



## PATIENT SAFETY UPDATE:

# What's Happening With the PDMA?

By Amanda M. Traxler

As *IG Living* reported in October-November 2007, the federal drug pedigree requirement that was first introduced as part of the Prescription Drug Marketing Act (PDMA) in November of 1988, and that was most recently to be implemented in December 2006, was once again put on hold due to a court challenge to its constitutionality. Had it been put into effect, the PDMA would have mandated a pharmaceuticals distributor to document every entity that has had possession of a vial or bottle of medication the distributor handles. As noted in the earlier article, a common belief is that requiring a pedigree—documenting a product's path from manufacturer to the patient—is the most effective way to regulate responsible distribution practices and secure the pharmaceutical supply chain. These practices would deter drugs from entering secondary distribution channels, where they are at risk of diversion into the gray, or secondary, market.

On July 10, 2008, the U.S. Court of Appeals for the Second Circuit affirmed the preliminary injunction issued by a federal district court in the Eastern District of New York on Dec. 8, 2006. Due to the fact that the court upheld the preliminary injunction, the Food and Drug Administration (FDA) "does not intend to initiate any enforcement actions against any wholesaler solely for:

- Failing to include lot numbers, dosage, container size, or number of containers on a pedigree; or
- Failing to provide a pedigree that goes back to the manufacturer so long as the pedigree otherwise identifies the last authorized distributor of record that handled the drugs."<sup>1</sup>

Where does that leave us? Much in the same place as before. Given that the preliminary injunction was upheld in July 2008, securing the pharmaceutical supply chain through the PDMA will likely not be happening anytime soon.

"It's going to remain status quo for quite a long time," said Patrick M. Schmidt, CEO of FFF Enterprises, Inc., a biopharmaceuticals distributor based in Temecula, Calif., and also the publisher of *IG Living*. "I think we will need to be prepared for continuous delays."

But that doesn't mean that everyone is sitting idly by. For many industry players, working to guarantee safety for the patient and the distribution channel is a top priority. For example, FFF has been voluntarily providing pedigrees for its customers since 2004, with its own proprietary Verified Electronic Pedigree™ system.

However, the fact remains that there is still work to be done. And, an important concept for consumers to grasp is that they shoulder part of this responsibility. Many patients do not realize, for example, >

that they can ask for a product's pedigree. As stewards of their own health, patients should remember to maintain a partnership with their healthcare providers and request what is essential to their health and safety—especially when it comes to ensuring that their immune globulin (IG) is not compromised at its final stop in the distribution channel, with a healthcare provider.

While outside of the scope of the PDMA (which solely deals with distributors and pedigrees), IG can still be vulnerable to re-entering the secondary market once it has reached a healthcare provider if that provider resells it and does not follow the "own use" policy, which means that it's not allowed to be sold or exchanged again.

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*Adam Fein, PhD*

### The Importance of a Safe Channel

According to Chris Ground, senior vice president of national accounts for FFF, the distribution channel for IG must be secure for three reasons: to maintain the efficacy of the product by handling it properly; to avoid possible counterfeiting; and to avoid inappropriate pricing, or price gouging, during times of short supply.

All are necessary to making sure, Ground says, that "the manufacturer's intent, which is maintaining product efficacy, is followed in the supply chain."

To Schmidt, the solution of securing the supply chain lies in not engaging in secondary distribution.

In other words, IG should move only from a manufacturer to an authorized distributor of record (ADR) to a licensed healthcare provider, and that's it. When a product follows this path, it is in the primary distribution market. When one distributor resells product to another, the secondary distribution market enters the picture. Other examples of being diverted to the gray market include when hospitals and physician offices sell overstocked drugs back into the marketplace or when wholesalers and distributors see a chance to make a quick buck and sell product to each other.

Adam Fein, PhD, an expert on pharmacy economics and the pharmaceutical supply chain, recognizes the large role that the secondary market has in drug counterfeiting—especially during times of short supply—and would no doubt appreciate Schmidt's solution.

"Legislators should recognize that the Heparin situation does not represent the most common way in which a counterfeit drug could enter your neighborhood pharmacy," Fein has written in his blog about supply channels. (The Heparin situation refers to batches of the blood thinner that were contaminated during manufacturing and that caused hundreds of allergic reactions, many of which were fatal.)

"Instead, it's much more common for a counterfeit drug to slip into the system when someone buys from an unreliable secondary source or intentionally counterfeits or compromises an authentic medicine," Fein wrote. "This process has been the entry point for almost every case investigated by the FDA in which a counterfeit or adulterated drug ended up in your local pharmacy. We cannot be complacent."<sup>2</sup>

During times of shortage, all drugs are vulnerable to entering the secondary market. According to Fein: "Even legitimate pharmacists sometimes purchase in the secondary market. For example, a 2004 study found that two-thirds of hospital pharmacy directors use secondary wholesalers as a resource to obtain needed supplies during a product shortage."<sup>3</sup>

That includes IG. According to a February 2007 study titled "Analysis of Supply, Distribution, Demand and Access Issues Associated With Immune Globulin Intravenous," which was done by the Office of the Assistant Secretary of Planning and Evaluation: "Distribution of IGIV [aka IVIG] occurs through an authorized and a secondary channel. The IGIV marketplace has struggled with channel integrity and includes a significant secondary market outside of the authorized distribution channels. The secondary market is characterized by fluctuating prices and product availability. While the size of the secondary market is unknown, our analysis shows that it likely exceeds 10 percent of the total grams available for distribution."<sup>4</sup>

In other words, the gray market is perpetuated by both bad guys and good guys, all of whom engage in purchasing practices that directly create opportunities for counterfeiting, tampering, drug diversion and theft of drugs.

"When drugs are diverted into the gray market, they are no longer safe," Schmidt said. "In the shadowy landscape of the gray market, these drugs are now vulnerable to mishandling, tampering, counterfeiting, and unfair pricing. Worse, they put patients' lives at risk."

### The Manufacturer Perspective

While no manufacturer intends for a product to be compromised anywhere along its supply chain, IG manufacturers especially don't want that to happen.

According to Ground, the care put into the manufacture of all IG products is noteworthy.

"I've been to most of the fractionation plants [where IG is made], and I've talked to most of the people who give the tours, the scientists and the PhDs," Ground said. "Then I've talked to the engineers who built the technology, and it's striking to me to listen to the scientist or the engineer who has worked so tirelessly. They talk with such reverence about the product. They're so respectful of that protein and what they've done to maintain the integrity of it throughout a rigorous and complex manufacturing process."

When it comes to making plasma products, safety is of ultimate concern from the get-go.

Take, for example, PediGri® On Line, a tracking program of Grifols, a plasma product manufacturer based in Barcelona, Spain. Launched in the United States in September 2008, PediGri® On Line allows registered healthcare providers to access specific quality and safety information about the individual plasma sources that contributed to each vial.

Once IG leaves a plant, though, a manufacturer has no control over it.

"Manufacturers end up with this bottle of product," Ground said, "and they have to trust who they're giving that product to so it will get to a patient. When they put it in the distribution channel, they lose control. That's why they should be so very careful about choosing a distribution channel that will afford the same respect for that vial of protein as they do."

Taking another safety measure, Grifols laser etches each vial of Flebogamma® 5% DIF with a unique identifier that includes the lot number and a filling sequence production number. Even if the label is missing, the laser etching is permanent and legible. A deterrent to tampering, it also allows Grifols to reference a video of a particular vial being filled while also allowing easier tracking of individual vials.

In practice, most manufacturers ship IG only to ADRs. According to Ground: "Most manufacturers authorize only four or maybe five distributors."

For example, Octapharma, a biopharmaceuticals company based in Switzerland, reduced the number of its ADRs to five in an effort to secure its supply channel since entering the U.S. market in 2004. Further, Octapharma's direct-distribution requirements also indicate that its products are not for resale. If, for example, Octapharma learns that Octagam® has been resold by a healthcare provider, it asks its distributor to not sell to that provider again.

### The Distributor Perspective

Manufacturers aren't alone in their concerns about product safety. With its 8 Steps to Guaranteed Channel Integrity™, FFF has instituted industry best practices to secure its supply channel for IG and the

other products it distributes.

Schmidt explains: "This standard is simple. My company calls it the 'Responsible Distribution Channel.' Drugs in this channel move only from the manufacturer to a sole distributor to a sole customer—with no gray in between. This guarantees channel integrity."

First and foremost, FFF's distribution channel provides a secure chain of custody that ensures biopharmaceutical products move only from the manufacturer through a single distributor to a healthcare provider licensed by the Drug Enforcement Administration (DEA).

"We sell only to DEA-licensed facilities," Ground said. "They take on the responsibility to ensure it gets to the patient appropriately."

Further, once IG is sold, it's supposed to be for "own use." According to Ground, any facility that violates this by reselling the IG will not be allowed to order product again from FFF.

Additionally, six other critical steps are taken to maintain the safety of the products. One step already mentioned is providing pedigrees. Regarding these, Schmidt says that no entity should be exempt, including manufacturers as well as ADRs.

With its commitment to safety, Schmidt considers FFF more than just a distributor.

"We're not just distributors," Schmidt said. "We're in the management of these critical-care pharmaceuticals."

That distinction is what makes the FFF business model unique.

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Especially during challenging, short-market conditions, another of the eight steps—interactive allocation—assures responsible, demand-based distribution of critical-care products. By ensuring product goes where the need is greatest, healthcare providers aren't forced to resort to secondary-market purchasing to accommodate critical demand. This is what FFF refers to as "Interactive Allocation," its term for responsible, patient-focused distribution of critical-care products. ➤



“If we had 1 million grams and one of our competitors had 1 million grams,” Schmidt said, “we could treat more patients than they could.”

Based on their strong relationships and regular interaction with their customers that helps them gauge and meet demand, FFF salespersons, whom Schmidt calls “service providers,” help ensure that patients receive needed products during times of short supply. Just as important, FFF’s practices help deter IG re-entering the supply chain in the secondary market.

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### Focusing on a Solution

Fein agrees that the ability to validate pedigrees is a fundamental requirement in order for pedigrees to make the supply chain safer. In fact, he lists that as his first rule of three that he considers key to supply-chain safety. Altogether, Fein says that anyone licensed to purchase drugs (such as a physician or a pharmacist) must:

- Demand pedigree documents (electronic or paper) from wholesalers and be able to validate the authenticity of these documents;
- Purchase only from wholesale distributors in the “Normal Distribution Channel” or wholesale distributors that are willing and able to supply pedigree.

Fein’s third rule places an important duty on patients:

- Consumers must (a) refuse to do business with any pharmacy that does not adhere to the preceding two rules, and (b) be able to validate a pharmacy’s compliance with these rules.

Fein contends that consumers and political representatives seem intent on ignoring the third rule.<sup>5</sup> Further, he contends that many industry websites about drug safety fail to address this issue.

“The industry sites do not help consumers identify legitimate pharmacies nor do they provide a way to validate that a pharmacy

is behaving ethically in its sourcing practices. ‘End-to-end’ visibility is a long way off, so we in the industry must confront the pharmacy buyer problem sooner or later, regardless of the endless appeals that are likely to dog the FDA’s attempts to implement the PDMA.”<sup>6</sup>

While Fein’s first two rules focus on the vulnerabilities to IG while it moves from manufacturers to distributors, Fein’s third rule focuses on another distinct area of vulnerability: the last stop in the channel, which is when IG has already landed at a pharmacy or at an infusion clinic. If every pharmacy were following “own use” policy, then there would be no reason for concern at this point.

### The Last Stop

Denise Hasenstab knows about the importance of Fein’s third rule. Her situation, which was reported in the December-January 2007 *IG Living*, demonstrates that IG can even be vulnerable when in the hands of the healthcare provider. In “Is Your Infusion Clinic One of the Good Guys,” *IG Living* detailed the Orange County, Calif., resident’s civil lawsuit against her infusion clinic for altering or replacing her IG injections with saline solution for seven years. Hasenstab—who is now healthy—was awarded \$300,000 in a civil suit. The clinic, which is still open, admitted only to faulty record-keeping.

Though what truly happened has yet to be determined, the criminal side of the case is not closed. In December 2008, Hasenstab told *IG Living* that the San Diego district attorney is currently looking into the clinic. Further, the medical board has filed several complaints against the doctor.

“The medical board team turned it over to the district attorney of San Diego. I received a letter from them, and I was pretty surprised because I had written it off because I had reported this a couple of years ago,” Hasenstab said.

According to Hasenstab, if the case moves ahead, the district attorney may be able to prosecute on criminal charges.

“I just don’t want to get my hopes up too high,” Hasenstab said, “but I am certainly happy to help in any way to bring awareness to other people because I would hate for anybody to go through what I went through.”

As a consumer who is also a nurse, Hasenstab counsels that consumers can—and must—be proactive about verifying their IG has not been compromised.

### What Patients Can Do

Where patients ultimately receive their IG, then, is the last stop of the distribution channel. With this in mind, patients must be aware that they can do the following to verify their IG:

- Ask your healthcare provider for the product's pedigree;
- Know the brand name of your IG, as well as what it looks like (bottle, shape, color, size);
- Monitor your own therapy in a diary in which you verify and log what product you receive at each infusion;
- If you receive infusions at a clinic, verify that your doctor is board-certified;
- Talk with your healthcare providers about where they buy their drugs and whether they follow "own use" policy;
- Ask your pharmacist if the pharmacy has a policy of not dealing in the secondary wholesale market;
- Be conscious of new or different side effects from those you've had previously or that are disclosed with the drug's packaging;
- If the drug is ineffective from the start or stops being effective, take it back to the pharmacy;
- Look at the packaging: Is it clear, clean and sealed? Look particularly at the quality and preciseness of the labeling;
- Be sure to keep samples of your medicine for evidence and comparison;
- Observe your symptoms and monitor your own levels; if your numbers are not what they should be, check with your physician;
- Check for warnings and announcements from the FDA and from state pharmacy boards and boards of health. Also explore the pharmacy's website;
- If you or your doctor suspect a medicine is bad, you or your doctor should submit a report to the FDA on its MedWatch site. Forms can be found at [www.fda.gov/medwatch/report/consumer/consumer.htm](http://www.fda.gov/medwatch/report/consumer/consumer.htm).

Ensuring the safety of the supply chain will require more than the PDMA. Ultimately, it will take the cooperation of healthcare consumers, providers, distributors and manufacturers to secure a safe channel. While industry initiatives are key to continuing progress, another part, no doubt, is raising patient and provider awareness. If, as the old adage goes, knowledge is power, then patients and their providers should not hesitate in becoming proactive about this important issue. ■

## Are State Efforts Worthwhile?

With federal requirements stagnant, many states have attempted to deal with the issue on a state level by enacting pedigree legislation. According to the Healthcare Distribution Management Association website, as of Nov. 20, 2008:<sup>7</sup>

- Eight states have enacted legislation;
- Ten states have enacted legislation, with rules pending;
- Twenty-one states have no legislation or regulations;
- Ten states have adopted final rules;
- One state has rules pending, but no legislation;
- Zero states have vetoed legislation;
- Zero states have proposed legislation.

According to Adam Fein, PhD, an expert on pharmacy economics and the pharmaceutical supply chain, "This approach has created a disparate patchwork of inconsistent regulations for tracking pharmaceuticals in the U.S. supply chain."<sup>8</sup> These systems, which are often incompatible, merely raise costs, reduce product availability, and lower safety, says Fein.

"We urgently need to replace these well-intentioned but disorganized, uncoordinated, and underfunded state-level mandates... Complying with a grab bag of state laws does little more than add unnecessary costs without an equivalent increase in safety."<sup>9</sup>

<sup>1</sup> Backgrounder re: RxUSA Wholesalers, Inc. vs. HHS, [www.fda.gov/CDER/regulatory/PDMA/PDMA\\_backgrounder.pdf](http://www.fda.gov/CDER/regulatory/PDMA/PDMA_backgrounder.pdf).

<sup>2</sup> Fein, A. Securing America's Pharmaceutical Supply Chain, [www.pharmalot.com/2008/05/the-op-ed-securing-the-supply-chain](http://www.pharmalot.com/2008/05/the-op-ed-securing-the-supply-chain).

<sup>3</sup> Fein, A. Drug Channels, Dec. 10, 2006, [www.drugchannels.net/2006/12/thank-you-for-buying-counterfeits.html](http://www.drugchannels.net/2006/12/thank-you-for-buying-counterfeits.html).

<sup>4</sup> U.S. Department of Health and Human Services, Office of the Assistant Secretary of Planning and Evaluation (ASPE), Analysis of Supply, Distribution, Demand and Access Issues Associated With Immune Globulin Intravenous, (IGIV), February 2007, [www.aspe.hhs.gov/sp/reports/2007/IGIV/index.htm](http://www.aspe.hhs.gov/sp/reports/2007/IGIV/index.htm).

<sup>5</sup> Ibid.

<sup>6</sup> Ibid.

<sup>7</sup> Distributor Licensing and Pedigree Requirements by State, HDMA website, [www.healthcaredistribution.org/gov\\_affairs/.state/state\\_legis-static.asp](http://www.healthcaredistribution.org/gov_affairs/.state/state_legis-static.asp).

<sup>8</sup> Fein, A. Securing America's Pharmaceutical Supply Chain, [www.pharmalot.com/2008/05/the-op-ed-securing-the-supply-chain](http://www.pharmalot.com/2008/05/the-op-ed-securing-the-supply-chain).

<sup>9</sup> Ibid.