Antibiotic: Is it or isn't it?

The answer could mean a lot for some companies' profits.

Antibiotics are arguably the most important class of medicines in modern history. But this doesn't mean that inclusion in this esteemed therapeutic category is something pharmaceutical companies are seeking for new drugs. In fact, at least two firms have recently put up big fights just so the FDA wouldn't call their products antibiotics. At stake are millions of dollars of revenue and, potentially, company survival.

The first case is that of CollaGenex Pharmaceuticals a Pennsylvania-based company whose main product is Periostat (doxycycline hyclate), a drug against gum disease that works by inhibiting enzymes that destroy periodontal support tissue. Since its approval by the FDA, in capsule form in 1998 and in tablet form in 2001, the drug has accounted for more than 80% of the company's annual revenues. CollaGenex also has several co-promotion and marketing deals for other companies' drugs, including Merck's Vioxx.

Both West-Ward Pharmaceutical and Mutual Pharmaceutical, have submitted Abbreviated New Drug Applications (ANDAs) to the FDA for generic versions of Periostat. The threat the ANDAs pose to CollaGenex, which depends so heavily on sales of a single drug, is tremendous.

Periostat is open to such challenges because its active ingredient, doxycycline, has been the active moiety in antibiotic drugs marketed prior to November 21, 1997. The FDA Modernization Act (FDAMA) of 1997 specifically exempted all antibiotic drugs that had been approved before the Act from market advantages that other new drugs had under the Drug Price Competition and Patent Term Restoration (Hatch–Waxman) Act. Specifically, this means that the patents for pre-kit antibotics drugs could not be listed in the Orange Book, which is the compilation of drug patents that need to be challenged for generic market entry, and they were not eligible for added market exclusivity beyond the patent term.

So when the FDA approved Periostat as an antibiotic, it immediately was open to the possibility of generic competition. But CollaGenex objected to this classification.

The exemption in the FDAMA refers to an antibiotic as a drug that contains "any quantity of any chemical substance produced by a microorganism and which has the capacity to inhibit or destroy microorganisms in dilute solution (including a chemically synthesized equivalent of any such substance)." According to CollaGenex, and according to the approved label for Periostat, the 20-mg doxycycline dosage in each pill is too low to have the capacity to kill or inhibit any microorganisms. Thus, the company asserts, there is no "antibiotic" in Periostat.

In the right class? It's not used to kill microbes, but the FDA categorizes Restasis, a treatment for dry eye, as an antibiotic. (Used with permission. Copyright 2004 Allergan).

Mutual Pharmaceutical, on the other hand, argues that the wording refers to "any quantity" of a known antibiotic, regardless of whether it has antimicrobial activity at the present dosage. But right before the FDA was ready to approve Mutual's ANDA last July, CollaGenex filed suit against the agency in the U.S. District Court for the District of Columbia. The court was convinced of a likelihood of success for CollaGenex's claim and granted a preliminary injunction restraining the FDA from approving any generic Periostat ANDAs until a final ruling could be made on the drug's regulatory status.

A final outcome has not yet been reached in this matter. However, in November, CollaGenex settled its patent infringement case with West-Ward. In the settlement, West-Ward agreed to the judgment that CollaGenex's Periostat patents are valid and infringed by its ANDA filing.

Taking notice of CollaGenex's success, California-based Allergan decided in November to take its own legal action against the FDA in the same DC court on a similar issue. Restasis (cyclosporine ophthalmic emulsion), the company's drug for increasing tear production and reducing inflammation in patients with dry eye (keratoconjunctivitis sicca), was approved in 2002 as a nonantibiotic treatment. But in March 2003, the FDA reclassified the drug as an antibiotic, thus exempting it from Hatch–Waxman benefits.

The FDA first approved a cyclosporine-based treatment in 1983 for preventing solid-organ-graft rejection, and cyclosporine is on the agency's list of antibiotics. Allergan, however, rejects this designation outright. In a Citizen Petition (*www.fda.gov/ohrms/dockets/dailys/03/Jun03/061703/03P-0275-cp00001-vol1.pdf*) that the company submitted to the FDA before deciding to file the suit, it asserts that cyclosporine "has never been approved by the FDA or labeled for any antibiotic indications and should not be considered an antibiotic drug under the law." The drug has only and always been an anti-inflammatory agent. Allergan contends that the chemical was erroneously put on the antibiotic list when it showed weak antifungal properties in testing in the 1970s.

Perhaps of more general significance, Allergan argues that simply because Restasis is not labeled or approved for antibiotic indications it logically should not, for any purposes, be considered an antibiotic. This same contention could be made for Periostat. The challenge seems to be growing for the FDA to provide greater guidance on what it means to be an antibiotic.

—DAVID FILMORE ■