



Navigating the Direct Importation of Active Pharmaceutical Ingredients:

COMPLIANCE CONSIDERATIONS FOR COMPOUNDING PHARMACIES

Bradley S. Byars and Brad Howard, J.D. are attorneys with Brown & Fortunato, P.C.



Bradley S. Byars, M.H.A., J.D., LL.M. (Health Law)
Brad Howard, J.D.



Abstract The direct importation of Active Pharmaceutical Ingredients (APIs) presents significant opportunities for compounding pharmacies to optimize costs and expand their services. However, sourcing APIs from foreign manufacturers, particularly from countries like China, introduces complex regulatory challenges. This article examines the federal regulatory framework governing API importation, outlines due diligence measures that compounding pharmacies should undertake, and provides general guidance on state-level considerations. By adhering to these guidelines, compounding pharmacies can mitigate risks, better ensure compliance with applicable laws and regulations, and maintain the integrity of their compounding practices.

Compounding pharmacies operating under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FDCA) must adhere to stringent regulations enforced by the U.S. Food and Drug Administration (FDA). Non-compliance can result in severe consequences, including import refusals, product seizures, and legal actions.



Introduction

In the globalized pharmaceutical industry, compounding pharmacies are increasingly exploring the direct importation of APIs from international manufacturers to enhance their compounding capabilities and reduce costs. China, being one of the largest producers of pharmaceutical ingredients, has become a focal point for sourcing APIs. However, importing APIs directly from foreign manufacturers introduces a myriad of regulatory challenges that compounding pharmacies must navigate to better ensure compliance with federal and state laws and to safeguard patient safety.

Compounding pharmacies operating under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FDCA) must adhere to stringent regulations enforced by the U.S. Food and Drug Administration (FDA). Non-compliance can result in severe consequences, including import refusals, product seizures, and legal actions. This article explores the critical steps that compounding

Medi-Dose[®]
EPS[®]

Unit Dose Done Right

12 Colors

1D & 2D Bar Coding

Flexible Formatting

12345678901
Lot: 8675309
EXP: 02/25/25

1D & 2D Bar Coding

Ideal for USP <800> Meds

Cold Seal (No Machinery)

Tamper-Evident

Moisture Resistant

8 Sizes, 15 Options

Ultraviolet Inhibitor

Up to 12 Month Beyond-Use-Dating

Simple.

Reliable.

Medi-Dose.

Scan Me!

MediDose.com • 800.523.8966

Unit Dose,
Bar Coding,
Pharmacy &
Nursing Supply
Experts!

pharmacies should take when sourcing APIs directly from foreign manufacturers, particularly in China. It provides an analysis of the federal regulatory framework, discusses due diligence measures, and offers general guidance on state-level considerations with illustrative examples.



Federal Regulatory Framework

(I) FDA REGISTRATION AND LISTING REQUIREMENTS

Under federal law, foreign establishments manufacturing APIs intended for importation into the United States are required to register with the FDA. Specifically, 21 CFR §207.40(a) mandates that foreign drug manufacturers provide the FDA with information about their establishments and the drugs they produce.¹ This registration enables the FDA to monitor and inspect foreign facilities to ensure compliance with Current Good Manufacturing Practices (cGMP). Compounding pharmacies should verify that their potential API suppliers are registered with the FDA.

They can obtain the FDA Establishment Identifier (FEI) number from each potential manufacturer and confirm their registration status by accessing the FDA's Drug Establishments Current Registration Site (DECRS).² Ensuring that the manufacturer is registered with the FDA is a critical first step in establishing a compliant supply chain.

(II) COMPLIANCE WITH CURRENT GOOD MANUFACTURING PRACTICES

Compliance with cGMP is essential to ensure that APIs meet the required quality and purity standards. The FDA's cGMP regulations for drugs are outlined in 21 CFR Parts 210 and 211.³ Non-compliance can lead to enforcement actions such as Import Alerts or refusal of admission of products into the United States under 21 USC §381(a), which authorizes the FDA to refuse entry of adulterated or misbranded drugs.⁴ Compounding pharmacies should review the FDA's inspection records for each potential manufacturer to assess their compliance history. This includes examining any Form FDA 483 observations, Warning Letters, or Import Alerts issued against the manufacturer. The FDA's Inspection Classification Database allows users to search for inspection records by firm name or FEI number.⁵ Reviewing these records helps identify any compliance issues or patterns of non-compliance that may pose risks.

(III) IMPORTATION PROCEDURES AND PRIOR NOTICE REQUIREMENTS

Importers of APIs must adhere to FDA regulations regarding importation procedures. Under 21 CFR §1.281(a), prior notice must be submitted to the FDA for each shipment of imported drugs.⁶ This requirement enables the FDA to review and make admissibility decisions before the arrival of the product. Compounding pharmacies should establish procedures to ensure timely and accurate submission of prior notices and maintain complete documentation for all shipments to prevent delays or refusals at the port of entry.

Compounding pharmacies should obtain and verify these certificates to ensure that the APIs meet international quality standards. This step adds an extra layer of assurance regarding the integrity of the APIs being imported.

(IV) VERIFICATION OF EXPORT CERTIFICATES AND QUALITY STANDARDS

Foreign manufacturers should provide a Certificate of Pharmaceutical Product (CPP) or equivalent export certificates to verify that the APIs comply with cGMP standards and are authorized for export.⁷ The CPP confirms that the pharmaceutical product is authorized for sale in the country of export and that the manufacturer adheres to quality and safety standards. Compounding pharmacies should obtain and verify these certificates to ensure that the APIs meet international quality standards. This step adds an extra layer of assurance regarding the integrity of the APIs being imported.



Due Diligence Measures

(I) CONDUCTING THOROUGH SUPPLIER VERIFICATION

Conducting thorough due diligence on potential foreign API manufacturers is essential to ensure compliance and mitigate risks. Compounding pharmacies should verify the FDA registration of each potential manufacturer by obtaining their FEI number and confirming their registration status on the FDA's DECRS.² Additionally, reviewing the FDA's inspection records for each manufacturer helps identify any compliance issues.⁵ Accessing these records allows compounding pharmacies to examine any Form FDA 483 observations, Warning Letters, or Import Alerts issued against the manufacturer.

(II) ASSESSING MANUFACTURING PRACTICES AND QUALITY COMPLIANCE

Compounding pharmacies should ensure that the manufacturer possesses necessary export certificates, such as the CPP, confirming compliance with cGMP standards.⁷ Verification of these certificates adds an extra layer of assurance regarding the manufacturer's adherence to quality standards. Establishing quality agreements with the manufacturer defines each party's responsibilities regarding quality

standards, cGMP compliance, and audit rights. The FDA's guidance on quality agreements emphasizes their importance in ensuring product quality.⁸ Compounding pharmacies should consider conducting on-site audits or hiring third-party auditors to assess the manufacturing facilities and provide assurance of compliance with quality standards.

(III) IMPLEMENTING SUPPLY CHAIN SECURITY MEASURES

Ensuring the integrity of the supply chain for APIs is essential to prevent counterfeit or contaminated products. While the Drug Supply Chain Security Act (DSCSA) primarily focuses on finished drugs, its principles are relevant to APIs.⁹ Compounding pharmacies should confirm

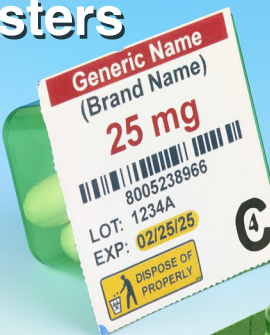
Medi-Dose[®]

EPS[®]

Unit Dose,
Bar Coding,
Pharmacy &
Nursing Supply
Experts!

MPB[™]

Multi-Purpose Blisters




All the features of our Medi-Dose System, in two larger and more versatile sizes, making them ideal for:

USP <800> Meds • Suppositories • Unit of Use Packaging
Compounded Meds • Larger Tablets & Capsules
Repackaging Unit Dosed Items • Anything that Fits!



Scan Me!

MediDose.com • 800.523.8966

that the manufacturer has robust supply chain security measures, including proper sourcing of raw materials and procedures to prevent contamination. This includes verifying the authenticity of suppliers, monitoring supply chain transactions, and employing secure logistics solutions.

(IV) PERIODIC TESTING AND QUALITY ASSURANCE

Implementing periodic independent testing of API batches at third-party laboratories is crucial for ongoing quality assurance. Regular testing helps ensure that the APIs meet quality standards and detect any potential issues early. Testing can include assays for potency, identification of impurities, and verification of physical characteristics. Selecting accredited laboratories with expertise in pharmaceutical analysis is essential. Maintaining detailed records of test results is also important for compliance and traceability.



General State-Level Considerations

In addition to federal regulations, compounding pharmacies must comply with applicable state laws governing the sourcing of APIs and compounding practices. While specific requirements vary by state, there are general considerations that pharmacies should be aware of.

(I) COMPLIANCE WITH USP STANDARDS

Most states require pharmacies to comply with the United States Pharmacopeia (USP) standards, including USP <795> for non-sterile compounding and USP <797> for sterile compounding.¹⁰ These standards mandate that all components used in compounding must



***Pharmacists, do you need
formulations with
references, stability &
compatibility information?***

*Log on to www.CompoundingToday.com
or www.IJPC.com to See How We Can Help
You Compound Quality Preparations
with Safety and Efficacy.*



 **CompoundingToday.com**

OUR COMPOUNDING KNOWLEDGE,
Your Peace of Mind®

www.IJPC.com | www.CompoundingToday.com | 800-757-4572 x1 | IJPC-subscriptions@IJPC.com

Implementing periodic independent testing of API batches at third-party laboratories is crucial for ongoing quality assurance. Regular testing helps ensure that the APIs meet quality standards and detect any potential issues early. Testing can include assays for potency, identification of impurities, and verification of physical characteristics. Selecting accredited laboratories with expertise in pharmaceutical analysis is essential.

meet identity, strength, quality, and purity specifications. Compounding pharmacies should ensure that APIs sourced from abroad adhere to these standards.

For example, in Alabama, all components used for compounding must meet the standards set forth in USP <795> and USP <797>. ¹¹ Additionally, pharmacies should ensure that all intermediaries involved in the supply chain, such as wholesalers, are licensed by the Alabama Board of Pharmacy under Alabama Code §34-23-32. ¹² In Florida, sterile compounding pharmacies must comply with USP <797> and Florida Board of Pharmacy Rule 64B16-27.797. ¹³ Non-resident pharmacies shipping compounded preparations into Florida must meet Florida's standards for API sourcing and quality assurance, as per Florida Statutes §465.0266. ¹⁴ Similarly, Ohio requires compliance with USP <795> and USP <797> for nonsterile and sterile compounding, respectively. ¹⁵ Pharmacies must maintain detailed records, including the source, lot numbers, and expiration dates of all APIs used, as mandated by Ohio Administrative Code 4729:7-2-04. ¹⁶ Compounding pharmacies should

review the laws and regulations of the states in which they operate or distribute products to ensure compliance.



Business and Operational Considerations

(I) VERIFICATION OF FOREIGN BUSINESS LICENSES AND REGISTRATIONS

Compounding pharmacies should verify that the foreign manufacturer is legally operating in their home country by requesting copies of their business licenses and certifications. Verification can be conducted through resources such as the National Enterprise Credit Information Publicity System of China. ¹⁷ Assistance from bilingual professionals may be necessary due to language barriers.

Medi-Dose[®] EPS[®]

NEW!

Unit Dose Done Right...Now For Ointments Too!

Unit Dose, Bar Coding, Pharmacy & Nursing Supply Experts!

Simple. Reliable. Medi-Dose

MediDose.com • 800.523.8966



(II) ASSESSING FINANCIAL STABILITY AND REPUTATION

Assessing the financial health and reputation of the manufacturer is important for ensuring a reliable supply of quality products. Pharmacies should request financial statements, credit reports, and references. Resources such as Global Trade Alert provide information on international trade developments, while business news outlets offer reports on specific companies.

(III) PLANNING FOR LOGISTICAL CHALLENGES

Compounding pharmacies should plan for logistical challenges associated with international shipping. Working with customs brokers experienced in pharmaceutical imports can help navigate customs requirements and potential delays. Familiarity with U.S. Customs and Border Protection (CBP) regulations is essential.¹⁸ Preparing for potential delays and ensuring compliance during the importation process helps in maintaining a steady supply of APIs.

Conclusion

Direct importation of APIs from foreign manufacturers presents significant opportunities for compounding pharmacies but also introduces complex regulatory challenges. Compliance with federal regulations, including FDA registration, cGMP adherence, and importation procedures, is essential. Conducting thorough due diligence, establishing quality agreements, and implementing robust quality assurance measures are critical steps in navigating these challenges. Compounding pharmacies must also be mindful of state-level considerations and ensure compliance with applicable laws and regulations. By adhering to these guidelines, pharmacies can successfully integrate direct API importation into their operations while maintaining compliance and ensuring the safety and efficacy of their compounded medications.

Brown & Fortunato is a Texas-based law firm with attorneys throughout the country representing health care companies nationwide.



References

1. U.S. Food and Drug Administration. 21 CFR §207.40(a). Code of Federal Regulations. Available at: <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-207>. Accessed November 19, 2024.
2. U.S. Food and Drug Administration. Drug Establishments Current Registration Site (DECRS). Available at: <https://www.accessdata.fda.gov/scripts/cder/drls/default.cfm>. Accessed November 19, 2024.

Medi-Dose[®] EPS[®]

LiquiDose[®] Labels

Labels to suit all your needs...
from solids, liquids and syringes
to ampules, IV's and equipment!

Unit Dose,
Bar Coding,
Pharmacy &
Nursing Supply
Experts!



Use Our Powerfully Easy MILT[®] Software
to Print Bar Codes, Graphics, Special
Fonts, Tall Man Lettering, Shapes,
Logos and Symbols.



Scan Me!

MediDose.com • 800.523.8966

3. U.S. Food and Drug Administration. 21 CFR Parts 210 and 211. Current Good Manufacturing Practice for Finished Pharmaceuticals. Available at: <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-210>. Accessed November 19, 2024.
4. U.S. Food and Drug Administration. 21 USC §381(a). Imports and Exports. Available at: <https://www.fda.gov/regulatory-information/laws-enforced-fda/federal-food-drug-and-cosmetic-act-fdc-act>. Accessed November 19, 2024.
5. U.S. Food and Drug Administration. Inspection Classification Database. Available at: <https://www.accessdata.fda.gov/scripts/inspsearch/>. Accessed November 19, 2024.
6. U.S. Food and Drug Administration. 21 CFR §1.281(a). Prior Notice of Imported Food. Available at: <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-1>. Accessed November 19, 2024.
7. U.S. Food and Drug Administration. Export Certificates. Available at: <https://www.fda.gov/industry/exporting-fda-regulated-products/export-certificates>. Accessed November 19, 2024.
8. U.S. Food and Drug Administration. Guidance for Industry: Contract Manufacturing Arrangements for Drugs: Quality Agreements. Available at: <https://www.fda.gov/media/86193/download>. Accessed November 19, 2024.
9. U.S. Food and Drug Administration. Drug Supply Chain Security Act (DSCSA). Available at: <https://www.fda.gov/drugs/drug-supply-chain-integrity/drug-supply-chain-security-act-dscsa>. Accessed November 19, 2024.
10. United States Pharmacopeia. USP Compounding Standards. Available at: <https://www.usp.org/compounding>. Accessed November 19, 2024.
11. Alabama Board of Pharmacy. Compounding Regulations. Available at: <https://albop.com/>. Accessed November 19, 2024.
12. Alabama Code §34-23-32. Licensing of Wholesalers. Available at: <https://codes.findlaw.com/al/title-34-professions-and-businesses/al-code-sect-34-23-32/>. Accessed November 19, 2024.
13. Florida Administrative Code Rule 64B16-27.797. Standards of Practice for Compounding Sterile Preparations. Available at: <https://www.flrules.org/gateway/RuleNo.asp?title=PHARMACY%20PRACTICE&ID=64B16-27.797>. Accessed November 19, 2024.
14. Florida Statutes §465.0266. Nonresident Pharmacies. Available at: <http://www.leg.state.fl.us/>. Accessed November 19, 2024.
15. Ohio Administrative Code 4729:7-2-01. Sterile Compounding Standards. Available at: <http://codes.ohio.gov/oac/4729:7-2-01v1>. Accessed November 19, 2024.
16. Ohio Administrative Code 4729:7-2-04. Record Keeping. Available at: <http://codes.ohio.gov/oac/4729:7-2-04v1>. Accessed November 19, 2024.
17. National Enterprise Credit Information Publicity System of China. Available at: <http://www.gsxt.gov.cn/index.html>. Accessed November 19, 2024.
18. U.S. Customs and Border Protection. Basic Importing and Exporting. Available at: <https://www.cbp.gov/trade/basic-import-export>. Accessed November 19, 2024.

Address correspondence to Bradley S. Byars at bbyars@bf-law.com 📧

Ask Questions and Share Ideas with Fellow Compounders

**IJPC'S
CNL**
(COMPOUNDERS'
NETWORK LIST)

SIGN UP AT:
IJPC.COM/CNL



**OUR COMPOUNDING KNOWLEDGE,
Your Peace of Mind®**

