Respiratory

An influx of specialty drugs has made its way to this dynamic market, alongside successors to the existing respiratory blockbusters for asthma and COPD. **Noah Pines** on how big pharma aspires to sustain sales, and how the biotech entrants have started to make inroads in the war on wheezing

The respiratory sector, long buoyed by sales from big pharma and mass-market brands, is seeing an influx of specialty drugs, alongside successors to existing blockbusters. The biotech entrants, some already approved and some moving through the pipeline, have started to open up new progress in the war on wheezing.

One of the most lucrative disease areas for drug makers has been chronic obstructive pulmonary disease (COPD). The current respiratory leaders include two COPD therapies: the once-daily, long-acting anticholinergic (LAMA) Spiriva, co-promoted by Boehringer Ingelheim and Pfizer, and GlaxoSmithKline's twice-daily Advair, which combines a long-acting beta-2 agonist (LABA) with an inhaled-corticosteroid (ICS) to attack asthma and COPD.

Spiriva had been the sole once-daily bronchodilator in the US until the 2011 launch of Novartis' once-daily LABA Arcapta Neohaler. BI is now studying a new once-daily LABA, olodaterol.

In February, an FDA advisory committee voted 15-1 to approve olodaterol as monotherapy, and it looks poised for a green light, although the FDA doesn't always follow the advice of its advisors. BI is also testing the new med in a fixed-dose combination with Spiriva, but other companies' LAMA/LABA combos could beat it to the punch.

GSK, which saw a key Advair patent take its last gasp in 2011, is also seeking to breathe new life into its portfolio with a new ICS/LABA co-formulation called Breo. (At press time, its March ad-com vote had been postponed.) Delivered via Theravance's inhaler Ellipta, the successor promises more convenient once-a-day dosing than Advair, which is known as Seretide abroad.

Despite the more than 10 approved therapies in the US, "In COPD, there is widespread under-treatment," observes BI's Tunde Otulana, MD, VP of clinical development and medical affairs, respiratory. "One possible reason may be because physicians don't have a sufficient number of options…to tackle the disease."

Better breathing through biology

But most of the marketed products do not address the biological cause of their diseases. Whether asthma, COPD or pulmonary arterial hypertension (PAH), "We need a better understanding," adds Dr. Mani Kavuru, a pulmonologist at Thomas Jefferson University Hospital, "so the search goes on for new targets and new biomarkers."

From that standpoint, cystic fibrosis (CF) is furthest along. Example: Two of the first three of the 21 applicants to get FDA's newly minted breakthrough status designation are Vertex Pharmaceuticals' CF drugs Kalydeco (ivacaftor), an orphan med which won FDA approval last year, and the experimental combination regimen of lumacaftor (VX-809) + Kalydeco.

Essentially, the designation, which took effect in 2012, is meant to get breakthroughs to patients more quickly. "We look for preliminary clinical evidence that the drug represents a very substantial improvement over existing therapy," Janet Woodcock, MD, director of FDA's Center for Drug Evaluation and Research, tells *MM&M* by e-mail.

Adds Woodcock, "We will work very closely with sponsors to determine how much data is needed for NDA filing, and how to scale up manufacturing, etc. The earlier the development program (in

TOP 50 RESPIRATORY PRODUCTS, 2012

Category leaders, ranked by US sales, and their media spend

Rank	Product	Manufacturer	US sales $ (millions)*	Vs. prior 12 mos.	TRx (millions)	Vs. prior 12 mos.	US DTC media $ (000s)	Vs. prior 12 mos.	US journal media $ (000s)	Vs. prior 12 mos.
1	**Advair Diskus**	GlaxoSmithKline	$4,887.7	2.0%	17.2	-5.0%	$110,936.2	-17.0%	$0.0	N/A
2	**Singulair**	Merck	$3,299.7	-31.0%	17.8	-36.0%	$290.5	99.0%	$0.0	N/A
3	**Spiriva Handihaler**	Boehringer Ingelheim	$2,832.1	15.0%	9.6	4.0%	$90,111.3	18.0%	$287.8	N/A
4	**Symbicort**	AstraZeneca	$1,299.9	21.0%	5.3	13.0%	$86,300.0	-8.7%	$460.0	10.0%
5	**Combivent**	Boehringer Ingelheim	$1,139.0	3.0%	4.1	-7.0%	$0.0	N/A	$57.3	N/A
6	**ProAir HFA**	Teva	$1,122.6	17.0%	25.4	10.0%	$220.6	25,586.0%	$2,619.1	76.0%
7	**Nasonex**	Merck	$1,107.6	3.0%	9.1	-3.0%	$46,465.7	16.0%	$0.0	N/A
8	**Flovent HFA**	GlaxoSmithKline	$1,038.0	5.0%	6.3	3.0%	$0.0	-100.0%	$0.0	N/A
9	**Budesonide**	Generic	$944.4	9.0%	2.8	-1.0%	$0.0	N/A	$0.0	-100.0%
10	**Ventolin HFA**	GlaxoSmithKline	$714.7	16.0%	17.2	9.0%	$0.0	N/A	$0.0	N/A
11	**Xolair**	Genentech/Novartis	$707.4	25.0%	N/A	N/A	$23.2	59.0%	$12.1	3.0%
12	**Fluticasone Prop**	Generic	$525.9	-10.0%	33.9	15.0%	$31.8	N/A	$21.0	N/A
13	**Pulmozyme**	Genentech	$458.2	9.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
14	**Qvar**	Teva	$423.1	25.0%	3.1	21.0%	$16.7	18,457.0%	$491.4	N/A
15	**Advair HFA**	GlaxoSmithKline	$362.4	18.0%	1.4	11.0%	$0.0	N/A	$0.0	N/A
16	**Xopenex**	Sunovion	$336.5	-31.0%	1.1	-8.0%	$0.0	N/A	$0.0	N/A
17	**Tobi**	Novartis	$332.1	15.0%	0.1	1.0%	$0.0	N/A	$0.0	N/A
18	**Revatio**	Pfizer	$323.8	1.0%	N/A	N/A	$0.0	N/A	$0.0	-100.0%
19	**Montelukast Sod**	Generic	$300.2	N/A	10.8	N/A	$0.0	N/A	$73.7	N/A
20	**Pataday**	Alcon	$299.1	13.0%	2.6	2.0%	$92.5	-25.0%	$508.7	-38.0%
21	**Proventil HFA**	Merck	$230.9	7.0%	4.1	0.0%	$0.0	N/A	$0.0	N/A
22	**Asmanex Twisthaler**	Merck	$227.5	-8.0%	1.3	-9.0%	$0.0	-100.0%	$0.0	N/A
23	**Pulmicort Respules**	AstraZeneca	$222.9	-1.0%	0.4	-17.0%	$0.0	N/A	$0.0	N/A
24	**Atrovent HFA**	Boehringer Ingelheim	$212.0	8.0%	0.8	-5.0%	$0.0	N/A	$0.0	N/A
25	**Patanol**	Alcon	$211.1	-12.0%	1.8	-22.0%	$0.0	N/A	$0.0	N/A
26	**Dulera**	Merck	$209.2	137.0%	1.0	152.0%	$43,590.2	16.0%	$93.7	-97.0%
27	**Albuterol**	Generic	$188.0	-6.0%	14.7	5.0%	$0.0	N/A	$0.0	N/A
28	**Brovana**	Sunovion	$173.0	16.0%	0.3	70.0%	$500.0	-92.0%	$1,037.7	N/A
29	**Veramyst**	GlaxoSmithKline	$141.4	-15.0%	1.3	-23.0%	$0.0	-100.0%	$0.0	N/A
30	**Azelastine HCl**	Generic	$141.3	-6.0%	2.4	0.0	$0.0	N/A	$0.0	N/A
31	**Xopenex HFA**	Sunovion	$140.2	-9.0%	2.5	-42.0%	$0.0	N/A	$0.0	N/A
32	**Astepro**	Meda	$126.2	10.0%	1.1	-2.0%	$0.0	-100.0%	$0.0	N/A
33	**Clarinex**	Merck	$121.3	-42.0%	0.7	-48.0%	$2.4	N/A	$0.0	N/A
34	**Triamcinolone Actn**	Generic	$116.2	64.0%	1.5	108.0%	$0.0	N/A	$0.0	-100.0%
35	**Pulmicort Flexhaler**	AstraZeneca	$116.0	-8.0%	0.7	-10.0%	$0.0	N/A	$0.0	N/A
36	**Patanase**	Alcon	$109.8	13.0%	0.8	0.0%	$0.0	N/A	$0.0	N/A
37	**Levalbuterol HCl**	Generic	$108.6	944.0%	0.4	>999	$0.0	N/A	$0.0	N/A
38	**Perforomist**	Dey	$98.8	14.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
39	**Serevent Diskus**	GlaxoSmithKline	$86.0	-16.0%	0.4	-12.0%	$0.0	N/A	$0.0	N/A
40	**Albut Sulf/Ipratro**	Generic	$82.4	5.0%	3.6	11.0%	$0.0	N/A	$0.0	N/A
41	**Adcirca**	Lung LLC	$77.5	47.0%	N/A	N/A	$0.0	-100.0%	$0.0	N/A
42	**Daliresp**	Forest	$71.4	338.0%	0.4	426.0%	$0.0	N/A	$7,807.2	-9.0%
43	**Foradil Aerolizer**	Merck	$68.6	-13.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
44	**Ipratropium Br**	Generic	$63.5	-4.0%	2.8	-3.0%	$0.0	N/A	$0.0	N/A
45	**Rhinocort Aqua**	AstraZeneca	$60.2	-26.0%	0.5	-29.0%	$0.0	N/A	$0.0	N/A
46	**Flovent Diskus**	GlaxoSmithKline	$58.5	39.0%	0.4	25.0%	$0.0	N/A	$0.0	N/A
47	**Zyflo CR**	Cornerstone	$56.9	61.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
48	**Alvesco**	Sunovion	$54.9	18.0%	N/A	N/A	$0.0	-100.0%	$0.0	N/A
49	**Levocetirizine Dih**	Generic	$48.0	-39.0%	3.3	37.0%	$0.0	N/A	$0.0	N/A
50	**Alrex**	Bausch & Lomb	$45.4	13.0%	0.3	-5.0%	$0.0	N/A	$93.3	177.0%

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

CLINICAL CORNER

With patents expiring and blockbusters hard to replicate, pharma labs industry-wide are turning to targeted approaches. The situation is no different for firms developing treatments for diseases of the airways.

But to develop more personalized therapies for asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF), researchers need to identify biomarkers earlier in clinical trials. Global CRO Quintiles thinks it has a more systematic and rational process.

It's based on measuring and analyzing sputum, which is among a new crop of indices being incorporated into respiratory trials, says Graham Clarke, PhD, who is based in the CRO's London facility where he directs respiratory and inflammation research.

Graham Clarke

Sputum can help spot patients who might produce a change in a biomarker. If it can predict a drug's safety and efficacy, sputum can cut the time it takes for a company to make a go/no-go decision on a respiratory therapy, Clarke says.

To harness this potential, Clarke's team developed an initiative called BioSpit. New for 2013, it is designed to harmonize methodologies in sputum analysis across data-collaboration centers. Clarke says it's the first of its kind to be introduced by a CRO.

"Since January," he adds, "we have two companies working on a proposal to incorporate the BioSpit initiative to [differentiate between phenotypes] in asthma and COPD." Clarke's facility will be a central hub to analyze the sputum data coming from these sites, he notes, adding that BioSpit "moves us in the direction where pharma is going."

Where does Clarke see the most promise for phenotyping in respiratory research? "CF has such huge potential for tailored medicine due to the heterogeneity of the disease group with DNA or coding approaches," he says, and "differences between CF phenotypes."

Identifying relevant biomarkers is a need at the start of trials. Later, there's a call for sponsors to be more efficient and timely. According to global benchmarks compiled by IMS Health's Clinical Trial Optimization Solutions group, the US is on par with Western Europe but lags behind Latin America, Asia and Eastern Europe in terms of the speed at which subjects are randomized for respiratory trials.

The US also leads the world in the number of weeks (18.6) it takes to get sites up and running to conduct trials for respiratory drugs. Substantial cost differences are apparent, with median cost per patient and cost per visit higher in the western markets, says IMS.

Trial sponsors also need better ways to keep trial sites engaged (i.e., to figure out which ones are good at coordinating their studies and maintaining enrollment). One company is applying principles of marketing research to get a better handle on some of these variables.

C-Score, developed by the firm Clinical SCORE, surveys people who manage the day-to-day clinical trial operations in physician offices (like clinical study coordinators) to offer visibility into how pharma firms stack up in their eyes on a range of image and efficiency dimensions.

the clinic) probably the more helpful the designation will be."

Products in the respiratory area, like Kalydeco, are blazing a trail along this pathway. The drug is the first oral agent that treats the underlying mechanism of CF. "The biggest substantial change is that we are now treating CF and not just the symptoms," says Julie Hoggatt, principal at Source Healthcare's *in*Thought Research.

"Vertex pushed the envelope with Kalydeco; in the respiratory space, nothing remotely comes close to what is happening in CF," adds Barclays senior pharmaceutical analyst Tony Butler, PhD.

Essentially it works by fixing a defective protein product, cystic fibrosis transmembrane conductance regulator (CFTR), which results from a faulty gene. The defect is responsible for the formation of thick mucus that builds up in the lungs, digestive tract and other parts of the body leading to the severe respiratory and digestive symptoms.

If Kalydeco has an Achilles' heel, it's that usage is limited to a small subset of people—those with the G551D mutation of CF, ages 6 and older. In the US, about 1,200 people, or 4% of the 30,000 people living with CF, have the G551D mutation. Vertex says that most of these eligible patients already are receiving Kalydeco. Worldwide, there are estimated to be approximately 70,000 people living with CF.

Next, Vertex is seeking to amplify Kalydeco's utility by combining it with lumacaftor (VX-809). Lumacaftor is thought to hoist the defective protein to the cell surface so that Kalydeco can debug it.

And by virtue of covering a wider span of mutations—people with two copies of the F508del mutation in the CFTR, which constitutes about 50% of cystic fibrosis patients—this booster has the potential to hike the number of CF patients treated.

At press time, the biotech had planned to initiate a Phase III development program for a combination regimen of lumacaftor and ivacaftor in people with CF ages 12 and older who have two copies of the F508del mutation by the end of the first quarter of 2013. Vertex has another CF mid-stage asset, VX-661, which some analysts say could widen the audience even further if successful.

According to an *in*Thought forecast, lumacaftor could be approved and launched in 2016, with the analysts projecting total US revenue of $436 million in the first year, with $890 million in worldwide revenue by 2017 as it reaches other markets.

*In*Thought anticipates VX-661 to follow in 2018 and to generate $717 million in revenue in its launch year, tacking on another $857 million in 2019. VX-661 may cannibalize lumacaftor, since both are used in the same capacity, but this depends on genotype overlaps that will present themselves with further study, the analysts say.

PAH—basically high blood pressure in the lungs—is another arena of orphan drug innovation in the respiratory diseases sector. The dominant players include the re-tasked PDE5s: Pfizer's Revatio (sildenafil) and Eli Lilly's Adcirca (tadalafil); oral endothelin receptor antagonists (ERAs) like Actelion's Tracleer (bosentan) and Gilead Sciences' Letairis (ambrisentan); and several intravenous and subcutaneous medications, with United Therapeutics' Remodulin/Tyvaso the most prominent. Jeffries' analysts estimate that there are approximately 30,000 treated PAH patients in the US, with the number growing by 10% annually.

PAH treatment has made great strides, says Kavuru, the Jefferson pulmonologist. "There has been palpable improvement. If you look at the number of patients transplanted, that has declined a lot over the last 10-15 years, and I would attribute that to the better medical therapy. What we need now has more to do with 'tweaking' things—side effects, the need to check liver functions, even cost." ■