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June 6, 2009
By fax to 301-847-3531

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Hamburg:

Subject: Request for investigation by Inspector General of DHHS

We are writing about a specific instance of regulatory failure in the Center for Devices and Radiological Health (CDRH) at the FDA: the case of AM2PAT, Inc., a small company that manufactured and sold syringes. Some of the syringes, as you know, were contaminated by bacteria that caused deaths and serious illnesses that were detected in December 2007. In February 2009 two officials of AM2PAT were sentenced to prison after pleading guilty to crimes related to these events.

Earlier today (June 6), in response to an article about this case,¹ you emphasized the importance of the FDA's role in ensuring the effectiveness and safety of medical products.²

Senior officials of AM2PAT were clearly responsible for this tragedy. However, the FDA bears much of the blame for allowing it to happen. The role of the FDA in this case and others like it is in need of investigation. Accordingly, we ask that you request an investigation by the Inspector General (IG) of the Department of Health and Human Services. Such an investigation is long overdue. A year before you took office as FDA Commissioner, many of the facts in the AM2PAT case were well known to the agency. However, up to now, the FDA's role in the AM2PAT case as a possible enabler of wrongdoing has not been publicly acknowledged either by the FDA or the Inspector General.

¹ Jewett, Christina and Deborah Shelton, "Dirty syringes: FDA failed to shut down troubled plant, and family says it paid the price." *Chicago Tribune*, June 6, 2009.

<http://www.chicagotribune.com/news/nationworld/chi-syringes-bd07-jun07.0.1073039.story>

and "Tainted Syringes Slipped Past FDA's Watch." *ProPublica*, June 6, 2009

<http://www.propublica.org/feature/tainted-syringes-slipped-past-fda-watch-607>

² Jewett, Christina. "FDA Commissioner Responds to Investigation of Agency's Oversight of Tainted Syringe Factory." *ProPublica*, June 6, 2009. <http://www.propublica.org/feature/fda-comissioner-margaret-hamburg-responds-to-am2pat-investigation-606>

666 Eleventh Street, NW
Suite 900
Washington, DC
20001-4542
Phone: 202-347-1122
Fax: 202-347-1116

www.POGO.org
pogo@pogo.org

501(c)(3) ORGANIZATION

The FDA's regulatory failure in the AM2PAT case is particularly clear-cut, as is the harm inflicted on patients. Many of the details have already been unearthed and confirmed by a federal prosecutor and are available in court documents as well as in accounts in the press. A report by the HHS IG on this well-documented, fairly straightforward case would throw light on the institutional weaknesses at the FDA that led to regulatory failures in other episodes that are more complicated and more difficult to investigate.

Why did the FDA fail in its duty to keep a dangerous medical product, AM2PAT's syringes, off the market? We believe that part of the reason is a culture within the FDA that habitually maintains a relationship with manufacturers that is too collegial and too tolerant. There is a reluctance by the FDA to take corrective action stronger than a Warning Letter, even when stronger action is clearly indicated, as it was at several points in the history of the AM2PAT case. There is an additional reason for the FDA's failure: the grossly inadequate resources available to the FDA for inspection and enforcement. This is mainly a budgetary problem that can, of course, be solved only by the White House and Congress.

The IG, with the facts in hand after its own investigation, can assess these possibilities and make recommendations to the Secretary of HHS and the Congress.

The case of AM2PAT, Inc.

AM2PAT was a small company in North Carolina that sold syringes until about 18 months ago. The syringes were prefilled with small amounts of heparin solution and saline solution for intravenous injection. The company was forced out of business in January 2008 when the fluid in some of its syringes, contaminated with bacteria (*Serratia marcescens*), caused severe systemic infections in patients. Several state public health agencies and the Centers for Disease Control (CDC) discovered the outbreak of infections in December 2007 and notified the FDA, which in turn sent out a nationwide warning to stop all use of the syringes immediately.

At least four patients died, and hundreds were harmed. Some suffered permanent, severe brain damage.

As shown by its own records, the FDA had known for a long time about safety problems at AM2PAT. Repeatedly, for at least two years before it finally took decisive action, the FDA was given ample warning that AM2PAT was failing to ensure the safety of its syringes. The likelihood of disaster is documented in the FDA's files in several ways:

Inspections by the FDA itself. Within its files, the FDA had its own official, detailed, and highly critical report (FDA Form 483, which resulted in a Warning Letter to AM2PAT) prepared after an inspection of the AM2PAT plant in August 2005.³ The Warning Letter specifies "significant violations," which are listed in nine categories. The violations seem more numerous, serious, and troubling than those in most Warning Letters.

³ The Warning Letter is posted in the FDA's Electronic Reading Room at <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2005/ucm075518.htm>

Syringes manufactured by AM2PAT were used routinely to deliver fluid from the syringe directly into the blood stream of immunocompromised or otherwise vulnerable patients. Several of the violations recorded in the Warning Letter were explicitly focused on possible breaches of sterility. In a facility that manufactures and ships syringes with injectable contents that are supposedly sterile, there are no violations more serious than those that endanger sterility. The findings of the initial inspection were so alarming that the FDA should have been in a high state of alert for all subsequent dealings with AM2PAT. The FDA's customary levels of vigilance were clearly not sufficient.

After the initial inspection, there were more FDA inspections based on indications of additional problems in the AM2PAT plant. These inspections, too, were documented in files prepared by FDA personnel and readily accessible to the agency's personnel.

Complaints filed officially by outsiders. Months before the December 2007 outbreak that struck down hundreds of patients, more than a dozen complaints about the syringes were filed in the FDA's online database (MAUDE). The database is easy to use and is readily accessible to all FDA personnel. The complaints were filed by medical personnel and other parties unconnected with the FDA. There were complaints, for example, about darkened or "dingy" syringes and about syringes holding liquid that contained floating debris. This type of debris (probably a silicone particulate) is known to be potentially dangerous.⁴

The finding of particulate contaminants in the syringe fluid should have served as a warning to FDA personnel that there might be, in addition, other types of violations – those that could jeopardize the sterility of the fluid. The possibility of such violations should always prompt immediate strong reaction by the FDA, at the very least including frequent surveillance. Even in the absence of demonstrable harm to patients, FDA managers should have considered the possibility of blockage of all shipments of syringes (by injunction if necessary). Civil penalties and prosecution would not have been unreasonable, even if not a single person was yet known to have been harmed.

Warning by a whistleblower. Months before the outbreak, a whistleblower working inside the AM2PAT plant sent the FDA an email identifying herself and warning explicitly about unsuitable conditions in the plant.

⁴ A release by ECRI Institute summarizes a warning about AM2PAT syringes containing particulate matter (probably a silicone particulate) suspended in normal saline. "B Braun – Normal Saline Flush Syringes: May Contain Particulate Matter." *Physician Practice E-News*, ECRI Institute, November 9, 2007. The release states: "Phlebitis and/or damage to vital organs (e.g., brain, kidneys, heart, lungs) may occur if this particulate matter is introduced into the bloodstream. Although less likely to occur, the potential exists for pulmonary embolism or silicone embolism syndrome to occur, possibly resulting in severe patient injury or death." http://www.ecri.org/documents/Physician_Practice_E-News.pdf

The above ECRI release also refers to (and provides a link to) a recall and press release dated September 14, 2007, posted by the FDA. This press release, though it does not name AM2PAT as the source of the syringes, has a similar warning about the effects of the particulate matter when introduced into the blood stream and also indicates that there was an "increase in customer complaints for particulate matter in the saline." "B. Braun Medical Inc. Issues Nationwide Recall of Normal Saline Flush Syringes with Lot Numbers Ending in 'SFR'." September 14, 2007. <http://www.fda.gov/Safety/Recalls/ArchiveRecalls/2007/ucm112275.htm>

These multiple, independent danger signs should *at the very least* have led to immediate suspension of AM2PAT's output of syringes followed by repeated inspections until FDA inspectors were satisfied that all the problems had been eliminated. Instead, the danger signs went largely unheeded by the FDA until December 2007.

Before the outbreak of lethal infections, the FDA's strongest action against AM2PAT was a Warning Letter, which the FDA's manual defines as "informal and advisory."⁵ Thus the sending of a Warning Letter, a mechanism commonly used by the FDA, is symptomatic of a relationship with manufacturers that is collegial and tolerant, rather than arms-length, formal, and peremptory. Manufacturers know that they can usually get away with cutting corners, as AM2PAT did. If the manufacturer is unlucky and gets caught (which is far from certain, because inspections are infrequent), the worst that usually happens is a Warning Letter. The manufacturer then corrects the violation – no big deal.

In December 2007, more than two years after the FDA's initial Warning Letter, the agency finally recognized the gravity of the problem when it received notification by the CDC that life-threatening infections were occurring in many patients receiving fluid from the syringes. The FDA then sent out a nationwide warning to stop using the syringes. By then the harm was done. Syringes containing bacterially contaminated fluid (saline solution and heparin solution) had already been shipped throughout the country, and the fluid had been injected into patients.

In February 2009, about a year after the outbreak of widespread infections and the closing of the AM2PAT facility, two of the plant's managers were sentenced to prison after pleading guilty to charges related to the shipment of the contaminated AM2PAT syringes. Federal agents are seeking the company's chief executive, who may have fled the country.

These three officials of AM2PAT were responsible for allowing the assembly and shipping of syringes whose infected contents caused at least four deaths and many serious injuries. However, the FDA bears much of the blame for allowing it to happen.

The culpability of the FDA is clear. Over a period of months if not years, FDA officials received repeated, documented warnings of serious problems at AM2PAT – warnings by its own agency personnel, by members of the public who sent the FDA damning descriptions of contaminated fluid in the syringes, and by a whistleblower on the AM2PAT premises. Nonetheless, the FDA failed to protect the public by barring the shipment of infected syringes. The FDA should simply have shut down the entire AM2PAT operation, thus preventing the final tragedy from occurring.

⁵ Sanctions stronger than the Warning Letter are available, but the FDA uses them far less often, and they were not used in the AM2PAT case until it was too late. The Warning Letter is "informal and advisory," according to Chapter 4 of the FDA's *Regulatory Procedures Manual* of 2009.
<http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm>

An analysis by the IG could provide answers to some important questions:

- o Was the FDA's regulatory failure in the AM2PAT case due to a shortage of field inspectors (investigators) assigned to that area (North Carolina) and thus too few inspections? Or were there enough inspectors, but poor inspections and poor inspection reports? Or were there reliable reports from the inspectors, but bad decisions in the FDA field office or in the CDRH headquarters in Maryland? Or were there regulatory failures distributed throughout the various steps of the CDRH surveillance and enforcement system?
- o Should FDA officials have concluded long before the outbreak of December 2007 that an immediate, peremptory prohibition on shipment of all AM2PAT syringes was necessary to protect patients?
- o Does the AM2PAT fiasco represent an unusual, almost unique regulatory failure by the FDA? (Based on reports in the press on other cases, this seems unlikely.) Or do similar failures occur from time to time, sometimes noticed, sometimes not? Or is the AM2PAT story typical of similar, less dramatic regulatory failures occurring fairly often in all the Centers of the FDA, but unreported by the press and unknown to the Congress?

FDA officials have known for more than a year about the agency's failures in the AM2PAT case, but the agency has issued no public statement about these failures. The silence on the part of FDA officials would by itself indicate the need for an investigation and report by the Inspector General.

Changes needed in FDA regulation: new companies and the 510(k) mechanism

The AM2PAT case provides a prime example of certain customary FDA practices that should be changed.

First, FDA should pay considerably more attention than it now does to newly established companies making medical devices – companies like AM2PAT that have no past record of dealing with the FDA. The FDA should, as a matter of routine, inspect such companies more carefully and more often than it now does.

Second, there is the issue of the Premarket Notification mechanism, also called 510(k). By making use of the 510(k) mechanism, new companies like AM2PAT are allowed to put potentially deadly devices on the market quickly and with little regulatory oversight by the FDA.

When using the 510(k) mechanism, a newly established company need only file papers with the FDA asserting that the device it plans to manufacture is “substantially similar” to some other device (a predicate device) previously marketed by *different* companies. The manufacturer is not required to submit test data for the actual devices that will be produced and marketed. In particular, there is no requirement for nonclinical test data under the Good Laboratory Practice regulation. Nor is the manufacturer required to describe the facilities or personnel for the manufacture of the device or to describe the details of the manufacturing process.

On receipt of the 510(k) notification, if the FDA accepts the manufacturer's claim of substantial similarity to a predicate device, it generally clears the device for marketing quickly and without requesting further information. The device can then be sold. Amazingly, the FDA's guidelines allow a new 510(k) device to be marketed immediately after FDA clearance of the device, without any direct evidence that the device is safe and without the manufacturing facility having been inspected even once.⁶ This policy is intrinsically dangerous to the public.

AM2PAT used the 510(k) mechanism for its syringes. The FDA cleared the syringes for marketing after what appears to have been a perfunctory examination of an uninformative two-page document filed by AM2PAT (see Attachment and footnote⁷). As is common for 510(k) notifications, the document contained no test data. The document contained the assertion, "Test data have been generated," but no actual data were included. Moreover, the document filed by AM2PAT contained no information about the company's specific plans for assembling its syringes – most importantly, about its plans for maintaining and verifying sterility. The rubber-stamp approval of AM2PAT's syringes is typical of many 510(k) devices cleared for marketing by the FDA.⁸

The OIG and the FDA Commissioner's office should consider recommending or requiring an immediate change in 510(k) policy.⁹ Specifically, when the manufacturer of a Class II or Class III device files a 510(k) notification form, the FDA should require that the manufacturer include information of the sort described above – especially if the manufacturer is newly established.

As with other problems at the FDA, more agency personnel will be needed if 510(k) requirements are tightened. This will require that the administration and the Congress provide the FDA with the much larger budget it needs.¹⁰

⁶ According to the current (May 2009) guideline for 510(k) notification, "The submitter may market the device immediately after 510(k) clearance is granted."
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm>

⁷ See the 510(k) notification by Dushyant Patel, president of AM2PAT, July 20, 2003, and the FDA letter of response, December 23, 2003, which cleared the syringes for marketing.
http://www.accessdata.fda.gov/cdrh_docs/pdf3/k032417.pdf

⁸ The lack of data in the 510(k) notification form could be remedied during the process of inspection. However, as noted, devices can be marketed immediately after clearance by the FDA and before any inspection. Moreover, as shown by the AM2PAT case, the lack of data delayed the recognition that AM2PAT did not meet the FDA's safety standards.

⁹ The actions recommended in our letter, above, are largely independent of reforms in the 510(k) mechanism recommended by the GAO in a January 2009 report, GAO-09-190, "FDA should take steps to ensure that high-risk device types are approved through the most stringent premarket review process." Responding to the GAO report, the FDA has announced some modest, long-overdue reforms: "FDA to review medical devices marketed prior to 1976: Action addresses GAO recommendation," April 8, 2009. The actions we recommend would be worthwhile whether or not the FDA implements the GAO recommendations.

¹⁰ A 510(k) submission containing large amounts of data would start to resemble a submission for Premarket Approval (PMA). For fiscal 2005, "the estimated average cost for the agency to review a 510(k) submission was about \$18,200, while the estimate for a PMA submission was about \$187,000," according to the January 2009 GAO-09-190 report. Thus,

We ask that you request an investigation by the Inspector General of DHHS.

Please do not hesitate to consult either of us if you have questions.

Sincerely,

Danielle Brian per NF

Danielle Brian
Executive Director
Project On Government Oversight
dbrian@pogo.org

Ned Feder

Ned Feder, M.D.
Staff Scientist
Project On Government Oversight
1100 G Street, NW
Washington, DC 20005
Phone: 202-347-1122
Fax: 202-347-1116
nfeder@pogo.org

cc: Daniel R. Levinson, Inspector General, Department of Health and Human Services

Attachment: Correspondence of AM2PAT president with FDA (referenced in footnote 7)

if 510(k) requirements were tightened as discussed here, the corresponding increase in the FDA budget would be considerable.

SOURCES OF INFORMATION ABOUT THE AM2PAT CASE

Articles

Avery, Sarah. "2 plead guilty in deadly tainted-syringes case." *McClatchy Newspapers*, February 24, 2009.

http://www.cleveland.com/nation/index.ssf/2009/02/2_plead_guilty_in_deadly_taint.html

Avery, Sarah and Sabina Vollmer. "FDA ignored debris in syringes." *The News & Observer* (North Carolina), February 25, 2009.

<http://www.newsobserver.com/news/wake/raleigh/story/1418047.html>

Baker, Mike. "FDA didn't inspect syringe plant despite reports." *Associated Press*, February 25, 2009.

<http://abcnews.go.com/US/wireStory?id=6960155>

"Timeline: Reports, Inspections of Syringe Factory." *Associated Press*, February 25, 2009.

<http://a.abcnews.com/print?id=6960166>

Jewett, Christina. "Could FDA Have Prevented Syringe Deaths?" *ProPublica*, February 26, 2009.

<http://www.propublica.org/article/could-fda-have-prevented-in-syringe-deaths>

This article has links to nine useful documents.

Jewett, Christina and Deborah Shelton, "Dirty syringes: FDA failed to shut down troubled plant, and family says it paid the price." *Chicago Tribune*, June 6, 2009.

<http://www.chicagotribune.com/news/nationworld/chi-syringes-bd07-jun07.0,1073039.story>
and

"Tainted Syringes Slipped Past FDA's Watch." *ProPublica*, June 6, 2009

<http://www.propublica.org/feature/tainted-syringes-slipped-past-fda-watch-607>

This article has extensive documentation through links to many useful documents.

Court documents

See, for example, "Criminal Complaint in the Case of United States of America v. Ravindra Kumar Sharma," U.S. District Court, Eastern District of North Carolina, case number 5:08-mj-1208, filed April 3, 2008 (14 pages). This document and others are available online from the PACER public access service.

DEC 23 2003

“510k Summary”

K032417

Preparation Date: July 20, 2003

Submitter: AM2PAT, Inc.
9400 Ransdell Road, Suite 10
Raleigh, NC 27603
Phone: (919) 552-9689
Fax: (919) 552-7400

Contact: Dushyant Patel, President

Device Name: Heparin Lock Flush Syringe

Device Common/Usual Name: Heparin Lock Flush Solution, USP

Device Classification Name: Catheter, Intravascular, Therapeutic, Short Term Less Than 30 Days

Product Code: NGT – Device, Flush, Vascular Access

Substantially Equivalent Devices:

Company	Product/Device	510k Number
EMT-Rx	Saline IV Flush Syringe	K002142
Becton Dickinson	BD PosiFlush™ Heparin Lock Flush Syringe	K011967
Baxter Healthcare	Heparin Lock Flush Syringe	K003245
Medefil, Inc	Heparin IV Flush Syringe	K020996

Device Description:

The proposed device is a sterile, single use, standard piston type syringe that is available in various fill volumes and syringe sizes containing either 10 or 100 USP u/ml Heparin Lock Flush Solution for Injection. units

The syringe uses a sterile, polypropylene luer lock fitting or blunt tip cannula. The piston syringe consists of a polypropylene barrel with a luer lock adapter assembled with a polypropylene plunger and a polyisoprene seal. The dispensing end of the syringe is covered with a tip cap closure.

Intended Use:

The AM2PAT Heparin Lock Flush Syringe and its predicate products are intended for prescription use to flush compatible intravenous administration sets and indwelling intravascular access devices.

Comparison to legally marketed devices:

The technological characteristics of the new device to legally marketed predicate devices are the same in that:

- All devices have the same intended use
- All devices are pre-filled with a heparin lock flush solution, USP
- All are single use disposable products
- All are sterile and pyrogen free
- All are manufactured using an aseptic process
- All are available in similar syringe sizes and fill volumes
- All use a polypropylene piston-type syringe
- All are packaged in a wrapper or polybag and sealed
- All use manual energy

Non-Clinical Testing:

The physical properties of the materials used to manufacture the Heparin Lock Flush Pre-Filled Syringe are tested by suppliers to ensure they meet either USP Class VI plastic test requirements or ISO 10993 Part 1 for all fluid path components. Materials that come into contact with the body have been tested and found to be safe and effective for their intended use. This information was submitted as part of 510 K002142 for the EMT-Rx Saline Flush Syringe. These materials are widely used in similar, and other medical devices and have been cleared through FDA.

Test data have been generated for stability and container/closure suitability. Performance testing indicates that the proposed device meets all functional requirements and supports its suitability for use.

Conclusion:

The Heparin Lock Flush Pre-Filled Syringe is substantially equivalent to the predicate devices cited with respect to indications for use, device design, materials, and labeling.



Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

DEC 23 2003

Mr. Dushyant Patel
President
AM2Pat, Incorporated
9400 Ransdell Road
Raleigh, North Carolina 27603

Re: K032417

Trade/Device Name: Heparin Lock Flush Syringe – 10 and 100 units/mL
Regulation Number: 880.5200
Regulation Name: Intravascular Catheter
Regulatory Class: II
Product Code: FOZ
Dated: December 17, 2003
Received: December 18, 2003

Dear Mr. Patel:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

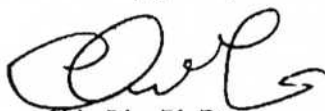
If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at (301) 594-4618. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address <http://www.fda.gov/cdrh/dsma/dsmamain.html>

Sincerely yours,



Chiu Lin, Ph.D.

Director

Division of Anesthesiology, General Hospital,

Infection Control and Dental Devices

Office of Device Evaluation

Center for Devices and

Radiological Health

Enclosure

K032417

Indications for Use

Applicant: AM2PAT

510(k) Number (if known): N/A K032417

Device Name: Heparin Flush Syringe – 10 and 100 units/mL

Indications for Use: Lock

The Heparin Lock Flush Syringe, 10 and 100 units/mL is intended for use in flushing compatible intravenous administration sets and indwelling intravenous access devices.

Susanna F. Bamu W

(Division Sign-Off)
Division of Anesthesiology, General Hospital,
Infection Control, Dental Devices

510(k) Number: K032417

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE
OF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use

OR

Over-the-Counter Use

(Per 21CFR 801.109)