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Quick Pulse

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FDA Bars More Than 30 Generic Drugs Made by Ranbaxy Laboratories in India

Citing Manufacturing Process Violations, Not Defective Products

The FDA has banned more than 30 generic drugs made by India-based Ranbaxy Laboratories because of manufacturing violations at two of its plants in Dewas and Paonta Sahib (including the Batamandi unit), India. The FDA also issued two Warning Letters to the drugmaker, which is one of the largest foreign suppliers of generic drugs to the U.S.

Among the generic drugs affected (*complete list on page 2*) are acyclovir, cephalexin, fenofibrate, clarithromycin, ciprofloxacin, loratadine, metformin HCl, pravastatin sodium, ranitidine, and simvastatin. Because Ranbaxy – which is being acquired by Daiichi Sankyo of Japan – is the sole manufacturer of the capsule version of ganciclovir (an antiviral drug), it will be allowed into the U.S. The others will not be allowed into the U.S. until the plants meet cGMP (current good manufacturing practice) requirements for drug manufacturing.

The FDA said that although it has not found any problems with the drugs produced at the plants, it has found repeated deficiencies in the company's drug manufacturing process. The agency said that there should be no drug shortages because other manufacturers can meet current market demands. Dr. Douglas Throckmorton, deputy director of the FDA's Center for Drug Evaluation and Research (CDER), told reporters, "To date we have seen no evidence of harm to consumers…and we have no reason to believe that the drugs already in the U.S. from these plants pose a safety problem. However, the FDA will monitor and conduct safety surveillance…The FDA will not approve any drug applications or abbreviated drug applications for drugs manufactured at those facilities (until FDA requirements are met)…This is a preventive action taken to protect the quality of drugs used each day by Americans."

The FDA told consumers not to discontinue taking their medication and to talk to their doctors. The agency also said that the announcement doesn't affect products made at Ranbaxy's other plants, which the FDA said meet U.S. cGMP requirements for drug making. Deborah Autor, director of the FDA's Office of Compliance in CDER, said, "These actions were taken proactively to address problems in manufacturing. The FDA has no reason to think that drugs already in the U.S. drug supply pose a problem."

Autor said that the FDA launched an investigation after it received letters in August 2005 suggesting fraudulent practices at the two plants. The agency inspected the plants in 2006 and found deviations from cGMP, including insufficient data collection, failure to document drug testing, and lack of personnel and lab instrumentation. In June 2006 the FDA issued a warning letter and worked with the company, including holding several meetings, to get corrections made.

Autor said, "Early this year the FDA inspected both facilities and documented significant violations at both locations. Because of the nature and the extent (of the violations), the FDA is taking steps, including issuing two warning letters, one for each plant, as well as the import alert…Specifically, the facilities manufacture a variety of…drugs such as penicillin, and the facilities' containment program designed to prevent cross-contamination was not adequate, and they had inadequate sterile processing operations…Today's actions are clearly warranted (due to) the extent of the violations…at these plants and not the products themselves…Additionally, no new drug applications or abbreviated drug applications will be approved until these deficiencies are addressed. The FDA has no evidence that the products are defective, but…the problems the FDA has found could impact the product… Ultimately, the deficiencies in the process reached the level where we think an import alert is justified – enough out of control that it is justified."

Some of the products made at the two facilities are used in the PEPFAR (President's Emergency Plan for AIDS Relief) program. Asked whether other countries will do the same thing, Murray Lumpkin, deputy commissioner of the FDA's Office of International Programs, said, "Our actions only have effect within the U.S. That is where our authority lies. We have been in contact with our WHO (World Health Organization) pre-qualification unit colleagues and (officials) in the U.S. government who implement the program, and we have informed them of our concerns and of our action today, but it will ultimately be up to each of them to make their own decisions."

The FDA inspected the Paonta Sahib facility in March 2008 and the Dewas factory in January and February 2008. In its warning letter addressing problems at the Dewas factory, the FDA documented cGMP deviations in the manufacture of sterile and non-sterile finished products and violations in the manufacture and control of APIs (active pharmaceutical ingredients). Specific concerns included:

- The facility's beta-lactam containment program appeared inadequate to prevent the potential for cross-contamination of pharmaceuticals.
- Inadequate batch production and control records.
- Inadequate failure investigations.
- Inadequate aseptic processing operations.

The letter to the Paonta Sahib factory followed an inspection at its Batamandi unit. Failures included:

- Lack of assurance that responsible individuals were present to determine that the company was taking necessary steps under cGMP.
- Inaccurate written records of the cleaning and use of major equipment.
- Incomplete batch production and control records.
- Inadequate procedures for the review and approval of production and control records for drug products.

Although Ranbaxy wrote to the FDA in response, the agency concluded that the response was inadequate and that warning letters were appropriate. This is the second time in less than three years that Ranbaxy has gotten warning letters. In 2006, the FDA cited the company for violations of U.S. cGMP at its Paonta Sahib factory.

Asked how the FDA can say that products already in the U.S. are safe, Dr. Throckmorton said, "Remember, the action we are taking today is aimed at the process. We're aimed at preventing an unsafe product from coming into the U.S. market. Issues have come up with the process whereby it's manufactured, not the product itself. That will lead to a safer product and prevent an unsafe product from coming on the market. We have looked at our Adverse Events Reporting System (AERS) and have seen no evidence for harm within that system."

Asked about specific testing on products, Autor said, "We have done sampling of products from both sites, and all the products met specifications. We will continue to do more sampling to get assurance of quality of the product. The violations in the letters relate to the processes themselves."

The FDA said that this action was not timed in any way to a Department of Justice court motion filed in July 2008, alleging a pattern of systemic fraudulent conduct by Ranbaxy. Autor said, "Today's action is the next step in an ongoing civil investigation. We continue to aggressively investigate those allegations and inspect Ranbaxy. The criminal case is on a separate track, and the timing of (this) action is not associated (with it) one way or another."

One day after the FDA action, Ranbaxy announced it has hired former New York City Mayor Rudolph Giuliani and his consulting firm, Giuliani Partners, to advise the company on resolving the issues with the FDA. Ranbaxy indicated it is "committed to a swift resolution to address these issues."

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Ranbaxy Drugs Barred from U.S. Entry

Finished drugs		APIs
acyclovir	isotretinoin	acyclovir
cefprozil	lamivudine	ciprofloxacin HCl
cefuroxime axetil	loratadine (OTC)	clarithromycin
cephalexin	metformin HCl	gabapentin
ciprofloxin HCl	nefazodone HCl	ganciclovir sodium
clarithromycin	nitrofurantoin	pravastatin sodium
fenofibrate	nitrofurantoin macrocrystalline	valacyclovir HCl
fluconazole	ofloxacin	
fosinopril sodium (with and without hydrochlorothiazide)	pravastatin sodium	
gabapentin	ranitidine	
ganciclovir sodium	simvastatin	
glimepiride	terazosin HCl	
	valacyclovir HCl	
	zidovudine (PEPFAR)	