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For FDA, Congress Readies a Bitter Pill

By Drew Armstrong, CQ Staff

Once every two years, the Food and Drug Administration dispatches teams of inspectors and lab technicians to every licensed drug plant in the United States to make sure manufacturing, quality control, and packaging and labeling systems all comply with federal regulations.

These sometimes surprise white-glove visits have bestowed an imprint of safety and reliability on the domestic drug manufacturing chain and led many experts to equate the FDA's seal of approval with a "gold standard" for the industry.

That's a marked contrast to the situation abroad, though, where the FDA lacks the clout and resources to show up on plant doorsteps, and instead must rely on an ad hoc system of checks by volunteer evaluators to track the quality and purity of drugs, vaccines and other products that are exported to the United States.

Inspection teams in China, India and other developing nations must make appointments to visit facilities and often depend on company representatives to comply with their requests and to provide translation services. Moreover, the agency does not have a firm fix on how many foreign establishments are subject to its so-called Good Manufacturing Practices inspections — estimates vary between 3,000 and 6,800 — and typically sends inspectors to visit about 7 percent of the plants it's aware of in any given year, according to government audits.

The contrast between foreign and domestic drug oversight, and the potential for safety problems it creates, was underscored by the recent health scare surrounding the popular blood thinner heparin. Top agency officials have admitted that before giving Baxter International Inc. the go-ahead to sell the medicine in the United States, they failed to inspect a plant in China that produced contaminated versions of the drug's active ingredient. At least 19 patients died, and hundreds others became severely ill.

SAFETY FIRST?: A Chinese worker loads pill capsules at the Tongrentang drug factory in Beijing last August. Safety concerns about Chinese drug manufacturing are prompting some in Congress to call for more overseas inspections by the Food and Drug Administration. (AFP \ TEH ENG KOON)

The heparin crisis has triggered a new round of calls for an overhaul at the FDA. The agency has undergone a series of congressionally mandated changes over the past two decades, often in response to problems discovered in food or drug supplies.

But compared with what lawmakers are planning now, those have been fairly modest. This time, there is reason to believe a real overhaul is in the FDA's future, if not this year, then perhaps in the next administration. First, there is wide consensus that the agency needs a restructuring that would enable it to keep up with a rapidly changing and increasingly

global food and drug supply chain. Second, high-profile crises like the one involving heparin have given lawmakers and critics of the FDA the best kind of A-ammunition to argue that the agency is insufficiently managed and cozy with the industry.

And then there is John D. Dingell, the powerful Michigan Democrat and chairman of the House Energy and Commerce Committee. Dingell is readying a fundamental FDA overhaul plan that, even if not enacted this year, will probably serve as a model for a Democratic presidential administration — and possibly even a Republican one.

Dingell would expand the FDA's regulatory authority to the developing world by setting aside money for a team of full-time inspectors overseas; authorizing country-of-origin labeling on drugs, medical devices and food products; and levying new user fees on manufacturers to finance spot checks at overseas drug plants and at U.S. points of entry. He is also holding oversight hearings to prod the agency's political leaders to make administrative changes or face pressure to resign.

The goal, says Dingell and Senate Finance ranking Republican Charles E. Grassley of Iowa, another prominent agency critic, is to refocus the agency's core mission beyond reviewing new products and make the FDA a more proactive regulatory body capable of keeping Americans safe from risks throughout a product's life cycle.

"They haven't got the vaguest idea who's producing these things, whether they're safe or not, whether they're using good A-manufacturing practices or not . . . or anything else that might relate to seeing to it that the safety of the American people is attended to," Dingell said of the agency's oversight of heparin and other imports.

Grassley is just as critical, saying the FDA's once-sterling reputation has become tarnished. "I believe the FDA was the world standard for decades and decades, but it's not today," he said. "Oversight is what's going to keep the FDA changing if it's going to change at all, and that's a pretty big 'if' as far as I'm concerned."

Senior FDA officials say they're taking steps to address the problems, but dismiss the need for tough new congressional directives to ensure drug safety. Commissioner Andrew C. von Eschenbach, in fact, suggests that Congress' past practice of layering new responsibilities on the agency in areas such as food and consumer product safety has left the FDA hard-pressed to keep the public safe.

"It is no secret in Washington that as the FDA's responsibilities have grown, the resources devoted to them have not kept pace. Strengthening the FDA for this new century will require an investment, providing our agency with a budget and authorities that are commensurate with the scale and scope of our mission," von Eschenbach said Feb. 29 in a speech at the National Press Club.

Taking Another Cut

Congress had an opportunity to impose major changes on the agency last year, when it renewed the 1992 Prescription Drug User Fee Act (PDUFA), which governs the prescription drug-approval process. Though Democrats approved incremental fixes, giving the FDA first-

time authority to require clinical studies of drugs after they are approved and to levy fines on manufacturers that don't adequately evaluate potentially dangerous side effects of some drugs, the lawmakers essentially punted on the question of imported drug safety, partly because they were caught in a crush of other A-legislation.

"We were under a bit of a time crunch with PDUFA," said Democratic Rep. Bart Stupak of Michigan, chairman of the House Energy and Commerce Oversight and Investigations Subcommittee. "We didn't get to put the time and effort we want in FDA reform."

Until the heparin scare, the need for such changes might not have been obvious. Under international agreements, the FDA had the ability to inspect manufacturing plants overseas. In fact, its plant certifications are a prerequisite for approving any new drug. But because the agency does not have full-time inspectors abroad, there is seldom any meaningful oversight after an initial inspection. It falls to the plant owner and the host country to keep operations up to code — a potential gap in the regulatory process, considering that some of those products, including the key ingredient in heparin, are made from animal organs.

The regulatory breakdown surrounding the blood thinner, not long after incidents involving tainted pet food and fish from China, has refocused Congress on the FDA's capabilities. Many public health experts say that is overdue at a time when China and India produce nearly 40 percent of the active ingredients in drugs consumed in the United States. Many of the substances are found in generic versions of name-brand products, ranging from antibiotics to asthma drugs.

TURNING UP THE HEAT: FDA critics Stupak, Grassley and Dingell (left to right) contend the agency's culture puts quick drug approvals ahead of stringent safety reviews and are pressing for major changes. (CQ \ SCOTT J. FERRELL)

In the case of China, the FDA acknowledges that regulators there do not inspect plants that produce drugs exclusively for export, meaning the agency's initial evaluation often amounts to the last check.

"You're importing from countries that have the regulatory framework that we had at the turn of the previous century," said David Kessler, who served as FDA commissioner from 1990 to 1997.

The FDA estimates that there are 566 plants in China making drugs or drug ingredients that are consumed in the United States. In fiscal 2006, the agency inspected 17 of those establishments. The Government Accountability Office, which issued three reports in late 2007 critical of the FDA's oversight, estimates that at that pace, it would take the FDA 13 years to perform at least one inspection of every foreign plant it is aware of.

It would be one thing to simply tick uninspected plants off a giant "to do" list. But tracking manufacturing flaws and product impurities is a much more imposing task because of the hydra-headed nature of international drugmaking.

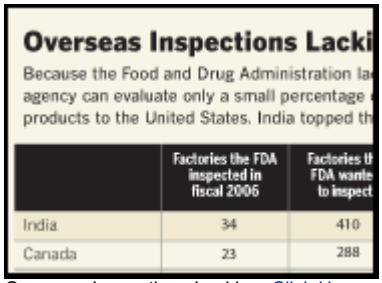
Consider that Deerfield, Ill.-based Baxter International obtained much of heparin's primary

ingredient from four Chinese manufacturers. The raw product is then shipped to processing plants, where it's converted into a sodium solution that can be injected into patients. (Heparin is administered in large doses to hundreds of thousands of patients with kidney disease while they undergo dialysis.) But instead of the pure heparin the company thought it was getting, the tainted batches contained a heparin-like substance, oversulfated chondroitin sulfate, which is extracted from cow and pig tissue and could have been added as an inexpensive filler to boost the volume of the drug being provided to Baxter.

The FDA first learned in January that Baxter International had advised the FDA in December that some patients were suffering unusual reactions. By February, the company had voluntarily pulled the drug from the market. But FDA inspectors have not yet determined the point at which the contaminant entered the supply chain.

The contamination is eerily reminiscent of the pet food safety scare last year, in which imported dog and cat food was found to be tainted with melamine, a chemical commonly added to animal feeds in China that previously was thought to be non-toxic in low doses. The substance is believed to have caused organ failure in some pets who ate the food.

"What do you think is going to happen if your active ingredients are being produced in plants overseas that have no regulation?" Kessler asked. "Should that be any surprise? You could predict that there would be risks."



Overseas Inspections Lacking: Click Here to View

The tainted active ingredient in Baxter's heparin came from the Changzhou SPL plant, which had been on a list of FDA-approved Chinese facilities. But that was due to a clerical mistake: The FDA mixed up the Chinese name of the plant with another that had passed an inspection. In fact, the suspect active ingredient came from a facility that had never been evaluated.

Public health experts and former agency officials cite a litany of ways in which the foreign oversight process is broken, including insufficient funds, a shoddy information technology system and benign neglect by top agency managers.

"Heparin is a pretty good example that the FDA can do a pretty good job reacting, but the prevention is a whole other matter," said Carl Nielsen, the agency's former director of import operations and policy, who left to become a consultant in 2005. "They're just not designed to stay ahead of foreign industry," he added, referring to the agency's lack of an overseas presence.

The agency's defenders depict it as a beleaguered bureaucracy that's frequently whipsawed between conflicting priorities. They say Congress put a priority on faster new drug reviews and approvals at the expense of safety considerations, prompted by the AIDS crisis in the late 1980s and early 1990s.

Congress enacted PDUFA in 1992 to create a dedicated funding stream for new drug reviews by forcing drug companies to pay a user fee with every new drug application. The fees greatly expanded the FDA's resources to review new medicines and cut median review times from about three years in the late 1980s to about 16 months a decade later.

"The FDA focuses where the Congress focuses," said Rep. Joe L. Barton of Texas, the ranking Republican on the Energy and Commerce Committee. "If we're focusing on drug and device review times," that's what the agency will do, he said. "We didn't focus as much on the food imports and drug imports."

Indeed, while the agency fortified and streamlined its U.S. drug evaluation program, pharmaceutical manufacturers were expanding operations to cheaper labor markets overseas and opening up new supply channels. Experts say the FDA has kept a careful watch on the applications for new drugs but did not expand its reach to identify new manufacturing defects or possible health risks from flawed medicine, unless they arose as part of clinical trials on drugs the agency was already evaluating.

"The costs of the prescription-drug user fees are that for many years, the agency focused on meeting the standards in the Prescription Drug User Fee Act," Kessler said. "It drew attention and resources from other aspects of the agency's portfolio."

Most congressional Democrats and some Republicans such as Grassley say the problems stem from an agency culture that is too focused on meeting deadlines and that encourages cozy relations between regulators and the drug industry.

"The logic behind it was sound," Stupak said of the expedited drug approval laws, adding, "But we've allowed them to use it for everything." There is a consensus among agency critics that a "culture of approval" pervades the FDA bureaucracy, with decreasing emphasis on thorough science and safety.

Nielsen says the agency's reputation for safety and competence has suffered a major blow with the heparin scare, opening the door for ambitious overhaul efforts.

"There's finally the disclosure of what FDA's capacity is," said Nielsen. "I think the public and even the Hill have this presumption that the FDA, bless their heart, is really trying to get this done."

He added: "I call it the FEMA-Katrina syndrome. . . . Globalization, a voluminous increase in imports, the movement of industry overseas has created a massive storm of products that are made overseas, and all of the weaknesses are showing through."

Modernizing the Mission

The idea of wrenching the agency into this new world is being driven by Dingell, the tenacious dean of the House and a longtime adversary of drug companies and regulators alike. The 81-year-old chairman is writing a wide-ranging plan patterned on legislation he introduced last year — before the heparin scare — at the same time that he is advancing legislation to give the FDA authority to regulate tobacco products.

Dingell has been characteristically quiet about his legislative plans. But he addressed the heparin scare and related safety concerns in a scathing Feb. 14 letter that he and other Energy and Commerce Democrats sent von Eschenbach, characterizing the FDA's efforts as lacking in almost every category.

"Clearly to date, you have been unable to assure the public these products are safe because you have been unable to competently address the systemic weaknesses in this program," the letter read. "Because of such inaction, American lives are unnecessarily being placed at risk."

Specific details of the plan are still being worked out, but the general parameters are known. They go far beyond the customary congressional prescriptions — more money to fortify surveillance in a particular area, for example — and seek to make the FDA's core mission and its organization more compatible with the complicated world it's supposed to oversee.

"They've established with great clarity that they have neither the budget nor resources," Dingell said. "The leadership of the agency is engaged in the most diligent form of self-deceit that you can find this side of damnation."

The plan would create a system to fund foreign drug plant inspections by levying new fees on manufacturers who make medicine abroad or use ingredients that are processed overseas. Dingell's 2007 bill envisioned raising $300 million annually to cover the inspection and testing of the drugs upon entry into the United States and to inspect overseas facilities.

Dingell would also give the agency funding for its first full-time foreign drug inspection force to replace the volunteers it now relies on to evaluate far-flung factories. It is unclear how many individuals the FDA would employ, or where Dingell proposes to find the money to pay them.

Dingell and Stupak believe imposing fees on drug companies could win the support of some in the Bush administration who adamantly oppose spending more general revenues to enlarge the FDA's workforce. But the White House in the past has expressed reservations about imposing fees on industry, considering them the equivalent of new taxes. A spokesman said the administration could not comment until Dingell introduced a bill.

Even if Dingell and the administration agree on a financing mechanism for more inspections, experts question how effective the reviews would be. Grassley is concerned that having big drug companies fund plant inspections, much as they do drug reviews under PDUFA, will make the agency beholden to manufacturers and more apt to overlook production flaws.

"Let me compare it to having meatpackers pay for meat inspection with the USDA," Grassley said, referring to the Agriculture Department. "That's always been in presidents' budgets over a long period of time. We generally don't buy it because we think people's confidence in our meat supply will be diminished."

Some former FDA officials believe it will take a strong push from Congress to ramp up inspections, because von Eschenbach and other top officials prefer to forge stronger collaborations with Chinese regulators and maintain just a handful of FDA staff members overseas.

"There's always been a lack of funding and availability for FDA inspectors to inspect international facilities," said one former high-ranking FDA executive-turned-lobbyist, who spoke on the condition that he not be identified. "The FDA puts a lot of responsibility on the manufacturer to make sure whatever products they're bringing in meet the specifications."

Dingell's plan isn't confined to the agency's overseas responsibilities. It would bar the FDA from closing any of the 13 field labs it maintains across the country to evaluate whether drugs and food products comply with federal standards. The agency cut its field inspection staff by 16 percent between fiscal 2003 and 2007 to save money and announced plans to close seven of the labs last year. It backed off after members of Congress, such as Dingell, voiced strong opposition.

Dingell's plan would also crack down on companies that violate drug import regulations. Manufacturers and importers could be fined as much as $500,000 for bringing contaminated or adulterated food or drugs into the country, and individuals could be subject to fines as high as $100,000 for similar offenses.

The Senate also has plans to fortify the agency's oversight, but not with a single legislative fix. Its fiscal 2009 budget resolution would add $375 million to the agency's budget, most of which would be used to buttress existing inspections. "That won't solve it. It will help," said Grassley.

The agency would probably need both sources of new money — Dingell's proposed user fees for inspections and the Senate funds — to begin confronting the issue. The Senate's $375 million line item is almost equal to the amount a recent government audit said was required to improve the agency's information technology systems, hire and retain key personnel, and maintain its current drug safety functions.

Dingell's plan would also address the importation of food products by making importers pay fees to finance tests and overseas inspections. And his plan would notably give the agency the authority to restrict food imports only to those ports of entry that have an FDA field office, with some exceptions for low-risk items. The plan would give the FDA first-time authority to automatically order a recall of imported foods suspected of posing a danger, instead of counting on manufacturers or importers to voluntarily recall the products.

Finally, Dingell's plan would require that imported foods, drugs and medical devices be labeled with the countries of their origin, A-replacing the voluntary system currently in place. Such proposals have triggered controversy in the past, because they require additional record-keeping and because some products contain ingredients from multiple countries.

The plan would stop short of another controversial proposal — splitting off the FDA's food inspection functions into an independent agency — possibly because such a move would erode the House Energy and Commerce and Senate Finance committees' jurisdiction over food safety.

Drug and biotech industry groups are closely watching Dingell and Grassley's effort and publicly echoing von Eschenbach's contention that the agency primarily needs more money to carry out its widespread duties.

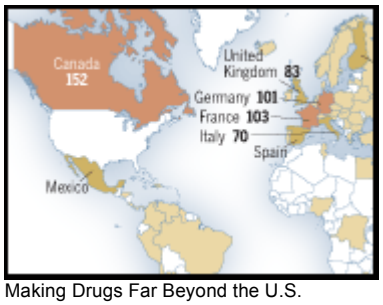
"We believe it is in the best interest of the public health and safety for Congress to significantly increase appropriated resources to help the FDA," Ken Johnson, the senior vice president of the Pharmaceutical Research and Manufacturers of America, said in a statement.

The Agency's View

The FDA's leaders acknowledge the dramatic new world they are confronting: In his Feb. 29 address at the National Press Club, von Eschenbach used the word "change" or "changing" at least 37 times in describing the agency's efforts or safety risks around the globe. But though he conceded in a March 26 address to the Food and Drug Law Institute's annual conference in Washington that the FDA may "fail in its mission to protect and promote the health of every American," von Eschenbach has yet to ask Congress for new powers over drug imports — even though he has done so for foods.

"The FDA of the 20th century is not adequate to regulate the food and drugs of the 21st century, a time when we live in a world where we can catch a fish in Chile today and eat it in Chicago tomorrow," von Eschenbach said Feb. 29. "The perils are many, with . . . drugs and vaccines containing ingredients obtained from sources around the world and manufactured and distributed through complex supply chains, as in the recent case of heparin."

Even some agency critics concede that the agency responded rapidly to the heparin scare once it became apparent, and quickly sent inspectors to China to assess the scope of the problem.



Making Drugs Far Beyond the U.S. Border: Click Here to View

The agency declined repeated requests to interview any FDA officials for this article, including von Eschenbach. In a statement, von Eschenbach said, "The need for radical and rapid change over the past two years has guided a systemic and systematic transformation at FDA. The challenges I face today as commissioner are perhaps unlike those of my predecessors as I attempt to guide the agency in responding to its day-to-day exhausting responsibilities while simultaneously guiding this transformation."

Murray Lumpkin, the FDA's deputy commissioner for international and special programs, said in a conference call with reporters in response to the heparin scare that agency personnel are collaborating with Chinese regulators more closely than in the past to head off future crises.

"I would characterize it as very cooperative. This is the kind of relationship that did not exist during the time of melamine a year ago," Lumpkin said, referring to the pet food contamination scare.

Over the next 18 months, the agency plans to place more staff in China as part of an initiative dubbed "Beyond Our Borders" that calls for deploying a small corps of inspectors in five foreign regions. The FDA has also taken the lead role in Bush administration efforts to forge an agreement with Chinese regulators that requires any exported food or drugs to meet U.S. standards. The agreement would still rely on Chinese inspectors to do the actual enforcement.

It's unclear how much the initiative would improve safety. While there would be more permanent FDA staff overseas, experts say the agency would still lack the resources to examine the thousands of plants. And absent an expanded budget dedicated to such a program, the agency is not likely to dedicate serious resources on its own. That doesn't sit well with Dingell or his allies, such as Stupak.

"Quite frankly, I think it's mostly PR," Dingell said of the Beyond Our Borders initiative. "I

think it's either pathetic or comical, or both. I think it's nothing that will accomplish anything that you or I will be able to identify."

Forcing Change?

To bring agency chiefs more in line with their thinking, Dingell, Stupak and Grassley are planning oversight hearings and launching investigations that are designed to raise questions about the judgment of von Eschenbach and his lieutenants. The goal is twofold: to build political support for legislative changes, even among staunch agency defenders, and to try to force von Eschenbach to resign.

A Feb. 12 Energy and Commerce oversight hearing, for example, focused on the FDA's controversial 2006 decision to approve the antibiotic Ketek over the objections of some of its career scientists and product evaluators. The agency instead accepted clinical trial results based on fabricated data from a physician hired by the manufacturer, Sanofi-Aventis LLC, who made up patient entries and results.

There is evidence that the experience with Ketek might prompt lawmakers who are generally averse to regulation to consider more of it in the case of the FDA. During the hearing, Texas Republican Rep. Michael C. Burgess, who fought against tougher federal regulations during last year's PDUFA reauthorization, appeared increasingly exasperated, and at one point asked, "When are we going to get to the point where we actually legislate on this issue?"

Grassley has launched 10 investigations into various aspects of the FDA's regulatory decisions, while Stupak and Dingell have started at least half a dozen. In addition, California Democrat Henry A. Waxman, chairman of the House Oversight and Government Reform Committee, is weighing whether to launch his own inquiries. The ongoing investigations take up such issues as whether physicians who examined drugs and devices for FDA approval also had ties to drug companies and whether FDA evaluators intentionally overlooked fraudulent data submitted as part of drug reviews.

"They've lost that fervor to be a regulatory agency," said Connecticut Democratic Rep. Rosa DeLauro, another frequent agency critic and chairwoman of the House Appropriations subcommittee that oversees the FDA budget.

One Energy and Commerce inquiry concerns whether von Eschenbach committed perjury during a March 22, 2007, subcommittee hearing on Ketek, by giving misleading statements about what the agency knew about falsified records and what information regulators factored into their decision to approve the drug. Should the panel conclude that von Eschenbach did, the case could be referred to the Department of Justice.

Stupak wants nothing short of mass resignations within FDA's senior leadership, saying, "I want them all gone. Get them out of there." While others in Congress are more measured in their remarks, they are pleased that Dingell has put the FDA in the spotlight, saying change is overdue. "I say praise the Lord that they're doing the work that they're doing," Grassley said of Dingell and Stupak's efforts.

Lawmakers also say they see a pattern of senior FDA officials squelching dissent within the

ranks of career employees — a charge agency officials deny. That is important, experts say, because the FDA has long relied on its scientific expertise. A strongly worded safety warning usually has been sufficient to discourage consumers from using a suspect medicine — and to force manufacturers to pull a product, in spite of the fact that the FDA cannot actually order the recall of a drug.

"They have this idea that 'we're the FDA and everybody trembles,' but everybody laughs behind their backs, like, 'You don't scare us. We know you're not going to do it. You threaten a lot but you're not going to do it,' " Stupak said of the current regime.

The perceptions are fueled by accounts from some former agency officials. David Ross, the FDA's former associate director of oncology drug products, says he was ordered by senior managers not to talk about his concerns with the Ketek trials.

"People in the field were stunned when Ketek got approved," Ross said. "There's an absolute lack of integration between the inspection-slash-enforcement functions and the review functions," said Ross. "Manufacturing inspections and chemistry are off in their own world. They get done at the last minute. . . . Nobody wants to hear, 'We're ready to approve, but there's a problem with manufacturing.' "

But he added, "At the end of the day, if you can't make the drug to spec, then all those clinical results are meaningless."

Ross said the agency's broader mission has been compromised by a singular focus on getting drugs approved faster. "The underlying disease is there's an obsession with meeting deadlines to the exclusion of all else," said Ross.

Some observers take a more nuanced position, noting that every drug has benefits and risks, and that policies that encourage bringing more new products to market inherently protect the public health.

"You either come down to the side of corporate America and you can trust them, or you feel like corporate America is fundamentally flawed and you can't trust them," says the former high-ranking FDA executive-turned lobbyist.

To Kessler, the future of the agency rests on whether its leaders have the will to exercise regulatory powers. With enough prodding and resources from Congress, the former agency chief believes, the FDA can restore its clout and become the world's premier consumer safety agency.

Recalling a 1991 case in which the FDA seized 2,000 cases of orange juice made from concentrate that had been labeled as "fresh" in violation of FDA regulations, Kessler said, "You could certainly poke fun at the day we seized thousands of gallons of Citrus Hill orange juice. But all it took was one federal marshal with a warrant and some yellow tape to change what was put on the food label in this country."

FOR FURTHER READING: *Tobacco regulation (HR 1108, S 625), p. 886, 2007 CQ Weekly, p. 2384; food safety, CQ Weekly, p. 544; Senate fiscal 2009 budget resolution (S Con Res 70), p. 633; drug approval law reauthorization (PL 110-85), p. 48; original law (PL 102-571), 1992 Almanac, p. 418; Dingell's 2007 FDA bill is HR 3610.*