

Bioprocessing

High purity alcohols in biopharma: Insights in navigating compliance

Alcohols used in bioprocessing require specific conditions to enable their safe storage, shipping, and usage. These conditions are dictated by multiple U.S. regulatory bodies through the development of safety, environmental, and alcohol-specific guidelines. An in-depth, working knowledge of the guidelines and permitting requirements includes an understanding of the substantial reporting obligations and the specifications around payment of excise taxes. The goal of the regulatory bodies with respect to alcohol is to protect the workers, the public, and the revenue.¹ The risks associated with storing alcohols can be mitigated by collaborating with companies who already have the necessary permits and authorizations to support compliant operations.

Thermo Fisher Scientific, a global supplier of bioprocessing equipment and consumables hosted an industry [webinar](#) where professionals in bioproduction and regulatory compliance discussed the safety and regulatory considerations associated with alcohols in bioprocessing. Speakers for the event included:

- Amanda Kelty, Director, Regulatory Compliance, Greenfield Global
- Jai Murthy, Ph.D., Director, Bioproduction Product Management, CGMP Chemicals and Services, Thermo Fisher Scientific
- Todd Newsome, Sr. Manager, Regulatory Compliance and Environmental Health and Safety, Thermo Fisher Scientific

Industry observations for use and supply of alcohols

The bioprocessing workflow includes numerous applications for alcohols including cleaning and sanitizing, equipment and column cleaning and storage, facility sterilization, clean-in-place applications, and final dose formulation. Like nearly all chemicals used in bioproduction, alcohols come with several challenges to their safe and efficient use.

Unforeseen supply shifts in upstream alcohol production can drastically slow or halt operations in downstream bioproduction facilities. For example, a shutdown of a major grain distillery can highlight the need for risk mitigation plans that include alternate sourcing strategies for raw materials. Geopolitical events, accidents, and natural disasters are just a few examples of unforeseen circumstances that could affect supply.

Lead times can change dramatically and unpredictably. In some cases, a single-sourcing strategy may be the only option for a given chemical; however, a multi-sourcing strategy engaging three or more suppliers offers the strongest reliability and the lowest risk of shifts in lead times that could cause production delays.

Governing bodies for industrial alcohols

Multiple governing bodies oversee the use of alcohols at the federal level to protect workers and the public from injury or other hazards. At the local level, municipal authorities may also have regulations governing the storage and transportation of industrial alcohols to ensure community safety. Overall, a network of governing bodies collaborates to uphold the responsible production and usage of industrial alcohols while safeguarding public health and the environment.

Safety regulations

At the international level, organizations like the International Organization for Standardization (ISO) establish guidelines for the production, handling, and transportation of industrial alcohols to promote uniformity and safety across borders. Within the US, the Department of Transportation (DOT), the National Fire Protection Association (NFPA), and the Occupational Safety and Health Administration (OSHA) oversee safety issues with respect to alcohol production. OSHA enforces its best practices for fire

hazard prevention through local building and fire prevention codes for flammable liquid storage. NFPA's flammable and combustible liquids code² covers storage and handling of these chemicals and is enforced by OSHA and many states and localities. The flammability of alcohols necessitates specific storage conditions to mitigate potential environmental and occupational hazards, including separate spaces for each category of alcohol according to its flash and boiling points (see Table 1). Pure, specially denatured, completely denatured, and reagents each have their own listed uses, formula requirements, and permitting and tax-related regulations.

Given the complexity of NFPA 30, it is important to have a strong understanding of these requirements. Fire Safety Consultants or Loss Insurance Underwriters can help companies understand applicable standards and ordinances that must be upheld to remain compliant and protect workers, the public, and the environment. DOT's regulations permit the shipping of combustible liquids

Environmental regulations

Environmental oversight is provided by the United States Environmental Protection Agency (U.S. EPA). Reporting requirements from the EPA cover many aspects of environmental safety:

- **Toxic Release Inventory (TRI) reports** inform the EPA about toxic chemical releases and a company's pollution prevention activities. The specific requirements for these reports depend on the industry sector and the types of chemicals being stored.
- **Tier II chemical reports** are submitted to the appropriate State authority which dictates the specific requirements and frequency of reporting.
- The **Clean Air Act (CAA)** requires inventory level monitoring and permitting of any CAA chemical levels in excess of established minimums (even if the excess is only held for a short duration). Note these minimums should be kept in mind prior to scaling up to determine whether permits should be updated.

Common challenges with alcohol use in biopharma

- Supply chain uncertainty
- Hazards associated with alcohol handling
- Misunderstanding regulatory compliance
- Potential to result in financial losses
- Lack of awareness around taxation implications

and some flammable liquids, but the NFPA 30 requirements are more stringent than those of the DOT for transport and covers storage and handling requirements, as well.

Alcohol-specific regulations

The Alcohol, Tobacco, Tax and Trade Bureau (TTB), a bureau under the Department of the Treasury, also provides specific oversight related to compliance to protect the public and revenue. In

	Examples	Flashpoint	Boiling Point
Category 1	Vinyl chloride, heptane, pentane, ethyl ether	Below 73.4°F (23°C)	At or below 95°F (35°C)
Category 2	Gasoline, isopropyl alcohol, acetone, ethanol	Below 73.4°F (23°C)	Above 95°F (35°C)
Category 3	Kerosene, mineral spirits, diesel fuel, turpentine	Below 73.4°F (23°C) At or below 140° (60°C)	Above 95°F (35°C)
Category 4	Mineral oil, oil-based paint, glycerin, ethylene glycol	Above 140°F (60°C) At or below 199.4° (93°C)	Boiling point above 95°F (35°C)

Table 1. OSHA's Flammable Liquid Categories

addition to oversight of the alcoholic beverage industry, the TTB issues permits for distilled spirit plants (DSPs) for industrial facilities. These permits require extensive monthly storage, processing, and denaturing reports. Additionally, they require a designated, fixed bonded area for any tax-free alcohols which must be separate from any tax-paid materials. Tax-free alcohol is tracked in proof gallons and must also be tracked from all sources. Use of tax-free alcohol is limited to those that do not bring a profit. Federal Excise Tax is required for material removed from bond and shipped to a location that is not authorized by the TTB for tax-free withdrawal.³

The TTB permit also dictates that specially denatured alcohols (SDAs) can only be blended on the bonded premise of a DSP, and the DSP is responsible for validating the permits of any shipment recipients. SDAs are tracked in liquid gallons. Some companies have an Industrial Alcohol User Permit (IAUP) from the TTB which authorizes them to withdraw pure ethanol tax-free. Permit holders must track all gallons received from all sources, not to exceed the annual permit limit.

Note that the TTB requires notification of any changes to the conditions under

which the permit was acquired. Figure 1 outlines these requirements. In addition to the federal agencies described here, state and local regulations may also apply.

Potential consequences of non-compliance

Sometimes a lack of training or awareness or changes in roles within a company lead to non-compliance with one or more of the regulations associated with alcohol production. Non-compliance can lead to operational shutdowns, explosions or fires, serious harm or possible death among employees, legal ramifications, financial penalties, or a damaged reputation for the company. As such, companies are encouraged to have staff who fully understand the regulations of all local, state, and federal agencies and who can diligently adhere to the reporting and other requirements.

Distributor's role in compliance

A DSP-bonded facility is legally approved and bonded to store large volumes of alcohol in a tax-free status. Bonds represent legal agreements between a company, the TTB, and a surety company that taxes will be collected and paid when required. Bonds generally cover what is transferred and stored.

Do-it-yourself or work with an existing DSP-bonded collaborator

Companies can choose to create their own DSP-bonded warehouseman or collaborate with another DSP-bonded warehouseman company. Companies wishing to work on their own should be aware that acquisition of all the appropriate permits and registrations can take 6-8 months, a distilled spirits surety bond will need to be established, and the company will be responsible for semi-monthly tax returns and monthly reports of storage and operations to the TTB.³

Specialized facility permitting allows for unique storage of highly hazardous flammable liquids. Enhanced fire protection, chemical containment, and ventilation systems could be required and will protect against risks associated with the flammable inventory while enabling compliance with requirements of the regulatory bodies. Compliance with each of these requirements would be the responsibility of an external DSP-bonded warehouseman.

Tax requirements

Distributors are responsible for calculating the excise tax when spirits are removed from the bonded premises. The excise tax on taxed alcohols is calculated by multiplying the number of proof gallons

by the distilled spirits tax rate (\$13.50 as of this writing) and is paid to the TTB. The distributor must also file the semi-monthly excise tax returns. Accurate, timely payments help the company avoid penalties and interest charges, and could lead to less frequent audits.

An external DSP-bonded warehouseman can set up proactive interactions with tax authorities, covering the tax costs to TTB upfront and including those costs in the invoice to the company to be paid when they take possession of the material. The customer and the distributor with whom they are collaborating can customize terms to best fit the needs of both companies.

Protecting the revenue through safety, traceability, and supply chain transparency

Companies working with an external distributor should consider confirming

that initial and periodic risk assessments are conducted including security protocols that incorporate access control, video surveillance, intrusion detection, visitor management, and employee background vetting.

Traceability and reporting can help support the line of sight and safety of the inventoried materials. Full documentation from source to finished product, EPA waste generation reports, monthly storage reports, and semi-monthly excise tax returns should be meticulously kept and safely stored. Similarly, efforts to create supply chain transparency can help improve risk management, provide visibility for order management, enhance quality control, and protect revenue. To do so, distributors must proactively communicate regarding orders and change control, appropriately handle

and document resolution of material nonconformities, and accurately maintain inventory control through cycle counting bonded areas and reconciliation of alcohol stored, received, and sold. According to Todd Newsome, Sr. Manager, Regulatory Compliance and Environmental Health and Safety, Thermo Fisher Scientific, “The inventory must be 100%, 100% of the time, down to the lowest proof count.” Proprietors must maintain accurate inventory records in accordance with 27 CFR Part 19 Subpart V. The physical inventory must be accounted for in proof gallons and reported to TTB on a monthly basis as part of the DSP’s storage operations.

Periodic audits from TTB allow the distributor to demonstrate their full control of the alcohol from the time it is transferred to the time that it is shipped,

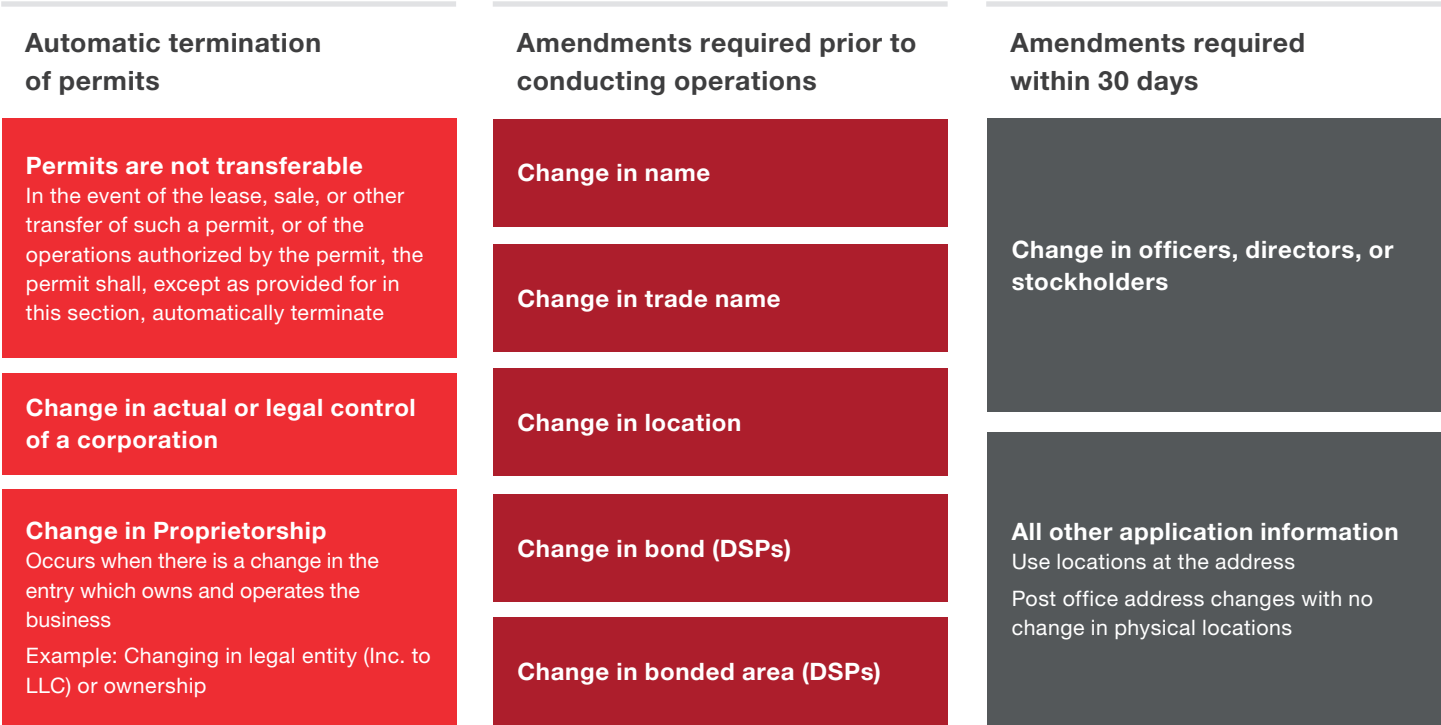


Figure 1. Requirements for compliance for TTB permits

9 features to look for in alcohol and logistics collaborators



Fire protection



Traceability & reporting



Quality of material



Security protocol



Supply chain transparency



TTB & regulatory compliance



Proof gallon & tax management



Organizational change control



Reliability & scalability

and the tax is determined. Being ready for unscheduled audits can result in improved risk management, enhanced quality control, and protected revenue.

The compliant storage and distribution of industrial-use alcohols requires an in-depth, working knowledge of several regulatory standards, frequent reporting, and timely payment of applicable taxes. Working with an existing DSP-bonded warehouseman with the appropriate experience can help support compliant operations.

Sources:

1. Alcohol and Tobacco Tax and Trade Bureau. (n.d.). TTB mission, vision, and values. Alcohol and Tobacco Tax and Trade Bureau, U.S. Department of Treasury. Available at <https://www.ttb.gov/about-ttb/mission-vision-values>. Last accessed April 25, 2024.
2. NFPA. NFPA 30 Flammable and Combustible Liquids Code. (2024). Available at <https://www.nfpa.org/codes-and-standards/3/0/nfpa-30>. Last accessed April 25, 2024.
3. Need to determine use of spirits—industrial or nonindustrial, 27 CFR §19.472. (2024). Available at: <https://www.ecfr.gov/current/title-27/chapter-I/subchapter-A/part-19/subpart-S/section-19.472>. Last accessed April 25, 20



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Pictured is the Thermo Fisher Scientific DSP-bonded warehouse in Riverside, CA. Thermo Fisher has several DSP-bonded facilities throughout the U.S.

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