatic improvements in exercise tolerance.

With a once-daily dosing profile, Opsumit continues to strengthen Actelion's posture in this life-threatening, rare disease that constricts the flow of blood through the pulmonary vasculature. And in December, United Therapeutics received a surprise FDA nod for Orenitram (treprostinil), becoming the first oral prostacyclin analogue for PAH and the company's fifth marketed medicine for PAH.

In idiopathic pulmonary fibrosis (IPF), California biotech InterMune has been generating buzz over its candidate Esbriet (pirfenidone) with the ASCEND data. Top-line results showed that pirfenidone nailed one primary and two secondary key endpoints of reducing disease progression while boosting patients' performance on the six-minute walk test distance (6MWD) and in terms of progression-free survival (PFS). IPF is a rare, potentially fatal lung condition that affects up to 132,000 Americans and whose prevalence is increasing. There are currently no FDA-approved medications to treat IPF—a reason why the category is getting attention.

As part of its pipeline commitment to IPF, Boehringer Ingelheim inked a deal with Duke University to develop an IPF patient registry and biomarker bank, the focus of which is to classify potential blood or genetic markers of the disease. The research partnership with Duke Clinical Research Institute "represents an important step to understanding a disease for which there has been a minimal amount of understanding," said Tunde Otulana, MD, SVP, clinical development and medical affairs, Boehringer Ingelheim, in a recent press release.

"Our partnership with Duke Clinical Research Institute represents an important step for our company," added Otulana. "We believe this approach will allow us to accomplish together certain research goals that we might not otherwise have achieved separately." ■