Compounding Drivers and Problems Dissected by Merck Pharmacy Expert at April PDA Annual Meeting

Root causes of the problems in the pharmacy compounding arena range from the absence of training in pharmacy schools to commercial pressures that prompt established pharmaceutical firms to leave the market and force hospitals to rely on less qualified providers to fill their immediate patient needs, Merck Engineering BioSterile Validation Director Chris Smalley commented at the April PDA annual meeting held in San Antonio, Texas.

Smalley’s insightful analysis of the current high-profile issues in the compounding arena was informed by both his extensive pharma experience as well as by the first two decades of his career, which was spent in the U.S. military as a licensed pharmacist performing hospital compounding.

As a hospital pharmacist, Smalley prepared IVs and total parenteral nutritional (TPN) packages. He explained that his training in pharmacy school in the 1970’s included laboratory courses that taught various types of compounding and evaluated the student’s ability to perform them.

“I couldn’t pass compounding lab until I could make capsules,” Smalley commented. “We made suppositories. We made powder…. And we made sterile products,” including hand-filling ampules with syringes. “I learned about aseptic technique.”

Over the intervening three decades, the pharmacy school curriculum has shifted towards clinical pharmacy – focused on drug/patient issues – and hands-on pharmacy compounding is no longer usually taught, Smalley pointed out.

Smalley commented during the Q&A after his presentation that pharmacists and those inspecting them – especially at the state level – generally have not had the training or the skills to either perform compounding or evaluate those who do.

“The New England Compounding Center (NECC) was inspected by the Massachusetts State Board of Pharmacy several times,” he pointed out, and “it continued to operate.”

Pharmacists have a role in healthcare, “but they are not being taught compounding pharmacy anymore. And yet a pharmacist goes out and gets a license and is entitled to do things like making TPN solutions and do compounding. It is a real concern of mine.”

Smalley explained that the American Society of Healthcare Pharmacists published a book that provides instructions on how to perform various types of compounding. “I don’t think reading a book would help you
manufacture sterile products in your facility. They might have book knowledge, but it has a lot to do with skills.”

**USP Forum Also Stresses Training Concerns**

At a two-day forum on microbiology that took place at USP headquarters in Rockville, Maryland in March, 2013, a panel of experts that was convened to review compounding issues also pointed to training in pharmacy compounding as a key driver of the sterility issues that have been surfacing *(IPQ May 29th, 2013)*.

In focus during the session were the aseptic practice, training, laboratory and regulatory concerns that have surfaced among sterile compounders in the US and how the 2008 version of USP’s sterile compounding chapter <797> should be refined to help address them.

**A basic message that emerged is that, compared to pharmaceutical manufacturers, the technicians doing sterile pharmacy compounding have a much harder job with generally much less training and expertise to accomplish it.**

Participating on the panel were two members of USP’s Sterile Compounding Committee, Keith St. John and Erik Kastango, and two members of the USP Microbiology Expert Committee to which it reports, Jim Agallaco and Russ Madsen. Kastango is heading the committee that is looking at revising USP <797>.

“Pharmacy schools do not train pharmacists on aseptic processing or control or sterility assurance,” Kastango commented. “All of that stuff is tribal lore. It is verbal tradition. So it is going to be, ‘I go to my new tribe. I go to my new facility. And I am going to get trained by Keith. And I am now here. Keith leaves and Russ gets hired and so now I am going to train Russ.’ So you have this rotation over time of what people understand.”

**Madsen supported the training observation with data from a Wall Street Journal article that reported on a study looking at contamination rates in pharmacy compounding operations.**

The study showed that pharmacists who were doing media fills in compounding had a contamination rate of about 4%. For technicians in the same pharmacies, the contamination rate was about 8%. “Compare and contrast that with what we see in the pharmaceutical industry for aseptic processing. It is down around 0.1% or better,” Madsen emphasized.

“So we see orders of magnitude differences. And I relate this to training and skill, and trying – without the benefit of scale-up, without the benefit of process development, working with a very wide variety of materials and products – to produce sterile compounded products. It is very difficult on its face.”

**Cost Pressures, Drug Shortages Drive Compounding**

During the Q&A at the April PDA meeting, Smalley also pointed to changes that have taken place in the pharmaceutical industry over time that have driven the growth in pharmacy compounding, including less pharmacist presence, an increasing focus on costs and profits, and the resulting drug shortage problems.
In the 1970’s as a newly-graduated pharmacist, Smalley had the opportunity to tour pharmaceutical plants. At that time, “the head of packaging was a pharmacist. The manager of production was a pharmacist. The manager of quality was a pharmacist. There used to be a very nice interconnection between industry and pharmacy. It has become very separated. It has become difficult for us to talk.”

At that time, Smalley recounted, Parke Davis and Eli Lilly were the two largest pharmaceutical manufacturers. “They made everything. I could buy ammonium chloride in perchlorate tablets,” taken by people with tuberculosis to improve their airflow. “I am sure that it was not a big contributor to the bottom line. But that was the focus of pharmaceutical companies like Parke Davis and Eli Lilly – to make product available that met the need of patients.”

In “most” pharma companies today, Smalley maintained, the focus has shifted to the financial contribution of products to the company’s bottom line, with products periodically dropped that meet patient needs but are not profitable. Compounding pharmacies step in to fill the gaps when these products that patients need are not commercially available.

The decreased profits from products with thin margins and those about to go off patent can also play out in drug shortages, Smalley explained.

Referencing the narcotic drug oxycontin, currently in short supply, Smalley commented that “if oxycontin was a big moneymaker, there would be no shortage. There would be some manufacturer out there pulling their hair out to make sure that the product was on the market because they were making a good buck.”

Existing products and those going generic that have very thin margins and do not contribute a lot to the bottom lines of the companies “wind up having this problem like oxycontin.” There is little financial incentive for industry to resolve the drug shortage issue with these products, the Merck official maintained.

Smalley recounted an experience he had at Wyeth regarding an oral antibiotic that went off patent and the company’s actions at the time that inadvertently led to a shortage of the drug.

“The day the product went off patent,” he explained, “Wyeth did not wait to see what the sales were going to be or how much it was going to earn. They closed the plant, laid everyone off, and began deconstructing the plant, because they knew it was not going to be a big profit contributor.”

Because the generic firms had not yet geared up production and did not anticipate that Wyeth would immediately leave the market, a “significant” shortage situation resulted that lasted “for about six or nine months. That happens a lot.”

Drug shortages are “driving a lot of our compounding right now,” Smalley stressed. “The increasing amount of drug shortages is accelerating the need and demand for compounding.”

Voluntary Outsourcing Registration of Concern
During the Q&A after his presentation, Smalley also expressed concern regarding the voluntary approach that has been written into the Drug Quality and Safety Act (DQSA) for pharmacy compounders registering as “outsourcers,” ([IPQ December 28, 2013]) noting the potential for abuse of the system.

FDA recognizes that some drug availability is going to have to be managed by compounding pharmacies as provided for in DQSA and the follow-up outsourcing registration draft guidance.

In exchange, facilities are supposed to voluntarily enroll so that they can be inspected to assure that they meet relevant CGMP requirements – one of the qualification criteria for the “outsourcer” status. “But the key word is ‘voluntary,’” Smalley said. “So, in the end, who do you think is going to enroll? The ones that really need the help? Or the ones that are in pretty good shape?”

The comment drew a question from a participant, who asked whether a hospital would be more likely to source compounded products from an FDA-registered facility, and whether they would face any liability if there were issues with a product that had been obtained from a compounding that was not registered.

Smalley responded with an analogy to demonstrate the two facets of the issue: Whether people are aware of registration or accreditation programs, and if so, whether they perceive them to provide any value.

He pointed to USP’s program for accreditation of nutritional supplements. “A manufacturer can enroll in the USP program and get a symbol on their product that says that it meets USP standards for their nutritional product,” he explained. “Maybe it has not been publicized enough, so maybe it is a matter of awareness. But are people willing to pay 20% more to pick a bottle off the shelf that has that label – that so-called seal of approval?”

If someone purchases an electric product in the U.S., Smalley maintained, that person would probably be unwilling to buy a product that did not have an underwriters laboratory label on it. “The fact of the matter is that about 20% of the electrical products in the United States are illegally imported from countries like China, and the UL label has been counterfeited onto that product,” he commented.

While there “should be a willingness to pay a little bit more” to assure product quality, ultimately Smalley suspects that the ability to provide the desired product reliably, in a timely manner, and at a reasonable cost, would be the primary deciding factors for a hospital pharmacy director making sourcing decisions. Whether the firm is enrolled in the FDA program would likely be a secondary consideration.

Smalley also expressed concern that there will be compounders that do not enroll as outsourcers and try to “fly below the radar.”

There are going to be “thresholds” for detection, he commented, such as whether products are introduced into interstate commerce or exceed a certain volume. “There are going to be people out there who are going to say, ‘I understand what that threshold is and I am going to stay below that threshold,’” because of a perception that meeting the FDA requirements would be cost-prohibitive.

“It scares me,” he emphasized, “the whole concept of…having thresholds is just a struggle.”
MERCK’S CHRIS SMALLEY ON DRIVERS FOR INCREASED STERILE COMPOUNDING

At the 2014 PDA annual meeting, Merck BioSterile Validation Engineering Director Chris Smalley reviewed some of the more high-profile contamination events with compounded injectables and then discussed three drivers for the increased reliance of healthcare practitioners on sterile compounding:

● the lack of commercially-available products
● drug shortages, and
● cost pressures.

I am going way back before NECC. In 2001, eleven people in Northern California developed bacterial infections from injections with compounded betamethasone – a steroid. Three died.

In 2002, seven people became ill and two died from fungal infections caused by contaminated methylprednisolone, another steroid, made by a compounding pharmacy in South Carolina.

In 2011, contaminated steroids were injected into the eyes of patients in Florida for macular degeneration. There is a product on the market for macular degeneration, but it is extremely expensive. What happens is, the price pressures cause people to consider going to alternate products. There is, in fact, a product that is commercially made, but it does not have as an indication the injection in the eye for macular degeneration. The manufacturer does not make that claim. And compounding pharmacies have arisen that will make that product and will make that claim.

And here, thirteen people, instead of having the macular degeneration stopped – since sometimes you are not curing the macular degeneration but you are stopping the degradation – got a contaminated steroid product that damaged their eyes.

So maybe in 2001, and in 2011, you didn’t hear about it because we have a threshold of how many deaths it takes get our attention nationally. The New England Compounding Center probably hit that threshold with 50 deaths. And what was the product? A steroid injection. And 720 additional people were injured. [Editor’s Note: For more on the compounding problems and the regulatory environment that preceded the NECC crisis, see IPQ’s November 2012 Special Report.]

Okay, 50 deaths probably hit our threshold. Now everyone is interested and everyone is excited. And what you noticed is, every product that we have been talking is a steroid.

What makes this popular? What makes this demand for compounding pharmacies? Physicians do not want to inject a preservative-containing product, intrathecal – into the spinal canal. So what is our root cause?

Lack of Commercially-Available Products

Our root cause is that we are not making commercially available products. There is a need, and the physicians are demanding this from pharmacists. I can tell you, I have been standing in the pharmacy when the pharmacist has said, ‘that’s not commercially available. I can’t give you what you need.’
And of course the pharmacist winds up first telling the nurse, because the nurse is the one who wants the product to give to the patient. The nurse in turn tells the physician. The physician, in turn, calls the pharmacy and dances on the pharmacist’s face and says, ‘why can’t you give me what I need? I am the captain of this ship.’ Physicians regard themselves as being the captain of the ship. ‘This is what I want. You are responsible as the pharmacist for giving me what I want, for giving me the meds I need to treat my patient. Get it.’ There is a lot of pressure on the pharmacist.

So let’s continue to talk about what drives some of these things…. Sometimes products are commercially available as they are listed in the catalogue, but they are not available at the time the pharmacist needs them.

**Drug Shortages**

These are recalls from us – the pharmaceutical industry. [In December 2013] Baxter initiates a worldwide voluntary recall of 5% dextrose injection and normal saline solution, 0.9% sodium chloride injection for IV solutions. Okay. A doctor writes an order for a patient. What am I going to do? I am going to take 5% dextrose and I am going to put enough sodium chloride in to get it up to 0.9%. I am going to start compounding, because the product is not commercially available to me.

[Also in December 2013] Hospira issues a voluntary recall of one lot of Lidocaine injection of 2%, 5 ml in 5 ml vials due to the presence of particulate matter. We receive an awful lot of particulate matter recalls. Recently there was a recall where one company found a particle in a vial that was on stability, notified FDA, and wound up recalling the whole lot.

That lot gets recalled. I need Lidocaine 2%. Now I probably have Lidocaine 50% on my shelf. So what am I going to do? I am going to take Lidocaine 50% and dilute it and make up smaller vials. I am now compounding, because commercially available products have been withdrawn from the market. These recalls creating drug shortages are getting to be more and more of a problem….

Drug shortages are driving a lot of our compounding right now. Earlier I talked about how product simply wasn’t commercially available, and now I am talking about how the increasing amount of drug shortages is accelerating the need and demand for compounding.

A Pfizer facility caused a drug shortage…. [There] is an instruction to me as a pharmacist at a hospital from the director of pharmacy to prepare these compounds because these compounds were no longer being made available. The one I want to highlight for you is oxytocin, 10 units in a 500 ml normal saline solution bag. How many people know what oxytocin is normally used for in a hospital? Wow. Didn’t get a lot of hands raised.

It is crucial. If you have a doctor in the delivery room, if you have an OBGYN, and the delivery is scheduled, their hair is going to be on fire if they don’t have oxytocin available. That is the best way I can characterize it.

This is the instruction to the pharmacist: ‘Currently, oxytocin 20 units of 100 and 1000 ml in normal saline solution must still be made in the pharmacy and stocked in the Women’s Care Unit.’ One of the reasons I point this out is because earlier I said that prescriptions are made based upon the physician’s order for a patient. This points out how we are beginning to detach ourselves from that philosophy. Pharmacies in hospitals will
compound these and stock them in the nurse’s unit before the doctor’s order has been received, so that when the doctor wants the oxytocin it is there and he can give it to the woman who is going to deliver.

So we begin to detach ourselves. No one is being evil. No one is being malicious. But philosophically we are beginning to separate the concept of filling to an order. In fact now, even within the hospital, we are compounding to stockpile in anticipation of that order.

So when we talk about these compounding pharmacies not filling to an order – and in fact, this is what FDA has been trying to achieve with the new law – hospitals have been doing this for a while.

**Cost Pressures**

Cost remains a big concern. Everyone is on a tight budget. The Affordable Care Act (ACA) actually cuts reimbursements further. For those of you who are not familiar with some of the things hospitals are struggling with in the ACA, if someone is admitted to a hospital with one of three types of conditions, such as a heart attack, and they are discharged from the hospital, if they need to be re-admitted to the hospital within a certain time-frame, the hospital will not be paid for the re-admission. The hospital is being told that when it discharges that patient there have to be more effective after-care activities that are taking place to ensure that the patient is not being re-admitted. And by the way, if you need to re-admit the patient, you are not going to be reimbursed for your cost.

The cost demands are extreme on hospitals. I can tell you within the next three years you are probably going to 20% of hospitals in the United States go out of business.

I want to talk more about this third factor. I actually have the article right here. ‘US Medicine’ is a publication that services healthcare providers in the military and also in the Veterans Administration. I continue to receive it, even though I am now retired, as a courtesy.

It talks about how Walter Reed, one of the premier hospitals in the US military system, has saved $700,000. The gist of the article is that by using a closed transfer device, they can now, on average, get ten doses out of nine single dose vials. They know that there is over-filling in single dose vials. So by using a closed transfer system, they now know by the time they open up nine vials, they have enough overfill to that they can get a tenth dose.

They are so proud of it that they published an article. [The pharmaceutical industry is] making single dose vials with the intention that the single dose vial, obviously, will be used one time. Maybe you do it that way because you are able to reduce or eliminate a preservative in that single dose vial. Remember earlier the demand for intrathecal use was ‘let’s get the preservatives out.’ So now you want to use that single dose vial, and nine vials will be combined to give ten doses, and they will save $700,000. It is that important to them. They do not realize the risk that they are putting on the patients.

Between drug shortages, product not-available, plus savings, this is why as an industry we have to be interested in compounding pharmacy.
For a pharmacist, I would tell you, whatever your role is, it is to ultimately meet the needs of the patient. You might regard your customer as being the physician. You might regard your customer as being the healthcare system. But ultimately the needs of the patient need to be met. All of these forces are impacting on what is causing more pharmacy compounding – skills, cost, and availability. But ultimately we have to ensure the patient is not being harmed.

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