

# THE WALL STREET JOURNAL.

A8 Thursday, March 18, 2010

THE WALL STREET JOURNAL.

## U.S. NEWS

# FDA Is Easing Way for Drug Cocktails

Agency Draws Up Guidelines for Approving Two or More New Drugs Together to Fight Deadly Diseases Such as TB, AIDS

By MARK SCHOOF

The Food and Drug Administration is devising guidelines that could accelerate testing and approval of multidrug regimens for some of the world's most deadly diseases.

At least two pharmaceutical consortia are poised to take advantage of the forthcoming policy: a group of 10 drug companies and several nonprofit organizations convened by the Bill and Melinda Gates Foundation to develop medicines to fight tuberculosis; and pharmaceutical giants Merck & Co. and AstraZeneca PLC, which are jointly testing two anticancer agents.

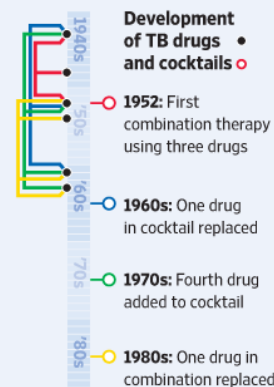
Many diseases, such as AIDS, tuberculosis and cancer, require multidrug combinations. Such drug cocktails can prevent the development of drug resistance, because the microbe or cancer cell needs to undergo more mutations to escape several drugs than to escape just one. By attacking the disease in different ways, drug combinations also improve the chances of therapeutic benefit.

Traditionally, the FDA has required each new drug to be tested and approved individually. Afterwards, multidrug regimens are usually developed through additional, time-consuming clinical trials.

At least since the mid-1990s, when cocktail therapies slashed the death rate from AIDS, the agency has been urged to streamline its approval process for multidrug regimens. In 2007, a report for the agency's own Science Board declared that the FDA's evaluation methods hadn't kept

### In the Pipeline | Tuberculosis compounds currently in development

Developer	Experimental drug	Class	How it kills the TB bacteria
<b>Tibotec</b> Johnson & Johnson subsidiary; <b>Global Alliance for TB Drug Development</b>	TMC-207	Diarylquinolone	<b>Disrupts cellular energy production</b>
<b>Otsuka Pharmaceutical</b>	OPC-67683	Nitroimidazole	<b>Disrupts synthesis of lipids and proteins</b>
<b>Global Alliance for TB Drug Development</b>	PA-824	Nitroimidazole	<b>Disrupts synthesis of lipids and proteins</b>
<b>Lupin</b>	LL 3858	Pyrrrole derivative	<b>Not well understood</b>
<b>Sequella</b>	SQ-109	Ethylenediamines	<b>Affects cell wall, may have other mechanisms</b>



Sources: Global Alliance for TB Drug Development; Stop TB Partnership's Working Group on New TB Drugs; WSJ reporting; Zhenkun Ma and Christian Lienhardt, article in Clinics in Chest Medicine

pace with the use of products in combination.

Now the FDA is drafting guidelines on how testing and approving multidrug cocktails composed of new, experimental drugs—something the agency has never done before, according to an FDA spokeswoman.

"This represents a bigger issue—the strengthening of regulatory science" to encompass scientific advances, FDA Commissioner Margaret Hamburg said in an interview Wednesday.

After the draft guidelines are published, as early as this summer, the agency will solicit public comment and then finalize the rules. The guidelines are expected to lay out

what research would be required in the test tube, animals and humans to determine side effects, proper dosage and each drug's contribution to any therapeutic benefit from the total cocktail.

The new guidelines would apply only to medications for life-threatening illnesses for which good treatment options do not already exist, and for which drug combinations—as opposed to single agents—are believed to be necessary. "This isn't for your garden-variety drugs," Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, said in an interview. Testing drugs together can make it more difficult to tease out which drugs or drug interactions

cause certain side effects. "Society wouldn't tolerate this degree of uncertainty" except for drugs to treat dire illnesses, she said.

Dr. Hamburg, who earned accolades for stemming drug-resistant tuberculosis when she headed New York City's health department, has met twice in the past year with the Gates Foundation, which solicited her commitment to testing multidrug combinations against the disease.

Spread by airborne bacteria, tuberculosis typically causes patients to cough up blood and kills about 1.8 million people every year. It is currently treated with drugs that are decades old, and about a third of patients contract a strain that is resistant to at least one first-line drug.

Multidrug-resistant cases—exceeding half a million annually—take two years to treat with drugs that often cause severe side effects but only cure about half of patients.

A regimen of entirely new drugs, which the tuberculosis bacterium has never before encountered, could potentially cure even those patients whose strain is now resistant to every current drug. In the last few years, at least nine experimental drugs have entered early-stage human trials, offering an unprecedented opportunity to mix and match drugs to come up with the best regimens, said Peter Small, head of the Gates Foundation's tuberculosis efforts.

In March 2009, Bill Gates met privately in New York with chief

executives of 14 drug companies. A representative of Sanofi-Aventis SA said the meeting helped catalyze that company's participation in the current tuberculosis collaboration. On Thursday in Washington, D.C., the foundation is expected to unveil the collaboration, in which all partners agree to share data and test new drugs in combination treatments early in the development process.

For companies, sharing the cost of clinical trials and bringing proven combinations to market more quickly might save money. But if a regimen fails, it could give every drug in it a bad reputation, which could be costly to overcome, even for drugs that ultimately prove safe and effective. And there are thorny questions on how competing companies would share data, decide which drugs to combine into regimens, and market their drugs.

The Gates collaboration, known as the Critical Path to TB Regimens, includes drug giants Pfizer Inc., GlaxoSmithKline PLC, and AstraZeneca, as well as small biotech firms such as Sequella Inc. Helping launch the collaboration were the nonprofit Global Alliance for TB Drug Development and the Critical Path Institute, set up by the FDA and the University of Arizona to develop new drug-evaluation methods. Also participating are the Treatment Action Group, a nonprofit advocacy organization; and the European and Developing Countries Clinical Trials Partnership, an initiative of the European Union.