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U.S. HOUSE OF REPRESENTATIVES
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Fact Sheet

FDA's Testimony to Congress on the Flu Vaccine Shortage

On November 17 and 18, 2004, acting FDA Commissioner Dr. Lester Crawford testified before two House committees that FDA bore no responsibility for the flu vaccine shortage, maintaining that FDA made no mistakes that contributed to the loss of half the U.S. flu vaccine supply. Yet a review of the record shows that Dr. Crawford's testimony disregarded FDA documents, contradicted statements made by senior FDA staff, and distorted facts about FDA's regulatory system. As explained in this fact sheet:

- Dr. Crawford testified that problems found by FDA at the flu vaccine manufacturing plant in June 2003 were "corrected" by the company. In fact, FDA inspectors determined in October 2004 that a number of key problems were "not corrected from previous inspection of 2003."

- Dr. Crawford testified that the problems found at the June 2003 inspection had no connection to the 2004 vaccine shortage. In fact, the manufacturer of the flu vaccine, Chiron Corporation, identified as the source of contamination of this year's vaccine supply a specific manufacturing weakness that FDA had cited in June 2003, but which was never addressed.

- Dr. Crawford testified that an 80% drop in FDA enforcement actions against manufacturers of biologics (including vaccines) that occurred after 2001 had nothing to do with a change in FDA enforcement policy. He stated that the steep falloff in enforcement could be explained by the fact that "there are not as many people to regulate." In fact, the number of FDA-regulated biologic manufacturers has declined only slightly from 2001 to the present.

- Dr. Crawford testified that after reports of bacterial contamination became public in August 2004, there was "no need" for FDA to communicate with British regulators about the Chiron plant because FDA had "all the information we were asking for." In fact, British regulators obtained critical information that was not available to FDA because the British regulators conducted two on-site evaluations and reviewed the company's draft internal investigation report.

- Dr. Crawford testified that FDA would have shut down the Chiron facility "a few hours later" after the British did "due to the time change." In fact, there is no support for the claim that FDA — which was taken entirely by surprise by the British action — would have acted within hours. According to FDA's chief enforcement official, even under the best case scenario, FDA would have had to fly inspectors to England and wait for their inspection report before acting.

- Dr. Crawford testified that FDA's lot release program fully protects the public from any tainted vaccine. In fact, lot release involves testing a sample of vaccine and needs to be coupled with good manufacturing practices to ensure safety.

The June 2003 Inspection

In June 2003, FDA inspectors identified 20 problems in the manufacturing practices of the flu vaccine manufacturing plant in Liverpool, England, which was then in the process of being acquired by Chiron.[1] Asked by Rep. Waxman about this inspection report, Dr. Crawford testified that the company "responded very well, they corrected the problems."[2] Asked by Rep. Eshoo, "You seem to be insisting that there is not any nexus between what was found in 2003 in contaminations, and what happens in 2004, is that correct?" Dr. Crawford responded, "that is clearly correct."[3]

Dr. Crawford's testimony, however, is contradicted by FDA's October 2004 inspection report of the same manufacturing plant. This report details several deficiencies in manufacturing practices that were "not corrected from previous inspection of 2003."[4] For example, FDA inspectors found that the plant had failed to address a vulnerability to contamination at the connections where vaccine passed from one sterile vaccine tank to another. In June 2003, FDA had cited the company for failing to study whether the number of these potentially hazardous connections could be reduced. In October 2004, FDA inspectors determined that "there is no documentation that adequate corrective action has been conducted."[5] FDA inspectors also found that problems investigating high bacterial levels were not remedied following the 2003 inspection, observing that the company was still unable to find the root cause of contamination problems.[6]

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[1] U.S. Food and Drug Administration, *Inspectional Observations, Form 483, Evans Vaccines, Ltd.* (June 10, 2003).

[2] House Committee on Government Reform, *Hearing on the Nation's Flu Shot Shortage*, 108th Cong. (Nov. 17, 2004).

[3] *Panel I of a Hearing of the Health and Oversight and Investigations Subcommittees of the House Energy and Commerce Committee*, Federal News Service (Nov. 18, 2004).

[4] *Inspectional Observations, Form 483, Evans Vaccines, an Affiliate of Chiron Corporation* (Oct. 15, 2004).

[5] *Id.*

[6] *Id.*

When presented with the October 2004 inspection report, Dr. Crawford responded: "The 2003 production was okay. That proves that they had made the corrections."[7] This response is false. Flaws in good manufacturing practices can exist even when tests of final product do not show contamination. According to the World Health Organization, "Good quality must be built in during the manufacturing process; it cannot be tested into the product afterwards."[8]

In the case of the Chiron plant, uncorrected flaws in manufacturing practices proved to be significant. According to FDA, the company's own investigation identified faulty connections between vaccine tanks as the most likely entry point for contamination of this year's flu vaccine.[9] Had this and other problems been fixed when they were noted by FDA 2003, the flu vaccine shortage might have been mitigated or prevented.

Change in Enforcement at FDA

Following the June 2003 inspection, senior FDA officials "downgraded" the recommendation of FDA inspectors for official enforcement action to a request for voluntary action.[10] The "downgrading" was consistent with an abrupt 80% drop in the number of official enforcement actions taken by FDA against makers of biologic drugs, including vaccines, after a new level of review was added by political appointees in the fall of 2001.[11] See Figure 1.

When presented with this information, Dr. Crawford testified that the decline in the number of enforcement actions was the simple result of consolidation in the industry. He stated, "Well,

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[7] *Panel I of a Hearing of the Health and Oversight and Investigations Subcommittees, supra* note 3.

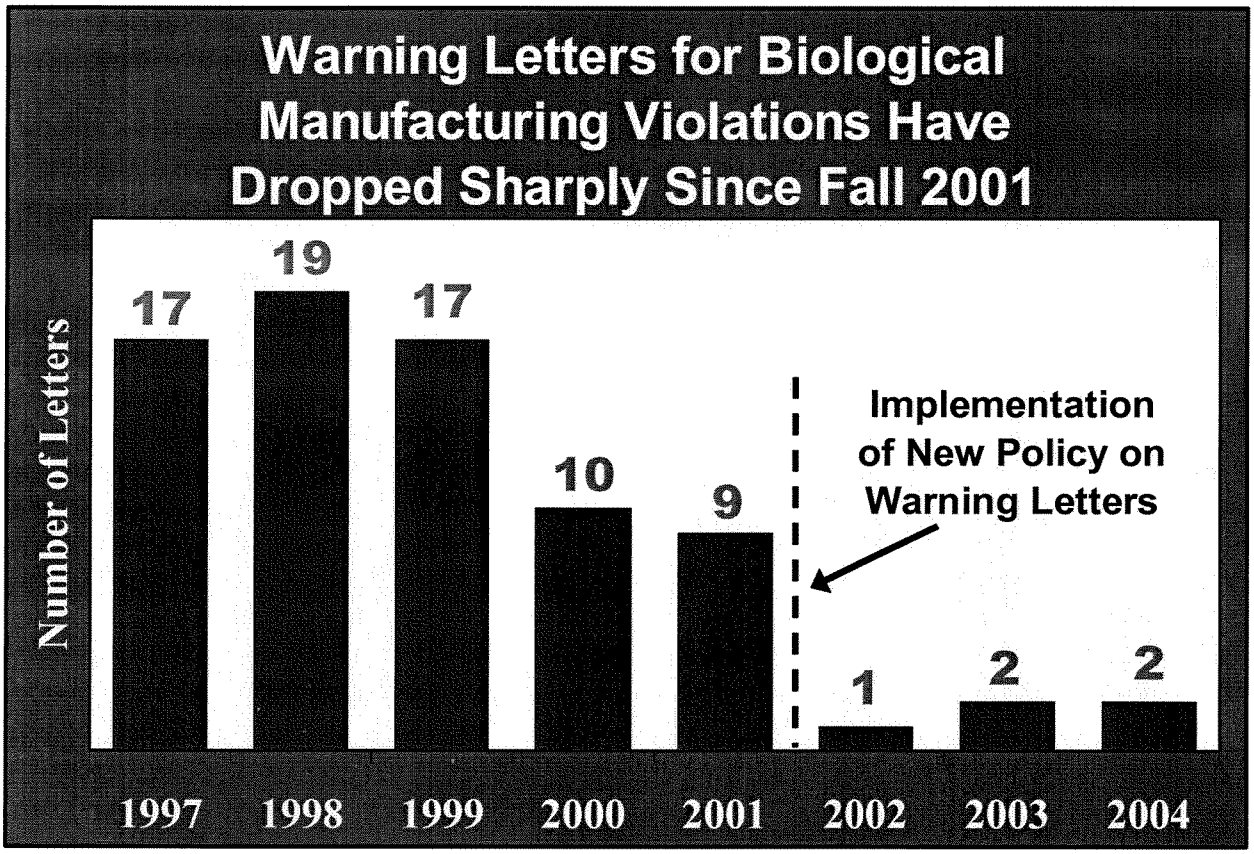
[8] World Health Organization, *Good Manufacturing Practice (GMP) in Pharmaceutical Production* (July 28, 2004) (online at http://www.who.int/medicines/organization/qsm/activities/qualityassurance/gmp/orggmp.shtml).

[9] U.S. Food and Drug Administration, *supra* note 4, at 5.

[10] U.S. Food and Drug Administration, Briefing for Government Reform Committee staff (Nov. 15, 2004); John Eltermann, U.S. Food and Drug Administration, *Notes of Internal FDA Discussions* (Oct. 5, 2004).

[11] The new policy provided for review of proposed enforcement actions by the FDA Chief Counsel. *New FDA Procedure May Lead to Fewer, Stronger Agency Warnings*, Bloomberg News (Dec. 13, 2001). The data on the decline in warning letters was obtained by counting warning letters for manufacturing violations issued by the Center on Biologics Evaluation and Research. *See* Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Warning Letters (2004)(online at http://www.fda.gov/cber/efoi/warning.htm); and U.S. Food and Drug Administration, Warning Letters by Issuing Office (2004)(online at http://www.accessdata.fda.gov/scripts/wlcfm/indexissuer.cfm). Warning letters for misbranding, research irregularities, and other non-manufacturing problems were not counted.

there is not as many people to regulate, not as many companies . . . we have not lessened our profile in terms of evaluating these companies."[12]



Dr. Crawford's response is wrong. The number of biologics manufacturers did not fall by 80% at the end of 2001. According to FDA records, there has been only a modest decline in the number of FDA-regulated establishments that make biologics. In April 2001, there were 340 such establishments.[13] There were 326 in July 2002, 320 in April 2003, 291 in January 2004, and 274 in October 2004.[14]

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[12] House Committee on Government Reform, *supra* note 2.

[13] U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, *Licensed Establishments and Products* (Apr. 4, 2001) (online at http://web.archive.org/web/20010620230424/http://www.fda.gov/cber/ep/part1.htm).

[14] U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, *Licensed Establishments and Products* (July 19, 2002) (online at http://web.archive.org/web/20020805101104/http://www.fda.gov/cber/ep/part1.htm); U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, *Licensed Establishments and Products* (Apr. 8, 2003) (online at http://web.archive.org/web/20030415044726/http://www.fda.gov/cber/ep/part1.htm); U.S. Food and Drug Administration, Center for

The number of inspections of biologics manufacturers has also not dropped substantially. According to FDA records, the number of FDA inspections of biologics manufacturers rose from 2,084 in fiscal year 2001 (which ended just before the new policy took effect) to 2,195 in fiscal year 2002.[15] There subsequently were 2,151 inspections in fiscal year 2003, an estimated 2,022 in fiscal year 2004, and plans for 2,255 in fiscal year 2005.[16]

Communication with British Regulators

After Chiron announced in August 2004 that several lots of vaccine had been contaminated by bacteria, both British regulators and FDA officials had jurisdiction to investigate. Because of confidentiality laws, British regulators could not share information about their investigation without permission from the company. FDA never sought to obtain this permission. Dr. Crawford testified that there was "no need" to do so, because FDA had "all the information we were asking for."[17]

In fact, FDA's efforts in understanding the conditions at the Chiron facility lagged considerably behind those of the British regulators. After the August announcement by Chiron, British regulators conducted two on-site visits, convened two high-level committees, reviewed a draft of the company's internal investigation, and shut down the facility for violations of manufacturing standards on October 5, 2004. By contrast, FDA relied almost exclusively on a series of conference calls with the company, conducted no inspections of the facility, did not review the draft of the company's internal investigation, and was taken by surprise by the British action.[18]

Had FDA obtained approval from Chiron to talk to British regulators, FDA would have learned about the ongoing problems at the facility and accelerated preparations for the flu vaccine shortage.

Biologics Evaluation and Research, *Licensed Establishments and Products* (Jan. 15, 2004) (online at http://web.archive.org/web/20040217112652/http://www.fda.gov/cber/ep/part1.htm); U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, *Licensed Establishments and Products* (Oct. 31, 2004) (online at http://www.fda.gov/cber/ep/part1.htm).

[15] U.S. Food and Drug Administration, *Justification of Estimates for Appropriations Committees, Fiscal Year 2003*, 107 (2002); U.S. Food and Drug Administration, *Justification of Estimates for Appropriations Committees, Fiscal Year 2004*, 81 (2003).

[16] *Id.;* U.S. Food and Drug Administration, *Justification of Estimates for Appropriations Committees, Fiscal Year 2005*, 173 (2004).

[17] House Committee on Government Reform, *supra* note 2.

[18] Rep. Henry A. Waxman, Memorandum to Democratic Members of the Government Reform Committee, *Re: Summary of FDA Documents* (Nov. 17, 2004). An FDA official who was present at the plant for another reason received information about the contamination in August. However, this meeting, which took place at the company's request, did not constitute a planned evaluation or inspection.

When FDA Would Have Acted

Dr. Crawford testified that FDA was not far behind British regulators in taking action against Chiron. In response to a question about when FDA would have acted to shut down the facility, he stated, "We asked that the company give us its final data by October 5. That conference was scheduled later on the morning that the U.K. announced its results. So we would have been a few hours later, due to the time change."[19]

Contrary to Dr. Crawford's testimony, there is no support for the claim that FDA would have shut the plant later in the morning of October 5. When the British closed the plant, Secretary of Health and Human Services Tommy G. Thompson said that the Administration "had no idea" that closure of the facility was imminent.[20] Even under the best case scenario, senior FDA officials have said that the earliest this action could have been taken was over a week later.

According to Associate Commissioner for Regulatory Affairs John Taylor, who is in charge of enforcement at FDA, the investigation report from Chiron was due by Friday, October 8. After receiving and reviewing the report, Mr. Taylor told congressional staff, FDA would not have immediately shut the facility. Instead, it would have scheduled an inspection. After the British announcement on October 5, FDA did set up and conduct an emergency inspection as quickly as possible. It occurred from October 10 to 15, 2004. Only after this inspection could FDA have suspended the company's license.[21]

This additional delay would likely have had significant consequences for public health. Across the country, including on Capitol Hill, many organizations scheduled flu vaccination days between October 5 and 15. When the British shut the Chiron facility, these campaigns were canceled so that vaccine could be redirected to those at highest risk. Had the British not acted, there would have been less vaccine available to those at high risk of hospitalization and death from influenza.

The Lot Release Program

Dr. Crawford testified that FDA's lot release program alone would have protected the public by keeping Chiron's vaccine off of the U.S. market. In response to a question from Rep. Bilirakis, he stated, "with our lot release program we would not have allowed it in circulation, or to be marketed."[22]

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[19] *Panel I of a Hearing of the Health and Oversight and Investigations Subcommittees, supra* note 3.

[20] *U.S. Will Miss Half Its Supply of Flu Vaccine*, New York Times (Oct. 6, 2004).

[21] U.S. Food and Drug Administration, Briefing, *supra* note 10.

[22] *Panel I of a Hearing of the Health and Oversight and Investigations Subcommittees, supra* note 3.

This testimony is highly misleading. Under the lot release program, manufacturers test samples from each lot of vaccine prior to sale.[23] According to the World Health Organization, "it is impossible to be sure that every unit of a medicine is of the same quality as the units of medicine tested in the laboratory" by sampling alone. That is why the world's leading regulatory agencies combine product testing with the inspection of facilities for good manufacturing practices. It is the combination of testing with inspections of manufacturing practices that assures safety.[24]

In the case of the flu vaccine, the lot release program could have mistakenly cleared lots of vaccine that included contaminated doses. This did not happen because the British regulators shut the facility on the basis of violations of manufacturing standards.

Conclusion

At the opening of the Government Reform Committee hearing, Rep. Waxman said, "It is essential for FDA to learn from its mistakes. But so far, the Administration has been unwilling to even admit them." FDA has still not provided a candid account of the actions taken by the agency in overseeing the flu vaccine facility in Liverpool, England. Dr. Crawford's testimony before Congress includes multiple evasions and misstatements that are at odds with the FDA's own documents and the statements of other FDA officials. As a result, the agency remains poorly positioned to prevent future threats to U.S. vaccine supplies.

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[23] 21 CFR 610.1.

[24] World Health Organization, *supra* note 8.