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# The COPD Pipeline XXIII

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## State of the COPD Pipeline

As of the end of May this year, clinicaltrials.gov shows 425 ongoing clinical trials for 'COPD', trials that are currently recruiting subjects. Adding 'emphysema' and 'bronchitis' to the search term only raises the total to 510. An unscientific scan of these trials indicates that fewer than half involve a drug that has not yet been approved. But how does our pipeline compare with the pipeline for other common disorders, again limiting the search to ongoing trials? For the search term 'cancer' it's 11,900; for 'coronary' it is 5,200; and for 'diabetes' it's 2,275. Even 'arthritis', a potentially serious but rarely fatal condition, shows 949 ongoing trials—almost twice as many trials as for the third commonest cause of death in most of the world.

What is the pharmaceutical industry doing to address this situation? The 2012 report of Phrma, Medicines in Development, states that there are 54 medicines for COPD in later stages of the pipeline (1). That pipeline, it seems, consists largely of classes of agents that have been available for many years, but which will be available in longer-acting form and in fixed dose combinations. The Phrma report also gives 3 examples of entirely novel agents that biopharmaceutical researchers are exploring. These are "an adult stem cell therapy that targets a protein in the blood that is often elevated in COPD" (would that be TNFα? an interleukin? CRP?), "a monoclonal antibody that acts on IL-1 receptors" and "a medicine that targets the underlying inflammation in COPD". This is good news that I will address in a subsequent column.

## New Fixed-Dose Combinations

A significant number of new bronchodilator combinations, mostly of once daily agents, are approaching FDA approval within the next months or years. Table 1 provides the list of these agents and their development status as of time of writing. Where known, their delivery formulation, e.g. MDI or DPI, is also shown. There may be others that I have missed. Few head-to-head comparisons between these agents have been published, to my knowledge.

GSK's fixed combination of fluticasone furoate (100 µgm) and vilanterol (25 µgm) was approved by the FDA on May 10 this year for "reduction of acute exacerbations of COPD and for the long-term maintenance treatment of airflow obstruction in COPD". It will be known as *Breo Ellipta* in the United States and *Relvar Ellipta* in Europe. The delivery device, *Ellipta* is novel. The directions call for a single inhalation once daily. In phase III studies a statistically significant increase in the incidence of pneumonia was seen in the fluticasone arms, so a box warning seems inevitable.

One notes that no new mechanisms of action are present in any of the combinations; they are thus combinations and permutations of classes of drugs that are well known. The MABA's (muscarinic antagonist/ beta-agonists) could be

**Keywords:** Combination bronchodilators, H5N1 influenza vaccine, REMS

**Table 1.**

| | | |
|---|---|---|
| LAMA/LABA Combinations | | |
| Forest | Aclidinium/formoterol DPI | Ph III |
| GSK/Theravance | Umeclidinium/vilanterol (Anoro) DPI | NDA* |
| BI | Olodaterol/tiotropium Respimat | Ph III |
| Novartis | Glycopyrrolate/indacaterol DPI | Ph III |
| Pearl | Glycopyrrolate/formoterol MDI | Ph II |
| ICS/LABA Combinations | | |
| Merck | Mometasone/formoterol MDI | NDA* |
| GSK/Theravance | Fluticasone/vilanterol (Relvar/Breo) | Approved |
| Mylan Specialty | Fluticasone/formoterol Neb soln | Ph II ->III |
| Pearl | PT002/009 MDI | Preclinical |
| Novartis | Mometasone/indacaterol DPI | Ph II |
| MABA+ | | |
| GSK/Theravance | GSK961081 | Ph II |
| AstraZeneca | AZD2115 | Ph II |
| ICS/LAMA/LABA Triple Combinations | | |
| GSK | Fluticasone/vilanterol/umeclidinium | Ph I |
| GSK | Fluticasone/GSK961081 | Ph II |
| GSK | Advair/umeclidinium | Ph III |
| Pearl | PT010 ICS/LABA/LAMA | Preclinical |

*NDA, New Drug Application.
+MABA, muscarinic antagonist/beta agonist.

considered a new class of agents; they contain 2 pharmacophores (a beta-agonist and an anticholinergic moiety) on a connecting spine. One notes also that some triple combinations are in development. Additional discussion of the merits and drawbacks of some combinations is available (2).

### Vaccine for H5N1 Avian Influenza

Protection against the H5N1 virus was almost absent in older subjects last season. A novel formulation uses attenuated rather than killed virus. The new formulation will also protect against H9 epidemics and will be administered by nasal insufflation instead of parenteral injection. The risk associated with an attenuated virus formulation is that, by genetic reassortment with transmissible virus genes after administration, the attenuated virus may re-acquire its potency. This risk has been addressed by an innovative genetic 'trick' the details of which are described in the report (3).

### REMS

A new acronym to be learned by many of us who consult with and advise pharmaceutical companies about a product in development, it stands for Risk Evaluation and Mitigation Strategy. Put in place by the FDA in 2007, the REMS program was a response to a need to understand and measure the safety or potential risk associated with a drug or biologic. When a potentially approvable drug appears to have a risk of causing harm, it is necessary for both the sponsoring manufacturer and the Agency, to determine whether the drug's benefit outweighs its risks. The FDA has the authority to require a REMS and, quite often, the pharmaceutical company will anticipate the need and offer a REMS during the development program. The REMS programs, of which there are or have been about 200 so far, typically require the development and distribution of information for patients and health care professionals, patient and prescriber registries, or training for prescribers. It is not certain if a specific clinical trial could be a component of a REMS.

I believe at its initiation, the REMS program was intended to address concerns such as the long-term use of opioid analgesics, but its use has since escalated. In our field, in 2011 FDA required a REMS that included a "Medication Guide written specifically for patients, and a plan to educate healthcare professionals about the appropriate use of LABAs." Almost all the products we use in treating our COPD patients are subject to a REMS requirement or have been through and already received approval of a REMS; this includes every product with a LABA or an ICS, as well as Chantix and Zyban, Tracleer and Bosantin, but not tiotropium or roflumilast. Most REMS have been required and performed post-marketing, but one notices that a REMS may be offered by the sponsor at the time of application for approval (NDA) to be performed in Phase IV.

Does the REMS program work? This is a matter of contention and uncertainty. A study by the Office of Inspector General found that compliance was deficient or could not be determined in about half the REMS they reviewed. In part, this was because the FDA lacks authority to enforce compliance because Congress did not grant it to the Agency. Nor has the FDA taken whatever action it has against a sponsor that is non-compliant. Information about the REMS program is available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htttp://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm.

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The information in this column was made available to the author through Citeline's Trial Trove ©. For more information on Trial Trove, please visit www.citeline.com.

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