Due Diligence in Drug Compounding M&A Deals

A Practical Guidance® Practice Note by
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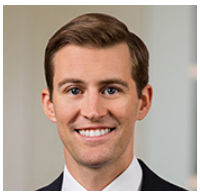

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This practice note addresses key topics related to due diligence in merger and acquisition (M&A) deals involving compounding pharmacies. Due diligence in transactions involving compounding pharmacies is as personalized as the medicine compounded by the pharmacies themselves. Proper due diligence in this area will help attorneys reduce regulatory risk to their clients. This practice note includes strategies for attorneys conducting due diligence relating to federal and state oversight of drug compounders, contracts with payers, and compounding standards.

This practice note focuses primarily on due diligence involving entities operating pursuant to Section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA) (also referred to as 503A compounding pharmacies). If the deal involves entities operating pursuant to Section 503B of the FDCA (hereafter referred to as 503B outsourcing facilities), the process is similar but will differ in several aspects, including but not limited to compounding standards, permissible activities, and federal and state oversight.

This practice note addresses the following topics:

- Drug Compounding Background
- Sections 503A and 503B of the FDCA
- Licensing Review
- Compliance Assessment
- Personnel Licenses
- FDA Inspections and Form 483
- Disciplinary Actions
- Contracts
- USP Considerations
- Additional Due Diligence Considerations

For information about due diligence considerations in transactions involving pharmaceutical companies, see Regulatory Due Diligence for Pharmaceutical and Biologics Company Transactions.

Drug Compounding Background

Drug compounding is a specialized subset of the practice of pharmacy. Pharmacy compounding is performed in local communities and, like many other businesses, often involves interstate commerce.

As part of the practice of pharmacy, drug compounding is regulated by state law, but unlike much of pharmacy practice, it is also regulated by federal law. In particular, the FDCA includes two distinct sections on drug compounding: Section 503A, 21 U.S.C. § 353a and Section 503B, 21 U.S.C. § 353b.

Section 503B(d)(1) of the FDCA defines compounding to include "the combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug or bulk drug substance to create a drug." In other words, compounding is generally a practice in which a licensed pharmacist, a licensed physician or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient. For example, compounding provides tailored therapy to patients who may not be able to use commercially available formulations due to dosing requirements, allergies, or rare diseases.

The type of drug compounded (sterile or nonsterile) and the starting material (bulk drug substance or FDA-approved finished product) both factor into the due diligence analysis in drug compounding M&A deals. A host of laws, regulations, and both governmental and nongovernmental standards create the framework for the regulation of nonsterile and sterile drug products. Nonsterile medications typically include oral and topical dosage forms, while medications that are required to be sterile typically include those administered through intravenous infusion or injection, including intraocular (injection into the eye) or intrathecal (injection into the spine).

Although events from 2012 involving the New England Compounding Center (NECC) did not arise out of an M&A deal, they provide examples of areas where proper due diligence can be key to ensuring that significant regulatory issues are uncovered at the time of a transaction. In 2012, 753 patients in 20 states were diagnosed with a fungal infection after receiving injections of preservative-free methylprednisolone acetate manufactured by the NECC. According to reports, the NECC compounded and shipped more than 17,000 vials of steroid injection, compounded in a potentially unsafe manner relating to possible insanitary conditions within the pharmacy. It was alleged that the NECC failed to properly sterilize compounded drugs, failed to test drugs for sterility, failed to wait for test results prior to dispensing and distributing drugs, used expired drug ingredients, failed to properly clean the facility, and failed to take action when environmental monitoring detected deviations. Accordingly, the Drug Quality and Security Act (DQSA) was passed after the NECC tragedy to address many of these issues. The DQSA created Section 503B of the FDCA and for the first time created a new category of compounders known as outsourcing facilities.

Sections 503A and 503B of the FDCA

As a first step in developing the framework and basic terms for your due diligence work, you should determine which section of the FDCA governs the compounding pharmacy's operations: Section 503A or Section 503B.

Compounding pharmacies that engage only in patient-specific compounding are likely operating under Section 503A of the FDCA, 21 U.S.C. § 353a. Section 503A applies to all state-licensed pharmacies engaged in compounding drugs, including retail pharmacies, hospital pharmacies, and pharmacies specializing in drug compounding that compound and dispense product based on a prescription or order for an identified individual patient (and in some limited instances, based on a history of receiving valid prescription orders).

In comparison, Section 503B of the FDCA, 21 U.S.C. § 353b, applies to outsourcing facilities. Outsourcing facilities register with the FDA and may compound an unrestricted amount of office stock medications for sale directly to hospitals, physicians, and other healthcare entities including but not limited to ambulatory surgery centers, dialysis centers, and home infusion providers.

Drugs compounded in accordance with Section 503A or Section 503B are subject to all provisions of the FDCA that apply to conventionally manufactured drugs, with several exceptions. The major exceptions are described in the table below.

503A	503B
• Current good manufacturing practice requirements (21 U.S.C. § 351(a)(2)(B)) • Labeling with adequate directions for use (21 U.S.C. § 352(f)(1)) • Premarket approval requirements (21 U.S.C. § 355)	• Labeling with adequate directions for use (21 U.S.C. § 352(f)(1)) • Premarket approval requirements (21 U.S.C. § 355) • Drug supply chain security requirements (21 U.S.C. § 360eee-1)

Generally, the FDA is responsible for oversight of 503B outsourcing facilities, but states also regulate them. In Fusion IV Pharm., Inc. v. Sodergren, 809 F. App'x 438 (9th Cir. 2020), the U.S. Court of Appeals for the Ninth Circuit affirmed the ability of states to regulate and license 503B outsourcing facilities in addition to federal registration and regulation. The role of state regulators is discussed in more detail below.

A rule of thumb is that the FDA exerts greater oversight over 503B outsourcing facilities and defers to state regulatory bodies to oversee most of the activities conducted by 503A compounding pharmacies. Nevertheless, the FDA will get involved in the oversight of 503A compounding pharmacies in certain circumstances, such as if the FDA believes a 503A compounding pharmacy is acting like a 503B outsourcing facility (i.e., compounding medication without receiving patient-specific prescriptions) without registering with the FDA.

Two activities that neither 503A compounding pharmacies nor 503B outsourcing facilities may do, except in some very limited circumstances, is compound drug products identified as presenting demonstrable difficulties for compounding or compound drug products that are essentially copies of commercially available drug product. Thus, reviewing a compounded product list during due diligence review must involve screening for drugs presenting demonstrable difficulties for compounding and essentially copies of commercially available drug. Compounding from bulk drug substances is a third activity that requires attention during your due diligence review. Sections 503A and 503B of the FDCA differ on when it is permissible to compound from bulk drug substance. Further, the FDA continues to develop policy on compounding from bulk drug substances. To show commonalities and differences, the FDA published a chart that compares and contrasts 503A compounding pharmacies and 503B outsourcing facilities.

A compounding pharmacy that compounds controlled substances will also be subject to the Federal Controlled Substances Act and corresponding Drug Enforcement Administration (DEA) registration. The compounding, handling, and storage of controlled substances is another area of potential compliance concern in M&A deals.

Because of the dual enforcement efforts of federal and state regulators, compounding pharmacies and outsourcing facilities must comply with applicable state laws in addition to applicable federal laws. Most states have a state pharmacy practice act or other statute from which pharmacy regulations are derived, and a state-controlled substances act or the equivalent. In most states, the board of pharmacy oversees laws and regulations relating to state-controlled substances. However, several states (e.g., Hawaii), have a separate regulator that enforces controlled substance and regulated chemical laws.

Licensing Review

Due diligence in the drug compounding space should begin with a review of all licenses, registrations, permits, and endorsements. Reviewing licensure status and the related activities allowed by each license is crucial because each state differs and states may have updated their licensure requirements since the pharmacy's last renewal. A review is not complete until it is determined what activities each license permits the holder to engage in.

For example, most states offer a variety of license types or designations that may permit different activities such as pharmacy, nonresident pharmacy, mail-order pharmacy, compounding sterile pharmacy, manufacturer, outsourcing facility, or wholesaler. You should review state permit laws as part of due diligence in each and every instance because state licensing schemes are subject to change. The following state licensing requirements provide a sample of the types of licenses and license designations found in the drug compounding space:

- California requires a sterile compounding pharmacy license in addition to a pharmacy or nonresident pharmacy license for 503A pharmacies that compound sterile drug products for injection, administration into the eye, or inhalation.
- Florida requires a similar permit as nonresident pharmacies must obtain a nonresident sterile compounding permit from the Florida Board of Pharmacy in order to ship, mail, deliver, or dispense compounded sterile products into the state.

- Texas issues a variety of classes of licenses, one class being specific for compounding sterile preparations.
- Tennessee issues sterile compounding modifier registrations.

For 503B outsourcing facilities, state regulation varies greatly. As mentioned, California provides a specific license: an outsourcing facility license. Other states may regulate an outsourcing facility as a pharmacy, as a wholesale distributor, or manufacturer, or not at all.

In 2017, the Government Accountability Office published a survey of state regulatory bodies, including a table on state regulation of outsourcing facilities. This report provides a good starting point for state regulation of outsourcing facilities, although many states have enacted new licensing acts and regulations since its publication. Compliance with state law is crucial when considering regulatory compliance for enforcement history and contract reviews with payers for risk calculations.

Compliance Assessment

For 503A compounding, most states incorporate the applicable U.S. Pharmacopeia (USP) General Chapters and standards but each state has unique intricacies that can often be overlooked in drug compounding due diligence. Examples of specific state rules that may be uncovered during due diligence are discussed below.

Tennessee requires pharmacies to hold a sterile compounding modifier on the pharmacy registration. To maintain compliance with this registration, compounding pharmacies must submit to the Tennessee Board of Pharmacy, on a quarterly basis, a report listing the quantity of high-risk or batch sterile products, as defined by USP standards.

Missouri provides substantial rules on sterile compounding. Missouri has established three risk levels for sterile products: Risk Level 1, Risk Level 2, and Risk Level 3. Sterile products are characterized by risk level based on compounding attributes including but not limited to the starting material, storage conditions, and beyond-use dates. For a complete description of the Missouri Board of Pharmacy's risk levels and regulation of sterile compounding, see Missouri Board of Pharmacy General Rules, Mo. Code Regs. Ann. tit. 20, § 2220-2.200.

Compounding pharmacies must pay close attention to state prescription drug monitoring program (PDMP) rules and laws. All states except Missouri have a statewide PDMP. PDMPs are statewide databases that collect data on the prescribing, dispensing, and purchasing of controlled substances. Almost all states that have a PDMP also have laws requiring dispensers, including pharmacies, to submit reports on the controlled substances dispensed. The frequency and interval at which pharmacies must submit these reports vary by state. Reporting intervals range from monthly to daily to real time. Below are some examples of state reporting intervals:

- California requires dispensing pharmacies to provide specified dispensing information on a weekly basis to its PDMP database.
- Oregon requires dispensers to submit reports no later than 72 hours after dispensing the controlled substance.
- Georgia and Maryland require dispensers to submit reports to their PDMPs within 24 hours of dispensing. Coincidently, both states also require pharmacies to submit a "zero report" when the pharmacy does not dispense any controlled drug substance during the previous 24-hour reporting period.
- Oklahoma requires controlled substance dispensing to be reported within five minutes of a controlled substance being delivered to a customer or his or her designee. This five-minute reporting period also applies to Oklahoma pharmacies that deliver controlled drugs by mail or courier to patients in or out of state as well as out-of-state pharmacies mailing prescriptions to patients in Oklahoma.

These different state requirements demonstrate why a thorough review of all laws and regulations for all states in which a compounding pharmacy operates is necessary to identify the applicable requirements and determine compliance.

Personnel Licenses

You must review state pharmacy personnel licensure requirements as part of every due diligence process. Fully understanding state licensing constructs for all pharmacy personnel may limit the potential for risk in a transaction. This review should be in addition to the standard review for exclusion and debarment as well as background checks typically done during due diligence.

Pharmacists and pharmacy technicians are licensed at the state level. All states require pharmacists to hold a license to practice pharmacy. Some states have additional requirements for the pharmacist-in-charge. Also, some states may require that out-of-state, or nonresident pharmacies employ a pharmacist who holds a license in the nonresident state, whereas other states recognize license reciprocity. Some states may also require pharmacy technicians to hold a license.

For example, the following states require the nonresident pharmacist-in-charge to hold a state license or registration: Alabama, Arkansas, Idaho, Iowa, Kansas, Kentucky, Louisiana, Maryland, Michigan, Mississippi, Nebraska, Nevada, New York, Oregon, Oklahoma, Tennessee, Texas, and Virginia.

FDA Inspections and Form 483

The FDA inspects 503B outsourcing facilities on both a risk-based schedule and for cause. In comparison, the FDA usually inspects 503A compounding pharmacies when there is a complaint or when the FDA is made aware of the need to inspect them. States inspect both 503A compounding pharmacies and 503B outsourcing facilities. When an inspection occurs and the FDA inspector makes an observation during the inspection that may be an issue under the FDCA, the FDA will issue a Form 483 to the pharmacy at the conclusion of the inspection. Observations on Form 483s, however, do not constitute a final Agency determination of whether any condition is in violation of the FDCA.

As part of due diligence, you should review every Form 483 that the FDA has issued to the pharmacy. A review of Form 483s and the pharmacy's responses provides a picture of the firm's compliance with compounding regulations. Response to a Form 483 should be timely. Firm records and documentation following an FDA Form 483 response will show whether the firm resolved any alleged FDA observations.

For more information about the FDA investigations and responding to Form 483s, see FDA Form 483 Inspection Observations and Responses.

Disciplinary Actions

A disciplinary action from the state board of pharmacy provides the state equivalent of an FDA Form 483. Violations resulting in state board discipline may bring concurrent sister-state disciplinary actions as well. In other words, discipline in one state may automatically trigger discipline in another state.

For example, the Alabama Board of Pharmacy has historically issued disciplinary citations for sister-state actions, such as failure to timely report disciplinary actions issued to the pharmacy by another state board of pharmacy. A pharmacy that has a written process in place to evaluate and assess which states require reporting sister-state actions will likely be a lower-risk target for an M&A deal as compared with a target firm that is licensed in multiple states but does not have a written policy or procedure for reporting sister-state actions. Timely reporting of such actions when required may decrease the pharmacy's exposure.

You should also investigate whether disciplinary actions have been taken against the pharmacy by other regulators. For example, the DEA issues discipline relating to controlled substances. You should review any violations and make sure that the violations are explained.

Finally, organizations such as the National Association of Boards of Pharmacy and URAC provide accreditations, including Verified-Accredited Wholesale Distributors and Specialty Pharmacy Accreditation, respectively. The records from these independent third-party accreditation processes may include additional critiques of and valuable due diligence information about pharmacies that have undergone the accreditation processes. Other third parties may audit compounding pharmacies and the associated reports may also inform you about the pharmacy's risk profile and value. For example, the pharmacy may contract directly with a third-party auditor to demonstrate to a board of pharmacy prior to the board issuing a license or renewal that the pharmacy has remedied previous observations on an FDA Form 483.

For information about FDA enforcement activity involving pharmacies and compounding, see FDA Warning Letters Tracker.

Contracts

A thorough due diligence review of a compounding pharmacy's vendors, payers, and purchasing organizations will help you to determine performance and future obligations. Your review of vendor contracts should include a review of vendor qualification history.

Depending on the types of payers the pharmacy accepts, fraud and abuse concerns can arise from payer contracts. For example, the Anti-Kickback Statute and the False Claims Act can introduce increased risk to a due diligence regulatory risk calculation. Pay particular attention to any policies addressing the following:

- Acceptance of discounts or rebates from manufacturers or distributors
- Formulary placement payments by payers
- Patient cost-sharing reductions or waivers
- Participation in patient assistance programs

- Acceptance of manufacturer coupons
- Payments by manufacturers or other third parties for administering patient adherence programs
- Physician marketing or educational programs

Payers often perform audits of compounding pharmacies. Parties paying for services, such as pharmacy benefit managers, want to make sure they are not overpaying and that pharmacies are acting in compliance with all contractual and regulatory obligations. Repercussions of audits include charge-backs of fees determined to have been paid in error, penalties, contract cancellations, and additional investigations. You must review these audits to determine the risk profile and value of a firm.

USP Considerations

The USP is a scientific nonprofit organization that sets public standards for identity, strength, quality, and purity of medicines. The FDCA recognizes and mandates USP standards for compounding. Determining firm compliance with USP compounding standards is foundational to determining risk, especially in light of the FDA's adopting them in guidance documents relating to 503A compounding pharmacies.

Four USP General Chapters deal specifically with compounding: <795>, <797>, <800>, and <825>. Below is a summary of each chapter:

- USP General Chapter <795> provides standards for compounding quality nonsterile preparations. According to the USP, General Chapter <795> is intended to benefit patients and reduce risks such as contamination, infection, or incorrect dosing.
- USP General Chapter <797> provides standards for compounding quality sterile preparations.
- USP General Chapter <800> provides standards for safe handling of hazardous drugs to minimize the risk of exposure to healthcare personnel, patients, and the environment.
- USP General Chapter <825> provides standards for the safe handling of radiopharmaceuticals containing radioactive materials.

Additionally, the USP publishes monographs with specifications for identity, strength, quality, purity, packaging, and labeling for substances and dosage forms. Whether a firm compounding from bulk drug substances adheres to the USP monograph, if available, is part of compliance with most state regulations and the FDA. States may require full compliance with <795>, <797>, <800>, and <825>, or they may incorporate aspects of them into their regulations.

Additional Due Diligence Considerations

Section 503A of the FDCA has a mechanism in place that could be used to limit the amount of compounded prescriptions a 503A pharmacy may distribute out of state. Specifically, the FDCA limits distribution of compounded drugs outside the state by a pharmacist, pharmacy, or physician located in a state that has not entered into a memorandum of understanding (MOU) with the FDA to 5% of its total prescription orders dispensed or distributed. The FDA is providing a 365-day period for states to decide whether to sign the MOU before the FDA intends to begin enforcing the 5% limit in states that do not sign.

The limit on interstate distribution of compounded drugs is another difference between pharmacies compounding under Section 503A and outsourcing facilities that are registered with the FDA under Section 503B. The MOU and statutory 5% limit will not apply to drugs compounded by outsourcing facilities under Section 503B.

With limited exceptions, neither a 503A pharmacy nor a 503B outsourcing facility may compound drugs appearing on the list codified at 21 C.F.R. § 216.24 of drug products withdrawn or removed from the market for reasons of safety or effectiveness. The same prohibition applies to drugs presenting demonstrable difficulties for compounding. However, the FDA has not fully established a list of such drugs. Developments in this list will require a keen eye during due diligence. The FDA is developing a list of drug products that present demonstrable difficulties for compounding in consultation with the Pharmacy Compounding Advisory Committee (PCAC) and the notice-and-comment rulemaking process. You and your client should monitor the FDA docket and the Federal Register for PCAC meetings and proposed developments.

For information about upcoming FDA meetings and regulatory developments, see FDA Drug Regulatory Activity Tracker.

Lastly, from a regulatory perspective, although the major players involved in drug compounding at the federal level are the FDA and the DEA, you should review the opinions and materials of other agencies, such as the Centers for Medicare & Medicaid Services (CMS), the Department of Justice (especially in enforcement trends), and the Office of Inspector General (OIG). In particular, Advisory Opinions

issued by OIG about the application of OIG's fraud and abuse authorities, the CMS Pharmacist Center, and DOJ actions and press releases can inform due diligence review in drug compounding M&A deals.

For information about OIG Advisory Opinions affecting pharmaceutical companies, see Drug and Medical Device OIG Advisory Opinions Tracker.

Lee Rosebush, Partner, BakerHostetler

With a background as a defense, regulatory, and registered patent attorney who has also worked as a registered pharmacist, Lee Rosebush provides his clients with legal counsel that is grounded in first-hand experience. Whether his clients are confronted with legal issues related to the naming of a drug, clinical trials, marketing, promotions, or advertising, Lee possesses a strong understanding of the pharmaceutical industry which, combined with his attention to detail and experience working with biologics, medical device, and healthcare companies, gives clients a single source for regulatory and litigation counsel. With post-graduate degrees in finance and business, Lee is frequently sought out to help expedite corporate deals involving healthcare entities. He also advises private equity and public and private companies in due diligence matters and buy-sell transactions.

Lee's ability to smoothly shift between the legal, governmental, and pharmaceutical environments further helps him to efficiently secure operating licenses or assist drug manufacturers avoid compliance actions from governmental agencies. Active with the Drug Quality and Security Act (DQSA), as well as the Federal Food and Drug Administration's (FDA) regulation of pharmacy compounding, Lee speaks and writes on both issues, and is passionate about orchestrating and advocating for pharmacists and pharmacies. Additionally, Lee is Leader of BakerHostetler's Pharmacy and Reimbursement team and Co-Leader of the FDA, Products Promotion, and Defense team.

Lindsay Holmes, Associate, BakerHostetler

Lindsay Holmes focuses her practice on regulatory and transactional matters, primarily in the healthcare and life sciences industries. She has experience advising clients on Food and Drug Administration (FDA) regulatory matters, including food, drug, device, dietary supplement and cosmetic issues, as well as matters related to 503B outsourcing facilities operating pursuant to the Drug Quality and Security Act (DQSA), and entities subject to the Drug Supply Chain Security Act (DSCSA). She also has experience assisting clients with matters related to the U.S. Department of Agriculture (USDA) and Drug Enforcement Agency (DEA) compliance. In addition, Lindsay helps pharmacy, wholesaler and third-party logistics provider clients navigate state licensing and pharmacy practice act issues. Her background also includes counseling clients on data privacy and security matters, fraud and abuse, and Medicare Part D.

Marc Wagner, Associate, BakerHostetler

Marc Wagner's knowledge of pharmaceutical compliance adds value to his developing practice. He has experience performing research on FDA guidance documents, food additives and standards of identity, Prescription Drug Monitoring Programs, Investigational New Drug Applications, and state board of pharmacy rules and regulations. Additionally, Marc's educational and professional background in pharmacy provides him with a substantial understanding of a variety of pharmaceutical compliance measures, including pharmaceutical compounding, 503B Outsourcing Facilities, pharmacy reimbursement, FDA labeling requirements, HIPAA standards, and Drug Enforcement Administration requirements.