# Respiratory

The respiratory field, in which several launches are under way, is branching out, from long-time dominant fixed-dose combinations to a therapeutic arsenal that includes biologics and gene therapy. **Rebecca Mayer Knutsen** investigates the innovation and the intrigue

Companies in the highly competitive respiratory market continue to crank out a steady stream of product launches while stockpiling the pipeline with innovations. Struggling to gain a foothold amid generic competition and patent cliffs, pharma giants are gobbling up respiratory assets and asset families at a frenetic pace.

The days of lung brands basking in the limelight of a starring role are long gone. Today's respiratory illnesses, including asthma and COPD, require a therapeutic arsenal. The global asthma market is grappling with the generic erosion of leading brands, including GlaxoSmithKline's Advair, AstraZeneca's Symbicort and Merck/Kyorin's Singulair.

While the respiratory space has been traditionally difficult for generic companies to penetrate, Teva and other generic firms appear ready to pounce on an otherwise-brand-centric market, adds Joshua Owide, GlobalData's director of healthcare industry dynamics.

While GSK long ago staked its claim as the category leader, recent lagging sales have prompted others to attempt to inch their way in. But many experts have their money on GSK's return before competitors can establish a beachhead. GSK's Breo, a once-daily version of megablockbuster lung drug Advair, is approved for COPD and is awaiting approval for asthma. Its cousin Anoro is approved for COPD.

Owide points to less-than-impressive uptake of the newest members of GSK's respiratory portfolio as the company's latest setback. Last year it welcomed once-daily treatments Arnuity for asthma and Incruse for COPD—both delivered with the Ellipta inhaler, the next-gen version of the Diskus device.

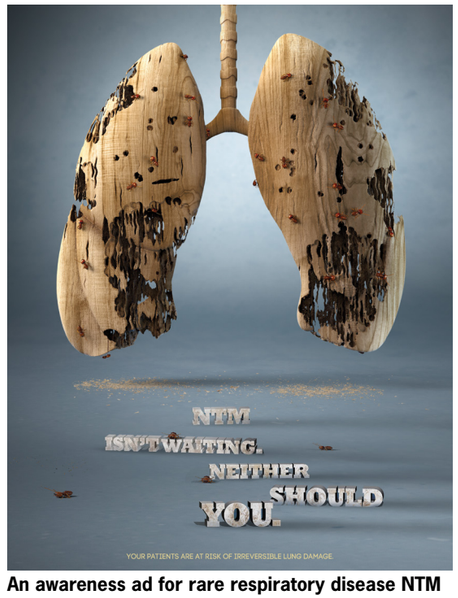
Overall sales keep Boehringer Ingelheim, AstraZeneca and Novartis an echelon below GSK. "These firms have invested heavily in new products and are poised to gain ground," Owide observes.

Boehringer Ingelheim is aiming for a shot at the throne by expanding its product slate—with, among others, COPD drug Striverdi Respimat. Meanwhile, Merck has found its asthma market position threatened by a weak pipeline and the generic erosion of Singulair.

In 2014 US sales were up 23%—to $1.5 billion—for Symbicort, AZ's twice-daily combination inhaled corticosteroid (ICS) and long-acting beta2-adrenergic agonist (LABA) for COPD, including chronic bronchitis and emphysema. Evaluate Pharma analysts predict GSK's mepolizumab (awaiting approval for the treatment of severe asthma) and Actelion's selexipag (filed for PAH) will rake in sales of $1.16 billion and $1.25 billion respectively by 2020.

"Respiratory disease treatment options haven't changed dramatically over the last few decades," says Christelle Perros-Huguet, PhD, SVP and chief scientific officer of the inflammation and immunology research unit at Pfizer. The current standard for asthma and COPD—one or more inhaled bronchodilators administered alone or in combination with an inhaled corticosteroid—leaves a large segment of patients poorly served, she says.

"These highly personal diseases affect patients differently depending on their condition, disease severity and preferred mechanism of delivery for asthma and COPD therapies," adds Michael Austwick, executive director, US Respiratory Franchise at AstraZeneca.




**An awareness ad for rare respiratory disease NTM (ad courtesy of Area 23)**

Brad Peebles, SVP at Area 23, says opportunities abound in areas of unmet need, including rare-disease nontuberculous mycobacterium (NTM). Insmed, its client, is developing orphan drug Arikayce for the treatment of NTM lung infections. Similarly, Mark Arnold, managing director of NEoN, commends its client, Barcelona-based Grifols SA, for its focus on rare diseases such as alpha 1 antitrypsin deficiency.

Meanwhile, the respiratory drug market wants in on some M&A activity. AstraZeneca sent a ripple through the market with its recent move to acquire rights to Actavis's branded respiratory line in the US and Canada, while Roche acquired InterMune to gain rights to Esbriet for the treatment of idiopathic pulmonary fibrosis in the US (see sidebar). "While it appears deals might shift toward specialty areas within the respiratory segment, there is also room for M&A activity relating to patent-expired intellectual property," Owide says.

Big companies have payer leverage and bundling possibilities and smaller companies boast enticing R&D programs, Makovsky Health EVP Gil Bashe explains. Pharma giants are scrutinizing sector innovators like Alnylam and Applied Genetic Technologies as "to-watch" acquisition targets.

## TOP 25 RESPIRATORY PRODUCTS

Category leaders, ranked by 2014 US sales, and their media spend

| Rank | Product | Manufacturer | US sales $ (millions) | Vs. prior 12 mos. | TRx (000s) | Vs. prior 12 mos. | US DTC media $ (000s) | Vs. prior 12 mos. | US journal media $ (000s) | Vs. prior 12 mos. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **Advair Diskus** | GlaxoSmithKline | $4,813.0 | -7.2% | 13,962.6 | -13.2% | $4,069.9 | -95.0% | $0.0 | N/A |
| 2 | **Spiriva Handihaler** | Boehringer Ingelheim | $3,329.0 | 9.7% | 9,610.7 | 0.9% | $56,245.7 | 8.0% | $380.0 | -68.0% |
| 3 | **Symbicort** | AstraZeneca | $2,245.8 | 41.6% | 7,963.1 | 30.6% | $92,357.7 | 38.0% | $2,493.0 | 295.7% |
| 4 | **Proair HFA** | Teva | $1,148.8 | 24.3% | 29,326.8 | 11.3% | $0.0 | -100.0% | $2,143.0 | 12.5% |
| 5 | **Nasonex** | Merck | $1,183.7 | 2.4% | 6,832.5 | -12.6% | $0.0 | -100.0% | $0.0 | N/A |
| 6 | **Flovent HFA** | GlaxoSmithKline | $1,141.9 | 7.0% | 5,659.7 | -2.9% | $0.0 | N/A | $0.0 | N/A |
| 7 | **Budesonide** | generic | $1,039.2 | -0.2% | 2,665.7 | 3.6% | $0.0 | N/A | $0.0 | N/A |
| 8 | **Xolair** | Genentech/Novartis | $1,034.1 | 25.9% | 213.9 | 15.3% | $0.0 | N/A | $129.0 | 73.7% |
| 9 | **Combivent Respimat** | Boehringer Ingelheim | $892.1 | 52.3% | 2,906.7 | 50.0% | $0.0 | N/A | $0.0 | -100.0% |
| 10 | **Ventolin HFA** | GlaxoSmithKline | $811.0 | 7.0% | 17,857.5 | 1.2% | $0.0 | N/A | $0.0 | N/A |
| 11 | **Qvar** | Teva Respiratory | $695.3 | 31.7% | 4,433.5 | 22.8% | $0.0 | N/A | $698.0 | -6.9% |
| 12 | **Dulera** | Merck | $587.3 | 74.7% | 2,181.0 | 50.3% | $27,883.5 | -32.0% | $0.0 | N/A |
| 13 | **Pulmozyme** | Genentech | $537.2 | 8.7% | 129.6 | 3.5% | $0.0 | N/A | $0.0 | N/A |
| 14 | **Advair HFA** | GlaxoSmithKline | $437.4 | 5.6% | 1,279.0 | -0.7% | $0.0 | N/A | $0.0 | N/A |
| 15 | **Montelukast Sodium** | generic | $313.8 | -32.6% | 32,822.5 | 10.2% | $0.0 | N/A | $0.0 | N/A |
| 16 | **Fluticasone Propionate** | generic | $302.3 | -21.7% | 43,662.5 | 16.1% | $0.0 | N/A | $0.0 | N/A |
| 17 | **Proventil HFA** | Merck | $292.5 | 15.3% | 4,544.2 | 3.1% | $0.0 | N/A | $0.0 | N/A |
| 18 | **Brovana** | Sunovion | $281.8 | 39.8% | 351.8 | 5.8% | $0.0 | N/A | $14.0 | -97.8% |
| 19 | **Asmanex Twisthaler** | Merck | $242.1 | 9.5% | 1,232.2 | 1.2% | $0.0 | N/A | $0.0 | N/A |
| 20 | **Atrovent HFA** | Boehringer Ingelheim | $240.3 | 10.1% | 791.0 | 1.2% | $0.0 | N/A | $0.0 | N/A |
| 21 | **Pulmicort Respules** | AstraZeneca | $236.1 | -5.1% | 443.5 | -3.1% | $0.0 | N/A | $0.0 | N/A |
| 22 | **Albuterol** | generic | $218.4 | -2.5% | 15,384.1 | 2.3% | $0.0 | N/A | $0.0 | N/A |
| 23 | **Levalbuterol HCL** | generic | $198.8 | -28.1% | 925.8 | -11.5% | $0.0 | N/A | $0.0 | N/A |
| 24 | **Pulmicort Flexhaler** | AstraZeneca | $142.0 | 14.1% | 774.5 | 9.7% | $0.0 | N/A | $0.0 | N/A |
| 25 | **Tudorza Pressair** | Forest | $137.2 | 91.6% | 540.8 | 71.7% | $0.0 | N/A | $12.0 | -99.8% |

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

### Asthma

While Advair is still no. 1, long-time market-dominant fixed combinations of ICS/LABA inhalers are gradually losing their glory. Biologic therapies in development will grab the lion's share of the asthma market by 2023, predicts Eirini Vavatsikou, PhD, GlobalData's analyst covering immunology.

"Allergy and asthma care and the patient experience will change completely in the next 10 years," predicts Mike Tringale, SVP of external affairs at the Asthma and Allergy Foundation of America. He notes that the industry will soon see a host of new solutions, including injectables, biologics and monoclonal antibodies that work with the immune system to stop the root cause of inflammation or other causes of lung constriction.

"Gene therapy is going to change this category altogether in a few years," Bashe says. Owide, for his part, points to companies actively bringing biologic therapies into the respiratory market, following the success of Genentech/Novartis's asthma biologic Xolair (omalizumab), which has surpassed the $1-billion mark in sales. And the success of the anti-IgE injectable therapy "is clearly reflected in the current crop of late-stage development candidates from several companies that target the interleukin (IL)-4, IL-5 and/or IL-13 pathways," Pfizer's Perros-Huguet says.

Benralizumab and tralokinumab, investigational biologic agents out of AstraZeneca's biologics R&D unit MedImmune, show improvements for patients with specific, severe forms of asthma. Benralizumab is also in early Phase-III development for COPD.

But the lingering question remains: Who is going to pay for biologics? "Patients are already feeling the financial burden of using bronchodilators, steroids and other medications," Tringale notes.

### COPD

The global COPD market is predicted to grow to nearly $175 billion in 2018 from about $12 billion in 2013. Although bronchodilators continue to drive the market, more efficacious and convenient products entering the market will fuel growth and command greater value.

Amazingly, more than 30% of COPD patients are relying on three or more therapies to tackle their condition. The pharma winners will seek an innovative path that combines the best of the corticosteroid, long-acting beta agonist and muscarinic antagonist approaches. "Therapeutic potential centers around a bundle of therapies that can arrest respiratory illness," Bashe says.

Vavatsikou explains that ICS/LABA/LAMA triple-fixed com-

## CLINICAL CORNER

Patients with idiopathic pulmonary fibrosis (IPF), who had previously contended with a borderline-deserted therapeutic market, have witnessed the approval of two first-in-class medications to treat the chronic lung condition. InterMune's Esbriet (pirfenidone) and Boehringer Ingelheim's Ofev (nintedanib) gained FDA approval last year to treat IPF.

IPF is a condition in which lung tissue progressively scars over time, resulting in shortness of breath, coughing and difficulty participating in everyday physical activities. Ofev and Esbriet act on and block multiple pathways that may be involved in the scarring process. About 100,000 Americans suffer from the rare and fatal lung disease, with a dismal prognosis of fewer than five years.

Gil Bashe

"We will continue to support the development and approval of new drugs, especially those that help patients with serious or life-threatening conditions for which no drug treatments are available," says Badrul Chowdhury, MD, PhD, director, division of pulmonary, allergy and rheumatology products, in the FDA's Center for Drug Evaluation and Research.

Within the sector, Makovsky Health EVP Gil Bashe identifies Boehringer Ingelheim and Roche as power players with blockbuster products. "The products have unique positioning and indications," he says. "Innovation that can change the human condition will gain support and these are two products that fit that mantra."

According to Chowdhury, researchers don't fully understand how Ofev and Esbriet combat idiopathic pulmonary fibrosis, but the drugs seem to inhibit important pathways that help to prevent scarring.

"Neither drug is a cure," Chowdhury stresses. "IPF may still progress after patients use these drugs, but each drug has been shown to significantly slow the progression of the disease."

As reported by Eirini Vavatsikou, PhD, a GlobalData analyst covering immunology, the IPF market is forecast to reach $1.1 billion across the six major markets of the US, France, Germany, Italy, Spain and UK by 2017. GlobalData attributes the astronomical growth in the IPF market over the next few years to the global launch of the two products and the availability of the first generation of pharmacological treatment options.

According to Joshua Owide, GlobalData's director of healthcare industry dynamics, Bristol-Myers Squibb recently entered into an option agreement to acquire Galecto Biotech, which is developing a treatment for IPF. Under the agreement, BMS will gain worldwide rights to the company's lead asset, TD139, a novel inhaled inhibitor of galectin-3 in Phase-I development for the treatment of IPF and other pulmonary fibrotic conditions.

"The key to success is developing products that address unmet needs," Bashe notes. "High patient care costs tend to open the minds and pocketbooks of payers."

binations will hit the market in 2019 with products from Chiesi Pharmaceuticals and GSK joining already-approved LABA/LAMA fixed combinations, including Novartis's Ultibro and AstraZeneca's Duaklir.

GlobalData analysts predict that BI's LABA/LAMA combining Spiriva and olodaterol will lead the drug class by 2023. Vavatsikou sees no room in the bronchodilator market for a blockbuster. Novartis appears to be ahead in the marketing game, as witnessed by the successful uptake of the LAMA monotherapy Seebri, the LABA monotherapy Onbrez and the praised LABA/LAMA Ultibro.

Emerging science targets underlying inflammation as an important driver of disease pathophysiology, Perros-Huguet notes. The COPD field recently witnessed the approval of roflumilast, an oral phosphodiesterase type-4 inhibitor, to reduce the risk of disease exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

Pfizer has explored the utility of a different anti-inflammatory mechanism—p38 kinase inhibition—as a potential COPD therapy. "Our experience highlights this enzyme as a key integrator of several intracellular processes intricately involved in COPD disease pathology," Perros-Huguet says.

Earlier this year Mylan entered into an agreement with Theravance Biopharma to collaborate on developing TD-4208 and its commercialization, upon FDA approval. Delivered via the mist of a nebulizer (rather than by a handheld device), TD-4208 is a once-daily long-acting therapy for COPD. Analysts commended Theravance for its choice, as Mylan has a solid reputation for successfully manufacturing and commercializing complex respiratory products.

Bashe advises COPD brand leaders to encourage physician engagement, payer commitment and patient compliance. "Patients in this category are often non-compliant," he explains. "It's not just staying true to therapy. It's stepping back from behaviors such as smoking that impact disease progression and putting the patient in the center of care."

### Cystic fibrosis

CF shot into the spotlight when President Obama used it as a model for a "precision medicine" initiative that zeroes in on treatments targeting a precise defect in the primary cause of the disease. To date, all CF medicines have addressed the symptoms of the disease but not its underlying cause: the defective Cystic Fibrosis Transmembrane Conductance Regulators (CFTR) protein. Several CFTR modulator drugs are currently in clinical trials.

"These drugs have the potential to treat CF at its cause, to improve lung function, nutrition and growth," says Thomas G. Keens, MD, director, Cystic Fibrosis Care Center, Children's Hospital Los Angeles. "Vertex is the leader, but other major companies are joining this innovative drug development."

Vertex Pharmaceuticals' breakthrough combo drug VX-809 (lumacaftor) and Kalydeco (ivacaftor) targets patients with two copies of F508del, the most common CF mutation. The FDA recently expanded the drug's indications to include treatment of the R117H mutation. ProQR Therapeutics NV is developing QR-010, a preclinical antisense nucleotide, to target the f508del mutation.

Bashe identifies immunotherapies as the respiratory category to watch. "Innovation can change the face of patient care for high-cost illnesses including lung diseases emphysema and CF," he says. ■