



Pharmacist[®]

Managing Quality in the Generic Drug Supply Chain



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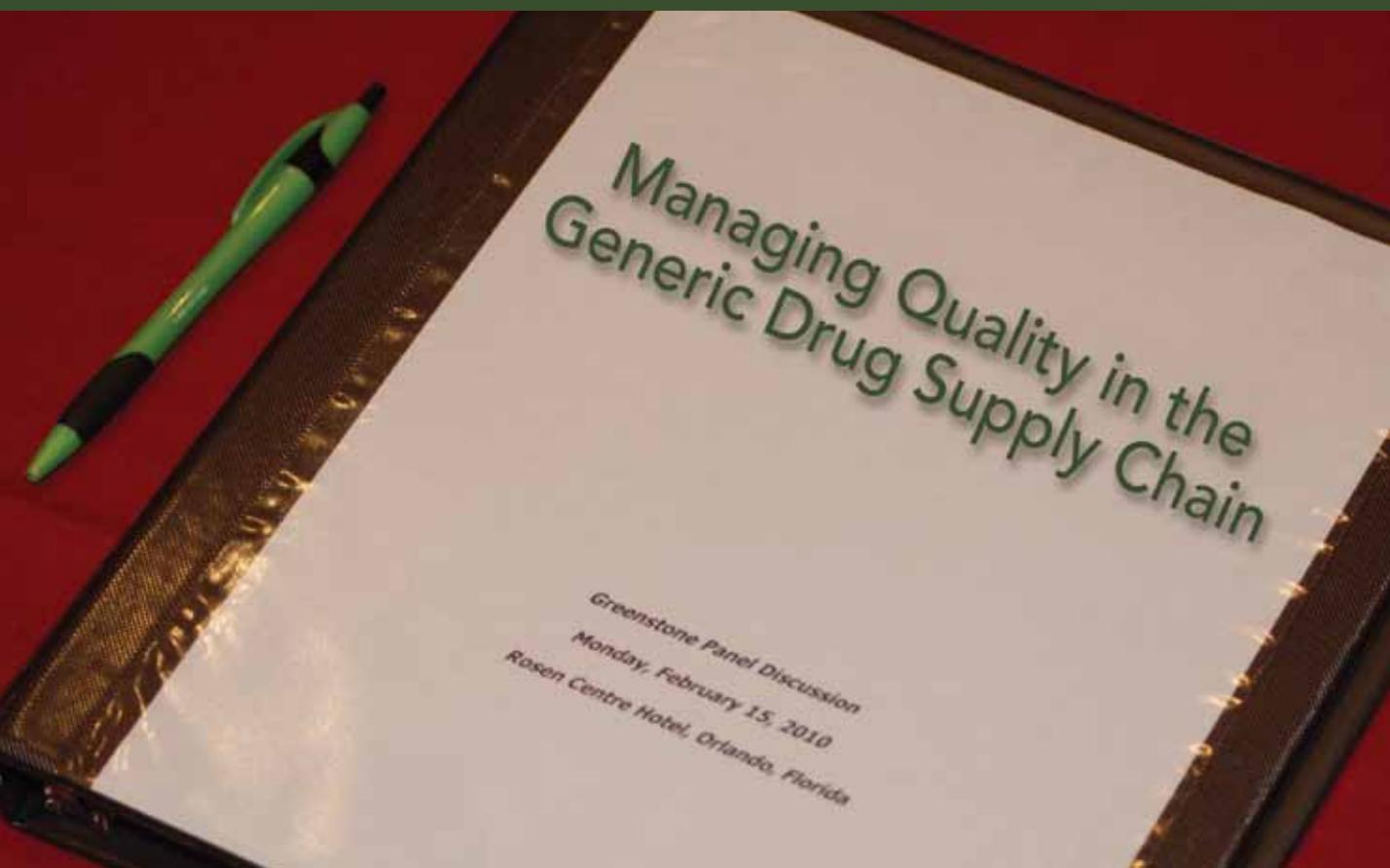


Photo by Linda Allen

Generic drugs are well entrenched in the United States drug supply chain. According to the latest data from IMS Health, generic drugs account for nearly 75% of all prescriptions dispensed in the U.S. today, and another \$89 billion of branded drugs are considered at risk to generic competition through 2014 as their patents expire.¹ Since the passage of the Hatch-Waxman Act (also known as the Drug Price Competition and Patent Term Restoration Act of 1984), cost-saving generic drugs have become a mainstay in the U.S. health care system. It is estimated that in the last decade alone, generic medications saved the U.S. health care system more than \$734 billion, with approximately \$121 billion in savings in 2008 alone.² In fact, it is estimated that generic drugs save Americans \$1 billion every three days.²

As a result of the Hatch-Waxman Act and FDA generic drug approval and manufacturing

protocols, the majority of today's pharmacists and their patients have a wide array of generic drug products available to them. This was clearly evident in the results of an exclusive generic survey conducted by *U.S. Pharmacist* that centered on pharmacists' perception of generics, the industry that manufactures them, and the distribution system that delivers them into retail and institutional pharmacies. The survey uncovered that approximately 90% of the 2,500 pharmacists polled were confident that generic products equaled the brand drugs in safety and efficacy.³ The results were similar when pharmacists were asked how their patients accepted generic substitution. Other concerns by pharmacists include counterfeit drugs and other issues directly related to the drugs' importation history and country of origin. Nearly all the pharmacists surveyed (95%) felt that a drug's country of origin affects the safety of a product. Survey topics included

the pharmacists' perception of "at-risk" and "authorized generics." Throughout the survey quality issues surfaced as one of the major factors pharmacists consider when choosing one company's product over another.

While the data indicate the future looks bright for the generic pharmaceutical industry, this success has also created concerns. Production requirements have increased exponentially over the years as generic manufacturers attempt to keep up with greater demand for their products. Competition is at a fever pitch while generic manufacturers and distributors vie for their share of today's exploding generic drug market and the burgeoning generic products still to come. In many cases, any share of market is really in the hands of the pharmacists they serve. Retailers have become more selective based on the quality of products and the level of service they receive. This fact was confirmed in the results culled from the *U.S. Pharmacist* generic survey.³ More than half of the pharmacists polled felt they have control over which generic

company's product to stock.

For this reason, many generic pharmaceutical manufacturers have undertaken measures that go well beyond FDA protocols to assure their customers that quality is paramount at every level of the product's production and distribution. One such company is Greenstone LLC, a division of Pfizer. To that end, earlier this year Greenstone held a panel discussion in conjunction with the ECRM Retail Pharmacy Generic Pharmaceuticals meeting in Orlando, Florida, to discuss its role in managing quality in the generic drug supply chain. Key opinion leaders representing critical components of the pharmacy supply chain, including mass merchandisers, retailers, and wholesalers, were invited to attend and actively participate in the open forum.

Panel Participants

Mike Sweitzer, General Manager, Greenstone LLC, moderated the panel discussion and kicked off the meeting by introducing the distinguished guest panelists. Each panelist is considered a stakeholder in understanding quality issues related to generics and is a specialist in their respective fields. They included Alexandra K. Finucane, Esq., Vice President, Legal and Government Affairs, Epilepsy Foundation of America; health care advocate Bonnie S. Muheim, representing the American Autoimmune and Related Diseases Association; and Pete Stevenson, Vice President and Team Leader, Established Products Business Unit, Pfizer Global Manufacturing.

Defining Quality

Sweitzer's opening remarks centered on the meaning of

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understanding how to take the medication and the importance of the consistency in the supply chain that brought the product to market."

Mike Sweitzer,
General Manager,
Greenstone LLC



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quality, particularly as it relates to generic products. Sweitzer emphasized that quality comes in many forms and means something different to each person who touches a generic product in the drug supply chain. For retailers, quality might describe the level of service they are receiving from the wholesaler or distributor who supplies them with the product; for patients, quality is more about the consistency of the color, shape, or size of the product they are being dispensed; and for the manufacturer, quality is about delivering a consistent product that meets or exceeds FDA regulatory requirements and safety standards and about providing their business partners with superior customer service. In the final analysis for Sweitzer, quality is centered primarily on the pharmacist and patient.

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manufacturers is to come up with the right value proposition with which to supply the industry.”

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Vice President/Team Leader,
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Sweitzer highlighted some revealing data from a small study conducted by Cylon Securities and reported by CNBC’s Mike Huckman. The study showed that 65% of the 25 pharmacists polled said they are concerned about generic drug safety, and more than half (56%) said they do not think generics are identical to brand-name pills. (When *U.S. Pharmacist* polled a much larger sample, pharmacists’ impressions of generic drugs compared to brand-name drugs were more favorable.³) Only a slim 15% admitted they trusted brand-name drugs more than generics. Another three-quarters of the respondents felt that the drug bottle should display the manufacturer’s name and country of origin. Sweitzer said pharmaceutical manufacturers have to do a better job of communicating and defining what “quality” really means to pharmacists, patients, and partners in the supply chain.

“Anytime there is a disruption in the quality of product in the supply chain it creates a negative ripple effect in the industry,” said Sweitzer. “It’s immediate and can be long-term.” As a key link in the supply chain, Sweitzer feels strongly that generic manufacturers and distributors have to better “understand and address pharmacists’ issues” when it

comes to the distribution of generic drugs. “Ongoing high-profile actions against generic manufacturers undermine confidence in the safety and ability to supply.”

Epilepsy and NTI Drugs

The FDA defines a narrow therapeutic index (NTI) drug as one that contains “certain drug substances subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation.”⁴ Other definitions of NTI drugs vary. For example, the North Carolina

Board of Pharmacy defines an NTI drug as “those pharmaceuticals having a narrowly defined range between risk and benefit.” Basically, an NTI drug is characterized by small changes in bioequivalence and/or bioavailability that could negatively impact its effectiveness in certain patients. Examples of drugs considered by the FDA as NTIs include digoxin, lithium, phenytoin, theophylline, and warfarin.

The substitution of NTI drugs is of great concern to panelist Alexandra Finucane, Vice President, Legal and Government Affairs, Epilepsy Foundation of America. She explained that the foundation’s primary goals for the approximately 3 million people who have epilepsy are threefold: “Ensuring access to all available treatments today for seizures of epilepsy; eliminating all the barriers to inclusion in society that people with epilepsy or seizures continue to face; and promoting research into a cure and better treatment of seizures.”

Finucane said that medication was a key element in helping to control often-disabling seizures suffered by many epilepsy patients. “About 60% of those people can have their seizures controlled with current medications,” said Finucane. “Another 20% are able to achieve partial control of their seizures with medication cocktails, and about 20% cannot control their seizures with any current treatment.”

She explained that the

Generics Fast Facts

- Three-quarters of total prescriptions dispensed were branded and unbranded generics.
- Through 2014, \$89 billion are at risk to generic competition in the United States.
- Generic medicines saved the American health care system more than \$734 billion from 1999 to 2008, with approximately \$121 billion in savings in 2008 alone.
- Generics save \$1 billion dollars every three days.
- A 3% increase in the national overall generic utilization rate could yield approximately \$10 billion in additional savings, \$1.4 billion for the Medicaid program alone.

Epilepsy Foundation has been a very strong supporter of generic drugs because “the major expense of people with epilepsy is the cost of medications. However, there has been an historic problem for some people with epilepsy and the drugs they take.” She said that over the past 30 years many patients with epilepsy took one or more of three major drugs. At one point the FDA classified these drugs as NTIs; however, according

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Alexandra Finucane,
General Counsel, Epilepsy
Foundation of America



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to Finucane, the FDA no longer includes them in that classification because “[the FDA] didn’t think it was necessary.”

She said that over the years, as branded epilepsy drugs have been converted to generics, there was “a small but significant portion of people with epilepsy who experienced seizures when switched from a brand to a generic, generic to generic, and generic to brand. Any form of switching will, for some people, result in either seizures or unacceptable side effects.”

Finucane also discussed the value of manufacturers with the ability to consistently supply the market. She cited incidences of patients receiving “jelly bean” bottles, medication bottles with assorted generic drugs because the pharmacist did not have a 30-month supply of drugs on hand and chose to combine multiple generics to fill the prescription. Finucane’s recommendations to the audience were for more research into drug switching and better education among patients and pharmacists about generics.

More Data Needed

The concern is that some of these patients might have seizures that could result in severe injury or

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Bonnie S. Muheim,
American Autoimmune
and Related
Diseases Association



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even worse consequences, depending on the type of seizure and the patients’ circumstances.

Finucane said that despite the Epilepsy Foundation’s best efforts to convince the FDA that there is a problem in the switching process, the agency says there is no data to confirm that fact and, as far as the foundation is concerned, substituting generics is safe and effective.

“We recognize that major studies do need to be done,” said Finucane. And while in recent years the FDA has been more receptive in providing feedback and guidance on what should be in those study protocols, it has not provided any support beyond that. “In the meantime, [the FDA] will continue to think that the generic versions of the epilepsy drugs are identical.”

Short of getting the FDA to recognize that switching to a generic can be harmful, Finucane said that pharmacists should be cognizant of patients with epilepsy who are switched to a generic. They should counsel patients to see if there have been adverse effects as a result of a switch. “We have found if there are going to be breakthrough seizures it’s going to be within one to three or four months after the switch,” said Finucane. This has potential implications for

medication therapy management. “We have also told people that if they are concerned about this issue because they’ve had problems in the past to ask their pharmacist to put a note in their record indicating that they cannot be switched and to keep them on the same manufacturer’s supply,” Finucane said.

Autoimmune Disease

Another area of concern discussed by the group was the quality of medications taken by patients with autoimmune disease. Bonnie Muheim, a health care communications

consultant speaking for the American Autoimmune and Related Diseases Association on behalf of 50 million Americans who suffer from one or more autoimmune diseases, told the group that patients with autoimmune diseases are particularly prone to changes in their drug therapy since many are suffering from multiple comorbidities.

“Switching from brand to generic, or from generic to generic, is one of the chief concerns for patients with autoimmune diseases,” said Muheim. She said that switching often changes the formulation of one product to another, which “can alter the absorption rates and affect the binding sites in autoimmune patients.” She believes that better communication between the physician and pharmacist could prove valuable.

She also said that in some cases the fillers that are used in various generic formulations may not be identical to the branded product, or even to another generic product. “What might seem insignificant or inconsequential to a lot of people is not insignificant for patients with autoimmune disease.” She explained that a good example is patients with celiac disease, a gastrointestinal disorder that is exacerbated by the ingestion of gluten. She views this problem as an opportunity for the industry to guarantee quality, gluten-free medications and an educational moment for pharmacists to help make their patients aware of the various formulations of the generics that they dispense.

Quality in the Manufacturing Process

Speaking on behalf of Pfizer Global Manufacturing, panelist Pete Stevenson, Vice President and Team Leader, Established Products Business Unit, said that quality in manufacturing requires both internal and external controls.

Stevenson explained that because of the global diversity of its manufacturing facilities, quality

standards at Pfizer are applied universally across its manufacturing network and that monitoring both external and internal manufacturing facilities across the network is a big task. “Right now, Pfizer is operating 79 manufacturing and 170 distribution sites worldwide. Last year, we had 100 inspections by the health authorities...this year we expect about 150.”

He added that 25% of Pfizer’s manufacturing is outsourced, which affords the company the ability to flex its own internal capacity, to optimize the economics of “make vs. buy” decisions, and to use different technologies. Most (about 90%) of Pfizer’s contract business is in the U.S. or Europe. In order to make sure that quality standards are evenly applied across all manufacturing sites both here and abroad, Stevenson said that Pfizer is continuously improving its quality standards by using internal and external benchmarking.

Internal Supply

When referencing internal benchmarking, one area of importance to Pfizer is having quality systems in place that cover all elements of the supply chain—from procurement through manufacturing to distribution. Stevenson said quality control systems are applied to “the entire supply chain, from raw materials through the plants, API, drug prod-

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uct formulation, and packaging...all the way through the distribution channels.”

“You just cannot *test* quality into a product,” he said. “The quality has to be designed in and ensured by effective quality systems.” He explained that by design he means the robustness of the formulation technology, which must be done right from the start by working collaboratively with research. Also important is the reliability of the equipment and how well colleagues are trained to work on that equipment. “The point is that it’s very much a systems approach.”

External Supply

Stevenson emphasized that Pfizer, like other U.S. manufacturers, is challenged when it comes to benchmarking external supply sources. He said that governments in emerging markets are still developing their standards and working to improve regulatory compliance.

Another factor is that while the manufacturing capacity in these countries is improving, it is still limited. He said that more inspections need to be done by the FDA to keep pace with similar inspections of plants in the U.S.⁵ How does Pfizer approach this situation?

He admits “it is unlikely to expect that we as an

industry are going to do everything perfectly; that we’re going to eliminate all the recalls and eliminate all the complaints, all the supply disruptions.”

“Not all products are equal. Some are a bit easier to make than others, but I have confidence in the ability of our outsourced manufacturers who make all of those products,” said Stevenson. He added that assuring quality controls are maintained becomes increasingly important “as you move up the complexity chain to products that utilize extended-release or aseptic manufacturing designs or those with active coatings and so forth; these are not the easiest things to manufacture.”

Stevenson assured the audience that quality control is a key element in Pfizer’s manufacturing process here and abroad as well as in developing countries. The company has an outstanding track record in quality and supply reliability. It maintains those strict quality standards by applying rigorous controls to all of its partners both internally and externally, thus protecting patients who take Pfizer products. “A secure supply chain is paramount in protecting the patients who use our products.”

Observations

Describing today’s business climate as “the generic perfect storm,” Jim Cannon, Senior Director of

Sales and Business

Development, Greenstone

LLC, said managing quality in the generic supply chain is of critical importance today in the face of “overcapacity in the marketplace, the continuing influx of competitors, government regulation, and pricing pressures.”

Cannon said a generic company that is committed to managing quality positively impacts the outcome of any shortfall in its production and distribution processes before it has a negative impact on its customers.

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to expand, this will be a challenge for all drug manufacturers.”

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Vice President /Team Leader,
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One comment from the audience came from a senior generic purchasing executive of a national drug chain. He said that it all comes down to “trusting the source of supply, based on both our personal history and the history of the company. We are also looking at the ability of a company to supply [its product] on a consistent basis.” He said the comments related to switching are a valuable lesson in that it is not all about cost but “the quality assurance we get from manufacturers.”

Third-Party Formularies

All of the audience participants agreed that the quality of a company’s product and services was a key item in whether to stock medications from one generic company over another, but they expressed frustration that much of the decision-making process is oftentimes out of their hands.

One retailer summed it up by referring to pharmacy benefit manager (PBM) formularies that sometimes mandate one drug be dispensed over another. “It’s fine to say that a particular patient who has been on a brand drug should not be switched to a generic, but in many cases that decision is pretty much taken out of our hands as a retailer and out of patients’ hands as well. There are financial incentives to switch to a generic, and it’s oftentimes at the suggestion of the patient.” Specifically addressing the two panelists representing patient advocacy groups, he suggested “the development and design of the formulary with the PBMs is of great concern.”

Another audience participant said she thinks the tide may be turning among PBMs that adhere to strict formulary controls. “Some [PBMs] have issued a policy that anyone who is well controlled on one of the brand-name products can stay on that if they need to at comparable copays to their generic counterparts.” She said that while that thinking is “certainly not across the board, we’re asking other PBMs to institute similar types of programs for patients who are living this problem.”

Responding to the audience’s comments, Muheim said that proper communication is

Blockbuster Drugs Expected to Lose Exclusivity in the U.S. Through 2011

2010	2011
Aricept	Actos
Arimidex	Alimta
Cozaar	Femara
Gemzar	Keppra
Hyzaar	Levaquin
Seretide	Lipitor
Taxotere	Oxycontin
	Plavix
	Seroquel
	Sifrol
	Xalatan
	Zyprexa

important for patients to make the right decision on whether they should switch or not.

“Physicians and pharmacists need to work together to communicate and educate the patient. Patients who are well educated and who better understand their illness will be in more control of their medications.”

Finucane agreed. “We find that [patients with epilepsy] assume that all generics are the same because that is what they’ve been told. So they go ahead and make the switch and have seizures.” She said it’s only after the fact they realize that the onset of their seizures may have been caused by the switching of medications. And while Finucane admits that educating patients is important, she feels it is equally important “that pharmacists be aware of this potential problem for people who take medications for seizures.” She added that in the end, the cost savings to insurers would be huge. “If you’re saving money on lower cost generics but spending it all on hospitalization costs, repeat visits to physicians, and different medication, there’s no savings whatsoever.”

According to another audience participant, the solution may be as simple as convincing the PBM that switching is not in their interest. “Generic manufacturers have to exhibit their

quality control to PBMs. This can be very important when it comes to disease states like epilepsy and autoimmune diseases.” He felt that third-party payers would be willing to enter into long-term agreements with specific generic companies if those companies can assure them consistent quality and supply of their product.

The Future for Generics

The generic market will continue to grow exponentially into the future. In the next two years alone, some 20 drugs, many of them considered “blockbusters,” will be losing their patent exclusivities to generics. Moreover, through 2014, \$89 billion are at risk to generic competition in the U.S.¹ As a result, the generic industry will become more crowded and competitive than it is today. This will force generic companies to differentiate themselves from their competitors. For some, that means focusing on niche markets like biotech drugs, injectables, or orphan drugs; for others, it means competing head-on with competitors, which will only drive prices lower.

“It’s not only cost, but also the quality of the product that will drive market share,” said Pfizer’s Stevenson. And it is likely that “quality” will be defined as quality in the consistency of supply chain, quality in the production of the product, and quality in the breadth of a company’s portfolio of products. “So the real chal-

lenge to us as manufacturers is to come up with the right value proposition with which to supply the industry,” said Stevenson. “Companies have tried different ways to reduce the cost of their product without sacrificing any of its quality control. For us, it was setting up controls in our manufacturing facilities that would allow us to scale up or scale down capacity very quickly depending on demand. As the industry continues to expand, this will be a challenge for all drug manufacturers.” In the end, the value proposition for customers is strengthening the value of the supply chain without sacrificing the reliability of the product.

Greenstone’s Sweitzer summed it up best: “Generic manufacturers need to provide the best value proposition, which is a finely tuned balance of product quality, reliability of supply, and competitive costs coupled with a strong sensitivity to patient needs.” ❖

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