

Classified Information: Shipping Biological Substances

The regulations surrounding the shipment of biopharmaceutical substances can be difficult to judge correctly. Michael Gotz at QuickSTAT offers some helpful pointers



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It is self-evident in the biopharmaceutical industry that science is intermeshed with business and regulatory concerns. This principle is readily apparent when it is necessary to ‘classify’ biological substances for shipping purposes. The shipper of a life sciences substance must comply with national and international transportation regulations to determine whether or not it is ‘classified’ as an infectious substance and thus considered dangerous goods. This scientific/medical decision impacts the manner in which the commodity is prepared for shipment as well as the type and availability of transport.

This is particularly significant if, for instance, a clinical trial is conducted in a region where dangerous goods airlift is severely limited – either by regulation or by the airlines themselves. In such cases it can be difficult to get patient samples from the investigator site to the laboratory in the timely manner required for temperature-sensitive shipments. The following discussion is intended as a guide to applying regulatory criteria to the classification of biological substances so as to comply with the law and ensure the timely, successful delivery of critical shipments.

THE REGULATORY ENVIRONMENT

The starting point in the classification process is identifying the regulations. The primary source for international law governing the classification, preparation and transportation of dangerous goods is the United Nations which, through a number of committees, produces a body of law relative to each mode of transport. In turn, national governments promulgate regulations which, for the most part, are ‘harmonised’ with the UN laws, meaning they are essentially the same, regardless of their

governmental origin. All regulations thus agree on the following passage taken from the IATA’s Dangerous Goods Regulations (DGR): “No person may offer or accept dangerous goods for air transport unless these goods are properly classified, documented, certificated, described, packaged, marked, labelled and in the condition for shipment required by these Regulations.” The regulations are enforced by governmental regulatory authorities, such as the Federal Aviation Administration (FAA), Civil Aviation Authority (CAA) and similar agencies in most countries. Infringement of the regulations carries stiff penalties, including large monetary fines for civil infractions and jail time for intentional/criminal violations.

The first step is to define ‘dangerous goods’ as applied to biopharmaceutical shipments such as patient samples. Since we are only concerned with whether or not a particular commodity is considered infectious and, hence, dangerous goods, the following definition applies:

Infectious substances are substances which are known or reasonably expected to contain pathogens. Pathogens are defined as micro-organisms (including bacteria, viruses, rickettsiae, parasites, fungi) and other agents, such as prions, which can cause disease in humans or animals.



It is the shipper's responsibility to apply regulatory criteria to determine whether a particular shipment meets this definition.

THE CLASSIFICATION CRITERIA

An infectious substance meeting the above definition must be categorised as either Category A or Category B. Category A substances meet the following criterion:

An infectious substance which is transported in a form that is capable of causing permanent disability or life-threatening or fatal disease in otherwise healthy humans or animals.

In the case of Category A, the rule makers have provided specific guidance in a chart of "Indicative Examples of Category A infectious substances". This chart may be found in the IATA or ICAO regulations or online (1). A perusal of this chart finds the majority of the listings come with a caveat: they are considered Category A only if shipped as cultures. Those remaining are quite exotic diseases such as sabia virus, variola virus and monkeypox.

Shippers of Category A infectious substances are few and far between. They are required to package and document the shipment in a highly specialised manner, which requires a fair amount of training and dangerous goods certification. Most shipments of infectious substances fall into Category B. The criterion for this category is expressed simply:

An infectious substance that does not meet the criteria for inclusion in Category A.

So, if a particular substance is adjudged to meet the definition of an infectious substance as provided above, but does not appear in the Category A list nor seem to meet the strict criterion of Category A, then it must be in Category B. Consequently, in this category fall such commonly transported commodities (patient samples primarily) as HIV, HPV, hepatitis A, B and C, adenovirus, malaria, and so on.

Given the definition of infectious substances and the existence of the two categories, one could easily imagine that a discussion of classification of biological substances might end here. But, as we shall see, there is no clear-cut universal principle of categorisation; rather, it is open to interpretation and exception. Questions linger.

What if the infectious pathogen has been neutralised? The regulations address this issue as follows:

Substances in a form that any present pathogens have been neutralised or inactivated such that they no longer pose a health risk are not subject to these Regulations.

What if the existence or non-existence of pathogens in a human specimen is not known due to a lack of testing?

In determining whether a patient specimen has a minimal likelihood that pathogens are present an element of professional judgment is required... based on the known medical history, symptoms, and individual circumstances of the source, human or animal, and endemic local conditions.

In addition, certain types of biological substances are exempt from the regulations, including blood and blood products collected for the purpose of transfusion, tissue and organs transported for transplant, substances containing microorganisms not considered to pose a significant health risk, biological substances containing no known pathogens, and biological products which are manufactured and packaged in accordance with the requirements of appropriate national authorities (such as vaccines).

APPLYING THE CRITERIA

In the final analysis, there are three scenarios when considering whether or not to classify a biological substance as dangerous goods:

- ◆ Scenario 1: The substance is known or reasonably expected to contain an infectious pathogen – in this case classify it as Category A or Category B
- ◆ Scenario 2: The substance has a minimal likelihood that infectious pathogens are present, the pathogens have been neutralised or the commodity is specifically exempted from the regulations – here, classify it as non-infectious, not dangerous goods
- ◆ Scenario 3: No testing has been done and there is a limited medical history, so the existence or non-existence of infectious pathogens is impossible to pre-determine – classify it as Category B

This third scenario is quite common. Patients enrolled in a trial for one disease, cancer, for example, may not have been screened for the presence of infectious pathogens. Most shippers prefer to take the conservative approach and classify such samples as Category B until a determination to the contrary is made.

However, it must be pointed out that the regulations require classification to be as precisely in compliance with the criteria as possible. It is against the law to classify an infectious substance as non-dangerous, but it is just as wrong to classify a biological substance as infectious if this is unlikely to be the case. An example of the latter condition is the classification of a known infectious virus that has been neutralised and is not able to reproduce in healthy cells. If when administered to a patient the virus does not create infection, the criteria for classification as non-infectious should be considered in the final determination. The classification of a biological substance is often fraught with grey areas and it takes training and experience to get it right. But there are professional transportation and regulatory specialists around with whom one can consult and a second opinion can be quite useful.

SHIPMENT PREPARATION

The regulations require the shipper to prepare the package in compliance with specified packaging, marking, labelling, and documentation rules. Category A substances are shipped under the 'proper shipping names', 'Infectious substance, affecting humans, UN 2814', or 'Infectious substance, affecting animals, UN 2900'. The UN numbers are assigned for positive identification, especially important for identifying complex chemicals. Category A substances must be packaged in expensive, highly durable boxes

with complex marking and labelling, and must be accompanied by a Shipper's Declaration for Dangerous Goods. The mandatory format for completion of this form is not self-evident and thus requires training and instruction.

Category B substances are shipped as 'Biological substance, Category B, UN 3373'. Packaging, marking, labelling and documentation is not nearly as stringent and can be accomplished after brief – but mandatory – training. The shipper is not responsible for a complex Shipper's Declaration but rather for the completion of certain information on the air way bill. For passenger aircraft transport, this task is performed on the shipper's behalf by the freight agent or courier, but for integrated freight air carriers it is usually done by the shipper.

TRANSPORT CONSIDERATIONS

The regulations contain provisions for the transport of completed packages of dangerous goods. These rules, while intended to be universally applied, can in fact be modified and made more stringent by an individual airline's policies and procedures. At the extreme end, for example, are airlines that do not accept dangerous goods at all. Other airlines accept only some types of dangerous goods but not others. Of course, the airlines who accept all biopharmaceutical commodities are the most useful to the life sciences industry. As indicated earlier, the classification decision may have an impact on the availability of air transport. If a clinical trial involving UN3373 specimens is conducted in a part of the world served primarily by one international air carrier, and that carrier does not accept this commodity for carriage, a significant challenge is presented.

This example deserves a detailed discussion because it comes up fairly frequently. In such a case, the science comes first: the shipper has the responsibility to determine with as much certainty as possible whether the commodity is in fact a Category B substance or whether it meets the criteria for classification as non-hazardous. For instance, a neutralised pathogen may have been administered to the patients, but the classification decision maker may be taking a carefully conservative road in calling the samples Biological substance, Category B.

It is not my purpose to question or criticise the classification, merely to suggest that because there are transport consequences arising from the classification decision, it is very important to be as precise as possible. In any case, the science must not be manipulated in the interests of business. An infectious substance or patient sample that has not been tested may not suddenly be transformed into a non-hazardous shipment.

If the shipment remains Category B, then business considerations do come into play. It is up to the professional freight agent or courier company to locate

suitable transport that accommodates the time and temperature-sensitive nature of the shipments, and at the same time complies with dangerous goods regulatory requirements. This may seem like a daunting task, but that is what the speciality courier companies are able to do, and its something that most shippers are eager to delegate.

It is in choosing a transport provider for a clinical trial or other life sciences shipment that science and business interests coincide. Usually these types of shipments are highly dependent on timely transport owing to temperature considerations and study protocols. If the samples are allowed to thaw or are otherwise made useless, the impact on the biopharmaceutical company can be tremendous. It is therefore in everyone's best interest that selection of the transporter be made in a timely manner prior to the first shipment. Factors affecting this decision include the ability to replenish the refrigerant (dry ice or gel packs, for example), to obtain suitable air transport and to communicate with the shipper and consignee during the transportation process.

CONCLUSION

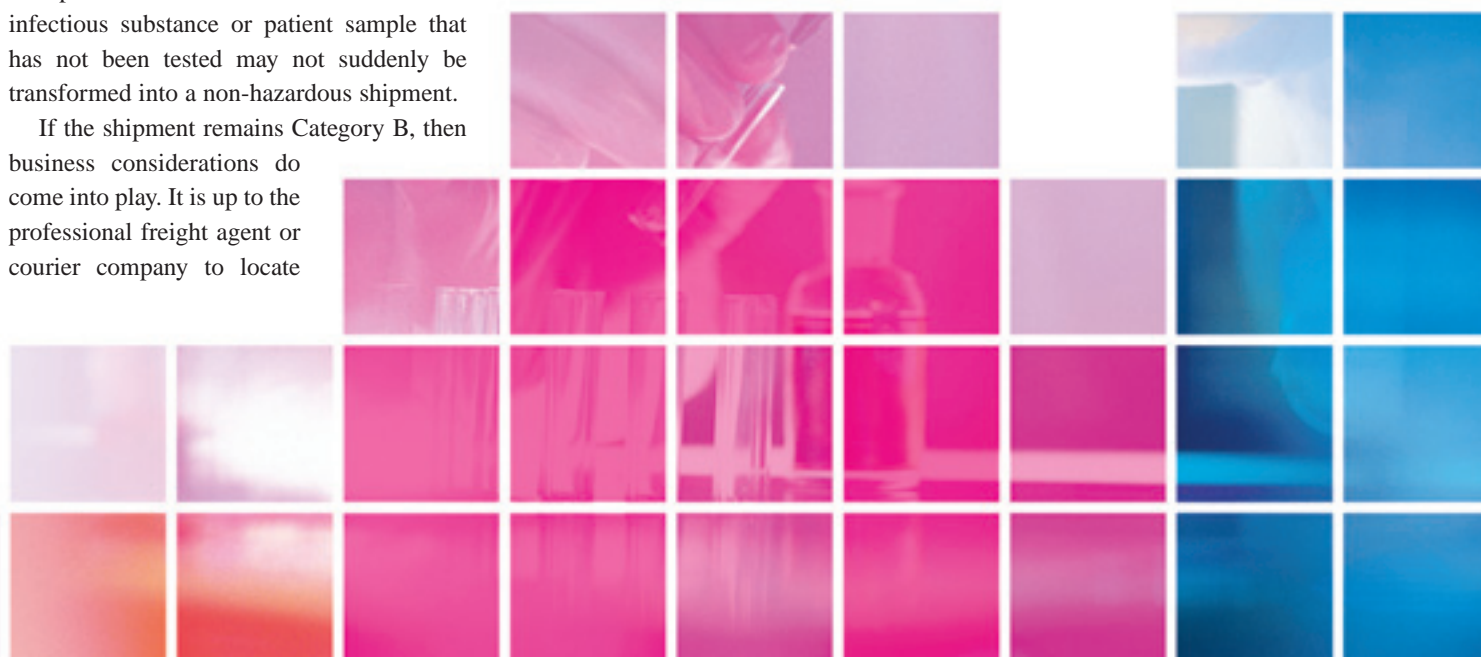
As we have seen, classification of biological substances for dangerous goods is the first step in the transportation process. It must be done strictly in compliance with the regulations, yet there are grey areas where only informed medical judgement is available to decision makers. Whatever the classification, the decision affects the manner in which the packages are marked, labelled and documented, and also has an impact on the availability of transport for the shipments. Mandatory training is inherent to this process, and speciality transport companies are willing to help.

It takes a team to navigate the challenging waters of biopharmaceutical transport. Success comes when scientists and medical personnel work alongside transportation professionals to ensure that science and business are effective partners. ♦

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Reference

1. www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm



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