



PHARMACY, MEDICINES & POISONS BOARD

**REGULATORY REQUIREMENTS ON
STORAGE AND EXPORT OF SAMPLES /
SPECIMENS COLLECTED FROM
PARTICIPANTS / CLINICAL TRIAL
SUBJECTS DURING CLINICAL TRIALS
FOR TESTING**

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1 Introduction

Samples or specimens collected from participants during clinical trials are often not tested at the clinical trial site and may have to be sent nationally or internationally to another testing laboratory.

Postal, airline and other transport industry personnel have concerns about the possibility of becoming infected as the result of exposure to infectious micro-organisms that may escape from broken, leaking or improperly packaged material. The packaging of infectious substances for transport must therefore be designed to minimize the potential for damage during transport. In addition, the packaging must ensure the integrity of the materials and so, in turn, timely and accurate processing of specimens.

Transportation of specimens is subject to regulation by the International Air Transport Association (IATA), which is stringent in its requirements for packaging, declaration and paperwork.

Informed consent is required from the clinical trial subject or his/her legal representative or guardian whenever a new sample is taken wholly or partly for use in research. Donors should understand what the sample is to be used for and how the results of the research might impact on their interests. Consent must also be obtained for storage and potential future use of samples.

In some clinical trials, clinical specimens may be tested initially at local laboratories, and any isolates that are recovered will then be sent to a central laboratory to confirm the identity of suspected pathogens and for antibiotic susceptibility testing. For example, in a clinical study involving skin infections, an investigator may be concerned with microbial testing only for *Staphylococcus aureus* as the primary target pathogen. If this pathogen were recovered from an initial specimen, it might be sent to a central laboratory for confirmation and additional testing.

Ensuring that clinical samples reach their destination safely, securely, and at the right temperature is a critical element in the clinical trial process. Cold chain or temperature control is playing a greater role in clinical logistics, as the process of transporting human clinical trial samples and investigational drugs becomes increasingly complex.

If clinical trials are to come in on time and on budget, it is critical for all parties associated with the transportation of biological substances - from the regulatory agencies overseeing transportation practices to the lab personnel, couriers and airline staff that handle the shipments - become fully familiar with and adhere to the proper packing and shipping practices.

Once samples/specimens are taken from clinical trial subjects they need to arrive in central laboratories in a defined transit time and in suitable packaging. Many samples have to be tested immediately and remain either frozen, or at refrigerated temperatures. Delays in transit times or incorrect storage conditions may lead to the loss of a sample and will negatively impact on the trial results.

Some types of transport media are better than others for particular applications. For instance, some media are designed for maintaining fastidious organisms. In clinical trials, the choice of transport medium depends in part on what target pathogens need to be recovered and also on the nature of the specimen being collected. Three major devices are employed to maintain viability of organisms during their shipment (Table 1).

In clinical trials, participants from many different countries are often enrolled in studies, and specimens collected from these participants are shipped over vast distances. Under such circumstances, it is imperative that the viability of organisms in the specimen be maintained until they reach the central laboratory. Deciding whether to ship specimens that are frozen, refrigerated, or kept at ambient temperatures depends on a number of factors, including the

type of study; countries where it is being performed; the local, national, and international shipping regulations that apply; the time of transit; and the target pathogens being sought.

Table 1 Major devices used to maintain viability of organisms

| Device | Shipping temperature | Disadvantages |
|--|----------------------|--|
| Refrigeration (with gel packs) | 2–8 °C | Weight and cost |
| Freezing (with dry ice) | approx -20 °C | Weight and cost |
| Ambient (no coolant) | 20–25 °C | Selective agents may have to be added to limit bacterial competition |

In recent years, clinical laboratories have shifted into a system in which many peripheral laboratories conduct only tests that can be completed the same day, while most specimens requiring culture and analysis are performed by a smaller set of “core” laboratories to which specimens are shipped. This change has led to increased reliance on the use of transport media to maintain the viability of pathogens during transit, which may take several days depending on the distances between the peripheral and core laboratories. In clinical trials microbiology as well as in routine clinical testing, properly collecting specimens and transporting them under appropriate conditions is critically important for maintaining microbial viability.

International regulations

The international regulations for the transport of infectious substances by any mode of transport are based upon the Recommendations made by the Committee of Experts on the Transport of Dangerous Goods (UNCETDG), a committee of the United Nations Economic and Social Council. The Recommendations are presented in the form of Model Regulations. The United Nations Model Regulations are reflected in international law through international modal agreements.

Air The *Technical Instructions for the Safe Transport of Dangerous Goods by Air* published by the International Civil Aviation Organization (ICAO) are the legally binding international regulations.

The International Air Transport Association (IATA) publishes Dangerous Goods Regulations (DGR) that incorporate the ICAO provisions and may add further restrictions.

The ICAO rules apply on all international flights. For national flights, i.e. flights within one country, national civil aviation authorities apply national legislation. This is normally based on the ICAO provisions, but may incorporate variations. State and operator variations are published in the ICAO Technical Instructions and in the IATA Dangerous Goods Regulations.

Rail Regulations concerning the International Carriage of Dangerous Goods by Rail (RID) apply to countries in Europe, the Middle East and North Africa. RID also applies to domestic transport in the 25 countries of the European Union through Council Directive 96/49/EC.

Road The *European Agreement concerning the International Carriage of Dangerous Goods by Road* (ADR) applies to 40 countries. In addition, modified versions of the convention are being used by countries in South America and South-East Asia. ADR also applies to domestic transport in the 25 countries of the European Union through Council Directives 94/55/EC.

Sea The *International Maritime Dangerous Goods Code* published by the International Maritime Organization (IMO) is of mandatory application for all 155 contracting parties to the International Convention for the Safety of Life at Sea (SOLAS).

Post The *Letter post manual* published by the Universal Postal Union (UPU) reflects the United Nations Recommendations using the ICAO provisions as the basis for shipments.

The World Health Organization serves in an advisory capacity to UNCETDG and ICAO.

2 Scope

This guideline applies to all samples / specimens collected from participants during clinical trials for the purpose of testing at a facility located outside the institute where trials are being conducted and for tests beyond the capacity of the trial institute.

3 Responsibilities of the Sponsor, Carrier and Receiver

3.1 Sponsor (shipper/sender)

The clinical trial sponsor is regarded as the shipper/sender and is the legal entity with the responsibility of ensuring that samples collected from clinical trial subjects are sent through the appropriate carrier to their destination.

The sponsor may delegate functions to the principal investigator.

The sponsor is responsible for the following:

- 3.1.1 Supply the necessary packaging material to ensure correct packaging of human samples for storage and shipment to the relevant testing laboratory.
- 3.1.2 Indicate the correct classification of the samples and the appropriate storage temperatures, storage conditions (e.g. protection from light).
- 3.1.3 Make advance arrangements with the receiver including investigating the need for import/export permits.
- 3.1.4 Make advance arrangements with the carrier to ensure:
 - that the shipment will be accepted for appropriate transport
 - that the shipment (direct transport if possible) is undertaken by the most accessible and convenient method of transport
- 3.1.5 Prepare necessary documentation, including permits for the sample exportation from national authorities, dispatch and shipping documents.
- 3.1.6 Notify the receiver of transportation arrangements once these have been made, well in advance of the expected arrival time.

Refer to **ANNEX 1** for Check-list for the principal investigator.

3.2 The carrier

The carrier is the transporter and is responsible for the following:

- 3.2.1 Provide advice to the sender regarding the necessary shipping documents and instructions for their completion.
- 3.2.2 Provide advice to the sender about correct packaging.
- 3.2.3 Assist the sender in arranging the most direct routing and then confirm the routing.
- 3.2.4 Maintain and archive the documentation for shipment and transport.
- 3.2.5 Ensure that samples are kept at the recommended storage conditions throughout shipment and to submit record of this to the sender and receiver.

3.3 The receiver

The receiver or consignee is responsible for the following:

- 3.3.1 Obtain the necessary authorization(s) from national authorities for the importation of the material.
- 3.3.2 Provide the sender with the required import permit(s), letter(s) of authorization, or other document(s) required by the national authorities.
- 3.3.3 Arrange for the most timely and efficient collection on arrival.
- 3.3.4 Should acknowledge receipt to the sender and maintain and keep records of all samples received.

Shipments should not be dispatched until:

- Advance arrangements have been made between the sender, carrier and receiver
- The sender has confirmed with the national authorities that the material may be legally exported
- The receiver has confirmed with the national authorities that the material may be legally imported
- The receiver has confirmed that there will be no delay incurred in the delivery of the package to its destination.

4 Abbreviations and Definitions

IATA: International Air Transport Association

ICAO: International Civil Aviation Organization

NRA: National Regulatory Authority

Sponsor: An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

WHO: World Health Organisation

5 Classification of infectious substances and diagnostic specimens

In the recent past, infectious substances were classified by reference to World Health Organization Risk Groups. For transport purposes the classification of infectious substances by risk groups was removed from the ICAO Technical Instructions in the 2005/ 2006 edition.

Infectious substances are now classified as Category A or Category B.

There is no direct relationship between Risk Groups and Category A and B.

There is a list of indicative examples of infectious substances included in Category A (see **ANNEX 2**), but there is no list for Category B.

As participants in clinical trials are treated for diseases, the samples / specimens that are collected for testing will fall into one of these categories. When these samples have to be transported for testing purposes, the correct classification is important to determine correct packaging and transport.

Infectious substances

For the purposes of transport, infectious substances are defined as substances which are known or are 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.

The definition is applied to all specimens except those explicitly excluded (see below).

Infectious substances are divided into two categories:

5.1 Infectious substance, Category A

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

Indicative examples of substances that meet these criteria are given in the table in **ANNEX 2**. They must be packed as described in section 6 below and must be accompanied by a Shipper's Declaration

Note: An exposure occurs when an infectious substance is released outside of the protective packaging, resulting in physical contact with humans or animals.

- (a) Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to United Nations number UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Dangerous goods are assigned UN numbers and proper shipping names according to their hazard classification and their composition. Proper shipping names are used to clearly identify the dangerous article or substance.

- (b) Assignment to UN 2814 or UN 2900 must be based on the known medical history and symptoms of the source human or animal, endemic local conditions, or professional judgement concerning individual circumstances of the source human or animal.

NOTE 1: *The proper shipping name of UN 2814 is INFECTIOUS SUBSTANCE, AFFECTING HUMANS. The proper shipping name for UN 2900 is INFECTIOUS SUBSTANCE, AFFECTING ANIMALS only.*

NOTE 2: *The table in Annex 2 is not exhaustive. Infectious substances, including new or emerging pathogens, which do not appear in the table but which meet the same criteria shall be assigned to Category A. In addition, if there is any doubt as to whether or not a pathogen falls within this category it must be transported as a Category A Infectious Substance.*

5.2 Infectious substance, Category B

An infectious substance which does not meet the criteria for inclusion in Category A. Infectious substances in Category B shall be assigned to UN 3373.

NOTE: *The proper shipping name of UN 3373 is "BIOLOGICAL SUBSTANCE, CATEGORY B"*

From January 1, 2007 the shipping names 'Diagnostic Specimens' and 'Clinical Specimens' is no longer permitted.

The new rules make shipping clinical trial and investigatory specimens easier, in that most commonly shipped infectious pathogens occurring in human bodily fluid samples are not found in Category A.

See **ANNEX 5**

For examples of Classification Scenarios and **ANNEX 3 & ANNEX 4** for Classification Flowcharts.

Note: Toxins from plant, animal or bacterial sources which do not contain any infectious substances or toxins that are not contained in substances which are infectious substances should be considered for classification in Division 6.1 and assigned to UN3172.

5.3 Cultures

Cultures are the result of a process by which pathogens are intentionally propagated. This definition does not include human or animal patient specimens as defined below. Cultures may be classified as Category A or Category B, depending on the micro-organism concerned.

5.4 Trial participant specimens

These are human or animal materials, collected directly from humans or animals, including, but not limited to, excreta, secreta, blood and its components, tissue and tissue fluid swabs, and body parts being transported for purposes such as research and investigational activities.

5.5 Biological products

Biological products are

- (a) those products derived from living organisms which are manufactured and distributed in accordance with the requirements of appropriate national authorities, which may have special licensing requirements, and are used either for prevention, treatment, or diagnosis of disease in humans or animals, or for development, experimental or investigational purposes related thereto.
They include, but are not limited to, finished or unfinished products such as vaccines.
- (b) those which do not fall under paragraph (a) and are known or reasonably believed to contain infectious substances and which meet the criteria for inclusion in Category A or Category B. Substances in this group must be assigned to UN2814, UN2900 or UN3373, as appropriate.

Note: *Some licensed biological products may present a biohazard only in certain parts of the world. In that case, competent authorities may require these biological products to be in compliance with local requirements for infectious substances or may impose other restrictions.*

5.6 Human material

All biological material of human origin, including organs, tissues, bodily fluids, teeth, hair and nails, and substances extracted from such material such as DNA or RNA.

5.7 Genetically modified micro-organisms and organisms

Genetically modified micro-organisms and organisms are micro-organisms and organisms in which genetic material has been purposely altered through genetic engineering in a way that does not occur naturally. Those genetically modified micro-organisms and organisms that do not meet the definition of an infectious substance but which are capable of altering animals, plants or microbiological substances in a way not normally the result of natural reproduction shall be assigned to UN 3245 and shipped following Packing Instruction P904 (ICAO/IATA PI913) – this is not considered further in this document.

5.8 Exceptions

Because of the low hazard they present, the following substances of biological origin are exempted from dangerous goods requirements and regulations:

- substances that do not contain infectious substances or will not cause disease in humans or animals
- substances containing micro-organisms that are not pathogenic to humans or animals
- substances in a form in which any pathogens present have been neutralized or inactivated such that they no longer pose a health risk

- environmental samples (including food and water samples) that are not considered to pose a significant risk of infection
- blood and/or blood components collected and shipped for the purposes of transfusion and/or transplantation
- dried blood spots and faecal occult blood screening tests
- decontaminated medical or clinical wastes.

Unless patient specimens comply with the following requirements, they must be assigned to UN 2814, UN 2900 or UN 3733, as appropriate.

Exempt Human/Animal Specimens

Human or animal specimens (clinical trial participant specimens) for which there is minimal likelihood that pathogens are present are not subject to the UN Regulation if the specimen is transported in a packaging which will prevent any leakage and which is marked with the words “Exempt human specimen” or “Exempt animal specimen”, as appropriate. The packaging should meet the conditions as described below under section

NOTE: *An element of professional judgment is required to determine if a substance is exempt under this paragraph. That judgment should be based on the known medical history, symptoms and individual circumstances of the source, human or animal, and endemic local conditions. Examples of specimens which may be transported under this paragraph include the blood or urine tests to monitor cholesterol levels, blood glucose levels, hormone levels, or prostate specific antibodies (PSA); those required to monitor organ function such as heart, liver or kidney function for humans or animals with non-infectious diseases, or therapeutic drug monitoring; those conducted for insurance or employment purposes and are intended to determine the presence of drugs or alcohol; pregnancy test; biopsies to detect cancer; and antibody detection in humans or animals.*

6 Labelling and Packaging for Storage and Export

Shipping of clinical trial participant samples should be conducted according to instructions given by or on behalf of the sponsor in the shipping order.

6.1 General preparation of shipments for transport

Because of the differences in the hazards posed by Category A infectious substances (UN 2814 and UN 2900) and Category B infectious substances (UN 3373), there are variations in the packaging, labelling and documentation requirements for the two categories.

The packaging requirements are determined by UNCETDG and are set out as Packing Instructions P620 (PI602 for ICAO/IATA regulations) and P650 – see **ANNEX 7 & ANNEX 9**. The requirements are subject to change and regular upgrade by the organizations mentioned. The current packaging requirements are described below.

Note 1: Hand carriage of Category A and Category B infectious substances and transport of these materials in diplomatic pouches are strictly prohibited by international air carriers. Exempted human or animal specimens may be carried in carry-on or checked baggage provided they meet the appropriate packaging requirements.

Note 2: Inner packagings containing infectious substances shall not be consolidated with inner packagings containing unrelated types of goods.

Shippers of infectious substances shall ensure that packages are prepared in such a manner that they arrive at their destination in good condition and present no hazard to persons or animals during transport.

6.2 Basic triple packaging system

This system of packaging shall be used for all infectious substances. It consists of three layers as follows.

- *Primary receptacle.* A primary watertight, leak-proof receptacle containing the specimen. The receptacle is packaged with enough absorbent material to absorb all fluid in case of breakage.
- *Secondary packaging.* A second durable, watertight, leak-proof packaging to enclose and protect the primary receptacle(s). Several cushioned primary receptacles may be placed in one secondary packaging, but sufficient additional absorbent material shall be used to absorb all fluid in case of breakage.
- *Outer packaging.* Secondary packagings are placed in outer shipping packagings with suitable cushioning material. Outer packagings protect their contents from outside influences, such as physical damage, while in transit. The smallest overall external dimension shall be 10x10 cm.

Each completed package is normally required to be correctly marked, labelled and accompanied with appropriate shipping documents (as applicable). The requirements for these aspects are described below.

6.3 Packaging for Exempt Patient Specimens

Patient specimens (human or animal) that have a minimal likelihood of containing pathogens must be packaged appropriately to further minimize the risk of exposure.

The packaging should consist of three components:

- (i) a leak-proof primary receptacle(s);
- (ii) a leak-proof secondary packaging; and
- (iii) an outer packaging of adequate strength for its capacity, mass and intended use, and with at least one surface having minimum dimensions of 100 mm × 100 mm.

For liquids, absorbent material in sufficient quantity to absorb the entire contents must be placed between the primary receptacle(s) and the secondary packaging so that, during transport, any release or leak of a liquid substance will not reach the outer packaging and will not compromise the integrity of the cushioning material.

When multiple fragile primary receptacles are placed in a single secondary packaging, they should be either individually wrapped or separated to prevent contact between them.

If such a packaging is used it should be marked “Exempt human specimen” or “Exempt animal specimen”, as appropriate.

See **ANNEX 6** for a graphic depiction of an Exempt Patient Specimen Packaging.

6.4 Packaging, labelling and documentation requirements for infectious substances in Category A (UN 2814 04 UN 2900)

6.4.1 Packaging (See ANNEX 7)

Infectious substances in Category A may only be transported in packaging that meets the United Nations class 6.2 specifications and complies with Packing Instruction P620 (PI602).

This ensures that strict performance criteria are met; tests for compliance with these criteria include a 9-metre drop test, a puncture test and a pressure test. The outer packaging shall bear the United Nations packaging specification marking (see ANNEX 8

), which indicates that the packaging has passed the performance tests to the satisfaction of the competent authority.

The primary receptacle or the secondary packaging shall be capable of withstanding a pressure differential of not less than 95 kPa. The United Nations packaging specification marking alone does not indicate that a test for this has been undertaken, and packaging users should ask their suppliers whether the completed package meets this requirement.

There is no comprehensive list of suppliers of packagings that comply with Packing Instruction P620 (PI602). However, an Internet search using a suitable international or national search engine usually provides appropriate information, as well as access to national regulations. Search phrases such as “UN packaging” and “UN infectious substance packaging” produce extensive results. Carriers and forwarding agents should also be able to supply details of local suppliers or local companies that can provide such information.

For surface transport there is no maximum quantity per package.

For air transport the limits per package are as follows:

- 50 ml or 50 g for passenger aircraft
- 4 litres or 4 kg for cargo aircraft.

Any primary receptacle with a capacity of more than 50 ml shall be oriented in the outer packaging so that the closures are upwards. Orientation labels (“UP” arrows) shall be affixed to two opposite sides of the outer packaging.

6.4.2 Marking

Packages are marked to provide information about the contents of the package, the nature of the hazard, and the packaging standards applied. All markings on packages or over packs shall be placed in such a way that they are clearly visible and not covered by any other label or marking. Each package shall display the following information on the outer packaging or the over pack:

- the shipper’s (sender’s, consignor’s) name and address
- the telephone number of a responsible person, knowledgeable about the shipment
- the receiver’s (consignee’s) name and address
- the United Nations number followed by the proper shipping name (UN 2814 “INFECTIOUS SUBSTANCES AFFECTING HUMANS” or UN 2900 “INFECTIOUS SUBSTANCES AFFECTING ANIMALS”, as appropriate). Technical names need not be shown on the package.
- temperature storage requirements (optional)
- when dry ice or liquid nitrogen is used: the technical name of the refrigerant, the appropriate United Nations number, and the net quantity

6.4.3 Labelling

There are two types of labels:

(a) Hazard labels in the form of a square set at an angle of 45° (diamond-shaped) are required for most dangerous goods in all classes;

(b) Handling labels in various shapes are required, either alone or in addition to hazard labels, for some dangerous goods.

Specific hazard label(s) shall be affixed to the outside of each package for all dangerous goods to be shipped (unless specifically exempted).

If required refer to “WHO/CDS/EPR/2007.2 Guidance on regulations for the transport of infectious substances 2007” for hazard labels.

6.4.4 Documentation

The following shipping documents are required:

To be prepared and signed by the shipper (sender, consignor):

- for air: the shippers Declaration for Dangerous Goods (Category A infectious substances)
- for international shipments: a packing list/proforma invoice that includes the shipper's and the receiver's address, the number of packages, detail of contents, weight, value (Note: for international transport, a minimal value shall be indicated, for customs purposes, if the items are supplied free of charge)
- an import and/or export permit and/or declaration if required.

To be prepared by the shipper or the shipper's agent:

- an air waybill for air transport or equivalent documents for road, rail and sea journeys.

For UN 2814 and UN 2900, an itemized list of contents shall be enclosed between the secondary packaging and the outer packaging. When the infectious substance to be transported is unknown, but suspected of meeting the criteria for inclusion in category A and assignment to UN 2814 or UN 2900, the words “suspected Category A infectious substance” shall be shown, in parentheses, following the proper shipping name on the document inside the outer packaging.

6.5 Packaging, labelling and documentation requirements for infectious substances in Category B (Clinical Specimens, Diagnostic Specimens, Biological Substances) (UN 3373)

6.5.1 Packaging (See ANNEX 9)

The triple packaging system continues to apply, including for local surface transport. Testing documents are not required, however. It may be possible to source packaging locally rather than finding an authorized supplier, provided that the packaging manufacturer and the shipper can comply fully with the requirements of P650.

As for P620, there is no comprehensive list of suppliers of packaging that comply with Packing Instruction P650. However, an Internet search using a suitable international or national search engine usually provides appropriate information, as well as access to national regulations. Search phrases such as “UN packaging” and “UN infectious substance packaging” produce extensive results. Carriers and forwarding agents should also be able to supply details of local suppliers or local companies that can provide such information.

To ensure correct preparation for transport, packaging manufacturers and subsequent distributors shall provide clear instructions to the consignor or persons preparing packages on how the packaging should be filled and closed.

For surface transport there is no maximum quantity per package.

For air transport:

- no primary receptacle shall exceed 1 litre (for liquids) or the outer packaging mass limit (for solids)
- the volume shipped per package shall not exceed 4litres or 4 kg for cargo aircraft

These quantities exclude ice, dry ice or liquid nitrogen when used to keep specimens cold.

6.5.2 Marking

Each package shall display the following information:

- for air: the shipper's (sender's, consignor's) name, address and telephone number
- for air: the telephone number of a responsible person, knowledgeable about the shipment
- the receiver's (consignee's) name, address and telephone number
- for air: the proper shipping name ("BIOLOGICAL SUBSTANCE, CATEGORY B")
- Temperature storage requirements (optional).

The following marking is used for shipments of Category B infectious substances.



- Minimum dimension: the width of the line forming the square shall be at least 2 mm, and the letters and numbers shall be at least 6 mm high. For air transport, each side of the square shall have a length of at least 50 mm
- Colour: none specified, provided the mark is displayed on the external surface of the outer packaging on a background of contrasting colour and that it is clearly visible and legible
- The words "BIOLOGICAL SUBSTANCE, CATEGORY B" in letters at least 6 mm high shall be displayed adjacent to the mark.

6.5.3 Documentation

Dangerous goods documentation (including a shipper's declaration) is not required for Category B infectious substances.

The following shipping documents are required:

To be prepared and signed by the shipper (sender, consignor):

- for international shipments: a packing list/*proforma* invoice that includes the shipper's and the receiver's address, the number of packages, detail of contents, weight, value (Note: the statement "no commercial value" shall appear if the items are supplied free of charge)
- an import and/or export permit and/or declaration if required.

To be prepared by the shipper or the shipper's agent:

- an air waybill for air transport or equivalent documents for road, rail and sea journeys.

A flowchart to help with the classification of infectious substances and patient specimens is shown in **ANNEX 4**

The Check-list may be used by the sponsor/principal investigator to ensure that the required documents are attached and correct - **See ANNEX 1**.

6.6 Over packs

"Overpack" is the term used when several packages are combined to form one unit and sent to the same destination by a single shipper. When refrigerants are used to protect contents, the overpacks may comprise insulated vessels or flasks. Whenever an overpack is used, the required marks and labels shown on the outer packaging must be repeated on the outermost layer of the overpack. This requirement applies to infectious substances in Categories A and B. Overpacks are also required to be marked with the word "overpack".

6.7 Refrigerants

Refrigerants may be used to stabilize infectious substances in Categories A and B during transit.

Ice or dry ice shall be placed outside the secondary receptacle. Wet ice shall be placed in a leak-proof container; the outer packaging or overpack shall also be leak-proof. Dry ice must not be placed inside the primary or secondary receptacle because of the risk of explosions. A specially designed insulated packaging may be used to contain dry ice. The packaging must permit the release of carbon dioxide gas if dry ice is used. ICAO/IATA Packing Instruction 904 shall be observed.

The secondary receptacle shall be secured within the outer package to maintain the original orientation of the inner packages after the refrigerant has melted or dissipated.

If dry ice is used to ship infectious substances in Category A, the details shall appear on the shipper's Declaration for Dangerous Goods. In addition, the outermost packaging shall carry the hazard label for dry ice and the appropriate marking. If dry ice is used to ship infectious substances in Category B, the package shall be marked "Carbon dioxide, solid" or "Dry ice" - this is not considered further in this document

If liquid nitrogen is used as a refrigerant, special arrangements shall be made in advance with the carrier. Primary receptacles shall be capable of withstanding extremely low temperatures, and packaging and documentation requirements for liquid nitrogen shall be observed. In particular, the outermost packaging shall carry the hazard label for liquid nitrogen.

For air transport, the handling label for cryogenic liquids shall also be affixed.

6.8 Infectious Substance and Diagnostic Specimen Comparison

| | Infectious Substance | Diagnostic Specimen |
|-------------------------------|-----------------------------|----------------------------|
| Regulated as a Dangerous Good | YES | YES |
| Shipper's Declaration | YES | NO |
| UN Specification Packaging | YES | NO |
| Primary Watertight | YES | YES |
| Secondary Watertight | YES | YES |
| Drop Test | 9 Meters | 1,2 Meters |
| Puncture Test | YES | NO |
| Stack Test | YES | NO |
| 95 kPa Pressure Test | YES | YES |
| Rigid Outer Box | YES | YES |
| Marking Requirement | YES | YES |
| Label Requirement | YES | NO |

7 General Acceptable Packaging

Proper packaging of clinical samples and environmental test samples includes four basic requirements:

1. Watertight Primary Receptacles
2. Watertight Secondary Receptacles
3. Absorbent Material
4. Sturdy Outer Packaging

NOTE: Internal filler or cushioning is recommended to protect fragile contents and limit movement.

For Biological Substance Category B (UN 3373) for both liquids and solids, cushioning material is required.

7.1 Watertight Primary Receptacles

All primary receptacles must have positive closures (such as screw-on, snap-on or push-on lids) that must be taped.

For Biological Substance Category B (UN 3373):

Primary receptacles may be glass, metal or plastic.

Positive means of ensuring a leak-proof seal, skirted stopper or metal crimp seal must be provided.

Reinforce screw caps with adhesive tape.

For liquid specimens, the primary receptacle(s) must be leak-proof and must not contain more than 1 L.

The primary or secondary receptacle(s) must be able to withstand, without leakage, an internal pressure producing a pressure differential of not less than 95 kPa in the range of -40 °C to 55 °C (-40 °F to 130 °F).

For solid specimens, the primary receptacle(s) must be siftproof and must not exceed the outer packaging weight limit.



7.2 Watertight Secondary Receptacles

To prevent contact between multiple fragile primary receptacles, individually wrap or separate each and place inside a leak-proof secondary receptacle.

For Biological Substance Category B (UN 3373):

Enclose an itemized list of contents between the secondary packaging and the outer packaging. For liquids, the secondary packaging must be leakproof; for solids, the secondary packaging must be siftproof.

These illustrations below are not intended to represent secondary containers for Biological Substance Category B (UN 3373). Secondary containers for Biological Substance Category B (UN 3373) must be certified by the manufacturer prior to use.



7.3 Absorbent Material

Place absorbent material between the primary and secondary receptacle, making sure that multiple primary receptacles are individually wrapped to prevent contact. Use enough absorbent material to absorb the entire contents of all primary receptacles.

For Biological Substance Category B (UN 3373) containing liquids, absorbent material is required between the primary and secondary receptacles.



7.4 Sturdy Outer Packaging

Sturdy outer packaging must be rigid, consisting of corrugated fiberboard, wood, metal or rigid plastic and be appropriately sized for content.

For liquids, the outer packaging must not contain more than 4 L.

For solids, the outer packaging must not contain more than 4 kg.

For Biological Substance Category B (UN 3373):

The minimum outer-container size in the smallest overall external dimension is 4 inches.

Each completed package must be capable of withstanding a 4-foot (1.2-meter) drop test outlined in IATA 6.6.1. The outer package must be rigid.



7.5 Unacceptable Outer Packaging

Styrofoam® boxes, plastic bags and paper envelopes are UNACCEPTABLE outer packaging.



Styrofoam Boxes



Plastic Bags



Paper Envelopes

Clinical Samples that are dried and non-infectious: Dried samples such as dried blood, tissue, saliva, hair.

Dried-blood samples on absorbent pads or cards for diagnostic testing must be enclosed in watertight plastic bags and shipped in a sturdy outer container or commercial envelope. Samples on glass or plastic slides must be adequately cushioned and may be shipped inside a sturdy outer container or flexible envelope packaging.

8 References

- 1 WHO/CDS/EPR/2007.2 Guidance on regulations for the transport of infectious substances 2007
- 2 Guidance Document. Infectious Substances, International Civil Aviation Organization Technical Instructions for the Safe Transport of Dangerous Goods by Air, 2005-2006
- 3 IATA, Diagnostic Specimen Transport Requirements, 2005
- 4 Wegerhoff F. It's a Bug's Life - Specimen Collection, Transport, and Viability. *Microbe / Volume 1, Number 4, 2006, 180 – 184.*
- 5 Clinical Samples, Biological Substance, Category B (UN 3373) and Environmental Test Samples, *FEDEX Pointers on Shipping* (including images)
- 6 Jie NS, Skinner R. Managing clinical trial logistics in Asia. *Business Briefing: Pharma outsourcing, 2005, 37-38*

ANNEX 1

| CHECK-LIST (to be completed by the principal investigator) | | |
|--|--|--|
| STORAGE AND EXPORT OF SAMPLES COLLECTED FROM CLINICAL TRIAL SUBJECTS DURING CLINICAL TRIALS FOR TESTING | | |
| A Trial information | | |
| 1 | Study Title | |
| 2 | Protocol Number | |
| 3 | Investigational product | |
| 4 | Unique code number | |
| 5 | NRA approval number of clinical trial | |
| 6 | Sponsor | |
| 7 | Applicant | |
| 8 | Trial site(s) | |
| 9 | Sponsor Contact Person: Address Telephone number Fax number Cell number E-mail address | |
| B Trial information relating to the sample | | |
| 1 | Does the protocol state whether the investigators intend to export the blood/plasma samples to an external laboratory for testing? | |
| 2 | Does the protocol state <ul style="list-style-type: none"> • the quantity of sample required • rationale for the transfer of sample • type of sample (e.g. whole blood, serum) • pathogens involved – indicate which • shipment procedure • labelling and storage conditions | |
| 3 | Is the written contract between the Principal Investigator and the testing laboratory in place (if different from the sponsor)? | |
| 4 | Is the specimen transfer agreement between the sample recipient and provider available? | |
| 5 | Is the number of years for which the samples are to be kept indicated in the informed consent and the protocol? | |
| 6 | Is an informed consent available for each sample? | |
| 7 | Is the reason for export stated in the informed consent? | |
| 8 | Does the reason for export indicate that testing is only for the research in question? | |

| CHECK-LIST (to be completed by the principal investigator) | | |
|--|--|--|
| STORAGE AND EXPORT OF SAMPLES COLLECTED FROM CLINICAL TRIAL SUBJECTS DURING CLINICAL TRIALS FOR TESTING | | |
| 9 | Check the classification flow chart to classify the samples. | |
| 10 | Check that the correct packaging materials are available | |
| 11 | Check the shipper's name and address (legal entity) | |
| 12 | Check that the correct storage conditions are indicated | |
| 13 | Does the transport company have the facilities to ensure the correct storage conditions? | |
| 14 | Is there a commitment from the recipient that the sample will not be used for other purpose other than for the intended purpose? | |
| 15 | Has disposal of left over specimen been described? | |

ANNEX 2

Indicative Examples of Infectious Substances Included in Category A in Any Form Unless Otherwise Indicated

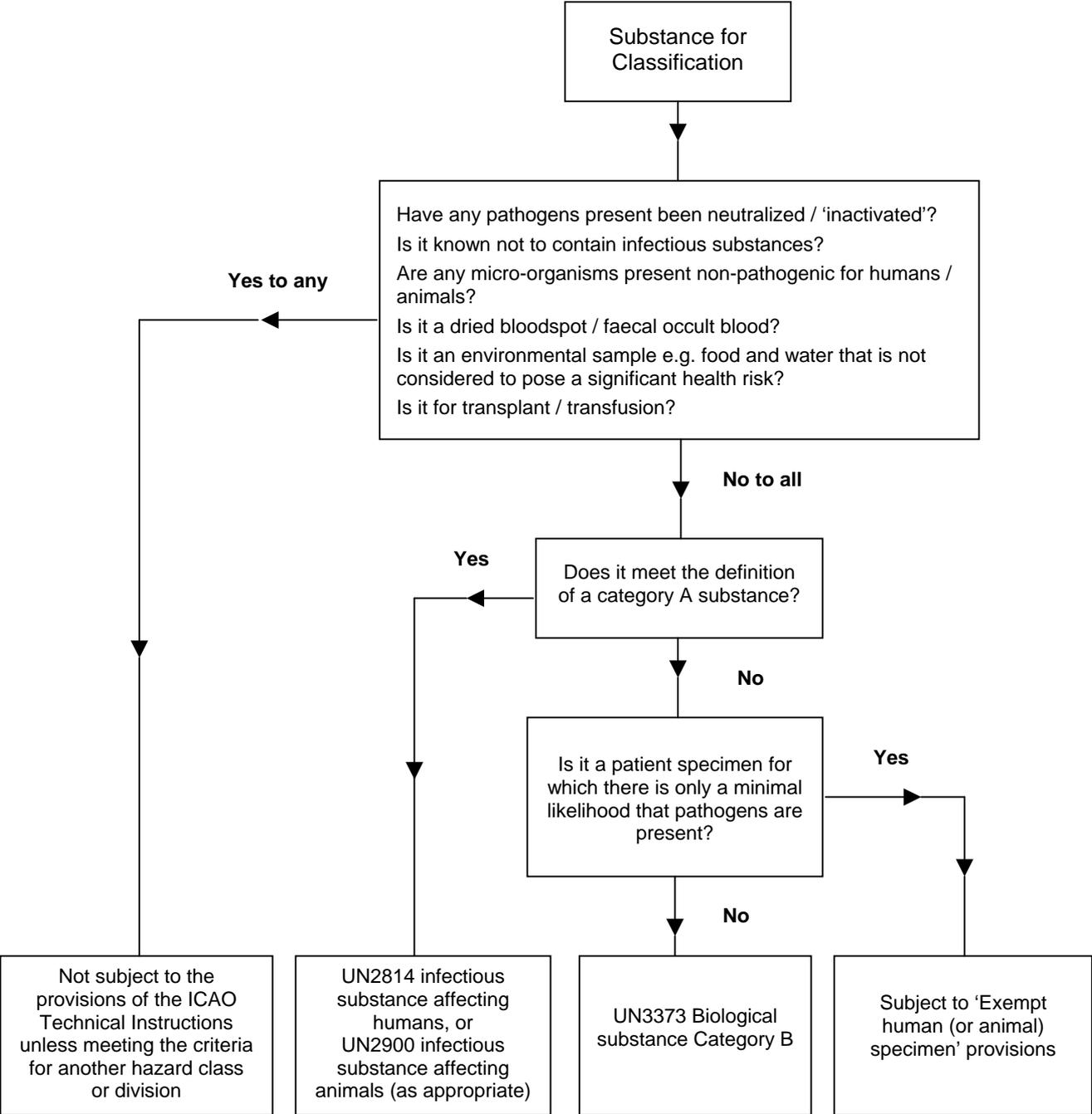
The micro-organisms written in italics are bacteria, mycoplasmas, rickettsiae or fungi.

| UN Number and Proper Shipping Name | Micro-organism |
|--|--|
| UN 2814 Infectious substance affecting humans | <i>Bacillus anthracis</i> (cultures only) |
| | <i>Brucella abortus</i> (cultures only) |
| | <i>Brucella melitensis</i> (cultures only) |
| | <i>Brucella suis</i> (cultures only) |
| | <i>Burkholderia mallei</i> – <i>Pseudomonas mallei</i> – Glanders (cultures only) |
| | <i>Burkholderia pseudomallei</i> – <i>Pseudomonas pseudomallei</i> (cultures only) |
| | <i>Chlamydia psittaci</i> – avian strains (cultures only) |
| | <i>Clostridium botulinum</i> (cultures only) |
| | <i>Coccidioides immitis</i> (cultures only) |
| | <i>Coxiella burnetii</i> (cultures only) |
| | Crimean-Congo hemorrhagic fever virus |
| | Dengue virus (cultures only) |
| | Eastern equine encephalitis virus (cultures only) |
| | <i>Escherichia coli, verotoxigenic</i> (cultures only) ¹ |
| | Ebola virus |
| | Flexal virus |
| | <i>Francisella tularensis</i> (cultures only) |
| | Guanarito virus |
| | Hantaan virus |
| | Hantavirus causing hemorrhagic fever with renal syndrome |
| | Hendra virus |
| | Hepatitis B virus (cultures only) |
| | Herpes B virus (cultures only) |
| | Human immunodeficiency virus (cultures only) |
| | Highly pathogenic avian influenza virus (cultures only) |
| | Japanese Encephalitis virus (cultures only) |
| | Junin virus |
| | Kyasanur Forest disease virus |
| | Lassa virus |
| | Machupo virus |
| Marburg virus | |
| Monkeypox virus | |
| <i>Mycobacterium tuberculosis</i> (cultures only) 1 | |
| Nipah virus | |

¹ For surface transport (ADR) nevertheless, when the cultures are intended for diagnostic or clinical purposes, they may be classified as infectious substances of Category B.

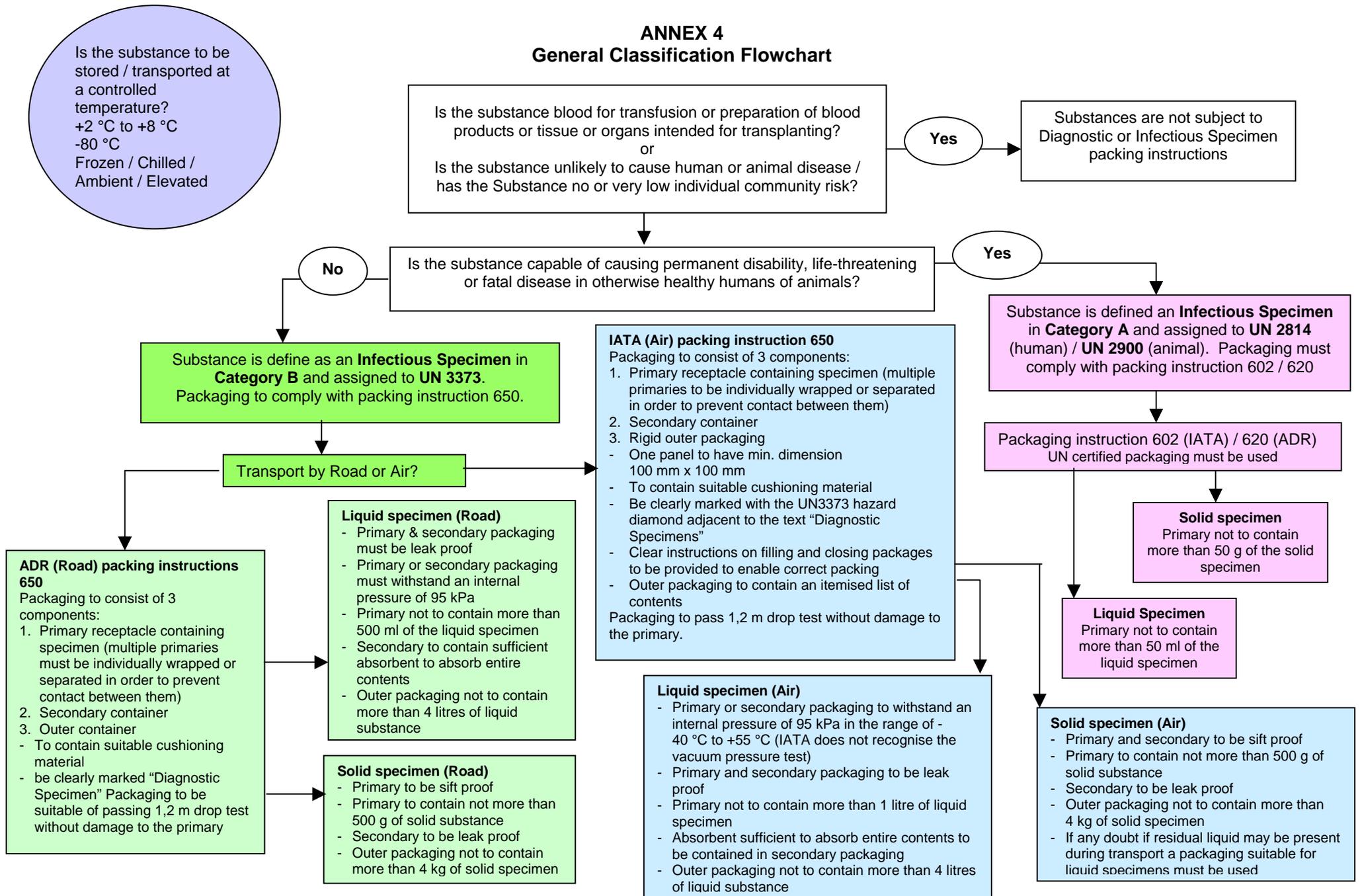
| UN Number and Proper Shipping Name | Micro-organism |
|------------------------------------|---|
| | Omsk haemorrhagic fever virus |
| | Poliovirus (cultures only) |
| | Rabies virus (cultures only) |
| | <i>Rickettsia prowazekii</i> (cultures only) |
| | <i>Rickettsia rickettsii</i> (cultures only) |
| | Rift Valley fever virus (cultures only) |
| | Russian spring-summer encephalitis virus (cultures only) |
| | Sabia virus |
| | <i>Shigella dysenteriae</i> type 1 (cultures only) ¹ |
| | Tick-borne encephalitis virus (cultures only) |
| | Variola virus |
| | Venezuelan equine encephalitis virus (cultures only) |
| | West Nile virus (cultures only) |
| | Yellow fever virus (cultures only) |
| | <i>Yersinia pestis</i> (cultures only) |

**ANNEX 3
ICAO Classification Flowchart**



DRAFT

ANNEX 4 General Classification Flowchart



DRAFT

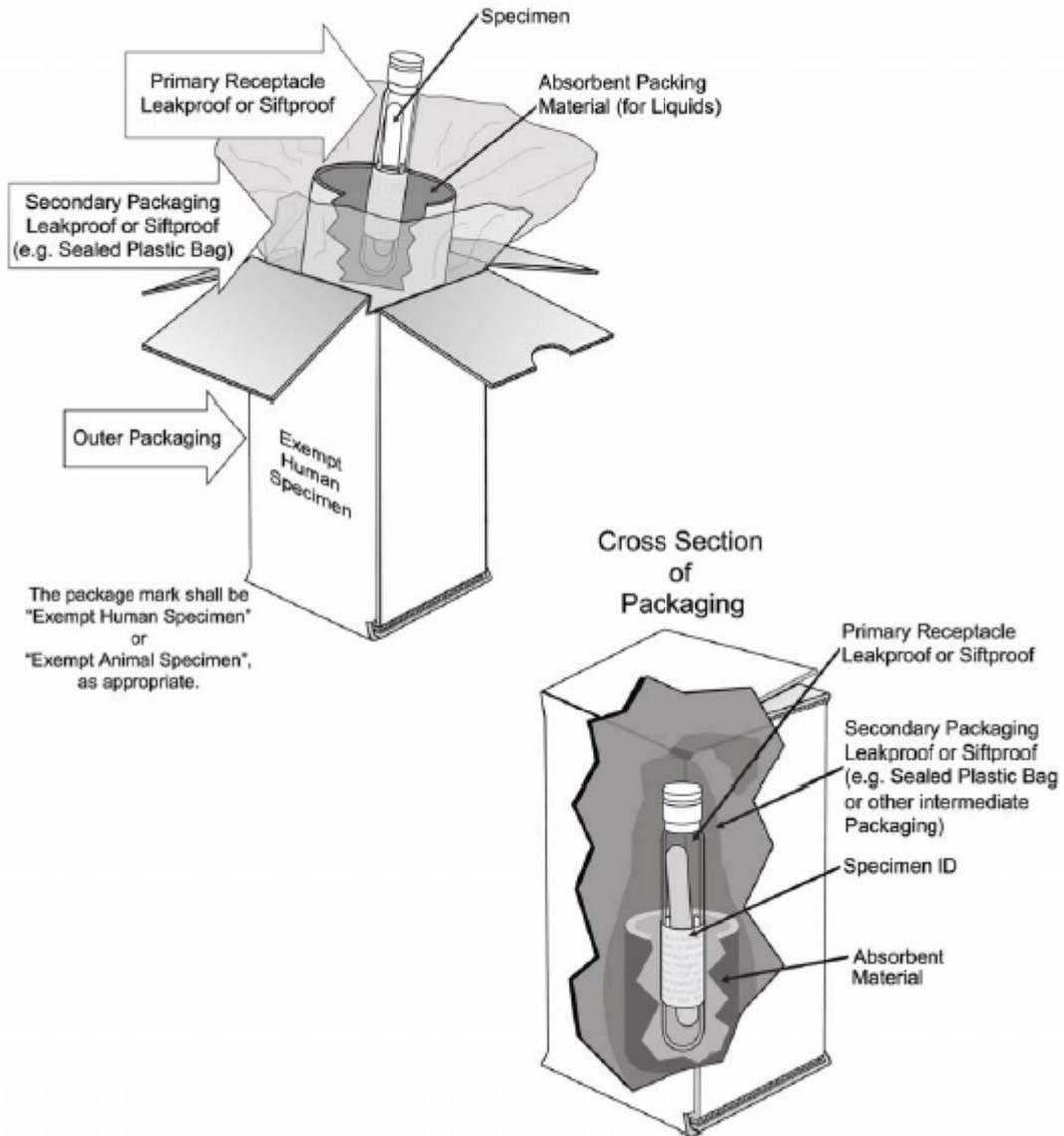
ANNEX 5
EXAMPLES - ICAO Classification Scenarios

1. A blood sample known or reasonably suspected to contain EBOLA VIRUS.
Appropriate classification: *Infectious Substances, affecting humans UN 2814.*
2. A culture of FOOT AND MOUTH DISEASE.
Appropriate classification: *Infectious Substances, affecting animals, UN 2900.*
3. A blood sample taken from a patient known or suspected to have a Category B pathogen, such as HEPATITIS B or HIV.
Appropriate classification: *Biological Substances, Category B, UN 3373.*
4. Culture of BOVINE TUBERCULOSIS.
Appropriate classification: *Biological Substances, Category B, UN 3373.*
5. Laboratory stock culture of a pathogen in Category B, e.g. INFLUENZA VIRUS.
Appropriate classification: *Biological Substances, Category B, UN 3373.*
6. Specimen containing a Category A or B infectious substance, treated so as to inactivate or neutralise the pathogens such that they no longer pose a health risk.
Appropriate classification: *Not subject to the transport requirements for dangerous goods, unless meeting the criteria for another class or division.*
7. Patient specimens other than those known or reasonably suspected to contain a Category A infectious substance e.g. those sent for testing for Cholesterol (blood), diabetes (urine), bowel cancer (faecal).
Appropriate classification: *this will depend on professional judgement i.e.:*
 - (i) If a professional judgement is made that there is only a minimal likelihood that pathogens are present, the specimen is not subject to the provisions of the ICAO Technical Instructions, providing they are packed in accordance with the provisions detailed under "Packaging for Exempt Patient Specimens" in this Guidance Document;
 - (ii) If no professional judgement is made, the specimen must be classified as UN3373.

ANNEX 6

ICAO

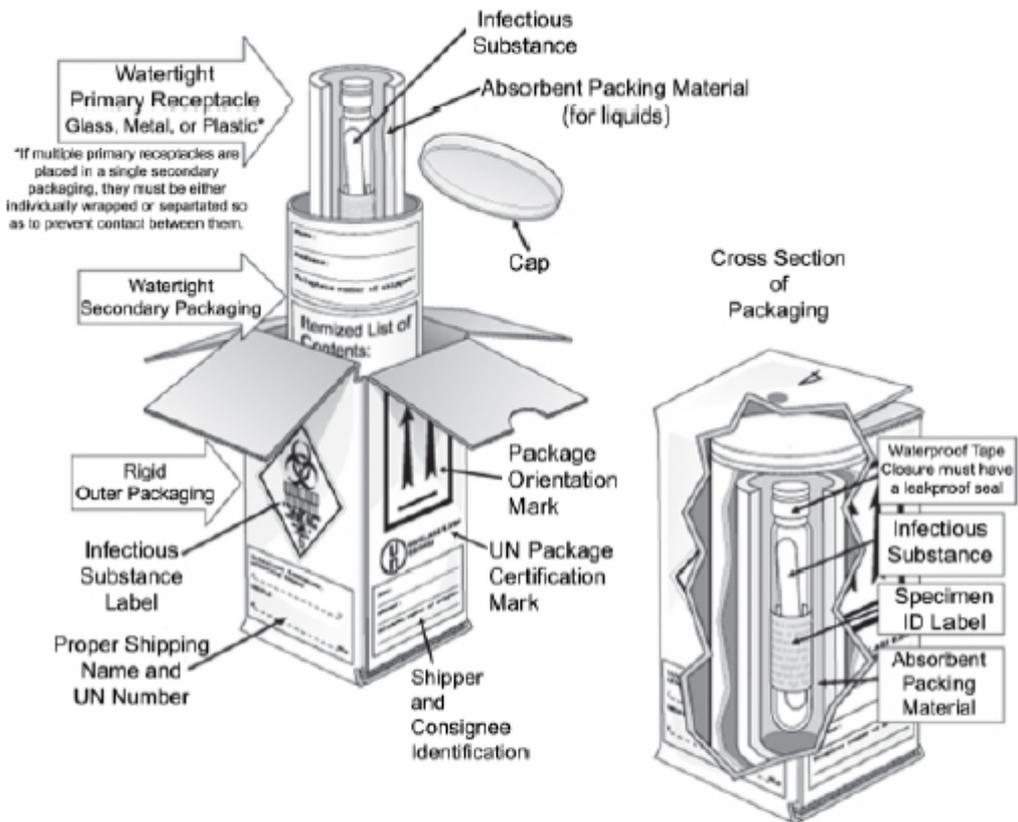
Example of Packing and Marking for Exempt Human Specimens or Exempt Animal Specimens



ANNEX 7

Packing, Marking and Labelling of Category A Infectious Substances

(See Packing Instruction 602)



Note: 1-The smallest external dimension of the outer packaging must not be less than 100 mm

Note: 2-The primary receptacle or the secondary packaging must be capable of withstanding without leakage an internal pressure producing a pressure differential of not less than 95 KPa

ANNEX 8

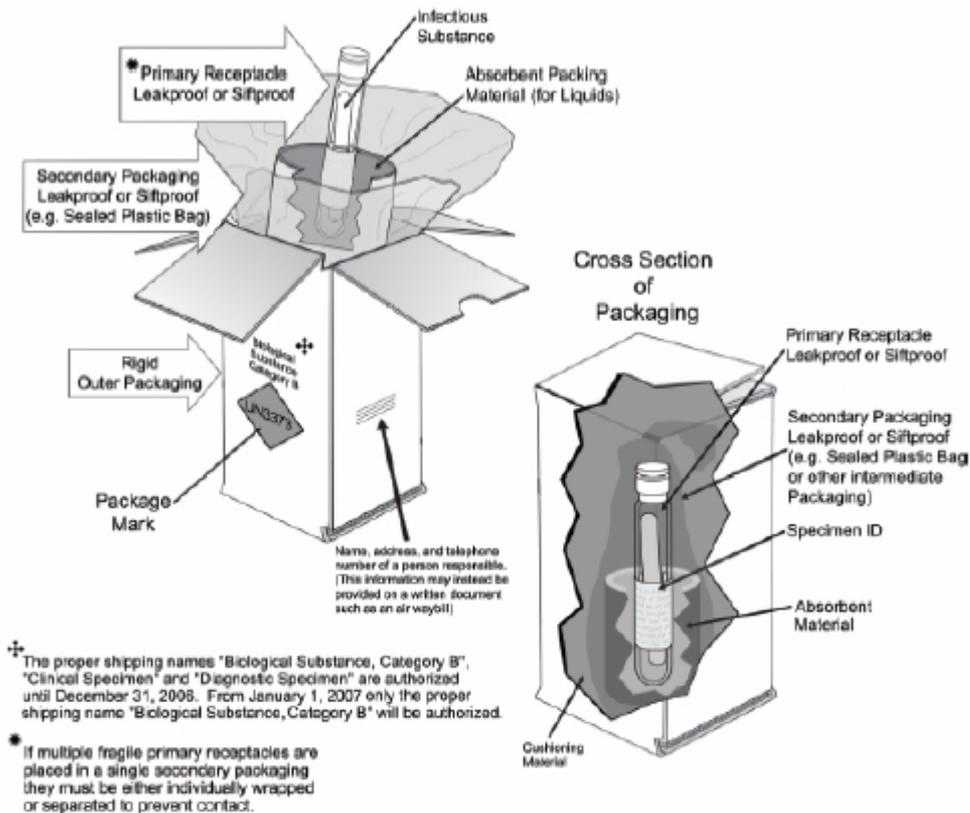
Package specification marking for Category A infectious substances (UN 2814 and UN 2900)

| | |
|--|-------------------------|
|  | 4G/Class 6.2/05/GB/2470 |
| <p>This marking comprises:</p> <ul style="list-style-type: none">• the United Nations packaging symbol• an indication of the type of packaging (in this example a fibreboard box (4G))• an indication that the packaging has been specially tested to ensure that it meets the requirements for Category A infectious substances (Class 6.2)• the last two digits of the year of manufacture (in this example 2005)• the competent state authority that has authorized the allocation of the mark (in this example GB, signifying Great Britain)• the manufacturer's code specified by the competent authority (in this example 2470) <p>Users shall be provided with clear instructions as to how the package should be filled and prepared for transport.</p> | |

ANNEX 9

Example of Packing and Marking for Category B Infectious Substances

(See Packing Instruction 650 for additional requirements; e.g. pressure differential and drop test)



Note: 1-At least one surface of the outer packaging must have a minimum dimension of 100 mm X 100 mm

Note: 2-The primary receptacle or the secondary packaging must be capable of withstanding without leakage an internal pressure producing a pressure differential of not less than 95 KPa