2015

# Pharmaceutical Compounding Roundtable:

## How can outsourcing facilities meet provider needs?

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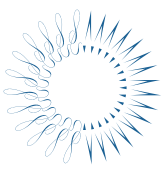

THE PEW CHARITABLE TRUSTS

# 2015 PHARMACEUTICAL COMPOUNDING ROUNDTABLE: How Can Outsourcing Facilities Meet Provider Needs?

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# OVERVIEW

In October 2015, The Pew Charitable Trusts (Pew) and the American Society of Health-System Pharmacists (ASHP) convened a stakeholder roundtable to discuss what compounded or repackaged products doctors' offices and clinics keep in stock, and whether and how "outsourcing facilities" — a new FDA-regulated source of compounded drugs — can provide them.

Providers sometimes need compounded drugs — specially tailored medicines prepared to meet unique patient needs — for treatment or procedures in their offices, which requires keeping a supply of these drugs on hand. This need was addressed by the 2013 Compounding Quality Act (CQA) which created a new sector of FDA-regulated drug compounders, called "outsourcing facilities," which are permitted to compound supplies of non-patient-specific drugs for providers. By contrast, traditional pharmacy compounding is done pursuant to individual patient prescriptions.

The CQA was a direct response to a fungal meningitis outbreak during which 753 patients were sickened, and 64 died. The outbreak was linked to contaminated compounded injections made at a single compounding pharmacy in Massachusetts. The CQA recognizes that facilities making higher volumes of compounded drugs should meet higher quality standards enforced by the FDA to better protect patients.

The Pew-ASHP conference "2015 Pharmaceutical Compounding Roundtable: How Can Outsourcing Facilities Meet Provider Needs?" had the following goals:

- Advance outsourcing facility awareness of compounded or repackaged drugs needed by practitioners, and advance provider awareness of outsourcing facilities as a source for compounded or repackaged products.
- Identify and understand barriers outsourcing facilities face in producing compounded or repackaged products, and facilitate discussion on how to overcome these barriers.
- Explore opportunities for standardization of certain compounded and repackaged products to support more efficient and viable production by outsourcing facilities.
- Educate participants about outsourcing facilities as created by the Drug Quality and Security Act (DQSA), and the differences between outsourcing facilities and traditional compounding pharmacies, including the quality standards applied.

The meeting focused on four therapeutic areas in which sterile compounded or repackaged drugs are routinely used: ophthalmology, pain management, anesthesiology, and parenteral nutrition. Participants included practitioners from within each of these sectors and representatives of the outsourcing facility sector, as well as other experts and stakeholders. Please see the Appendix for a complete list of participants.

These proceedings describe a roundtable discussion of the needs and opportunities of each therapeutic focus area, and summarize key findings. The conclusions of this report may not reflect the individual views of each participant.

# INTRODUCTORY REMARKS AND BACKGROUND

## Overview of the CQA and the outsourcing facility sector

To provide background and establish shared understanding, the roundtable began with presentations on the legal framework for the new outsourcing facility sector, and the outsourcing of sterile compounding by health-systems. Gabrielle Cosel, manager of the drug safety project with The Pew Charitable Trusts, presented an overview of the CQA of 2013, and described the differences between federal policies applicable to traditional compounding pharmacies, covered by section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA), versus the new "outsourcing facilities" sector under section 503B of the FDCA, created by the CQA.

The principal difference between these two categories is that outsourcing facilities under section 503B are permitted to compound supplies of drugs without prescriptions, but they must meet current Good Manufacturing Practices (cGMPs), which are the same quality standards applied to drug manufacturers. Conversely, traditional compounding pharmacies that are compliant with section 503A must compound pursuant to individual patient prescriptions, but they are exempt from the cGMPs.

The new outsourcing facility sector was the outcome of congressional deliberations on how to draw a better line between traditional pharmacy compounding and manufacturing. Over the years, this distinction had become blurred by the emergence of specialized compounding facilities preparing supplies of drugs for use in hospitals and clinics, rather than the more traditional patient-specific mode of practice. Congress recognized that providers relied on supplies of certain sterile compounded medicines, but also that higher quality standards were appropriate when drugs had the potential to reach many more patients across a larger market, resulting in broader patient exposure risk if a contamination event occurred.

In addition to meeting cGMPs, outsourcing facilities must report biannually to FDA the compounded drugs they make, as well as serious adverse events. They may also only compound from an active pharmaceutical ingredient (API) if it has been identified by FDA as a bulk drug substance that can be used for compounding because there is a clinical need. Both outsourcing facilities and traditional compounding pharmacies in compliance with 503A may not copy commercially available products (unless, for a 503B, the product is on FDA's drug shortage list), and may not make medications on FDA lists of drugs that are demonstrably difficult to compound, or drugs that have been withdrawn or removed from the market due to safety or efficacy concerns.

Over 50 outsourcing facilities across 24 states are currently registered with the FDA. While outsourcing facilities are now defined in the CQA, this sector is still becoming established, and business models and portfolios are still in flux. The success of this sector will likely be affected by utilization and provider demand, as well as clear regulatory oversight that upholds the distinctions between 503A and 503B entities.

## Overview of outsourcing of sterile compounding

Bona E. Benjamin, director of medication-use quality improvement and coordinator of drug shortages resources at ASHP's Center for Medication Safety and Quality, presented an overview of trends and opportunities related to health-system outsourcing of sterile compounding.

Ms. Benjamin began by describing the emergence of outsourced compounding, which grew out of an earlier shift in sterile drug preparation from nursing to pharmacy that began in the 1970s. This shift was driven by increases in the volume, scope, and complexity of sterile compounding such as for total parenteral nutrition (TPN) solutions, cardioplegia solutions, and pain medications administered

intrathecally (into the central nervous system). The need to comply with 2004 United States Pharmacopeial Convention (USP) standards on sterile compounding additionally drove reliance on pharmacy and pharmacy technicians.

Increased medication complexity and growth of pharmacy sterile compounding practice also led to outsourcing. While pharmacists are trained in compounding, few come out of school prepared to run a large, central sterile drug preparation facility. This highly specialized type of work requires a great deal of technical knowledge about pharmaceutics and quality control.

One of the earliest outsourced preparations was TPN, due to the number of ingredients needed, and the greater risk of patient harm if contamination occurs, as these products are more conducive than others to bacterial growth. Facilities specializing in TPN compounding emerged to meet provider needs, especially in the home care sector. In 2002, ASHP found that about half of 513 hospitals surveyed were outsourcing TPN.

Outsourcing continued to increase over the years, with particular growth in patient-controlled pain medicines and epidurals. As of 2011, 66 percent of hospitals reported using outsourced compounding. Ms. Benjamin noted that outsourcing by hospitals dropped precipitously after the fungal meningitis outbreak associated with compounded drugs in 2012, but is now beginning to return to pre-2012 levels. The most commonly outsourced products include intravenous pain medicine delivered via patient controlled pumps or IV-PCA (60 percent of responding hospitals), Pitocin/oxytocin (56 percent), epidural injections for pain (50 percent), TPNs (34 percent), drugs on shortage (34 percent), operating room syringes (29 percent), and intravenous opioids (27 percent).

Ms. Benjamin described several advantages to outsourcing sterile compounding, which for hospitals is a highly labor-intensive, training-intensive, and resource-intensive process. Sourcing these products from a specialized supplier can be a better route for difficult to compound drugs and drugs in shortage, and can allow health-system pharmacists to focus on patient care activities – reducing redundancy and operational inefficiencies, and limiting exposure to hazardous drugs. Outsourcing offers particular advantages for ambulatory care centers and other clinics that are less likely to have a pharmacist or significant compounding capacity on site. Ms. Benjamin suggested that outsourcing compounding can reduce the medication preparation burden for physicians, allowing them more time to focus on patient care as well.

According to Ms. Benjamin, there are particular advantages to sourcing sterile preparations from the new outsourcing facility sector created by the CQA. In addition to being able to compound supplies of commonly used drugs without first receiving prescriptions, outsourcing facilities can also set extended beyond-use dating (BUD) based on stability tests, allowing products to be safely kept on the shelf for longer periods of time. This sector will also adhere to Good Manufacturing Practices (GMPs), increasing safety for patients.

Ms. Benjamin described several resources available to health care providers interested in outsourcing sterile medications, including ASHP's Guidelines on Outsourcing Sterile Compounding Services and their Outsourcing Sterile Products Preparation: Contractor Assessment Tool. Both resources cover the new FDA-regulated outsourcing facility sector, and are available online.

## SESSION ONE: Perspectives from the Outsourcing Facility Sector

During session one of the roundtable, Central Admixture Pharmacy Services (CAPS), PharMEDium Services, LCC, Avella Specialty Pharmacy, and JCB Laboratories shared their experiences as members of the new outsourcing facility sector. All four companies were established prior to enactment of the CQA, from the early 1990s to the early 2000s. The products provided by these companies, used in both inpatient and outpatient care settings, include cardioplegia products, drugs requiring complex drug delivery systems, unit-dose controlled substances, anesthesia drugs in syringes, medications for postoperative pain pumps, continuous renal replacement therapy, ophthalmic formulations, and starter total parenteral nutrition solutions.

### Increased quality standards

The presenters described their experiences as outsourcing facilities, able to compound supplies of non-patient-specific products per federal law (as opposed to traditional compounding pharmacies limited to patient-specific compounding) and the significant quality enhancements they have made to meet the cGMPs required of the sector. These included upgrades to, and increased testing and validation of, facilities and equipment; hiring pharmaceutical quality experts, as pharmacists do not learn GMP in pharmacy school; product sterility, endotoxin, and potency testing for every batch; increased air and surface sampling; use of sterile gowns, masks, and footwear; and use of enhanced bactericidal and sporicidal cleaning and sanitation agents. Participants emphasized that cGMP compliance was significantly different from meeting USP <797> quality standards, and required significant financial investment.

### Product standardization

Participants also described attempts to initiate greater product standardization in order to take advantage of economies of scale. Although outsourcing facilities produce large lots of standardized medicines, they also receive requests for dozens of formulation variations due to varying provider preference. Participants cited ropivacaine and bupivacaine, local anesthetics, as examples. Clients may request these drugs in concentrations that vary only a few hundredths of a percent (e.g., 0.1 percent, 0.12 percent, or 0.15 percent), but there may not be evidence that these small differences improve the quality of patient care.

The presenters described limited success working with provider groups to identify formulations that could be standardized. Despite consensus on which standardized concentrations to use, not all providers will use them. Standardization would support larger batch sizes, better facilitate quality oversight, and reduce testing costs for each batch — costs that an outsourcing facility might otherwise have to pass on to customers. One presenter estimated that potency and sterility testing costs between $86 and $1,200 per batch, depending on the product. Presenters emphasized the overall goal is providing the safest possible product without an insurmountable cost increase to the facility and to customers, and that standardization can help achieve this. From the provider perspective, increased standardization might also streamline processes, increase safety, and reduce waste.

Increased standardization to address the challenges of small batch preparation is an important factor to the viability of the outsourcing facility business model. But presenters also described a number of additional challenges they face as their new sector is established. One such challenge was a need for greater provider awareness about the differences between outsourcing facilities and traditional compounding pharmacies, and consequent valuing

of the safety and quality of a drug prepared by an outsourcing facility compared to one prepared by a traditional compounding pharmacy operating under less stringent quality and safety standards.

## Oversight and regulation

Presenters also described regulatory oversight challenges. For example, the sector is currently relying on FDA draft guidance, inspection reports, and warning letters to make business decisions regarding their facilities. Facilities must respond to FDA inspectional findings with plans for corrective action, however in some cases there is no clear guidance from FDA on what the optimal corrective action would be. Outsourcing facilities are eager to have final FDA policy on applicable GMPs – the quality standard required of the sector – to provide certainty about the agency's expectations. Outsourcers also expressed a need for increased training and knowledgeable experts on Good Manufacturing Practices. Compounding is traditionally a pharmacy practice, but pharmacy training does not traditionally include GMPs – standards that were originally created for commercial drug production.

Finally, presenters described struggles with inconsistent regulation by the states. While outsourcing facilities register with and receive primary oversight from the FDA, many states also require these facilities to be licensed or registered with the state, but not in consistent manner. Some states require licensure as a manufacturer, some as a wholesaler, and some as a pharmacy. In at least one state, an entity licensed as a wholesaler may not also be licensed as a pharmacy. Only a few states have yet created a specific "outsourcing facility" regulatory category. Similarly to pharmacists, state inspectors are also not generally trained to know GMPs, complicating oversight.

In addition, federal law requires that outsourcing facilities employ a pharmacist to oversee compounding operations. According to participants, 12 states require this pharmacist in charge to hold an active state license. This means that the pharmacist in charge of an outsourcing facility shipping to those states might be required to hold 12 separate state licenses to be in compliance.

## SESSION ONE: Discussion

### Provider knowledge

Following presentations by the outsourcing facility participants, attendees engaged in a group roundtable discussion. A first, key discussion point was the status of provider understanding about compounding. Following the national meningitis outbreak in 2012 and 2013 linked to compounded injections, providers reported diminished trust in compounded drugs, and a greater desire to understand where these products are made, and to what quality standards they are held. Patient safety was paramount behind these increased concerns, but also provider liability. One provider described the numerous lawsuits against practitioners following the 2012-13 outbreak for lack of due diligence in ensuring the quality of the compounded drugs they were using with patients. The provider saw a lack of awareness among clinicians about the quality standards appropriate for compounding that persists to this day.

Those seated at the roundtable felt that hospital providers had a greater awareness of the new outsourcing facility sector, and the legal and patient safety reasons to purchase from them, but that similar awareness may not exist in physician communities outside of the hospital setting. Participants agreed that more education was needed, particularly regarding the distinction between traditional pharmacies and outsourcing facilities. Physicians may be accustomed to ordering compounded drugs from traditional pharmacies, and may not be aware of the new outsourcing facility sector, or that new federal requirements prohibit traditional pharmacies from compounding without a prescription. They may not understand that different and more stringent quality standards apply to outsourcing facilities. Providers may not have visited the traditional compounding facilities they source from, and may not even be able to visit when those facilities are in distant states. Purchasers may also not be aware that inspections of traditional pharmacies and outsourcing facilities differ significantly. In one company's experience, a 503A facility inspection lasted only a few hours, and was mainly focused on the paperwork — the clean room was not inspected.

For those that were sourcing from outsourcing facilities, providers at the roundtable reported difficulties in assessing FDA oversight of this sector. First, FDA's risk-based inspection schedule may be confusing to providers, who are accustomed to reviewing more regular, if less intensive, state inspections of traditional compounding pharmacies. But perhaps more importantly, because the sector is new, and newly held to a more strict set of quality standards, most FDA inspections of outsourcing facilities have identified compliance issues. It is hard for providers to distinguish between quality issues that should discourage purchasing from a given facility, versus issues that are reflective of a transitional time for the sector, and that companies are working to address — made additionally challenging by the lack of final FDA policy on the specific GMP criteria they will apply. Participants felt that additional, accessible information on how outsourcing facilities have addressed compliance concerns and resolved them would be of value. Participants also noted that while FDA inspectional findings are not something providers would typically use when assessing suppliers of compounded drugs, FDA's transparency when applying higher standards should also instill confidence.

### Cost and quality

A second, related topic of discussion was how providers that purchase compounded drugs value increased quality requirements. Providers, particularly those outside of the hospital community, may be accustomed to sourcing supplies of compounded drugs from traditional compounding pharmacies, and if they have not seen any quality issues that affect patients, they may not see a need to switch to outsourcing facilities that comply with stronger quality standards.

Lack of observed patient harms may lead providers to assume that products from a traditional pharmacy and from an outsourcing facility are equally safe. Without demonstrated benefits of quality enhancements, stakeholders may not be inclined to accept increased costs that may come with greater assurance of product quality. These costs would be normally borne by providers, but might also be borne by patients who are not covered by insurance.

But roundtable participants recognized that lack of observed problems with drugs compounded by a traditional pharmacy does not mean these issues do not exist. Contamination in a sterile product may not cause serious harms in all cases, and some adverse effects may not be noticed or reported, or may not be linked to a problem with a compounded product, particularly for very ill patients. Even when observed, adverse events may be inconsistently reported, as state reporting requirements differ. Lack of robust adverse event reporting means there may be a continued lack of awareness regarding the benefits of switching to outsourcing facilities with higher quality standards. But meaningful adverse event data may not be easily obtained or available at all. One provider participant noted that outcomes may be too rare to show anything meaningful, which is why we look to process measures, and why inspections of compounding facilities focus on issues like air contamination, rather than reported patient harms. Stricter sterile production controls do reduce the risk of contamination, and risk aversion is particularly important for compounding supplies of drugs without patient-specific prescriptions, particularly when those drugs reach greater numbers of patients. Participants circled back to provider education as a critical means to addressing this problem. As one provider put it, in the field of medicine, one catastrophe is one too many.

Participants from the outsourcing facility sector acknowledged that increased quality requirements may result in an increase in costs, but also that standardization and the ability to produce larger volumes would mitigate this to some degree. These participants also challenged assumptions about appropriate cost: because traditional pharmacies have been making supplies of compounded drugs outside of strict manufacturing production standards, costs and cost expectations have been driven down. Legislative updates in 2013 set clear baseline quality standards for facilities making supplies of compounded drugs, rather than individual patient-specific preparations, which can prompt a needed market reset. Meaningful enforcement of compounding laws will help ensure adoption of these patient protections by both 503A and 503B establishments, and therefore an even playing field for the industry.

## Outsourcing facility sector opportunities

The final theme for session one was a discussion of opportunities within the outsourcing facility framework that may be useful to providers, as well as any barriers to taking advantage of these opportunities.

First, outsourcing facilities have the ability to set longer beyond-use dates (the time frame in which a product can be used) for their products than traditional pharmacies. Longer dating provides advantages to providers such as improved inventory management and reduced waste which, by extension, can reduce costs. Participants noted, however, that FDA guidance on beyond-use dating is not yet finalized, and FDA is also exploring different limits on dating for repackaged drugs and repackaged, mixed, or diluted biologics. Final guidance from FDA that limits an outsourcing facility's ability to set extended beyond-use dates based on meaningful stability studies would take away the sector's ability to meet market demand

for products with a longer shelf life, an important market advantage over 503A pharmacies.

Second, participants discussed how product standardization could afford an opportunity to both reduce overall costs for outsourcing facilities and providers, as well as improve patient safety. Costs to comply with new batch testing requirements for outsourcing facilities can be reduced if batches are larger and needed tests are therefore fewer. Larger batches depend on movement away from many small specialized orders to more standardized product lists. In addition, longer beyond-use dating would also allow for larger batch sizes because orders could be larger and less frequent. Participants also discussed whether increased standardization could allow outsourcing facilities to combine orders from different providers, further increasing batch size and reducing costs.

## Summary points

Session one examining the outsourcing facility sector's ability to meet provider needs for compounded drug supplies yielded the following key takeaways:

- Increasing product standardization, which will permit larger batch sizes, will increase safety and efficiency, and reduce costs of batch testing. Participants called for greater provider collaboration to achieve this goal.

- Educating providers and institutions about the differences between outsourcing facilities and traditional compounding pharmacies, the quality standards that apply, and the regulatory liability risks of purchasing non-patient-specific products from a traditional pharmacy.

- Addressing questions about quality advantages to sourcing from outsourcing facilities given potential cost increases over products sourced from traditional pharmacies. This includes provider education on quality risks and liability exposure, pursuit of the strategies above to increase standardization to reduce costs, and ensuring clear regulation of outsourcing facilities to permit an even playing field.

- Establishing clear federal regulations over the entire outsourcing facility sector, including finalization of FDA GMP expectations, better standardizing of FDA inspections, and affirming the authority of FDA, rather than state, oversight of the sector.

- Strengthening collaboration between outsourcing facilities to ensure they have a clear voice in this new, rapidly evolving sector and are able to meet consumer needs.

## SESSION TWO: Compounded Drug Supplies Needed in Ophthalmology

Session two began with an in-depth presentation on compounded drugs used in ophthalmology by Dr. Suber Huang, MD, MBA, a practicing retina specialist with long-standing leadership in clinical care, translational research, and education. Dr. Huang is past president of The American Society of Retina Specialists, and is the current associate secretariat for federal affairs and chairs the Research, Regulatory, and External Scientific Affairs Committee for the American Academy of Ophthalmology.

### Provider concerns regarding access and cost

Ophthalmologists rely on certain compounded drugs to treat their patients. Dr. Huang described in his presentation how, following the outbreak of meningitis linked to compounded drugs in 2012-13, ophthalmologists reported concerns regarding product safety, sterility, and contamination, but also their continued ability to access certain compounded products for office use to treat patients.

Eye disease is a growing concern: according to the speaker, cases of age-related macular degeneration (AMD), diabetic retinopathy, cataracts, and glaucoma are each predicted to double by 2050. There are over 40 regularly-used compounded or repackaged ophthalmic products, including many that are anti-infectives, antifungals, antibacterial agents, and antiviral agents. Many are stocked in small quantities in physician offices for on-site administration to patients. Some of these compounded products represent important advances in care. For example, compounded Brilliant Blue G and Indocyanine Green retinal dyes allow providers to more precisely peel very thin retinal membranes in procedures to treat certain forms of macular disease.

Following the 2012-13 meningitis outbreak and updates to federal compounding law, Dr. Huang reported that physicians were concerned about continued access to compounded and repackaged products, as well as the potential for increased costs. The concern was focused on products purchased from compounders as "office stock" — non-patient-specific supplies that under federal law only outsourcing facilities have the clear legal authority to prepare.

Physicians rely on office stock compounded drugs particularly for treating emergent cases. If a patient comes in to the office with an infection of the eye, treatment may be needed within minutes or hours. A provider may not have time to write a prescription for a compounded product and wait for it to be filled. This time lag could be particularly challenging for remote or rural practices. While outsourcing facilities are allowed to prepare and ship non-patient-specific compounds, this may come with an increased cost for providers. In cases where patients have no insurance, or have incomplete coverage, these costs may be borne by the patient.

### Repackaged bevacizumab

One of the most frequently cited examples of a needed office-use product is repackaged bevacizumab (Avastin). Approved for treatment of metastatic cancer, bevacizumab has been used off-label for more than 10 years to treat several conditions of the eye, including age-related macular degeneration, diabetic retinopathy, and neovascular glaucoma. FDA-approved treatments also exist, such as ranibizumab (Lucentis), and aflibercept (Eyelea). These drugs are more costly than repackaged bevacizumab because they have gone through the full FDA drug approvals process, including significant clinical trials and product testing.

While bevacizumab has not been through the FDA approvals process for treatment of macular degeneration, some studies have been conducted. One of the largest, a study of 1,208 patients by the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) research group, found no difference in safety and efficacy between repackaged bevacizumab and ranibizumab.

Cost comparisons between FDA-approved treatments for macular degeneration and bevacizumab repackaged by a traditional pharmacy have been published, and bevacizumab is significantly less costly. But in later discussion, participants noted that establishment of the outsourcing facility sector adds a new dynamic. This sector will be held to stricter quality standards than traditional pharmacies, but cost increases for repackaged bevacizumab made by an outsourcing facility would be small compared to the cost increase of switching from repackaged bevacizumab to an FDA-approved drug.

Dr. Huang also described related challenges with FDA guidance on the repackaging of biologic products like bevacizumab. Draft FDA guidance proposes a conservative default beyond-use date for repackaged biologics of 24 hours for both traditional pharmacies and outsourcing facilities. Under the guidance, outsourcing facilities can apply dating of up to five days, but to do so must conduct microbial challenge studies and container-closure assessments to demonstrate the integrity of their product. Traditional pharmacies in the business of repackaging bevacizumab normally conduct sterility testing of a portion of each batch which takes two weeks to complete.

The speaker recommended an allowance for 90-day dating for repackaged bevacizumab, which some pharmacies have used when preparing bevacizumab injections. In guidance to date, the FDA, recognizing that outsourcing facilities will be required to meet stricter quality standards, has proposed allowing these facilities to set longer product dating based on stability studies. However, the proposed five-day maximum dating would likely significantly affect their ability to meet provider needs for this product.

Dr. Huang concluded his remarks with an appeal for stakeholders to pursue opportunities to improve safety and quality, but also to preserve timely, efficient access for patients to proven treatments.

## SESSION TWO: Discussion

### Supply landscape for compounded ophthalmic drugs

Following Dr. Huang's presentation, participants began with roundtable discussion of the current supply landscape for compounded ophthalmic products, and specifically repackaged bevacizumab. There was broad understanding among participants that certain drugs are important to have in stock to treat emergent cases, as well as recognition that federal law now establishes outsourcing facilities, and not traditional pharmacies, as the entities that may provide office stock drugs.

Discussion revealed a supply landscape still very much in flux. Some participants reported access issues, as well as provider confusion regarding where they could purchase the drug, given unfamiliarity with the new outsourcing facility sector, and potentially conflicting state laws on whether pharmacies can prepare "office stock" supplies. One participant felt that most ophthalmologists were reluctant to change compounding suppliers, and wished to avoid shifts that would complicate access and potentially increase costs.

Other participants commented on the ongoing push by FDA to enforce federal law, and the likely eventuality that traditional pharmacies will be greatly restricted or prohibited from providing office stock products in the future due to potential federal violations, even if their state laws allow it. They will decide it is not worth the risk of going out of business to compound drugs without prescriptions. The FDA continues to inspect compounding pharmacies that have not registered as outsourcing facilities, and many of these pharmacies have had to cease office stock production.

State policies are likely to continue to change as well. Most state office stock policies predated 2013 updates to federal law, during a time when federal policies on compounding were unclear. But participants acknowledged that compounding businesses may wait to change practices until state policies are clarified and these practices are challenged. Thus overall change may take some time.

### Quality, testing, and beyond-use dating

Some participants felt that sterility testing by traditional pharmacies was sufficient to ensure quality for ophthalmic injections. Others emphasized the importance of stricter GMP standards — and the importance of the required additional studies and testing — in reducing public health risks when drugs are prepared on a larger scale. One outsourcing facility participant described conducting potency testing on a product placed into commercially-prepared vials. They learned through this additional testing — required of the new outsourcing facility sector — that the drug was being absorbed into the vial stopper, which affected the medicine's strength. Not only does this mean a patient may not be getting needed treatment, it could also lead to harm.

Another outsourcing facility participant noted that when setting beyond-use dates for stability, traditional pharmacies may not actually test their drugs, but rely on studies that have been published in literature, while outsourcing facilities must conduct their own product qualification assessment, using analytical laboratories to develop a study for product stability and potency over time. Traditional pharmacies therefore have the advantage of a more rapid turnaround time, which is appealing to providers.

These more robust qualification and testing protocols do increase costs for outsourcing facilities. One participant reported an increase from $25,000 to $250,000 or more to begin to sell a new product. Another reported that despite major cost increases to meet new requirements, they have continued to sell a repackaged ophthalmic product for the same price to please their customer base. Yet there may be

some willingness among providers to pay more for greater quality. One provider participant noted that ideally compounded drugs would be sourced from the highest quality producers, and that some cost increases could be borne in the interest of this goal, particularly if they could still realize savings when compared to the alternate choice of using more costly FDA-approved products.

## The business case for outsourcing facilities

An appealing business case is necessary for outsourcing facilities to choose to produce a compounded product. Outsourcing facilities described the market for compounded ophthalmic drugs as compelling, but not without hurdles.

One such hurdle is ensuring an even playing field. Outsourcing facility participants emphasized that a level playing field was very important to the success of their evolving business model — and this includes removing the risk of being undercut by traditional pharmacies who continue to prepare supplies of office stock drugs.

Competition from traditional pharmacies could also affect market share. Participants discussed whether provider reticence to change sourcing from traditional pharmacies is preventing outsourcing facilities from understanding true levels of demand. The transitional nature of both state and federal enforcement likely slows these market shifts. And while the market shifts, participants emphasized the importance of continuing to ensure sufficient patient access to needed products.

Another business challenge for outsourcing facilities discussed at the roundtable was small batch requests. As discussed in previous sections, new testing requirements are making small batches much more expensive for outsourcing facilities to produce. Batch testing is required for any batch greater than one product. Because testing destroys the product, outsourcing facilities have to make additional products just to have products to test. One participant suggested a greater reliance on process quality to demonstrate product control, and a consequent relaxation of testing requirements for very small batches.

Efforts to increase standardization may help with batch sizes, but batches are often still not very large. One outsourcing facility described reducing their portfolio from 900 individual formulations to around 40. Batch sizes then increased from batches of two to 50 to batches of 50 to 100. While a help, it still doesn't go as far as it might in terms of amortizing testing costs.

Outsourcing facilities reported working with providers during standardization efforts to ensure that revised formulations still met their needs. But standardization has the potential to leave some customers with unmet demand for discontinued formulations, and may lead doctors to go to traditional pharmacies to source products that outsourcing facilities do not make.

Participants also discussed the potential to increase batch size through better market forecasting, allowing a larger batch to meet orders from several customers. This is not current practice, and would depend on good inputs regarding patient flow and clear communication and cooperation between the suppliers and providers.

Standardization not only helps producers stay in a market, it helps with market entry. Outsourcing facilities reported they would be reticent to spend the money to test products and conduct stability studies to support longer dating if there is not consolidation around a specific formulation. One

facility explained that if you ask ophthalmologists which antifungal drops they like to use, you will get a number of different answers. It is difficult to choose which product is worthwhile taking to market.

Finally, one participant noted the insurer reimbursement is also an important driver. Insurers must be willing to pay for compounded drugs made by outsourcing facilities, even where these represent a cost increase over products prepared by traditional compounding pharmacies. This issue may warrant further exploration for repackaged bevacizumab – on which government payers may have established policy.

## Summary points

Session two examining the compounded drug supplies needed in ophthalmology yielded the following key takeaways:

- The supply landscape is still in flux, and market shifts for office stock compounded ophthalmic products from traditional pharmacies to outsourcing facilities may take time, as will changes in state laws. This transitional time causes significant confusion, and there was a call for greater harmonization across state approaches.

- Outsourcing facilities need a viable business case to make compounded ophthalmic products. This depends on eliminating non-patient-specific compounding by 503A entities, clear demand, and ability to avoid small batch production where possible due to costly batch testing requirements.

- Cost is an important driver. There is the potential for some product cost increases by outsourcing facilities compared to traditional pharmacies. These differences could be mitigated by increased product standardization and increased batch size.

- Ophthalmologists highly value extended beyond-use dating for products, and outsourcing facilities' ability to meet this demand has clear implications for the success of their business model in ophthalmology. This issue is particularly critical for repackaged bevacizumab, a biologic, where proposed default dating under initial draft FDA guidance is no longer than five days, which participants described as an extremely narrow window of time in which to use ordered supplies.

- Participants reiterated a need for collaboration between practitioners and outsourcing facilities, and among individual outsourcing facilities, to engage on issues of standardization and provider needs.

## SESSION THREE: Compounded Drug Supplies Needed in Pain Management

Session three commenced with a presentation by two pain management specialists. Dr. Edward Michna is a staff anesthesiologist at Brigham and Women's Hospital and an assistant professor at Harvard Medical School. He has board certification in anesthesia, pain management, and palliative care medicine. He was the former chairman of the Pain Care Coalition and the former chair of the American Pain Society's Public Policy Committee. Brigham and Women's pain management clinics support 250-300 patient visits per day, 90 percent for chronic pain and 10 percent for cancer-related pain. Dr. Usman Latif is board-certified in internal medicine, anesthesiology, and pain medicine. He completed his fellowship in interventional pain medicine at Harvard, and currently practices at the University of Kansas Medical Center. The Medical Center has several pain clinics structured as Comprehensive Spine Centers, paired with a larger hospital or procedure suites. Nearly 2,000 patients are seen each month, with 10-15 percent growth each year for the last four years.

### Sourcing compounded pain medications and related challenges

In their individual presentations, the panelists touched on several important themes. First, they provided a practitioner viewpoint on the use of compounded products in pain management, and a number of recognized challenges regarding outsourced compounding.

According to Dr. Michna, compounded epidurals and patient-controlled analgesia pumps, which contain a syringe of pain medication administered by a doctor, are sourced now from outsourcing facilities. But for intrathecal pain pumps, special combinations of drugs are often needed, and providers may rely on traditional pharmacies to create these patient-specific formulations. Reliance on outside pharmacies is understood to be greater for providers that are not housed in or near a larger health-system, which may take care of patient-specific compounding in-house. Dr. Latif described a colleague in a small private practice in Texas who relies entirely on outside compounding pharmacies, while a colleague in a large private practice is sometimes able to get medicines from a nearby affiliated health center, and at other times must source them from a specialty pharmacy. Dr. Michna and Dr. Latif both reported that their large academic health centers have capacity to prepare compounding in-house, but outside suppliers are still sometimes needed.

The speakers described some hurdles associated with ordering patient-specific product as-needed from outside pharmacy suppliers. Coordinating patient refills and ensuring timely delivery is not always easy. Compounding pharmacies may be far from the clinic ordering the drugs, and patients may forget to let doctors know they are running low on medication until it is almost out. If refills are not ordered with enough lead time, patients will not have the product by the time their current pump supply is depleted. On occasion these logistical issues can lead to quality problems. For example, temperature or weather variations during transport can cause issues such as crystallization in a liquid drug. Issues like this mean the product must be reordered and compounding redone. Dr. Michna also described access interruptions when compounding pharmacies go off-line due to compliance issues, such as problems identified at contract testing laboratories.

Quality issues also arise due to inherent problems with medications and delivery systems. Intrathecal pumps themselves are not tested with the various compounded drug combinations used in them, and there is notable variability between compounding pharmacies regarding what buffering agents are used in drug solutions and how the solutions are prepared. Dr. Michna noted that 14 patient deaths have been linked to pump failures that the pump manufacturer has suggested are due to compounded products. Once removed from patients, the failed pumps showed corrosion. The manufacturer had recommended drugs used in pumps have a pH of not lower than three, but compounding pharmacies preparing the drug do not normally test for pH.

There is a significant lack of data on different preparations, from the effects of pH on hardware to product stability.

## Intrathecal pump standardization – challenges and opportunities

Compounded medication combinations for intrathecal pumps are traditionally ordered on a patient-specific basis, and are not highly standardized. As discussed above, for a business to be viable for outsourcing facilities, there must be sufficient standardization to avoid heavy reliance on ordering drugs as individual units or small batches.

Current differences in intrathecal pump formulations, according to many participants, are not clinically significant and different combinations have not been robustly compared. Identifying the most commonly prescribed items could lead to recognition and use of a more standardized set of products, which could allow outsourcing facilities to produce these drugs under GMP conditions. Providers would still be able to order other combinations and concentrations for specific patients from traditional compounding pharmacies, but utilizing a core set of standardized products could help minimize errors and patient risk.

During his remarks, Dr. Latif noted that standardization would only be successful if there was a compelling business case to do it, and that this requires sufficient data to perform financial tests such as viability analyses and profit projections. Dr. Latif proposed stakeholders develop a data-driven approach to identify the medicines most commonly sourced from compounding pharmacies and repackaging facilities. Those medications would have to be matched for identical concentration, identical additives, and identical total volume dispensed, as well as frequency of dispensing. One approach to this would be analysis of large-scale claims data. Once the medicines most commonly utilized are identified, they could be evaluated as candidates for standardization.

If standardized products also result in lower costs, this may further incentivize providers to prescribe those formulations instead of different variations. Insurers might also adjust reimbursement policies to incentivize this.

Finally, standardization may not only incentivize outsourcing facilities to enter a market, it could also incentivize manufacturers to prepare formulations that are not currently available as approved products, if sufficient need is demonstrated.

## Use of compounded steroids for epidural injections

Finally, the speakers touched on compounded steroids used for epidural injections – which was the product associated with the national meningitis outbreak in 2012-13. It was noted that some practitioners believe that steroids with preservatives contribute to nerve injury, but Dr. Michna believes there are no reported cases in the literature to support this. Rather, neurologic injuries have occurred with steroid injections both with and without preservatives. Dr. Latif described a colleague whose large private practice decided 10 years ago that using compounded steroid injections was not worth the risk, and instead they rely only on manufacturer supplied vials of local anesthetic steroids for injections. Most participants agreed that there is insufficient data supporting the need for preservative-free steroids for epidural injection, although an outsourcing facility participant noted that many doctors still order this product. In addition to ongoing, even if potentially unfounded, concern regarding preservatives and patient harms, some at the roundtable suggested this practice might be financially driven.

## SESSION THREE: Discussion

### Viability of standardization for intrathecal pain pump formulations

Participants saw value in standardization of intrathecal pain pump formulations, but also raised concerns about the viability of such efforts. According to participants, formulation variation is driven largely by private practice providers, and these practitioners are used to ordering specific formulations they believe work best for their patients.

There was broad agreement that most variation in intrathecal formulations was not clinically meaningful. For example, bupivacaine is prepared as 0.1 percent, 0.12 percent, and 0.125 percent solutions at different institutions. There is no meaningful data that these have a different impact on patient care. Participants also recognized that there is an essentially unlimited range in formulations used today in intrathecal pumps, some combining many different drugs. More than one participant described it as "the wild west."

There was good interest in studies to show the degree of unnecessary variation in products, and some participants felt that better data on this would help drive consolidation in and of itself. But others believed that calling attention to unnecessary variation would not be sufficient, and that practitioners would need to be additionally incentivized to change prescribing behavior. For example, financial incentives to use outsourcing facilities held to higher quality standards could be more impactful. Better cost and better dating for standardized products were both seen as likely drivers to consolidate prescribing, and insurer reimbursement practices, if changed, would be a powerful driver as well.

Participants also acknowledged that there will always be a need for special tailored formulations when patients don't respond to a more regularly prescribed product.

### Outsourcing sector opportunities

Outsourcing facility participants expressed some skepticism that formulation consolidation would occur in a way that allowed their sector to produce these drugs in a cost-effective manner. Two participants described making intrathecal preparations in the past, but leaving that market due to the high level of product complexity and variability. The facilities were not able afford to support the broad number of formulations with stability data. High concentration of active ingredients in some of these products means that they must be made from chemical starting materials, rather than adapted from manufactured products. This creates additional production challenges, as does dealing with controlled substances — subject to specific regulations. Participants also noted that doctors commonly tweak patient formulations over the course of treatment, which adds to ordering complexity, and can mean less lead time for a producer.

Yet participants also discussed how if standard formulations were identified and there was sufficient utilization, outsourcing facilities may be able to prepare larger batches of these products and supply a provider in advance, allowing for immediate use when needed. Having even just a few standard treatment options on hand and in stock would be valuable to practitioners, providing them an opportunity to start treatment immediately and avoid the delay of ordering a drug. This need may be particularly compelling for advanced cancer

patients. Outsourcing facilities at the roundtable were slightly more optimistic about the prospect of a few standardized products, rather than meeting the bulk of provider demand in the intrathecal medication space.

The availability of compounded drugs made under GMP was appealing to participants, and they saw great value in the potential for increased knowledge about medication stability, including stability in medication administration devices. The potential for longer dating on products was also appealing. Traditional pharmacies are limited in the beyond-use dates they may set, but outsourcing facilities may be able to conduct studies to establish extended dating which would reduce logistical challenges with reordering. Cost may go up if outsourcing facilities are the producers of these products, but there is a desire to explore possibilities to address quality and safety concerns. Immediate availability appeared to be a compelling driver for participants. Other drivers, such as reimbursement policies, could also affect this decision.

## Summary points

Session three examining compounded drug supplies used in the field of pain management yielded the following key takeaways:

- There is wide variation in the compounded medicines used in intrathecal pain pumps, and participants believed much of this variation is not clinically meaningful.
- Participants supported standardization of formulations, which will require additional research data, but also believed that prescribing practices would not change absent sufficient incentives, such as clear advantages to products with longer beyond-use dating, or changes in insurer reimbursement practices.
- An opportunity for outsourcing facilities to serve this market may exist for a small set of most frequently used products. Providers saw value in an option to source drugs that they could keep in stock to use for patients without delay.

## SESSION FOUR: Compounded Drug Supplies Needed in Anesthesiology

Session four began with a presentation by Dr. Beverly Philip, professor of anesthesia at Harvard University, and founding director of the Day Surgery Unit at Brigham and Women's Hospital. Dr. Philip is active in research in ambulatory anesthesia, particularly in the pharmacology of new anesthetic agents. She is vice president for scientific affairs of the American Society of Anesthesiologists, and has served in prior leadership positions with the Society for Ambulatory Anesthesia and The Joint Commission's Ambulatory Health Care Professional and Technical Advisory Committee.

### Lack of appropriately-sized pre-filled syringes

Dr. Philip explained that compounded or repackaged anesthesiology medications are utilized in many practice settings, including hospitals (operating rooms, procedure rooms, and intensive care units), ambulatory surgery centers, pain centers, and private practices.

However, her remarks focused on a related issue that may present opportunities for the outsourcing facility sector: the lack of appropriately-sized doses provided in pre-filled syringes and vials for needed medicines. Dr. Philip offered several examples, including neostigmine, which is available in a 10 mL vial, but the usual dose is two to five mL, and contrast media, normally available in 30-50 mL vials, but the patient dose needed is a few mLs.

Some medications are available in smaller vials but these may be significantly more expensive. Medicines packaged in larger volumes, while potentially cheaper, may only allow providers to break the medicine's seal for a single use, meaning any drug not used for one dose on the first patient must be thrown away. To avoid this waste, practitioners may seek to prepare several patient treatments out of one vial, which creates contamination and infection risk.

Another constraint is standards that limit "in-use" time, or the period beyond which a prepared medication may no longer be used, to one hour — which is known as "immediate use" policy. However, many drugs that are slowly administered over time exceed this limit. In addition, certain preparations may need to be prepared in advance to provide emergency treatment, but time limitations preclude a provider preparing drugs early in the day for later use.

Specific limitations are placed on medicines prepared outside of controlled environments, such as a pharmacy clean room, because the risk of contamination and patient harm is greater. Outsourcing facilities, which meet GMPs, are not subject to these limitations, and there is an opportunity for outsourcing facilities to help meet provider need for medicines in unit-dose packaging, and provide products with longer beyond-use dating. Provider education on these benefits will also be necessary, according to Dr. Philip.

### Drug shortages

Dr. Philip also spent some time describing the serious effects of drug shortages on anesthesiologists and their patients. According to a 2012 survey, almost all anesthesiologists experienced disruptions in their typical medication use practices due to drug shortages. Published reports suggest that patients have had less than optimal outcomes or have had longer operating and recovery times as a result of drug shortages, and many providers have had to use alternate agents, change procedures, or even postpone or cancel treatment. Drug shortages exacerbate the waste issues associated with a lack of appropriate vial sizes for needed drugs.

## SESSION FOUR: Discussion

### Opportunities for outsourcing facilities

Participants thought that the demand for appropriate vial sizes presents a clear opportunity for outsourcing facilities to help meet a provider need by performing sterile repackaging services. Recent draft guidance from the FDA states that outsourcing facilities may repackage single-use vials into smaller dosage forms, as long as GMP quality standards are met and dating is correctly set.

In fact, according to participants, many outsourcing facilities are already in this space, but there appears to still be an unmet need, and outsourcing facilities could work with providers to better understand what those needs are. Outsourcing facilities described this as an area of high engagement in their sector, and solicited more input from providers on the drugs for which unit-dose repackaging needs were most acute. Participants also again discussed the need for provider education about outsourcing facilities, that this sector provides a sourcing option where drugs are prepared under higher quality standards, and can have extended dating.

Pricing for some anesthesia drugs has made providers additionally sensitive to purchasing and waste issues. Yet low pricing may also be a factor in drug shortages: products that are less profitable may not be prioritized by manufacturing plants. It is also expensive for manufacturers to develop new packaging sizes, as these must be taken through FDA approvals.

Participants broadly agreed that solutions to unit-packaging concerns must either come from manufacturers or from outsourcing facilities. While some hospitals have the infrastructure to repackage unit-dose vials under strictly compliant clean rooms and procedures, many other care settings, such as ambulatory surgery centers, do not. Participants characterized the need for "right-sized" dosing forms as critical and also noted that there is a greater degree of agreement already on standard dosage forms for many drugs used in anesthesia, which would make the challenge of identifying products on which outsourcing facilities should focus easier. But there is still standardization work to be done to help consolidate prescribing. As one outsourcing facility put it — under the new regulatory paradigm, they have to build a model that is based on a certainty of larger or stronger demand, versus a certainty of any demand.

To support the ability of outsourcing facilities to repackage these sterile drugs, participants recommended that stakeholders work together to address barriers. Some participants raised concerns about FDA's draft repackaging guidance, which currently does not propose allowing outsourcing facilities to set longer beyond-use dates based on stability studies, but requires default beyond-use dates. In addition, the guidance requires beyond-use dates to not exceed in-use times printed on the manufactured product label, if one appears. Ropivacaine, for example, is labeled with a 24-hour in-use time. If held to this timing, there would be no provider-benefit for outsourcing facilities to repackage this product.

### Safety issues

Participants discussed quality and safety concerns related to repackaging supplies sourced from traditional compounding pharmacies. One provider described receiving a shipment of five mL compounded syringes from a pharmacy in Florida, but the volumes were not exact — they ranged from 4.8 to 5.2 mL. The pharmacy assured the provider that all vials had the same amount of active drug in them, but this did not reassure the provider about the quality of the compounded drug. Outsourcing facilities, under GMP, could alleviate some of these quality concerns.

Participants also acknowledged that some providers may be dividing vials into smaller doses in their own clinics or surgery centers, and that this increases patient risk. One provider noted that while this occurs with some frequency, health-system

accreditors are citing organizations for this practice during inspections. These pressures will counteract cost drivers, because health-systems will risk losing accreditation.

A final safety concern raised was product labeling. Labeling of medicines is not always consistent when done by different facilities, and when drugs are drawn up at bedside, poorly-labeled or unlabeled products are an issue. Greater labeling consistency is another potential advantage of increased sourcing from the outsourcing facility sector.

## Summary points

Session four regarding opportunities for outsourcing facilities to provide compounded and repackaged drugs for use in anesthesiology yielded the following key takeaways:

- There is a clear need in anesthesiology for medicine packaged in unit-of-use doses. The lack thereof causes waste, exacerbates shortages, and increases patient risks.

- There is a clear opportunity for outsourcing facilities to work to meet this provider need by repackaging sterile products for anesthesia. Increased communication between providers and outsourcers will help outsourcing facilities target specific products, and develop meaningful stability studies to validate them.

- Barriers to outsourcing facilities' ability to meet provider demands should be examined and addressed, such as potential limits on the beyond-use dates that outsourcing facilities may set based on stability studies.

- Standardization is less of a barrier in anesthesiology as in pain management, but additional efforts here are still needed.

## SESSION FIVE: Compounded Drug Supplies Needed in Parenteral Nutrition

Session five began with a presentation by Dr. Beverly Holcombe, a clinical practice specialist at the American Society for Parenteral and Enteral Nutrition. Prior to joining ASPEN, Dr. Holcombe was a senior clinical specialist in the pharmacy department at the University of North Carolina Health Care, and clinical professor at the UNC Eshelman School of Pharmacy for more than 25 years. Dr. Holcombe has served in several leadership positions at ASPEN, including serving on the board of directors.

### Sourcing of compounded preparations for parenteral nutrition

Dr. Holcombe described the complex nature of TPN solutions. Many contain 20 or more components, including amino acids, dextrose, electrolytes, and trace minerals. TPN preparation has become more difficult due to shortages of key ingredients, such as amino acids and saline.

Although TPN solutions are usually ordered in a patient-specific manner, TPN preparation has been outsourced by health-systems for many years because it is costly and difficult for health-systems to prepare in-house.

In 2011, nine patients died and 19 were infected due to contamination of parenteral nutrition admixtures from a compounding pharmacy. The contamination resulted from the preparation of amino acids from non-sterile active ingredients by the pharmacy. This event was devastating to the nutrition support community, and pushed them to work towards improving safety of parenteral nutrition. One initiative is a strong effort to standardize parenteral nutrition.

Dr. Holcombe expressed the belief that providers are increasingly open to standardization, and that, for example, there is some evidence for adult TPN that a set of standard formulations could meet about 80 percent of the patient needs.

### Opportunities for outsourcing facilities

While there are some commercially available TPN admixtures available for adults, most patient needs are met by compounded preparations. But there are also standardized formulations for these preparations. Dr. Holcombe described an opportunity for increased standardization to make production of non-patient-specific TPN solutions viable for the outsourcing facility sector, particularly for less complex formulations that are commonly used. Increased standardization in TPN products can minimize compounding steps and potential for error, and could lead to more rational usage and potential cost savings due to larger batches and less waste.

One immediate opportunity may be neonatal starter formulations. These formulations are used for preterm and low-birth-weight infants. Most premature neonates require TPN within hours of birth due to their small size and inability to take in enough nutrition through their gastrointestinal tract. There are a limited number of ingredients in these formulations, and thus there is greater opportunity to develop consensus among clinicians on a standard neonatal TPN formula that fits most infants.

In addition to formulated TPN solutions, outsourcing facilities could also provide TPN components during times of shortage. About 15 percent of the active drug shortages are related to nutrition and electrolyte products. Finally, as in anesthesiology, concentrations and sizes of commercially-available products are typically limited; outsourcing facilities could help prepare pre-filled syringes that have longer beyond-use dating, which could help prevent waste.

## SESSION FIVE: Discussion

### Viability of outsourcing facility preparation of non-patient-specific TPN solutions

As in other practice areas, outsourcing facilities are working with providers to decrease their current lists of TPN formulations. But these processes take time, and the complexity of TPN solutions makes this a difficult task: one participant reported working to reduce a list of 60-70 TPN formulations to 40, still leaving a notable degree of variation. For some products, such as calcium and heparin, participants felt providers were less likely to agree to standardization.

Traditional patient-specific TPN solutions are customized and rapidly delivered – an outsourcer could produce a finished preparation within three hours of receiving an order. This is a different model than preparing standing supplies of medicines that a provider would keep in stock. Though there has been some movement in this direction: for example, low-birth-weight infants need TPN solutions immediately. Individual hospitals have standardized neonate TPN formulations allowing them to be pre-ordered from the outsourcer in order to have these formulations on hand. However, every hospital serviced in this way has their own standard formulation – which continues to create a challenge for outsourcing facilities.

The complexity and variability of TPN formulations also make it challenging to design and conduct stability studies, which outsourcing facilities must do to establish beyond-use dating. Some outsourcing facility participants felt that certain TPN products were too complex for them to want to make, such as calcium gluconate and sodium bicarbonate. One participant reported denying requests to make these products, but also warned that providers seeking them would certainly go elsewhere to find them, and traditional compounding pharmacies that step in to capture that opportunity may lead to product quality and safety issues. Another participant described how during a time of increased demand for magnesium sulfate there were many mini bags and vials found to contain mold.

### Viability of outsourcing facility preparation of shortage drugs

Participants also discussed the possibilities around outsourcing facility preparation of TPN products when in shortage, as well as shortage drugs in general.

Outsourcing facilities described that their businesses re mainly focused on providing regular service, rather than making intermediate supplies and described a number of challenges related to producing shortage drugs.

Outsourcing facilities may not be able to get the starting products and ingredients needed to make drugs during a shortage. One participant described conducting studies on six to eight different electrolyte products but when it came time to launch them, the manufacturers, who were rationing sales, refused to sell them the starting drug.

This type of problem is related to a broader issue: the unpredictability of the shortage drug market. Outsourcing facilities cannot compound and distribute shortage drugs unless they are on the FDA drug shortage list. This list is not predictable, meaning an outsourcing facility takes on significant risk to invest in the ability to make a drug that may or may not go into shortage. Once a drug is in shortage, furthermore, there is no ability to predict how long it will stay in shortage. And once the manufacturer returns to the market, the outsourcing facility must stop selling that product.

Despite these challenges, there was clear interest at the roundtable for identifying ways outsourcing facilities could better help meet demand during shortages. One suggestion was for outsourcing facilities to prepare to make drugs that are frequently on the shortage list. Another proposal was to explore whether FDA could give outsourcing facilities greater market certainty once a drug goes into shortage – such as a minimum amount of time they would be allowed to produce the drug after the product was added to the shortage list.

## Summary points

Session five examining compounded drug supplies needed in parenteral nutrition yielded the following key takeaways:

- Parenteral nutrition products are complex, and have high variability. But there are opportunities to advance standardization, especially for less complex products such as neonatal starting formulations.

- Outsourcing facilities continue to deal with high variation in TPN solution requests. There are also TPN products that some facilities feel are too complex to produce — such as calcium gluconate.

- Producing shortage drugs is a difficult proposition for outsourcing facilities because the market is highly unpredictable, making up-front investments risky. Despite this, there was high interest among providers at the roundtable for outsourcing facilities to produce shortage drugs, and a desire to examine ways to make this possible.

## SUMMARY OF BARRIERS AND OPPORTUNITIES, AND NEXT STEPS

Roundtable participants spent the final hours of the conference reviewing key themes raised during the five sessions, summarizing barriers and opportunities, and discussing next steps. The conference findings were summarized into the following categories: awareness and education, valuing quality, standardization and GMP batch size challenges, opportunities for already-standardized products, cost and convenience, level playing field, and regulatory clarity.

Overall, conference participants recognized that this remains a transitional time for systems and policies that impact how compounded drugs are sourced.

### Awareness and education

Providers reported confusion following the 2012-13 outbreak of meningitis linked to compounded products, and an increased desire to insource compounded preparations. Participants agreed there was a need for greater awareness and education among providers about the existence of the outsourcing facility sector, the higher quality standards applied to them, and the opportunities to source compounded and repackaged drugs from these facilities. Education may be more acutely needed among private practice physicians than health-system providers.

Education on compounding law and federal oversight is also needed. Providers may incur liability if they source products from suppliers not in compliance with federal and state policies. In addition, providers sourcing from outsourcing facilities may still struggle to understand FDA oversight documents, such as inspectional findings known as Form 483s. Some of the findings in 483s, which use standardized language from federal regulations, may be alarming to providers, and it may not be easy for providers to assess how a facility is responding to these observations. Access to educational information could help providers make sourcing decisions during what is still a transitional time for this sector.

### Valuing quality

Participants recognized the importance of production quality and consistent standards. Good Manufacturing Practices — the standards that apply to outsourcing facilities — are significantly more rigorous than the standards applied to traditional compounding pharmacies, particularly in the areas of environmental monitoring, sterile gowning, cleaning, training, and testing. GMP inspections are conducted by the FDA, and these inspections are more comprehensive and robust than state inspections. Participants believed that providers must value this new paradigm if it is to be successful. Increased quality standards may be an abstract benefit for some, and there may not be a clear signal in terms of reduced patient adverse events. But adverse event reporting for compounded drugs is limited and inconsistent, which makes this a less useful metric for demonstrating value.

### Cost and convenience

Cost and convenience are clear, ongoing drivers for providers and their patients. Providers will need to have compelling reasons not to choose products that are the least costly, though if providers have an affordable option that is more convenient for them they may consolidate around it. For example, paying slightly more for a product may make sense to providers if it provides a better value — such as a product repackaged into a unit-dose form that has longer beyond-use dating. In addition, cost sensitivities are most often expressed by stakeholders in terms of price differences between compounded drugs and approved products. But drug cost differences between traditional pharmacies and outsourcing facilities are likely to be much smaller. As described above, the value of outsourcing facility quality will need to be made clear to providers. Increased standardization, and increased batch sizes, will also help reduce costs for outsourcing facilities which could translate into reduced product costs for providers.

### Standardization and GMP batch size challenges

Core issues affecting an outsourcing facility's ability to make a product are the degree to which that product is standardized and production batch size. The creation of the outsourcing facility sector came with new regulatory requirements, including stricter quality standards that include required sample

testing for every batch, even when the batch is small. This has created pressure to increase batch size and consequentially reduce a broad set of varying formulations to a smaller more standardized list. Outsourcing facilities are already working with providers on standardization efforts, but more progress is needed.

Providers agreed that in many cases slight formulation variations are not clinically meaningful, and saw value in standardization for a number of reasons, including decreasing medication errors. If standardization efforts can help outsourcing facilities serve providers, this would be valuable. There are some broader standardization efforts underway. ASHP, under a current standardization initiative, is working on a list of standardized medications particularly for continuous infusions. They are in the process of collecting available data in a format that can be used by different groups to encourage the standardization process. Participants also suggested using large-scale claims data to identify most frequently used formulations, and others suggested a comparison of the varying formulations outsourcing facilities are asked to make.

## Opportunities for already-standardized products

Some products needed by providers, such as medicines repackaged into unit-dose forms, are already standardized, but optimizing outsourcing facilities' ability to serve provider needs for these drugs warrants additional provider-supplier communication to identify which products are most needed. This will allow outsourcing facilities to make a business case to invest in the up-front studies needed to support production. As discussed earlier, provider education is also critical to ensuring that providers understand the option to source from outsourcing facilities, and the legal restrictions on sourcing non-patient-specific products from traditional pharmacies.

There is a great desire for outsourcing facilities to help supply drugs when in shortage, but the unpredictability of this market reduces the incentive to engage. Greater communication with providers about products that are more likely to be in shortage and would be in greatest demand could be useful, as well as further exploration of options to give outsourcing facilities a greater degree of market certainty when a drug enters a shortage.

## Level playing field

2013 federal law created the outsourcing facility sector, which may compound without patient-specific prescriptions, but is held to stricter quality standards. The law also clarified that traditional pharmacies may only compound pursuant to prescriptions for individual patients. The prescription requirement is a key defining parameter of the outsourcing facility business model. Therefore, if it is not adhered to, outsourcing facilities will not be operating on a level playing field because they will be complying with quality standards that their competitors are not required to meet. The FDA has been enforcing the prescription requirement, but provider sourcing decisions also play a role. Other stakeholders, such as insurers, may also have a role to play, both in terms of reimbursement policy as well as insurers that assess an organization's liability.

## Regulatory clarity

There was a resounding call for clear regulation and guidance from FDA for outsourcing facilities. This includes final policy on the Good Manufacturing Practices that apply to this sector. A number of participants raised concerns with the proposed limit of 30 days or less on beyond-use dating for outsourcing facilities in draft FDA guidances on both cGMP and repackaging of drugs and biologics. One of the main reasons providers purchase from outsourcing facilities is to obtain products with longer dating based on meaningful stability and sterility studies. Limitations on this market differentiator for outsourcing facilities will restrict their ability to meet provider demand, and providers may turn to traditional pharmacies or in-house preparation for their compounded drugs. There was also a call for greater harmonization across state policy approaches, and a need to address state conflicts, such as mutually exclusive licensure requirements.

## APPENDIX Roundtable Participants

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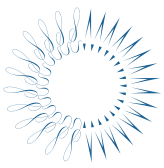

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