White Paper

Streamlining the importing & exporting of biological samples

MARK VANN
Operations Support Manager, Aliri

Aliri
BIOANALYSIS

SUMMARY

Import and export processes can cause major headaches for sponsors if they are not prepared with realistic timelines and proper permits and documentation for biological samples. By relying on experienced bioanalytical laboratory partners, understanding what paperwork their samples require and proactively planning for this part of the process, importing and exporting can become a seamless and fairly predictable phase in research and development.

In this white paper, we explain:

- How to determine which licenses and/or permits are required based on the type of biological material in a sample
- Which government agencies need to be involved for importing or exporting approval
- Key tips for planning timelines around the permit process

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INTRODUCTION

United States Customs and Border Protection works with partner government agencies to monitor and regulate all biological materials and substances that enter the country. Likewise, other nations strictly monitor biological samples entering their own jurisdictions. In order for samples to successfully reach their destination, most governments require items to be permitted in advance and properly labeled for easy processing.

While this practice sounds straightforward, it can be a challenging experience — one that causes significant timeline delays or unexpected expenses — if the proper government agencies are not notified and able to approve permits in advance of shipments in or out of the country. Identifying the correct agency or agencies and obtaining the right paperwork can be time-consuming and confusing for companies with little experience importing or exporting biological materials. For this reason, experienced sample collection sites, research laboratories or contract research organizations (CROs) typically handle this on behalf of sponsors.

Provided the proper paperwork is filed and approved, the import/export process does not have to be an unknown on the path to advancing development efforts. By incorporating strategic planning and ensuring the right information is provided to agencies with the first application, shipments of biological materials into or out of the United States can be achieved with minimal uncertainty in timeline and budget.

CATEGORIZING BIOLOGICAL MATERIALS

Properly identifying a biological sample prior to shipment in or out of the U.S. is critical, as it enables all of the appropriate permits or licenses to be obtained so that review goes smoothly in customs. Different types of biological specimens have different government agencies that require permits and approval, and many materials require permits from multiple government agencies. Animal specimens are the most frequently used in preclinical drug development, but samples involving genetically modified organisms, viral vectors, and cell cultures also require government permitting prior to entry to the U.S., regardless of the stage of research.

The U.S. Customs and Border Protection website provides extensive resources explaining biological sample importation requirements. In general, export procedures are more lax but still require permits in particular cases (discussed below). In all cases, a letter accompanying the shipment explaining the contents and their purpose, as well as detailing any approved permits, can be helpful. Without proper documentation, shipments can be destroyed, held in customs or even used to bring civil or criminal penalties against the relevant parties. Once a developer's substance is properly classified, the proper requirements for permitting, licenses, and paperwork can be identified and completed and provided with shipments for swifter review in customs.

TABLE 1. US Customs and Border Protection examples of biological materials for import purposes[1]

Category	Examples
Cell or tissue cultures	Recombinant or nonrecombinant products, tissue culture supernatants, hybridomas
Genetic materials	Recombinant, synthesized or inactivated chromosomes, genomes, plasmids, transposons or DNA/NA
Genetically modified or engineered organisms	Plants, insects, seeds or other organisms
Human and animal products	Diagnostic specimens such as urine, feces or saliva; histopathological slides; blood, plasma or clotting factors; monoclonal or polyclonal antibodies; antitoxins, antivenom, toxoids or antisera; vaccines; proteins, peptides, enzymes or extracts; test kits
Infectious substances, agents and toxins	Poliovirus, rabies, or hepatitis B virus cultures; anthrax, botulinum neurotoxins or ricin; African swine fever virus, Ebola virus, Rift Valley fever virus; *Xanthomonas oryzae* disease
Microorganisms	Live, inactivated or killed recombinant or nonrecombinant bacteria, fungi, yeast, viruses, protozoa, prions or helminths
Vectors and hosts	Scientific or laboratory research animals or insects

GOVERNMENT AGENCIES AND REQUIREMENTS

Importing

Typically, qualified and experienced research labs are well versed in the types of permits and licenses required for the work they commonly perform. In many cases, such labs maintain annual licenses for the most common products or species they handle, such as rats or cynomolgus macaque monkeys, and merely require permits to cover anticipated import shipments for particular projects, which they know how to quickly obtain. Labs that work with animals are often subject to inspection and oversight according to the Animal Welfare Act (1966) or the Public Health Service Policy on Human Care and Use of Laboratory Animals (1985), particularly if they receive federal funding.[2] The Institutional Animal Care and Use Committee (IACUC) may also be involved. Depending on the type of specimen, multiple permits may be required (see Table 2).

TABLE 2. Import permitting agencies by type of material (human or animal origin only)

	US Fish & Wildlife Service (USFWS): Office of Law Enforcement	**USFWS Division of Management Authority:** Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES)	**US Department of Agriculture (USDA):** Animal & Plant Health Inspection Service (APHIS), Veterinary Services	**Centers for Disease Control & Prevention:** Import Permit Program
IMPORTING	Animal materials	Threatened animal materials	Livestock or poultry animal materials, including those bred for lab use	• Knowingly infected human or animal materials • Non-human primate or bat materials
EXCLUDES	• Livestock or poultry animal materials • Human materials	• Non-threatened animal materials • Human materials	• Knowingly infected livestock or poultry animal materials • Animal materials not derived from livestock or poultry • Human materials	• Not-knowingly infected human or animal materials (except non-human primat and bat)
APPLY AT	USFWS ePermit website	USFWS ePermit website	APHIS website	CDC website
FREQUENCY	Annual, per site, per species	Per shipment(s), per species	Per shipment(s), per species	Per shipment(s), per species
FORM	General	3-200-37e (Appendix I); None (Appendix II, III)	VS16-3	General
APPROVAL	1-2 weeks	1-2 weeks	4-6 weeks	4-6 weeks
ACTION	License maintained by experienced labs	Permit maintained by experienced labs; exporters provided with copy of permit	Permit maintained by experienced labs; exporters provided with copy of permit	Permit maintained by experienced labs; exporters provided with copy of permit
IN LIEU	None	None	None	Exporter includes with shipment a letter stating material not known to be infectious

In general, all animal research should start with the USFWS, which licenses importation of all animal materials except livestock. Depending on whether the materials are infectious or from threatened species, additional permits may be required. Companies developing drug substances with biological origins may also need to consult Food and Drug Administration (FDA) and/or Drug Enforcement Administration regulations regarding permit and license requirements. Chemically synthesized materials containing or derived from animal products as well as other animal-, plant- or human-derived materials may also require permitting from the USDA.[3] Chinese hamster ovary (CHO) cell specimens only require USFWS permitting if the CHO cells still contain some animal DNA or other material.[4] Human specimens intended for laboratory research only and not for use in human therapeutics or clinical research do not typically require FDA permits; however, if they contain infectious material, CDC involvement may be required.[5]

Exporting

Exporting biological samples is typically easier than importing, as the onus is on the receiving laboratory or vendor to ensure that documentation meets their own governments' requirements for importation. US-based exporters shipping on behalf of sponsors can take steps to simplify the process, however, by providing copies of any licenses or permits for the originating lab as well as a letter stating details about the contents and their infection status (e.g., details regarding any testing performed or simply a statement indicating the contents are not known to be infectious).

Endangered or threatened animals are the exception to the rule of simple exportation processes, however. USFWS CITES tightly regulates exportation of threatened live animals or materials derived from those animals listed in any of its three appendix documents. The permitting process is complex and time-consuming, valid only for a specific number of shipments over a stated period of time, and species-specific. Both the laboratory and the sponsor must typically work together to complete the paperwork as documentation regarding animal origin, handling, parentage and more must be thoroughly filled out, along with justification for and a summary of the research and information on the receiving party. The method of material disposition may also be required. A copy can then be sent with the shipment for importing agencies in other countries to review.

In general, only infectious substances or materials/animals of interest to USFWS CITES require extensive export permitting processes (see Table 3). Receiving laboratories in other countries are responsible for obtaining their own permits, which may require communication with the sponsor or shipping laboratory in some cases.

TABLE 3. Export permit requirements for human and animal samples

	USFWS Division of Management Authority: CITES	**US Department of Commerce:** Bureau of Industry and Security (BIS)
EXPORTING	Threatened animal materials	• Knowingly infected human or animal materials
EXCLUDES	• Non-threatened animal materials • Human materials	• Not-knowingly infected human or animal materials
APPLY AT	USFWS ePermit website	BIS website
FREQUENCY	Per shipment(s), per species	Per shipment(s), per species, per nation
FORM	3-200-37e (Appendix I); 3-200-29 (Appendix II, III)	General
APPROVAL	4-6 weeks	4-6 weeks
ACTION	Permit maintained by experienced labs; foreign importers provided with copy of temporary permit	Permit maintained by experienced labs; foreign importers provided with copy of temporary license
IN LIEU	None	None

TIMELINES AND PLANNING

It is the responsibility of the sample collection site or laboratory to obtain and maintain permits for both importing or exporting. This includes the cost of permitting, which is absorbed by many CROs. Beyond verifying that the lab they have selected is in compliance with such licensing and inspection requirements, most sponsors do not have involvement in these background certifications and documentation regulations.

However, they may be required to supply information to labs to assist with proper documentation during the application process for new permits. In particular, most importation permits require labs and sponsors to provide details on the quantity of specimens being shipped, their volume, the anticipated number of shipments within a specific period of time, where they are coming from, and details about the materials. Furthermore, sponsors should be aware of what importing and exporting entails in terms of work and potential impact to timelines.

When planning for shipping samples internationally:

- **Don't instruct sample collection sites to ship to the receiving laboratory until the appropriate licenses and permits are obtained.** Sending materials before permits are in place and the lab is ready to begin work can jeopardize samples in transit by causing long customs delays.

- **Provide information to assist in permit applications as needed.** This can speed the process as laboratories complete permitting paperwork. Typically, information required includes only contact information on exporting or receiving sites, but for more complex cases may entail details on sample origin and treatment prior to their receipt by the lab.

- **Build application approval lead times into the study's timeline.** Note that it takes time to complete the applications before they can be submitted for review; the times provided in Tables 2 and 3 may be significantly longer if labs do not receive the required information from sponsors in a timely fashion for rapid submission. Working with government agencies can also be unpredictable, and timelines may be drawn out when application volume is high.

- **Use couriers who can replenish dry ice in transit.** Experienced biological sample and pharmaceutical carriers such as World Courier, MNX Global Logistics, Biocair, Marken and QuickSTAT specialize in handling critical samples and are familiar with dry ice restocking, temperature tracking, replenishment if caught in customs, and other needs for biopharmaceuticals and animal shipments. More standard carriers such as DSL, FedEx and UPS have replenishing services available by special request but are not as experienced in transporting such items and maintaining their integrity.

CONCLUSION

The U.S. government requires import permits for many reasons, but primarily to prevent the introduction of exotic diseases into people or the ecosystem. Proper documentation and oversight helps mitigate risk and minimize the chances of unforeseen outbreaks or specimen mishandling. For example, receiving facilities must meet biosafety level ratings to receive infectious agents. In addition, permitting requirements help reduce black market circulation of drug substances, threatened animals and other products by ensuring all items passing through customs have proper documentation.

For emerging drug companies and novel products, it can be challenging to navigate the permitting process and identify the right agencies for the right permissions if they tackle this process alone. Working with an experienced research partner can significantly streamline the process. Established CROs can simplify the process of biological sample categorization and documentation to make government agency and permit requirements clearer. Furthermore, CROs that maintain annual licenses for handling certain species of animals or types of human tissue may also save weeks for a sponsor's timeline, and absorb related licensing expenses as part of their regular cost of doing business. Knowledgeable CROs can also help avoid lost time in customs and fines due to insufficient documentation. Having a research partner manage and direct this process can provide significant clarity and a more seamless import/export experience for sponsors, making sample documentation, permitting and shipping a fairly stress-free part of drug development.

To learn more, watch our webinar about importing and exporting biological samples, or reach out to our experienced laboratory specialists today to discuss permit requirements for your material shipment needs.

About the author

Mark Vann joined Pyxant Labs (now Aliri) in 2018 and serves as Operations Support Manager, overseeing the inventory management of samples and compounds, international logistics, procurement, and special operations projects. Mark has worked with a variety of biotech and pharma companies to successfully import and export their biological samples.

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