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Teva *Plan B* OTC Application Fails Political Test After Clearing FDA Hurdle

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Teva Pharmaceutical Industries Ltd. faces an unprecedented challenge in its pursuit of OTC access for emergency contraceptive *Plan B One-Step* after a surprising rejection by Department of Health and Human Services Secretary Kathleen Sebelius.

Despite FDA's recommendation of approval, Sebelius said the label comprehension and actual use data Teva submitted in its February supplemental new drug application for *Plan B One-Step* (levonorgestrel 1.5 mg) do not fully cover younger consumers ("Teva's *Plan B One-Step* OTC Application Puts FDA On The Spot" – "The Tan Sheet," Feb. 14, 2011).

Sebelius' Dec. 7 memorandum to FDA Commissioner Margaret Hamburg couched HHS' decision in the lack of data for 11-year-old females, 10% of whom have reached reproductive age and would thus be in *Plan B*'s patient population.

"It is commonly understood that there are significant cognitive and behavioral differences between older adolescent girls and the youngest girls of reproductive age, which I believe are relevant to making this determination as to nonprescription availability of this product for all ages," Sebelius said.

Plan B One-Step and generic versions of the original two-dose *Plan B* manufactured by **Watson Pharmaceuticals Inc.** and **Perrigo Co.** remain available nonprescription from a pharmacist to consumers aged 17 and older, and with a prescription for younger patients.

Clinical Recruiting Faces Challenges

Practical problems inherent in evaluating younger adolescent subjects make it unlikely Teva will be able to clear the bar Sebelius set, says Dan Grossman, senior associate with the advocacy group Ibis Reproductive Health. The HHS secretary likely was motivated by political realities in denying *Plan B* OTC, he adds.

"It's very hard to recruit 11-year-olds into a study like this, [and] a tiny minority are sexually active. So I think that would be very hard data to produce," said Grossman, who coordinates Cambridge, Mass.-based Ibis' Oral Contraceptives Over-the-Counter Working Group ("Advocates For Switching Birth Control Pill Face Social, Risk Obstacles" – "The Tan Sheet," Jul. 26, 2010).

David McCammon, president of PEGUS Research, says OTC actual use trials accept all comers as subjects and typically do not set quotas for narrow age groups. He points out distinctions among subgroups may be arbitrary anyway.

"So the girl of age 12 understands [*Plan B One-Step*] and follows the label. What makes you think a girl age 11 wouldn't? It doesn't seem reasonable to me," McCammon said in response to Sebelius' memo.

Salt Lake City-based PEGUS, which conducts research in support of Rx-to-OTC switch applications, has never been told by FDA that it did not recruit enough young adolescents to warrant the standard indication for ages 12 and older.

"It does seem like a different set of decision-making is going on here that isn't done with other drugs," McCammon added.



Health and Human Services
Secretary Kathleen Sebelius

Photo courtesy of HHS

HHS' Plan B Interference Could Rattle Industry

Drug industry stakeholders voiced concern about the potentially far-reaching impacts of Health and Human Services Secretary Kathleen Sebelius quashing OTC access for *Plan B One-Step*.

For regulated industry, the HHS override of a scientific review suggests a new paradigm for the department's oversight of FDA, said food and drug attorney Stephen Mahinka.

The HHS hierarchy typically lacks the expertise to weigh in on drug safety and efficacy. "They don't get into FDA things for good reason," said Mahinka, a partner with Morgan, Lewis & Bockius.

Sebelius' rationale for overruling FDA Commissioner Margaret Hamburg on *Teva Pharmaceutical Industries Ltd.*'s supplemental new drug application for the emergency contraceptive is "potentially very expansive" and could emerge as a hurdle in other controversial drug areas, such as cancer treatments, he added.

Dan Grossman of Ibis Reproductive Health posited that the specter of HHS interference could become "a little bit of a black box" and stifle innovation in the area of Rx-to-OTC switches.

FDA Center for Drug Evaluation and Research official John Jenkins played down Sebelius' intrusion into the drug approval process.

Jenkins, director of CDER's Office of New Drugs, said members of the review team that handled Teva's application were disappointed that Sebelius overruled them. But he added that they understood the broader political controversy surrounding Plan B, and Hamburg's support for their conclusion gave the reviewers a boost.

"I think we appreciate the fact that the secretary, in making her decision, has owned the decision, so it was very transparent," Jenkins said Dec. 8 at the FDA/CMS Summit in Washington.

Wood Questions Plan B Scrutiny

During her Senate confirmation process in 2009, Sebelius wrote that "doctors and scientists will provide us guidance on who can safely and appropriately use Plan B" ("*Sebelius Plans To Leave Plan B Decision To Science*" – "*The Tan Sheet*," Apr. 20, 2009).

That response to a senator's inquiry came soon after a decision by the U.S. District Court for the Eastern District of New York that criticized FDA's previous rejection of a Plan B switch attempt and found the Bush administration had pressured agency reviewers. That ruling, in a lawsuit the Center for Reproductive Rights filed challenging FDA's first decision on Plan B OTC access, ordered FDA to extend nonprescription sale of the product to 17-year-olds and to reconsider universal access ("*Plan B Ruling Sets A Precedent That Could Give FDA Pause*" – "*The Tan Sheet*," Mar. 30, 2009).

A veteran of FDA during the original Plan B OTC review, Susan Wood says she believes the drug's safety data were sufficient to warrant universal OTC access following the original 2003 switch attempt and remain so.

Wood, who resigned as head of FDA's Office of Women's Health in 2005 over the Plan B controversy and now heads the George Washington University's Jacobs Institute of Women's Health, says the emergency contraceptive and the young female consumers who might use it are being scrutinized unfairly.

"For some reason, we have focused on young teens and this one particular over-the-counter contraceptive," she said. "Do we ever do subgroup analyses to ensure that people

over the age of 80, for example, can read and understand the label and use over-the-counter medications correctly in combination with who knows what else they're taking?"

Additionally, Wood pointed out the safety profile for levonorgestrel is much cleaner than that of many other OTC drugs.

"You can't kill yourself on Plan B. You can with acetaminophen," she added.

"It does seem like a different set of decision-making is going on here that isn't done with other drugs."

-PEGUS Research President David McCammon

Teva reportedly worked closely with FDA to develop and submit the SNDA data. In a statement, Hamburg said she and the Center for Drug Evaluation and Research found the drug safe and effective in adolescent females, whom the data showed understand Plan B is not for routine use and does not protect against sexually transmitted diseases.

Teva issued a statement commending FDA's positive finding and expressing disappointment at HHS' differing conclusion. The company now plans to review FDA's complete response letter and determine its next steps.

Political Considerations Loom

The political ramifications of Sebelius' decision were immediately apparent, as conservative organizations concurred and

women's health advocates and other liberal groups expressed outrage. President Obama said he was not involved with the decision but supports it.

Though the HHS secretary has legal authority to overrule an FDA determination, it appears that the department has never before publicly waded into the realm of science as Sebelius did in this case.

Under the health care reform law, HHS will require private health plans to cover Rx contraception purchases beginning in August 2012 ("Contraceptives Covered Without Cost-Sharing In HHS Prevention Rule" – "The Pink Sheet" DAILY, Aug. 1, 2011). Consumers will share the costs of branded OTC contraceptives such as Plan B One-Step or Watson's branded generic Next Choice, but can waive cost-sharing if obtaining the drugs with a doctor's prescription.

Conservative politicians and some insurance industry stakeholders objected to the expansion of essential benefits to include contraceptives, suggesting Sebelius' decision was calculated to avoid further controversy in advance of the 2012 presidential election.

But Wood said easier nonprescription EC access for all women should be a non-issue, just as it is for OTC contraceptives such as condoms and spermicides.



Teva's Plan B One-Step

"Who do they think they're impressing with this decision?" she mused. "I don't understand it."

FDA now must defend its earlier Plan B decisions in federal court against a November 2010 claim by CRR that the agency should be held in contempt for ignoring the earlier court order to reconsider universal OTC access to Plan B ("FDA Will Wait To Act On Plan B Petition Despite Contempt Complaint" – "The Tan Sheet," Nov. 22, 2010).

The U.S. District Court for Eastern New York will hear oral arguments in the case Dec. 13. 