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COMPOUNDING PHARMACIES: STEPS TO AVOID ISSUES WITH THE FDA, DEA, PHARMACY BOARDS, AND PATENT HOLDERS

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INTRODUCTION

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- In the fall of 2012, a meningitis outbreak linked to contaminated injectable drugs prepared by a Massachusetts compounding pharmacy killed 64 people and sickened many more. The disaster spurred increased regulation and oversight of compounding operations at the federal and state levels.

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- In particular, the Drug Quality and Security Act ("DQSA"), signed into law on November 27, 2013, sought to address public safety and welfare concerns by balancing of state and federal interests. In particular, DQSA reserved the oversight of traditional compounding on a small scale to the individual states, while expanded the federal government's regulatory authority in relation to manufacturers or entities registered as outsourcing facilities.

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- In part due to the DQSA, there is no uniform standard for pharmaceutical compounding. Rather, compounding standards vary widely depending on the entity and practice involved.

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- All traditional compounding pharmacies, which are typically regulated by state boards of pharmacies, are required to adhere to the guidelines laid out in the US Pharmacopeia ("USP") and relevant state law. In particular, USP chapters 795 and 797 are applicable to non-sterile and sterile compounding respectively.

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- In contrast, large-scale drug manufacturers and those that register as outsourcing facilities will fall under the regulatory authority of the Food and Drug Administration ("FDA") and its current Good Manufacturing Practices ("cGMP").

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- It is important to note that the FDA inspections are generally done using cGMP standards instead of USP guidelines. As the cGMP standards may be more stringent than USP 797 in some areas, such as air sampling, sterility testing, and validation of compounding methods, traditional pharmacies should be alert as to allegations of improper compounding based on incorrect standards.

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- To the extent that USP contains less restrictive compounding requirements than cGMP, pharmacies may prefer to remain a traditional pharmacy rather than voluntarily register as an outsourcing facility in order to reduce the likelihood of compounding violations.

TRADITIONAL PHARMACY

- The DQSA revived Section 503A of the Federal Drug and Cosmetic Act ("FD&C Act"), which sets forth the conditions under which a compounding pharmacy would qualify for exemption from the FDA's cGMP.

TRADITIONAL PHARMACY

- Specifically, Section 503A requires that compounding be conducted by a licensed pharmacist, physician, or practitioner pursuant to a "identified individual patient" prescription, or be done in anticipation of such patient orders in limited quantities based on order history. In essence, the FDA has interpreted this to prohibit all "office-use" compounding by 503A entities.

TRADITIONAL PHARMACY

- In direct contrast to the FDA's application of the statute, Congress has expressed that it did not intend to allow the FDA to prohibit pharmacy compounding for office use in states where it is expressly allowed and regulated.

TRADITIONAL PHARMACY

- The issue of office-use compounding was raised again most recently in the House Agriculture Appropriations Committee Report. In the Report, the Committee reiterated its position that the FDA was acting contrary to the congressional intent behind the DQSA.

TRADITIONAL PHARMACY

- In particular, the Committee directed the FDA to issue a guidance regarding how compounding entities can continue to engage in office-use compounding before the receipt of a patient-specific prescription consistent with the provisions of 503A.
- In addition, pharmacies must meet the multiple requirements set out in 21 U.S.C. § 353a(b) in order to qualify for a 503A exemption.

TRADITIONAL PHARMACY

- If the pharmacy meets the qualifications for a 503A exception, then the appropriate compounding standards are the more lenient USP guidelines and state regulations, not cGMP.

OUTSOURCING FACILITIES

- The DQSA also created a new voluntary category of outsourcing facilities. Unlike with traditional pharmacies, outsourcing facilities have greater ability to conduct interstate commerce. However, entities that register as outsourcing facilities are subject to the FDA's cGMP.

OUTSOURCING FACILITIES

- If a compounding entity does not register with FDA as an outsourcing facility and does not satisfy the conditions for 503A exemption, it will also be subject to the cGMP requirements of manufacturers and must comply with all of the requirements of the FDCA that are applicable to drugs made by conventional manufacturers.

STATE REGULATIONS & LICENSES

- Pharmacies should be aware of the requirements for compounding activities in any state in which they do business. While many state boards of pharmacy have directly adopted USP 797 as their regulations or have modeled their own regulations on USP guidelines, some states may have their own compounding standards that differ from or exceed the USP.

STATE REGULATIONS & LICENSES

- Furthermore, in the past several years, state legislatures have taken steps to impose additional restrictions on out-of-state compounding pharmacies that ship pharmaceuticals into their states. The additional requirements range from subjecting pharmacies to inspections to require special compounding licenses. Entities should be aware of state guidance in order to properly ensure compliance.

PERMITTED OFF-LABEL USES

- Off-label use refers to the use of medication in a manner not described in the U.S. Food and Drug Administration's approved drug label or insert. This includes the use of a drug for different subpopulations, different therapeutic purposes, different dosages or duration of use, or different modes of administration. Off-label prescribing has become a common practice, particularly in the areas of cancer treatment, pediatrics and HIV/AIDS care.

PERMITTED OFF-LABEL USES

- The FDA does not regulate the practice of off-label prescribing by physicians. In fact, the FDA states that "[o]nce a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling.

PERMITTED OFF-LABEL USES

- There is little state or federal regulation of when off-label prescribing is permitted; rather, it has been largely left to the professional judgment of physicians. Per FDA guidance, a physician has the "responsibility to be well informed" about a product and bases the decision for its off-label use on "firm scientific rationale and on sound medical evidence".

PERMITTED OFF-LABEL USES

- An important question to consider with regards to the permitted use of off-label drugs is whether health insurance plans will provide coverage for off-label uses. Plans often decline to do so citing that the unapproved use has not been shown to be safe or effective for the prescribed purpose and, therefore, the use is non-covered experimental or investigational. Of particular interest is the treatment of off-label uses by federal health care programs such as Medicaid and Medicare.

PERMITTED OFF-LABEL USES

- Whether a state Medicaid program will reimburse an off-label prescription is largely dependent on the drug's FDA-approved status. Under the Medicaid statute, a covered outpatient drug does not include a drug or biological used for a medical indication which is not a medically accepted indication.

PERMITTED OFF-LABEL USES

- The term “medically accepted indication” is defined as either an FDA-approved use or a use supported by citations included in, or approved for inclusion in, one of the following compendia: *American Hospital Formulary Service Drug Information*, *United States Pharmacopeia – Drug Information*, or the *DRUGDEX Information System*.

PERMITTED OFF-LABEL USES

- Thus, unless a particular off-label use for a drug is included in one of the listed drug compendia, a prescription for the off-label use of that drug may not be eligible for reimbursement under Medicaid.

PERMITTED OFF-LABEL USES

- States with drug formularies may also exclude a covered outpatient drug for the treatment of a specific disease or condition when the drug does not have a significant safety or efficacy advantage over a current formulary item. Accordingly, state Medicaid programs have varying rules as to the coverage and reimbursement of an off-label prescription.

PERMITTED OFF-LABEL USES

- With regard to Medicare Part D coverage, drug claims must be provided for medically accepted indications as a prerequisite for reimbursement. Medically accepted indications include both uses approved by FDA and uses supported by at least one citation included or approved for inclusion, in specified compendia.

PERMITTED OFF-LABEL USES

- With the exception of anti-cancer chemotheraphy regimens, citations to peer-reviewed medical literature, generally, will not support coverage for an off-label use that does not involve a medically accepted indication.

PERMITTED OFF-LABEL USES

- The Medicare Part B program will pay for a drug only if the use is “reasonable and necessary”. FDA-approved drugs used for indications other than what is indicated on the official label may be covered under Medicare if the carrier determines the indication to be medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice.

PERMITTED OFF-LABEL USES

- For anti-cancer chemotherapeutic regimens, medically accepted indications of an off-label use may be supported either in a specified compendia or in peer-reviewed medical literature.

PERMITTED OFF-LABEL USES

- Required coverage of off-label drug usage also varies among the states. Some states require health plans to cover off-label prescriptions for all FDA-approved drugs if the use is listed in a major drug compendia or supported by medical research. Other states chose instead to limit its coverage mandate to only off-label prescriptions used in conjunction with the treatment of cancer treatment or other life-threatening illnesses.

PERMITTED OFF-LABEL USES

- Although physicians are permitted to prescribe drugs for an off-label purpose, the FDA prohibits drug companies from actively marketing drugs for unapproved purposes. In recent years, the federal government has aggressively pursued off-label promotions using the vehicle of the False Claims Act.

PERMITTED OFF-LABEL USES

- The general theory postulates that, by promoting off-label uses, some of which are not listed in a compendia or supported by medical literature, the manufacturer or physician took action that then triggered a chain of events resulting in the submission of a claim to the government for a non-covered treatment.

PERMITTED OFF-LABEL USES

- For example, in 2013, Wyeth Pharmaceuticals, Inc. agreed to pay $490 million to settle allegations of a False Claims Action violations relating to its promotion of the prescription drug Rapamune. Rapamune was approved by the FDA for use in renal transplant patients. However, Wyeth sales representatives, under a financial incentive, marketed the drug to all transplant patient populations.

PERMITTED OFF-LABEL USES

- The government alleged that the marketing of off-label uses, some of which were not medically accepted, were not covered by federal health care programs and, therefore, resulted in the submission of false claims.

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PREPARING FOR FDA INSPECTION

FDA INSPECTION: OVERVIEW

- Section 704(a)(1) of the Federal Food, Drug, and Cosmetic Act. 21 U.S.C. §374(a)(1). It allows FDA investigators to enter, at reasonable times, facilities in which drugs are manufactured, processed, packed, or held for introduction into interstate commerce. In addition, Section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act allows the FDA to request, in advance of or in lieu of an inspection, within a reasonable timeframe, within reasonable limits, and in a reasonable manner, any records or other information that may be inspected under Section 704(a).

FDA INSPECTION: OVERVIEW

- There are three basic categories of inspections:
  - A COMPREHENSIVE INSPECTION is requested by FDA headquarters or the district office and can cover everything in the pharmacy subject to FDA jurisdiction. These inspections can take less than a day, or they may last for weeks.
  - An ABBREVIATED INSPECTION is an inspection that covers only critical factors that are identified in the Inspectional Guidelines, the FDA Investigations Operations Manual (IOM), or under an inspectional program from FDA headquarters.
  - A DIRECTED INSPECTION is triggered by an identifiable event, such as a recall, consumer complaint follow-up, competitor complaint, or other specific incident.

FDA INSPECTION: OVERVIEW

- Regardless of the type of inspection, the key issue will be whether the pharmacy is a manufacturer. If the inspector believes that the pharmacy is a manufacturer, he or she will issue an FDA-483 Inspectional Observations.
- The final decision as to whether a pharmacy is a manufacturer will be made by FDA headquarters in Silver Spring, Maryland.

FDA INSPECTION: OVERVIEW

- Key personnel should be familiar with their roles in dealing with the investigator. (Although pharmacy inspections ordinarily involve only one FDA investigator, the agency can send two or more investigators.) Once the inspection begins, it is crucial that the key personnel in all operations promptly be made aware of the presence of the FDA. If a corporate Inspection Leader is not available to respond to the FDA, other personnel need to understand the pharmacy's policies when answering the investigator's inquiries.

FDA INSPECTION: OVERVIEW

- FDA inspections are usually unannounced. Thus, the pharmacy must be prepared for an inspection at any time.
- Contacts with FDA investigators require the utmost professionalism. Investigators have a job to perform. The FDA's Investigations Operations Manual says that investigations "must always be conducted with tact, honesty, diplomacy, and persuasiveness." §5.2.5.4.

FDA INSPECTION: OVERVIEW

- Do not create an adversarial environment; it is counterproductive. On the other hand, the pharmacy must recognize that the investigator is not there to befriend it. No matter what the investigator says, the investigator is not there for the pharmacy's benefit.
- The investigator should be courteously received during the course of his or her visits. Usually, this attitude will achieve the best results for the pharmacy and establish a better long-term relationship with the FDA. Conversely, a series of confrontations with the investigator can cause an otherwise manageable situation to deteriorate rapidly.

FDA INSPECTION: OVERVIEW

- The degree of corporate cooperation will be reflected in the investigator's Establishment Inspectional Report ("EIR"). The EIR is an internal FDA document that comprehensively describes the inspection. The EIR describes all aspects of the investigation, e.g., the history of the pharmacy, pharmacy management, inspectional findings, the lay-out of the facility, discussions with management about problems, etc. The pharmacy's attitude will be reflected in the EIR, which will then go into the FDA's permanent file on the pharmacy. It is often helpful to obtain a copy of the EIR through a Freedom of Information Act request once the inspection has been concluded.

FDA INSPECTION: OVERVIEW

- An Inspection Leader must be assigned to deal with the FDA. This designated individual may also be appointed to handle the telephone communications. This leader should be aware of all aspects of the pharmacy's policies, operations, and record-keeping systems.
- Alternatively, an Inspection Group can be set up. This group would then assign a Leader who would be responsible for the group's actions. The group would be made up of persons familiar with the pharmacy's policies for dealing with the FDA and with the pharmacy's operations.

FDA INSPECTION: OVERVIEW

- The Leader and/or the group should accompany the investigator throughout the inspection.
- The FDA may follow-up the inspection with a telephone call. All telephone calls from the FDA should be handled by the pharmacy's Inspection Leader.

FDA INSPECTION: OVERVIEW

- The investigator should be made aware at the outset that there is a pharmacy policy for dealing with the FDA. This will help when questions arise on how to answer the inquiries made by the investigator. An FDA investigator will more readily accept a denial based on established policy than a refusal based on an "instant policy" created on the spot. In responding to issues such as the taking of photographs, access to corporate records, and signing affidavits, as well as other problem areas, politely explain that the investigator's request cannot be granted because of an existing pharmacy policy.

INSPECTION AUTHORITY

- If the pharmacy refuses inspection, the FDA's recourse would be to obtain a search warrant allowing it entry onto the premises. There is no legal basis for completely refusing an inspection, except if the FDA wishes to inspect at an unreasonable time. Refusal can lead to an FDA enforcement action. It also injures the relationship with the agency. Thus, refusal is almost never a viable option. However, the inspection must be at a reasonable time.

PROPRIETARY INFORMATION

- Special attention should be paid to records that contain proprietary information. These documents should be marked **"CONFIDENTIAL - TRADE SECRET,"** and this fact should specifically be called to the attention of the investigator. Make sure that the investigator notes that the material is considered trade secret information. This notation minimizes the risk that the information will be disclosed to third parties under the Freedom of Information Act ("FOIA"). Be aware, though, that too many claims of confidentiality may cause the FDA to view all claims of confidentiality skeptically.

PROPRIETARY INFORMATION

- Generally, FDA personnel are barred from disclosing any trade secret information to anyone outside the agency. 21 U.S.C. § 331(j); 18 U.S.C. § 1905. However, the FDA may release these documents to Congress. Congress is not bound by the same obligations to preserve confidentiality.

SIGNING OFFICIAL DOCUMENTS

- An official of the pharmacy may be asked to supply copies of shipping records or invoices, and then to sign documents identifying the source, verifying shipment, or confirming other information on the status of any sample the FDA collects. Or the pharmacy may be asked to confirm in writing its compounding and dispensing practices. This is usually in a form of an "affidavit" prepared by the FDA. The FDA has no authority to compel the pharmacy to sign anything.

ESTABLISH AN INSPECTIONS FILE

- After each inspection, the pharmacy should create a separate file. This file will include the notes taken during the inspection by pharmacy employees, the forms filled out regarding the inspection, duplicates of the records copied by the investigator, the FDA-482 Notice of Inspection, the FDA-483 Notice of Observations, the FDA-484 Receipt of Samples, the pharmacy's analytical results for samples tested, and any subsequent correspondence with the agency.
- Maintaining all information in a single file will make it easier to reconstruct the circumstances of the inspection years later, if necessary. Never show this file to the FDA, or to anyone outside the pharmacy who is not bound by confidentiality.

GIFTS

- Without question, gifts should never be offered to any investigator. It is a federal offense to give a gift to a federal agent.

MEALS

- The pharmacy should not offer to take the investigator to lunch. FDA employees are prohibited from accepting meals from regulated industry. It is not inappropriate to offer coffee, tea or a soft drink if that is the customary practice for all visitors.
- If the pharmacy wants to have lunch with the investigator, let him pick up his own bill. It is much better, though, to recommend a restaurant where the investigator can eat without being accompanied by a pharmacy employee.

FDA-483 (LIST OF OBSERVATIONS) RESPONSE

- At the inspection's end, the investigator will have an exit interview with management to detail the findings of the inspection and to obtain the pharmacy's comments.
- If no FDA-483 is issued, the investigator may still have some recommendations for how to improve the pharmacy's operations. Sometimes, an investigator will suggest some way in which a pharmacy can strengthen its claim to be a pharmacy, not a manufacturer. Or the investigator may make a suggestion about shelf-life testing.

FDA-483 (LIST OF OBSERVATIONS) RESPONSE

- In such a case, listen and take all suggestions under review but do not promise implementation. No further follow-up is necessary for this type of exit interview.
- If an FDA-483 is issued, the investigator is going to request a direct and immediate response. It would be advisable to review each point for clarification with the investigator, but make no comments regarding follow-up action unless the pharmacy is certain that a specific action can and will be taken. Explain that the list will be reviewed by management, and a written response soon will be mailed to the district office.

FDA-483 (LIST OF OBSERVATIONS) RESPONSE

- One section of the establishment inspection report ("EIR") specifically addresses the exit interview. Statements made during the exit interview will be reported in detail in the EIR. Do not reject observations out-of-hand, become defensive, or be unwilling to listen; on the other hand, make commitments sparingly. Any commitments will be recorded. The safest response is of the "We have no comment on that at this time" variety.

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QUESTIONS?

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THANK YOU

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