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 by 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.

GSK's return to inch their way in. But many experts have their money on GSK's return in combination with an inhaled corticosteroid (ICS) and a long-acting β2-adrenergic agonist (LABA) for COPD, including chronic bronchitis and emphysema. Evaluate Pharma analysts predict GSK's mepolimub (awaiting approval for the treatment of severe asthma) and Aclidex's selipipax (filed for PAH) will rake in sales of $12 billion and $1.25 billion respectively by 2020.

“Respiratory disease treatment options haven't changed dramatically over the last few decades,” says Christelle Perros-Huet, PhD, SVP and chief scientific officer of the immunology and immunology research unit at Pfizer. The current standard for asthma and COPD—more or less 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. 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 of unmet need, including rare-disease nontuberculous mycobacterium (NTM).}

"Allergy and asthma care and the patient experience will change completely with the next 10 years," predicts Mike Trianelle, 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, from several companies that target the interleukin (IL)-4, IL-5 and/or IL-13 pathways, Pfizer's Pheros-Huet says. Benralizumab and trilukinumab, investigational biologic agents out of AstraZeneca's biologics R&D unit MedImmune, show promising improvements for patients with specific, severe forms of asthma. Benralizumab is also in early Phase-III development for COPD. 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,” Trianelle 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 dominate 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. Vavatsikos explains that ICS/LABA/LAMA triple-fixed combi...
**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.

“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 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 Galacto 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 inhaling 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.”

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 Seebriz, 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 rolufilast, 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.