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Europe's Evolving Distribution Model

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The pharmaceutical distribution model in Europe is in need of change. Manufacturers are intent to bolster the integrity of the supply chain, and hence public safety, and to achieve a supply-and-demand equilibrium between markets. The challenge: European Union (E.U.) policymakers support parallel trading, which is fueled by national laws that cause price differentials between markets.

Under these conditions, the existing distribution model is no longer sustainable. Manufacturers, policymakers, and the public are concerned about the safety of products that reach the end-user. Public confidence in the current post-market surveillance process has been damaged, and public trust in manufacturers is at an all-time low.

The challenge facing manufacturers is that under the current distribution model, drugs often pass through a multitude of third parties before reaching the patient. Manufacturers sell products to a wholesaler, which is responsible for distribution and delivery to the pharmacist. The manufacturer has limited ability to monitor the integrity of its product once it transfers rights to a third party.

The inability of manufacturers to monitor downstream activities, and intervene when necessary, results in:

- Distortions in supply and demand
- Public safety risks
- Brand and trademark deformation
- Ineffective product recall

The complexity and ambiguity of the gray market for drugs in Europe give rise to an environment that favors counterfeiters. In a survey conducted jointly by Ernst & Young and the Economist Intelligence Unit (EIU) in late 2004, over one-third of European executives in the manufacturing, wholesaling, and pharmacy sectors believe that counterfeiting is an important or critical problem in the supply chain. The same proportion of respondents across regions — Asia-Pacific, Europe, and North America — believe there is a link between parallel trade and counterfeiting activities.

Current E.U. competition policy hinders manufacturers' efforts to monitor the integrity of the supply chain. They may have greater freedom in the future to verify that third parties handling their products adhere to existing regulations thanks to several E.U. federal court judgments. However, these developments are minor compared to those needed to address the frailties of the European supply chain.

Manufacturers are actively lobbying policymakers and regulators on the importance of consistent application and enforcement of regulations. They are arguing that manufacturers, wholesalers, and repackagers alike should abide by the same rules in each of the E.U. member states.

ONE STEP AT A TIME

Without government intervention, manufacturers may still be constricted in their actions. To date, European manufacturers have focused on reviewing their own internal controls over supply chain operations, according to the Ernst & Young–Economist Intelligence Unit Survey. Many have also reviewed and revised contracts with vendors and other third parties in their supply chain.

Companies are beginning to take more aggressive steps, however, to modify their supply chain strategy. Nearly one-half of European companies surveyed plan to spend more than $5 million to enhance the integrity of the supply chain between 2004–2006. In some cases, manufacturers are considering direct distribution. These incremental measures are aimed at providing greater public confidence in products and meeting demand while minimizing margin erosion.

New product launch strategies and pricing corridors, which are meant to establish upper and lower limits to prices throughout the region, are being applied at the supply chain level. These measures aim to minimize the arbitrage opportunities available to parallel traders.

Solutions vary among manufacturers and are tailored by several components that shape arbitrage opportunities: product characteristics; geography; and national pricing and reimbursement regulations.

Manufacturers are developing enhanced risk and opportunity analyses that assist in decision-making. For example, executives are testing and simulating product recall capabilities through innovative modeling techniques.

Timely information and knowledge management are vital as companies enhance their supply chain proficiency. Quantifying product volume flows is as important as tracking consumption and sales in order to determine the location of products in the distribution channel, and to enable accurate product tracking and market demand.

Equipped with more robust and timely data, manufacturers will be able to pursue a day-trading business model, which will enable them to pre-empt and reduce arbitrage opportunities through strict supply management.

Manufacturers acknowledge that the source of problems may sometimes lie within the company. Executives are re-examining and redesigning performance measurement systems in order to improve their understanding of the influence that incentive and reward programs have on employees and, in particular, on country managers.

CONCLUSION

Manufacturers, wholesalers, parallel traders, and repackagers are each preparing for and contributing to changes in the European pharmaceutical market. Executives are reviewing and reshaping their strategy to mitigate risk and tap new opportunities. ®

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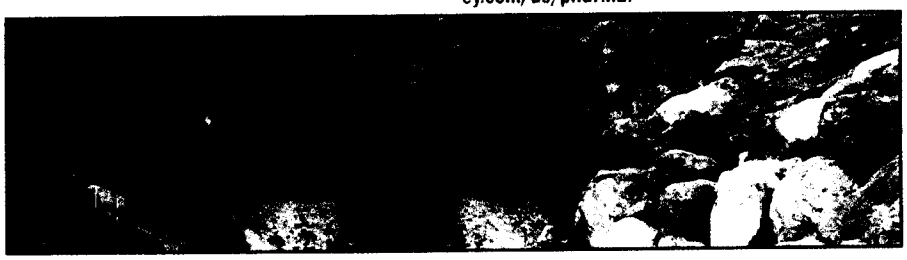

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Wyeth Urges Halt to Hormone Compounding, Questioning Its Safety

Wyeth's citizen petition to the FDA urging it to stop compounding pharmacists from producing "bioidentical hormone replacement therapy" focuses on safety concerns about the practice.

Compound pharmacies "are using unapproved ingredients to compound their products and are promoting their own BHRT formulations as wholesale substitutes for FDA-approved estrogen-containing hormone therapies," Wyeth's petition states.

In particular, Wyeth singles out BHRT products containing the hormone estriol, which is not an ingredient in any FDA-approved drug. Thus, the company says that compounding pharmacies using estriol "are engaging in manufacturing new, unapproved drug products rather than in traditional compounding activities."

Compounding pharmacists have been claiming that "bio-identical" hormone therapy is safer than commercial products.

Wyeth, manufacturer of the ***Premarin*** (conjugated estrogens) product family, has seen its hormone therapy franchise decline after 2002 when the Women's Health Initiative found increased cardiovascular and cancer risks from the products.

The findings resulted in class-wide black-box warnings, and Wyeth has used a number of direct-to-consumer campaigns to try to revive the category ("The Pink Sheet" July 25, 2005, p. 11).

The company is concerned about statements from compounding pharmacies that their bioidentical hormone products – which are plant-derived – are safer than FDA-approved hormone therapy products.

Borrowing a phrase from FDA's regulatory playbook, Wyeth notes these claims "lack clinical evidence." Further, Wyeth argues that promotional materials for BHRT products contain no information on side effects or contraindications.

Wyeth asks that FDA initiate "seizures, injunctions and/or warning letters" against compounders with any violative "manufacturing, labeling, advertising or dispensing practices." The agency should also issue an "alert or talk paper" informing the public and industry about the issue, Wyeth said.

The petition, submitted by Wiley, Rein & Fielding Partner Andrew Krulwich, also contains substantial discussion of how the pharmacists are manufacturing to create a "niche commercial market." Wyeth also presents numerous examples of allegedly violative advertising in an appendix.

However, the company's focus on safety issues may be a reflection of uncertainly regarding FDA's authority in the area following a 2002 Supreme Court decision that invalidated the pharmacy compounding section of the 1997 FDA Modernization Act on First Amendment grounds.

Former FDA associate chief counsel David Adams, now a partner at Venable LLP, has suggested that a petition modeled on an FDA warning letter may be an effective way to get the agency to respond to concerns about compounding, given FDA's limited resources ("The Pink Sheet" April 5, 2004, p. 35).

Despite questions about its enforcement powers, FDA has continued to take actions against compounders and issued a spate of letters in early 2004 ("The Pink Sheet" June 14, 2004, p. 41).

FDA remains under pressure to relax its oversight of compounding, though, and has been sued by a coalition of pharmacies in a Midland, Texas, federal court.

A response to Wyeth by the International Academy of Compounding Pharmacists, whose guidelines are cited in the petition, said that the action was simply "an attempt to restrict patients' access" to customized therapy. IACP said it is planning a formal submission to FDA, but an Oct. 27 press release focused mostly on legal arguments and did not address the ingredient issue directly.

"Compounding has been regulated by state boards of pharmacy, not FDA," IACP states. The group argues that because the products are made in small amounts and for individual patient needs, they are exempt from the Federal Food, Drug & Cosmetic Act.

IACP also criticizes the safety of Wyeth's products. "WHI studied Wyeth's products exclusively.... The physical components of BHRT are different from the components of Wyeth's synthetic hormones that were studied by WHI."

An extended volley of submissions in the docket between various parties might cause FDA to delay acting on the petition. ♦♦

Genentech/OSI Touting *Tarceva* Pancreatic Cancer Overall Survival Benefit

Genentech and marketing partner OSI are highlighting the overall survival benefit of combination use with ***Tarceva*** over gemcitabine (Lilly's ***Gemzar***) plus placebo for treatment of advanced pancreatic cancer.

Tarceva is "the first new therapy in nine years to demonstrate an improvement in overall survival in pancreatic cancer," Genentech and OSI said announcing approval of the new indication Nov. 2.

The Tarceva (erlotinib) supplemental NDA was cleared by FDA for use "in combination gemcitabine for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer."

For women and patients over the age of 65, "the benefit of erlotinib was uncertain," labeling concludes.

The epidermal growth factor receptor inhibitor was originally approved in November 2004 for use in patients with non-small cell lung cancer whose disease has progressed after at least one prior chemotherapy regimen. First-line use with Tarceva is explicitly discouraged in NSCLC due to failed studies in that patient group.

In their announcement press release, Genentech and OSI highlight the "statistically significant (23%) improvement in overall survival" seen with Tarceva in a pivotal pancreatic cancer trial.

A chart in Tarceva labeling shows that the difference in median survival was 6.4 months for 100 mg erlotinib-gemcitabine compared to 6 months for 100 mg gemcitabine-placebo. The statistical p-value was .028.

At one year, 23.8% of Tarceva-gemcitabine patients were alive, compared with 19.4% of gemcitabine-placebo patients.

While FDA found that a 12-day improvement in median survival was of questionable clinical benefit, the agency's Oncologic Drugs Advisory Committee felt that any extension in survival time, no matter how modest, represents a valuable benefit, especially in a particularly recalcitrant disease. The committee recommended full approval for the indication by a vote of 10 to three ("The Pink Sheet" Sept. 19, 2005, p. 3).

At the Tarceva review, the committee suggested that a study of sequential dosing of the two drugs might improve survival outcomes. However, such a study is not included in postmarketing commitments for the Tarceva indication. No new commitments are specified in the approval letter for the indication.

The difference in progression-free survival was also statistically significant, the companies noted. Median progression-free survival was 3.8 months for Tarceva-gemcitabine compared to 3.5 months for gemcitabine-placebo, according to the chart in labeling.

The companies added that although no tumor response was observed (8.6% for Tarceva-gemcitabine compared to 7.9% for gemcitabine-placebo), "the disease control rate" (complete response, partial response and stable disease) "was significantly improved (59% in patients receiving Tarceva plus gemcitabine versus 49% in the gemcitabine plus placebo arm, p=.036)."

Genentech/OSI presented their disease control rate analysis during the advisory committee meeting but the data are not included in labeling. Labeling only includes the tumor response analysis. Duration of response is also noted in labeling, a median 23.9 weeks for Tarceva-gemcitabine compared to 23.3 weeks for gemcitabine-placebo.

Labeling also contains a graph on a series of exploratory univariate subset analyses of survival in different patient groups.

EGFR-positive patients had a survival benefit while EGFR negative patients "did not appear" to have a benefit. However, wide confidence intervals make it so that "a survival benefit due to Tarceva in the EGFR negative subgroup cannot be excluded."

"[I]n patients with pain intensity score >20, female, locally advanced, age ≥65 years, or performance status 0 or 1, the benefit of erlotinib was uncertain," labeling concludes. The hazard ratios for those groups were very close, or equal, to 1.0 in the analysis.

OSI's international sales partner Roche is also pursuing a pancreatic cancer indication outside the U.S. The firm recently submitted a European application for the indication, OSI said.

OSI has halted studies of Tarceva in combination with Genentech's ***Avastin*** (bevacizumab) to treat renal cell carcinoma, after a *Phase II* study "did not support further development" of the combination. The company and its partners are conducting further *Phase III* studies in NSCLC lung, colorectal and ovarian cancers. ♦♦

GSK To Launch *Arranon* In Early 2006; Confirmatory Study To Follow

GlaxoSmithKline will launch ***Arranon*** (nelarabine) in early 2006, following FDA approval of the oncologic Oct. 28.

Arranon received accelerated approval for "treatment of patients with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens."

GSK attributed the lag between approval and launch to faster than expected approval; the company said it will be scaling up manufacturing in the interim.

The size of the sales force supporting Arranon's launch has not been determined, GSK said. The company said detailing efforts will particularly focus on pediatric oncologists.

Approximately 500 patients have relapsed or refractory T-ALL/T-LBL each year, of whom around 200 are children, FDA said in an Oct. 31 release announcing Arranon's approval.

Arranon was designated an orphan drug, qualifying for seven years of market exclusivity.

The approval is consistent with the recommendation of FDA's Oncologic Drugs Advisory Committee at its Sept. 14 review of the chemotherapy ("The Pink Sheet" Sept. 19, 2005, p. 7).

Arranon's safety and efficacy was primarily established in two open-label, single-arm *Phase II* trials, labeling states.

In a 39-patient cohort of pediatric T-ALL or T-LBL patients with at least two prior inductions, nine (23%) patients experienced a complete response (n=5, 13%) or a complete response without hematologic recovery (n=4, 10%).

In a 28-patient cohort of adult patients, five (18%) patients had complete responses and one (4%) patient experienced a complete response without hematologic recovery.

Labeling states that "randomized trials demonstrating increased survival or other clinical benefit have not been conducted." The approved indication is "based on the induction of complete responses," labeling notes.

GSK will conduct a *Phase III* confirmatory study of Arranon; the protocol will be the same as a protocol proposed during the advisory committee meeting.

The study, which will be conducted by the Children's Oncology Group, will include 640 newly diagnosed T-ALL patients between the ages of one and 30. Patients will be randomized in a 2x2 factorial design to 650 mg/m² nelarabine and two different formulations of methotrexate.

The primary endpoint is event-free remission at four years. COG will begin enrolling patients in April 2006, the approval letter states.

GSK is expected to submit a complete study report of a confirmatory trial by 2016.

FDA expects the safety phase of the trial to be completed by the fourth quarter of 2009, with accrual completed in Q04 2012, the letter says. Three-year follow-up should be completed in Q04 2015, with the complete study report available by the end of 2016.

During the advisory committee, panelists expressed concern about the long enrollment period for the trial, especially in light of the low completion rate of accelerated approval confirmatory studies.

Arranon labeling includes a boxed warning for neurotoxicity; nervous system events were reported in 64% of patients across *Phase I* and *Phase II* studies.

"Severe neurologic events have been reported with the use of Arranon. These events have included altered mental states including severe somnolence, central nervous system effects including convulsions and peripheral neuropathy ranging from numbness and paresthesias to motor weakness and paralysis."

"Full recovery from these events has not always occurred with cessation of therapy with Arranon. Close monitoring for neurologic events is strongly recommended, and Arranon should be discontinued for neurologic events of NCI Common Toxicity Criteria grade 2 or greater," the warning states.

Labeling also includes a precaution for hematologic adverse events.

GSK submitted the NDA (21-877) April 29. FDA approved Arranon one day ahead of nelarabine's six-month priority review action date. ♦♦

Novartis Iron Chelator *Exjade* To Launch In December With Broad Indication

Novartis plans to launch its oral iron chelating agent ***Exjade*** (deferasirox) in early December following its Nov. 2 approval for the treatment of chronic iron overload due to blood transfusions in adults and children over two years of age.

Exjade, which is dissolved in water or juice, is the only approved once-daily oral iron chelator.

"The approval of Exjade is expected to greatly enhance the acceptance of iron chelation therapy, especially for children, and offers a new alternative to the burdensome continuous infusion therapy," Novartis said.

Novartis said during its third quarter earnings call in October that Exjade could command a premium price over the company's parenteral therapy ***Desferal*** (deferoxamine), which is currently the first-line therapy for iron overload.

Desferal prices are as high as $30,000 a year in some markets, Novartis said, although 40% to 75% of the cost is associated with ancillary costs such as pumps that would not be required with Exjade.

Desferal requires a daily infusion of 8 to 13 hours for as long as a patient is receiving blood transfusions. Novartis has estimated the iron chelation market could grow dramatically with the availability of a more user-friendly product.

The company estimates incidence of iron overload to be between 100,000 and 250,000 patients, although the number of patients treated annually is currently between 25,000 and 35,000.

"We believe Exjade is a significant breakthrough that will fill an important gap in protecting patients from the cumulative toxicity of iron overload by making iron chelation therapy much more acceptable," Novartis said.

"Until now, patients may have avoided the potentially life-saving benefits of iron chelation because the standard therapy can be difficult to use."

The Exjade application (NDA 21-882) was based primarily on data from patients with ß-thalassemia, but Novartis requested a broader transfusional hemosiderosis indication that includes patients with a variety of blood disorders.

FDA's Blood Products Advisory Committee recommended approval for the transfusional hemosiderosis indication, although the committee split on whether there was adequate data to support use in children as young as two years of age ("The Pink Sheet" Oct. 3, 2005, p. 14).

Novartis' primary efficacy study measured liver iron concentration over 12 months in 586 adults and children randomized to either Exjade or Desferal.

"The percentage of patients achieving the primary endpoint was 52.9% for Exjade and 66.4% for deferoxamine," labeling states.

However, "the relative efficacy of Exjade to deferoxamine cannot be determined from this study."

Novartis estimates the market for iron chelation market could grow dramatically with the availability of an oral therapy.

Exjade tablets will be available in three doses: 125 mg, 250 mg and 500 mg. The recommended starting dose is 20 mg/kg body weight.

"After commencing initial therapy, it is recommended that serum ferritin be monitored every month and the dose of Exjade adjusted if necessary every 3 to 6 months based on serum ferritin trends," labeling states.

"Dose adjustments should be made in steps of 5 to 10 mg/kg and should be tailored to the individual patient's response and therapeutic goals."

As with Desferal, Exjade labeling recommends auditory and ophthalmic testing because of reports of side effects including decreased hearing and retinal disorders.

Novartis is implementing a patient support program: Exjade Patient Assistance and Support Services.

"Through a single point of contact with specially-trained operators, patients will be able to fill their Exjade prescriptions, obtain coverage and reimbursement assistance and choose to receive proactive Exjade education support," Novartis said.

Exjade received a priority review as well as an orphan drug designation. Exjade's U.S. approval is the first for the product worldwide. ♦♦

Novartis Catches Flu Fever: Second Bid Nets Chiron

Novartis' first priority upon the completion of its acquisition of Chiron will be to resolve the flu vaccine maker's outstanding manufacturing issues, Novartis Head of Pharma Development Jörg Reinhardt said during an analyst call announcing the deal Oct. 31.

The Swiss drug maker said it plans to acquire the outstanding 57.8% stake in Chiron that it does not already own for roughly $5.1 bil., representing a sweetened offer over its bid for the Emeryville, Calif. company in August.

The acquisition provides Novartis with entry into the global vaccines market, a dynamically growing segment. Chiron is the fifth largest vaccines player with 2004 segment revenues of $510 mil. The company's total revenues in 2004 were $1.7 bil., according to Novartis.

"Our plan is to turn around the Chiron vaccines business, which will require investments in R&D and manufacturing to increase quality and capacity," Novartis stated.

Novartis plans to develop a global vaccines leader in Chiron, Reinhardt said. In the short term, Novartis will focus on assuring quality processes and procedures, and completing a new egg-based manufacturing facility at Chiron's Liverpool, U.K. production center.

Longer-term plans call for investing in cell-based flu vaccine manufacturing during a three to five year period, Reinhardt added.

Despite strong growth potential in the flu vaccines market, Chiron has struggled with its manufacturing. Earlier this year, the firm suspended delivery of the ***Begrivac*** influenza vaccine to non-U.S. markets due to sterility concerns at its Marburg, Germany facility.

The Begrivac production suspension came after production of Chiron's U.S. flu vaccine ***Fluvirin*** was halted last year due to good manufacturing practice deviations at its Liverpool facility. The company has since addressed GMP issues raised by FDA in a "Form 483." Chiron's sBLA for production of Fluvirin was approved Sept. 14.

Nonetheless, Chiron expects that less than 18 mil. doses of the vaccine will be manufactured for the 2005-2006 flu season. The firm had released 1.5 mil. doses of the vaccine as of Oct. 17, but expects production capacity of 40 mil. doses of Fluvirin for the 2006-2007 season.

The vaccine maker stands to benefit, however, from efforts to develop a national avian flu vaccine stockpile. The company announced Oct. 27 that it had signed a $62.5 mil. contract with HHS to provide an avian flu vaccine to the Strategic National Stockpile in 2006 ("The Pink Sheet" Oct. 31, 2005, p. 28).

President Bush announced a $7.1 bil. pandemic flu preparedness plan Nov. 1 (*see related story p. 16*).

Novartis will create a new division for Chiron's blood testing and vaccine units to be headed by Reinhardt. The company will integrate Chiron's biopharmaceutical unit into its pharmaceutical division under Pharmaceuticals CEO Thomas Ebeling.

"We will run the vaccine and the diagnostic business separately as a division as we believe it is more important to have a very clear focus rather than a broad portfolio within pharmaceuticals," Novartis CEO Daniel Vasella said.

In addition to providing Novartis with its vaccines portfolio, the acquisition gives Novartis access to Chiron's blood testing and biopharmaceuticals units. Chiron's product portfolio includes the antibiotic ***TOBI*** (tobramycin solution), the oncologic ***Proleukin*** (aldesleukin), and the multiple sclerosis drug ***Betaseron*** (interferon beta-1b).

Novartis expects to achieve annual cost synergies of $200 mil. from the integration of Chiron within three years, the firm said.

Under the agreement, subject to shareholder and regulatory approval, Novartis would pay approximately $5.1 bil. in cash for Chiron's roughly 113 mil. outstanding shares. Novartis already owns a 42.2% stake in Chiron, stemming from a 1995 transaction.

The $45 per share bid represents a 23% premium over Chiron's Aug. 31 stock price, when Novartis made its original bid. Novartis had previously offered $40 per share – a 10% premium totaling $4.5 bil. That bid was rejected by Chiron's independent directors Sept. 5 as being "inadequate."

The deal marks the second high-profile acquisition of a vaccine manufacturer by a major pharma company this year. GlaxoSmithKline announced the acquisition of vaccine manufacturer ID Biomedical Sept. 7 ("The Pink Sheet" Sept. 12, 2005, p. 22).

Novartis recently closed the mergers of Eon Labs and Hexal into its generics unit Sandoz ("The Pink Sheet" Feb. 28, 2005, p. 21).♦♦

Avian Flu Plan From Administration Places Vaccines First, Antivirals Second

The Bush Administration's pandemic flu preparedness plans call for a dramatic expansion in the stockpiling of antivirals, an increase expected to be largely paid for by the states.

According to the HHS plan which was announced Nov. 2, "quantities of antiviral drugs sufficient to treat 25% of the U.S. population should be stockpiled."

This translates to enough doses for approximately 74 mil. people, up from the 4.3 mil. doses the federal government has presently contracted.

While the prospect of a significant increase in stockpile sales may initially seem appealing to antiviral manufacturers, the Administration's plan could create a situation in which firms are required to go through multiple negotiations with individual states, which could focus more attention on product pricing.

President Bush's pandemic flu preparedness plan includes $1.2 bil. for vaccine stockpiling and $1 bil. for antiviral stockpiling.

Individual states will shoulder 75% of the cost of antivirals for their residents in the case of a pandemic avian flu outbreak, with the federal government contributing the remainder of the costs, according to the HHS plan.

Part of the administration's $7.1 bil. strategy is a request for $1 bil. in antiviral stockpiles "so that we have enough on hand to help treat first responders and those on the front lines, as well as populations most at risk in the first stages," President Bush said during a Nov. 1 event at the National Institutes of Health.

However, "antiviral drugs cannot prevent people from contracting the flu." Therefore, as "the foundation of our pandemic response," the President is also asking Congress for $1.2 bil. for HHS to purchase 40 mil. doses of avian flu vaccine, which would be sufficient to inoculate 20 mil. people.

At a Nov. 2 Senate Appropriations/Labor-HHS Subcommittee hearing, Sen. Tom Harkin (D-Iowa) said that the plans released by the White House and HHS fail to adequately fund states' stockpiling and preparedness needs.

The plans allocate $100 mil. for state and local preparedness efforts.

Harkin attached an $8 bil. amendment to the HHS appropriations bill which placed a larger emphasis on state and local preparedness ("The Pink Sheet" Oct. 31, p. 28).

Harkin said that he fears state preparedness efforts could suffer in light of a financial burden. "It seems that the money will be allocated based on states' ability to pay."

"How are you going to ask Louisiana right now to come up with this money?" he asked HHS Secretary Michael Leavitt.

Leavitt responded: "We want to make sure [states are] buying into pandemic preparation and not just looking for a check from the federal government to put into the federal stockpile."

He added that the preparedness plans permit the federal government to assist state preparation efforts, but that "public health is a state and local function."

"We want them to have a plan, and we want them to have access to those antivirals and to be able to do it in a way that's consistent with their other preparation."

Leavitt also said that the states will be solely responsible for dissemination of antivirals. "We expect we'll be placing the bulk of the entire stockpile of federally purchased antivirals in the states."

However, "there is a view that antivirals [such as Roche's ***Tamiflu***] are synonymous with preparation; that just isn't the case. It is an important part of a comprehensive plan, but there are limits to it."

Roche and GlaxoSmithKline (which markets ***Relenza***) have seen considerable demand growth as governments and private entities make plans for a potential outbreak. Both firms have been emphasizing a willingness to partner with outside manufacturers to meet demand, but the firms want to maintain control over the production process.

Roche's production of Tamiflu (oseltamivir) was recently boosted by FDA approval of an additional specialized Tamiflu manufacturing site.

The approval allows Roche to manufacture Tamiflu in the U.S. for the first time. "By mid-2006, global production capacity for Tamiflu will have increased eight to 10-fold over 2003," the firm said Nov. 1.