

**001: Drug Shortages: A Conversation with Erin R. Fox,
Pharm.D., BCPS, FASHP**
Episode Transcription

Speaker 1: Welcome to the ASHP Official podcast, your guide to issues related to medication use, public health, and the profession of pharmacy.

Tom Kraus: Hi, this is Tom Kraus from the Government Relations team at ASHP. I'm joined today by Erin Fox. Erin leads the work of the University of Utah Drug Information Service. She's a national expert on drug shortages and the impact that they have on patient care. She's also the 2019 Zellmer Award Lecture winner. So congratulations, Erin, and thanks for joining us today.

Erin Fox: Thanks so much for having me, Tom.

Tom Kraus: So Erin advises a member of Congress and has worked closely with ASHP to come up with some policy solutions to address drug shortages and minimize their impact. So I'm going to ask Erin some questions today about some of the strategies that we can take to respond to drug shortages and hopefully we can learn a little bit about some steps that Congress and the FDA can take to address them. So Erin, can you give us a sense of the scale and frequency of drug shortages?

Erin Fox: Yeah. Drug shortages are such a frustrating problem because they've been so consistent, but I would say in the most recent years, probably beginning in the middle of 2017, we started to get a huge increase in the number of very common, very basic products. It's very frustrating because these are not going away. They are lingering and staying on, and my team right now is following just over 280 active drug shortages. So this is a lot for hospitals to deal with, and the frequency of these, almost a new shortage every week. Sometimes it feels like a new shortage every day is very frustrating for practitioners.

Tom Kraus: Do you have a sense of what's driving those shortages? Are there common causes that result in shortages?

Erin Fox: Yeah. One of the main reasons we have shortages is there are a lot of quality problems at manufacturing factories. So the other reason we have is for injectable products, there are usually only two or three companies that make these products in the first place. So usually one company will have a very large market share of that product, and if there's any type of a glitch, most of these companies make their products in a just in time manufacturing mode. They don't have a lot of redundancy, they don't have a stockpile. So even if one company has a problem, it almost always immediately results in a shortage. Even if other companies manufacture that product as well, they usually only have a small market share, maybe 10, 20%, and even if they're able to ramp up their production, it's not enough to make up the difference and really have good supplies and resolve the shortage.

Erin Fox: So those manufacturing problems are not just kind of picky FDA things. In some cases they're very, very egregious problems. Things like mold on the walls, and metal shavings in the vials, birds flying around the sterile fill facilities. These are really pretty severe manufacturing problems and they're taking a long time to fix, and so that's

**001: Drug Shortages: A Conversation with Erin R. Fox,
Pharm.D., BCPS, FASHP**
Episode Transcription

another reason why the shortages are lasting a long time, is it can take two or three years to fix a problem like that.

Tom Kraus: Some of those sound incredibly egregious. I hadn't realized the sort of pervasiveness of some of those quality challenges. Certainly we think of FDA as doing inspections to guard against some of the worst manufacturing challenges, but obviously FDA isn't everywhere all the time, and so there need to be ways that that companies are incentivized to address quality. I would think the manufacturers are in the best position to control that quality. So why isn't there more of an incentive for them to control the quality of their products?

Erin Fox: That's a great question and it's one that I have all the time. It's literally their job to manufacture these products. The way the system is set up is the companies devise processes for their own factories based on FDA's Good Manufacturing Practices guidelines and then the companies are supposed to follow them. Now, FDA inspects, but when companies sometimes intentionally choose to not follow their own processes or intentionally falsify data, which we're seeing more and more, those types of actions are very difficult for FDA to actually detect with their inspection based model that they have right now.

Tom Kraus: So some of those are some of the more nefarious examples. What about just a manufacturer that is operating in good faith trying to supply the market? How do things like price impact what their incentives are around manufacturing quality?

Erin Fox: That's a really good point. I mean, when you talk about what are some of the key reasons for shortages, economics is right up there, and part of that is a lot of these really basic hospital drugs are very, very low cost. They're almost treated as commodities. The incentives for hospitals are to use the very lowest cost products as possible in part because of the way that they're reimbursed on a DRG basis. So the incentive is for the hospitals to try to get contracts and really have the very, very lowest priced products. So as companies compete for that business, it's almost a race to the bottom. Then in some cases, these companies are underwater on some of the products that they're making. Now, they certainly make up the difference on other products, and so we shouldn't feel very sad that these companies are going to go out of business at any time, but it is a race to the bottom, and that can be very much an incentive for these companies to discontinue and stop making a critical product and maybe make a product that they could make more margin on, and that's because drug manufacturing is a business first and foremost.

Tom Kraus: So you've mentioned I think in the past in some conversations that as purchasers, it's hard for us to identify which are the manufacturers that have robust quality processes versus which are those that either cutting corners or for pricing pressure reasons just not investing in quality. How should we think about ways to incentivize quality?

Erin Fox: So I think one of the biggest arguments for incentivizing quality is adding transparency to the mix. So I talked earlier about those kind of those egregious things going on in some of those factories where you read about mold on the walls. Well, if you

**001: Drug Shortages: A Conversation with Erin R. Fox,
Pharm.D., BCPS, FASHP**
Episode Transcription

read a report like that, wouldn't you like to know all the drugs made in that factory and which company it is and then really avoid purchasing from that company and maybe reward another company that has higher quality? Not only are you rewarding that higher quality, but you're also hopefully going to have fewer shortages and fewer recalls, which take a lot of time. So because there is no requirement for any drug company to disclose the site of manufacturer, even the company that's manufacturing the product, it's impossible right now for hospitals to make a quality-based purchasing decision.

Tom Kraus: So a couple of the things you mentioned there overlap pretty significantly with some of the drug shortages, policy priorities that we've put forward as ASHP that we're trying to take to Congress to create some laws that create an incentive for manufacturing quality. One of those is around just metrics of quality. Some way that FDA can be in a position to monitor the quality systems of manufacturers and make that transparent so that purchasers can make purchasing decisions based on where they have some confidence in the quality manufacturing of products. You also mentioned manufacturing sites and quality manufacturing. So that's another area that we have identified where laws can be strengthened, but I thought there was some laws passed relatively recently that ASHP actually supported that did create some disclosure requirements. What was that law and has it produced meaningful results in addressing shortages?

Erin Fox: In 2012 we had the FDASIA law and that really required drug manufacturers to disclose to FDA if they were going to stop making something or have a shortage. That notification is not public in any way, but the intent is that FDA will use that information to try to prevent the shortage from happening in the first place. Once a shortage happens, there's not much that FDA has in their tool kit to really ameliorate that problem. They can do a few things. So they can look for imports. Although nine times out of 10 when FDA goes to look to import a product to alleviate a shortage, there's not another country that has enough of that product to share with the US market because we're so large, and so that's usually the rate limiting step with importation. FDA can also ask other companies to ramp up supply. That doesn't always work because they may not have capacity. In isolated cases, FDA can use their regulatory discretion and allow product that they normally wouldn't let stay on the market, like if it has glass shavings in the vial, they might say, "We are going to allow hospitals to continue to use this product but they must filter it." And then that will avoid a very critical shortage. So those are some of the things in FDA's tool kit, but none of those are really good at solving a shortage once it starts.

Tom Kraus: Okay. So there's an aspect of sort of anticipating, but if something's already underway, you're sort of limited in what you can do. So one of the things we can do is put a little more emphasis on quality manufacturing. You mentioned contract manufacturing. Can you just talk a little bit about how contract manufacturing plays into shortages?

Erin Fox: Sure. So contract manufacturing happens throughout the drug manufacturing market. Basically it's when one company's factory makes a product for another company and that company puts their label on it. For example, if we had the Tom Kraus brand Vancomycin, you might have a contract manufacturer make that for you and

**001: Drug Shortages: A Conversation with Erin R. Fox,
Pharm.D., BCPS, FASHP**
Episode Transcription

you would put your name on it. Of course we don't have that, but that's how it works, and again, if you were that drug manufacturer, you would not have to say which company did the contract manufacturing. So that's part of why we need that additional transparency if we're going to know which factories are truly doing a good job and which factories to reward.

Tom Kraus: And I assume that there are probably circumstances where you have two or three manufacturers might actually use the same contract manufacturer. So if that contract manufacturer ends up having a quality problem, it doesn't mean one manufacturer has a supply disruption, it means all three of them do.

Erin Fox: That's exactly right. You can get a false sense of security looking maybe in FDA's Orange Book or online to say, "Oh well, we should be okay. This product has maybe three or four suppliers." But in reality in your example, there really can be just one company making that entire supply. So that's something that's not visible to really anybody, and so that's another weak link in our supply chain.

Tom Kraus: Do manufacturers have any obligation to think about how they're going to react if they do find themselves in a shortage situation, whether that's because of their own manufacturing challenge, or because of an API supplier, or a contract manufacturer?

Erin Fox: They don't. There's actually no requirement for them to manufacture anything, of course, and there's no requirement as part of the FDA approval process or even an FDA inspection process, there's no requirement for them to have even a business continuity plan. Even kind of a basic what if plan. Now, certainly some companies do this, but these are companies that are making very, very high cost branded products. It's worth it to them to have that business continuity plan, but for companies that are making very inexpensive products, if they have a shortage, it doesn't really hurt their bottom line, and so there's no incentive for them to have any type of a business continuity plan. It's easier for them to just have that shortage.

Tom Kraus: Okay, so in those situations, one of the things we could think about is some relatively light touch way to say, "Manufacturer, do you have some kind of contingency planning in place? You're not obligated to do anything, but can you at least do a little bit of the forward thinking of how would you respond if you found yourself in this situation?"

Erin Fox: Yeah, no, that would be a great idea. As FDA is thinking about quality metrics and I noticed that they just reopened the docket for comments on FDA quality metrics. That might be something that goes into that scoring system. Does the company have a business continuity plan? That could maybe give them a little bit of a higher rating than a company that chooses not to plan ahead.

Tom Kraus: And you mentioned some of the other things that FDA can do to respond to shortages. Can you tell us a little bit about how compounding fits into that?

Erin Fox: Yeah. I think when FDA started the 503B process to allow compounding to help with shortages, I think they were a little more hopeful that it would provide better resources for people than it actually has. I think part of the reason it hasn't been very

**001: Drug Shortages: A Conversation with Erin R. Fox,
Pharm.D., BCPS, FASHP**
Episode Transcription

successful is 503B compounders are not allowed to compound anything until it appears on the FDA shortage list. Now, FDA takes some time before they post something on their shortage list. Our ASHP list has things much earlier on there, but FDA takes some time. It then takes those compounders, the ones doing a good job anyway, at least three to four weeks to make a good batch of compounded product and then ship it. But those compounders are kind of working in a bit of a vacuum because they receive no information from FDA about how long they will be allowed to sell that product. So they don't know how large of a batch to make. There is no information about how the duration of how long the shortage will last. So at any given time they could make a very large batch and FDA could take it off the shortage list and then they would be stuck with a large amount of product.

Tom Kraus: Okay. So just to make sure I understand. So because once something comes off that shortage list, that's when these 503B compounders are allowed to step into this space and they would come off as soon as FDA basically declare that the shortage is over.

Erin Fox: Yeah. So because the compounders don't have a lot of insight into whether or not FDA will post something on their shortage site, and when most hospitals have already had to make a plan to get by through the shortage and a lot of that planning requires large changes to the electronic health record. Those changes would have to happen again once you use a 503B compounded product. So it's just double the work for health system pharmacists to make those changes and you probably wouldn't go ahead and do that unless it was something extraordinarily critical and you were completely out.

Tom Kraus: If that's kind of how compounding factors into responding to shortages, are there incentives in place for traditional manufacturers to enter the space of products that are in shortage?

Erin Fox: A little bit. So FDA will certainly reach out to companies that either own an ANDA or have manufacturing capability and they will ask those companies to ramp up supply if they can. If a company wants to add a new product, FDA can kind of jump that company's application to the head of the line, give them a much faster approval. So that's really one of the things that FDA has in their tool kit. I remember maybe 10 years ago when we had a very severe methotrexate shortage, we had lots of news stories with lots of patients not being able to receive their treatment, and FDA was able to very quickly approve another company's product and that shortage was resolved actually very, very quickly. I'm not sure how fast that would have happened without all of the news stories because FDA didn't really have that ability to jump the line with applications at that time, but that is something in FDA's tool kit. But of course there has to be a facility that has the capability, and the capacity, and the willingness to make the product.

Tom Kraus: Sure. I seem to recall the now former FDA Commissioner Scott Gottlieb use some flexibility in his authority to say that FDA would expedite review of products with three or fewer sources of supply.

Erin Fox: Yeah, and he was actually aiming for improving competition to lower prices, but at the same time that also adding more suppliers really helps stabilize the supply chain

**001: Drug Shortages: A Conversation with Erin R. Fox,
Pharm.D., BCPS, FASHP**
Episode Transcription

for preventing shortages as well. So FDA did have that ability to accelerate approval for products that are in short supply, but also with that new guidance, it's great. Hopefully it will improve, but at the same time there aren't very many companies that are willing to do this type of manufacturing and so the facilities and capacity are limited.

Tom Kraus: One of the other issues that has come up when we think about drug shortages is how it relates to national security. This is actually a topic that ASHP hosted a summit on several years ago. What are the security concerns when it comes to shortages? I'm thinking a lot about sort of foreign sources of ingredients and foreign manufacturing. How does that play in?

Erin Fox: Yeah. I think there's a couple ways to think about shortages relating to our national security and I'm really happy that that topic, that this national security issue of shortages is rising to the top of several meetings that have occurred over the years. The first way to think about it is, do we have enough products to send our soldiers to war if we need to? Do we have enough products to take care of our own patients and keep our hospitals running? That's one way to think about it. But then when you think about where the raw come from, with more than 80% coming from foreign sources. If those foreign sources want to cut us off from those products, then we would be in a disastrous situation. So I think thinking about it from a national security perspective is really, really important. Especially thinking about antibiotics, the majority of those come from China. So thinking about being cut off from all of our antibiotics is a pretty scary situation and it deserves attention from a national security perspective.

Tom Kraus: Yeah, it certainly seems that there might be a vulnerability there when so much of our supply, especially of API and antibiotics is coming from foreign sources and in such a concentrated set of foreign sources, especially as now we're hearing about the sort of trade dispute between the US and China and how does that impact supply. That certainly seems like an area of risk and I'm glad that policymakers are starting to think about that. One of the requests that ASHP made of policymakers was to ask the Department of Health and Human Services and the Homeland Security Administration to look at these issues and actually come up with some recommendations to minimize those risks and presumably a lot of that would relate to having domestic sources of manufacturing.

Erin Fox: I'm really glad that that's being considered because it is such a scary situation to think about.

Tom Kraus: Another source of potential shortages that I've heard of is related to consolidation in the manufacturing industry. Do you have a sense of how that plays in? So I'm sort of thinking of situations where a couple of manufacturers combine and so then you end up with only one and that can have separate price implications, but what does that do for shortages and have we seen that happen?

Erin Fox: Yeah, we've definitely seen that happen, and I think what it does is it contributes to a more fragile supply chain for particularly for injectables, which is where we've seen most of the consolidation, but we talked about transparency earlier. Again, it

**001: Drug Shortages: A Conversation with Erin R. Fox,
Pharm.D., BCPS, FASHP**
Episode Transcription

could look like we have three suppliers, but maybe one company is really only making it. So we've seen a consolidation in the contract manufacturing department. We can also think about consolidation from the API, from the raw material perspective. There might even be eight suppliers, but if every single one of those suppliers is using raw material from one source in China, or one source in India, in a vulnerable area, that also creates a very fragile supply chain with just one mishap. One misstep can create some really severe repercussions.

Tom Kraus: Are there any other issues we should keep in mind in responding to shortages?

Erin Fox: There's one thing that I would like to maybe touch on if we could about the predictability of shortages. So right now everyone is really looking for a way to predict shortages and FDA is the closest to being able to do that, but not even FDA has all of the elements that you would need to truly predict a shortage. Some of the gaps that FDA has are they don't always know the true capacity at a factory, and if a company has approval to use two sources of products, then FDA doesn't always know which source of raw material that company is using. So to truly predict shortages, FDA is definitely the closest, but right now that is something that would be good for FDA to have more of those data points to be able to try to get to a predictive model and try to prevent those shortages from happening in the first place.

Tom Kraus: So we've touched on a few different themes that lead to shortages. You mentioned pricing pressure resulting in low investment in manufacturing quality. We talked about a lack of transparency into anticipated shortages, making it difficult for FDA to respond when there is a shortage. We also talked about a lack of contingency planning, making it difficult for manufacturers to respond to shortages. We talked about mergers and acquisitions leading to a consolidation in the number of manufacturers in the market, and finally we talked about national security risks, particularly those related to foreign sourcing of API. ASHP actually has identified policy priorities that address each of those different areas of concern.

We also want to make listeners aware that legislation was recently introduced that incorporates several of these priorities.

The introduction of this legislation is a first step to advancing these policy priorities. To become law, the legislation will need to be approved by the full Senate and the House of Representatives.

Listeners can see ASHP's policy solutions and let congress know they support this legislation by following the link in the show notes to this podcast, or in the advocacy section of ASHP.org.

Erin, thank you again for speaking with us today.

Erin Fox: Thanks very much.

Speaker 1: Thank you for listening to ASHP Official, the voice of pharmacists advancing healthcare. Be sure to visit ASHP.org/podcast to discover more great episodes, access

**001: Drug Shortages: A Conversation with Erin R. Fox,
Pharm.D., BCPS, FASHP**
Episode Transcription

show notes, and download the episode transcript. If you loved the episode and want to hear more, be sure to subscribe, rate, or leave a review. Join us next time on ASHP Official.