Integrated PharmaConsulting

AUTHOR: Chad Hopkins, PhD

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Shipping Practices for Early Stage to First-In-Human (FIH) Small Molecule Programs

Executive Summary

This whitepaper, prepared by Integrated Pharma Consulting, consolidates shipping guidance covering the handling, documentation, storage, and regulatory requirements for shipping Research and Development (R&D) materials, controlled or hazardous substances, and Current Good Manufacturing Practice (cGMP) materials. Adherence to these guidelines is essential to ensure compliance with applicable regulations, including Drug Enforcement Administration (DEA), Food and Drug Administration (FDA), Customs and Border Protection (CBP), Department of Transportation (DOT), and International Air Transport Association (IATA) requirements, protect proprietary information, avoid unexpected costs, and maintain the integrity of materials throughout the supply chain.

KEY INSIGHTS

▶ Proper classification and documentation are the foundation of compliant, cost-effective shipping.

▶ Phase-appropriate shipping conditions protect material integrity and reduce costly study repeats.

▶ Pre-IND import of cGMP materials requires specialized strategies.

▶ The client is responsible for all materials it owns, including third-party shipments.

1. Controlled and Hazardous Substances

1.1 Controlled Substances

A controlled substance is any drug or other substance listed under the Controlled Substance Act (CSA). The client, or client's vendor, must be registered and have permits from proper authorities (DEA if in the US) to receive, store, use, or ship controlled substances. Controlled substances may include final targets (e.g. opioids, amphetamines) or intermediates/starting materials that may be used in the production of such substances.

Key points:

- Any shipper or receiver handling controlled substances on behalf of the client must be notified of the applicable schedule and must verify their certification to handle such materials.
- To verify whether a compound is a controlled substance, consult the DEA database: https://www.deadiversion.usdoj.gov/schedules/schedules.html.

1.2 Hazardous Materials

Smaller companies generally do not ship hazardous materials for R&D purposes; hazardous waste is the primary exception.

A hazardous material is defined as a substance or material capable of posing an unreasonable risk to health, safety, or property when transported in commerce, as designated under the Hazardous Materials Regulations (HMR). Shipment of hazardous materials requires specialized training under both IATA and DOT standards.

Only personnel trained under IATA and DOT standards may ship hazardous waste or sign related shipment documents.

2. Storage

The majority of routine, non-cGMP R&D samples (mg-to-g quantities) are stored in-house or at a Contract Research Organization (CRO) under the following commonly achieved conditions: ambient (15–30°C), 2–4°C, −20°C, or −80°C with or without protection from light and/or air. A well-maintained inventory should be in place. Note that these conditions are not necessarily considered "controlled" as required with cGMP materials.

It is advisable for companies to review their internal policies and consult with their Regulatory Affairs (RA), Quality Assurance (QA), Environmental Health and Safety (EH&S), and Facilities Management teams prior to receiving hazardous, controlled, radioactive, or cGMP materials. Failure to have the proper permits and controls in place could result in health risks, violations, fines, and deviations resulting in loss of cGMP material classification.

When selecting a storage facility, key considerations include:

- If storing cGMP materials, what is the facility's regulatory inspection history? Were there any violations or other key findings?
- Is the facility (i.e. building design, HVAC, cleanrooms) qualified and does it have controls in place for storage of cGMP materials? Are the personnel properly trained? Is the equipment qualified and appropriately maintained? Refer to 21 CFR Parts 210 & 211 for more information about regulatory requirements for cGMP material storage.

- What level of cleanroom do you require? What level of cleanroom does the facility offer?
- What is the Occupational Exposure Limit (OEL) of the material to be stored and is the facility equipped to handle the indicated OEL (e.g. highly potent active pharmaceutical ingredients (HPAPIs))?
- Can the facility aliquot materials for shipping or only ship the entire container in the same manner as received (i.e. unopened)?

3. Documentation for R&D

3.1 Overview

Shipping documentation requirements can be extensive and vary depending on stage of program and level of control needed for the material. Always include phase-appropriate documentation and maintain consistency across all documents (e.g. shipping and storage temperature, ID, purity, hazards, etc.).

Documents that should accompany *non-cGMP R&D* material shipments include:

- Certificate or Results of Testing (COT, ROT) at minimum.
- Safety Data Sheet (SDS).
- Pro Forma Invoice.
- Airway Bill (AWB) / House Airway Bill (HWB) / Bill of Lading (BOL).
- Packing List.
- Any submission forms required by the receiving party.

Providing electronic copies to recipient is advisable. Documents for cGMP material shipments are described later.

3.2 Material Identification

To protect proprietary information, avoid including chemical structures, IUPAC names or any version thereof on shipping documents, including Certificates of Analysis (COAs) and Safety Data Sheets (SDSs).

Inclusion of batch numbers can prevent downstream regulatory complications. Per 21 CFR §210.3(b)(11), a batch number is defined as any distinctive combination of letters, numbers, or symbols from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch can be determined.

Information should be consistent across all documents (nomenclature, SDS, shipping invoice, COA, shipping log, etc.). Inconsistent nomenclature (i.e. ID) and batch numbering may cause errors in CRO/CDMO and pharmacy databases, potentially leading to deviations or need for amendments.

Consistency and "ID bridging" become increasingly critical for tracking the material's history as programs advance into GxP activities. Internal processes should be designed with this principle in mind.

4. HS/HTS Codes and Costs

4.1 Harmonized System (HS) and Harmonized Tariff Schedule (HTS) Codes

HS codes (universal, 6-digit) and HTS codes (country-specific, up to 10 digits) provide customs with descriptive product information. Incorrect classification can result in unexpected duties, refusal of entry, receipt issues and in extreme cases, destruction of material. The client is responsible for all materials it owns.

Key considerations for small molecules:

- The client primarily deals with Chapter 29 (DS or intermediates) and Chapter 30 (DP) codes. Be aware that not all CROs/CDMOs can receive shipments classified under Chapter 30; the client should verify with the recipient before initiating a shipment.
- Chapter 29 materials are taxed at varying rates and may be influenced by trade policies. Chapter 30 materials are typically duty-free in the US. However, refer to the next point.
- Maintain awareness of trade war implications and changing tariff landscapes.

4.2 Shipping Costs

Shipping costs are often underestimated during budgeting and comparison of manufacturing proposals. Both import duties and value-added taxes (VATs) can create substantial, unanticipated expenses. For example, international shipments may incur compounded tariffs and VATs that can increase costs by 20% (based on material valuation) or more depending on the country.

Strategies to reduce tax burden:

- Plan manufacturing sites carefully.
- Itemize purchase orders; allows for more accurate material valuation.
- Use bonds and drawbacks.
- Apply strategic HS/HTS coding.
- Select strategic ports of entry.
- Leverage free (or foreign) trade zones (FTZs).

5. General Shipping

5.1 Routine R&D Samples

Routine R&D samples are primarily produced by medicinal chemistry groups in mg-to-decagram quantities but may extend to early-stage non-cGMP process chemistry (g-to-kg). Well-established shipping lanes with CRO/CDMO partners generally minimize complications. Common issues include lack of or incorrect Toxic Substance Control Act (TSCA) forms, material descriptions, and Harmonized System (HS) codes.

Suggestions to help your shipping run smoothly:

- Designate a single point of contact.
- Always notify CROs before or at the time of shipment and provide shipping documents; this is both professional and relationship-building. Request the CRO to provide the same courtesy.
- Check with the CRO for requirements (CRO-specific submission forms, SDSs, project codes, contacts, addresses, etc.).
- Implement and maintain a system for tracking and archiving shipping documents.

5.2 Shipping Conditions

Most routine R&D samples can be shipped under ambient conditions. However, always confirm with the chemistry or process team, particularly as a project progresses and additional stability, impurity profile, and degradation data become available. Communication is especially important after a development candidate (DC) is nominated.

General recommendations:

- Ship early batches of DC drug substance (DS) at 2–8°C unless experimental data supports an alternative. Shipping at 2–8°C incurs minimum cost and reduces degradation risks that could complicate or necessitate repetition of downstream studies. Consider a compound sitting in a courier truck for 8–10 hours without air conditioning on a hot summer day which can reach upwards of 120°F (49°C) or higher in the cargo area. Are there data to support stability at those temperatures? The compound may need to be re-analyzed upon receipt to ensure no degradation and reported purity is still correct.
- Obtain pilot stability and forced degradation data on the DC early to support alternative shipping/storage configurations and to inform temperature deviation risks.
- Certificates of Analysis (COAs), or similar documents, and Safety Data Sheets (SDSs) should be consistent in reflecting the proper shipping and storage conditions.
- Obtain raw data used to generate the COA, especially for the DC, and keep on file. Do not include chemical names or structures on COAs or SDSs that may reveal proprietary information. These documents are seen by numerous people during the shipping process and can easily compromise intellectual property (IP). CROs may be insistent upon including names or structures, but this often stems from assigning correct HS/HTS codes and hazard communication.
- Drug product (DP) is typically maintained at ambient or controlled room temperature (CRT, 20–25°C), reflecting a balance between risk and developability, although exceptions certainly apply and should have supporting data and be agreed upon with the DP and analytical teams.

6. cGMP Material Shipping

6.1 General Shipping Requirements for cGMP Materials

Shipping cGMP materials requires heightened oversight and specific documentation.

Key recommendations:

- Documents must use language appropriate for materials intended for human use. *Do not* label materials "for R&D purposes only" if the batch may be used for human studies.
- Verify with recipient that document language is suitable and aligns with their requirements to release for human use.
- Leverage strategic HS codes (e.g., Chapter 98 "Prototype" for DS post-IND) to minimize import duties.
- The client, consignee or Importer of Record (IOR) is obligated to maintain records for 5 years per CBP law and CFR, exercising reasonable care throughout.
- A client representative should track each cGMP shipment and should follow up with both shipper and recipient for shipment/receipt confirmation, storage conditions verification, and terminal document collection.

> **!** **CAUTION**
> CDMO exportation requires closer oversight than CDMO importation. An experienced import/export broker can be a valuable resource

for cGMP shipments. The client is responsible for each shipment.

6.2 cGMP Documentation with an Active IND

The following documents should be made available to, and reviewed by, the client prior to shipment and be accessible to the receiving party, customs, broker, and FDA upon request:

- IND number.
- COA / COT / COC (unless under quarantine, ROA, or authorization memo).
- SDS.
- BSE/TSE statement.
- TSCA Statement.
- USDA 1105 Statement.
- Melamine Free Certificate.
- Pro Forma Invoice.
- AWB / HWB / BOL.
- Packing List with TempTale information (remind CDMO to equilibrate before recording).
- End Use Letter (EUL).
- Submission forms required by recipient.
- Photographs (internal and external; labels clearly legible). Customs will occasionally flag a shipment for further inspection; if photographs of internal packaging are available, opening of the secondary container may be avoided.

Clinical DS SDSs are controlled documents and should be reviewed and updated annually or when significant new data is obtained. These documents may be managed by third-party vendors or an internal quality management system (QMS).

7. Pre-IND Import Strategies for First-in-Human (FIH) Studies

7.1 The Pre-IND Challenge

Importing cGMP DS or DP intended for human use into the US prior to an active IND can present a challenge to teams. Without an active IND, standard import pathways are unavailable, requiring specialized planning.

Language on documents in this context follows 21 CFR §201.122(b): where no application is approved, the label must read *"Caution: For manufacturing, processing, or repacking"* and must be supplemented by the words *"in the preparation of a new drug or new animal drug limited by Federal law to investigational use."*

IMPORTANT

DO NOT label materials “for R&D purposes only” if the intent is to use the imported material for eventual human studies. This will result in the CDMO not releasing the material (or product made with the material) for human use.

7.2 Strategic Options for Pre-IND Import

Several mechanisms exist to enable pre-IND import of DS/DP intended for clinical trials. Each carries trade-offs in timeline, labor burden, cost, and efficiency. A recommended strategy is IFE/TIB (see Section 7.3).

Alternative strategies include:

- Conduct all activities outside the US and import post-IND (requires consideration of country-specific regulations if conducting manufacturing activities in more than one country).
- Conduct all activities (i.e. DS & DP manufacture, labeling, storage) in the US.
- Manufacture DS outside the US then import into a US Foreign Trade Zone (FTZ) for DP manufacturing and labeling; export from FTZ post-IND.
- Manufacture a cGMP DP demonstration batch in the US using a portion of imported cGMP DS (labeled as not for human use) to support IND filing; import remaining DS post-IND for bulk DP manufacturing intended for human use.
- Import intermediates and perform the final DS cGMP step in the US.

7.3 Current Strategy: Import for Export (IFE) / Temporary Importation Bond (TIB)

Import for Export (IFE) permits the importation of products that are unapproved or otherwise non-compliant with FDA regulations, provided they are imported for further processing and ultimately exported from the US. Products imported under IFE may not be distributed or sold domestically.

Temporary Importation under Bond (TIB) allows temporary importation of goods without payment of duty, with the intent to export or destroy the goods within three years of the importation date.

In combination, IFE under a TIB allows for import of cGMP DS into the US pre-IND for the manufacture of cGMP DP for human use without payment of duties.

Requirements for a successful IFE/TIB:

- All materials imported under TIB must be carefully tracked and accounted for to close out the bond by the end of the 3-year period.

- Materials must either be exported from the US or destroyed (per 19 CFR 10.39) by the end of the 3-year period.
- Liquidated damages are assessed at 2× the original duty for non-compliant closures.
- Exportation may be achieved for DP labeling and re-imported to a bonded warehouse in the US for storage until IND is active.
- Once material is exported from the US and the IND becomes active, subsequent shipments may be treated as normal cGMP shipments.

If you have a program that is in the manufacturing sites planning stages and need to ensure the drug product is packaged, labeled and ready to be distributed to the clinical sites as soon as your IND becomes active, reach out to Integrated Pharma Consulting at info@integratedpharmaconsulting.com. We have experience managing import/export activities and have successfully utilized IFE/TIB multiple times.

Integrated PharmaConsulting

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About Integrated Pharma Consulting, LLC

Founded to give early-stage biotech companies and academic spinouts access to senior preclinical & CMC expertise typically found only inside larger pharmaceutical organizations. With over 15 years leading preclinical R&D at Zentalis and Kalyra Pharmaceuticals, IPC provides strategic depth across the full translational continuum from discovery science to regulatory submission.