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Model requirements for the storage and transport of time and temperature sensitive pharmaceutical products

Version 2b

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1 Acronyms

| | |
|-------|---|
| CAPA | Corrective and Preventive Action (procedures) |
| EEFO | Earliest-Expiry-First-Out |
| GPS | Global Positioning System |
| IATA | International Air Transport Authority |
| PCCIG | Pharmaceutical Cold Chain Interest Group |
| PDA | Parenteral Drug Association |
| SKU | Stock-keeping Unit |
| SLA | Service Level Agreement |
| SMS | Short Message Service |
| SOP | Standard Operating Procedure |
| TTSP | Time and Temperature-Sensitive Pharmaceutical Product |
| UPS | Uninterrupted Power Supply |

2

3 Glossary

4 *Active systems:* Actively powered systems using electricity or other fuel source to
5 maintain a temperature-controlled environment inside an insulated enclosure under
6 thermostatic regulation (e.g. cold rooms, refrigerators, temperature-controlled trucks,
7 refrigerated ocean and air containers).

8 *Change control:* The processes and procedures to manage system changes.

9 *Controlled or hazardous TTSPs:* Temperature-sensitive pharmaceutical products
10 with high illicit value, poisons, narcotics, psychotropic products, inflammable or
11 explosive substances and radioactive materials.

12 *Dunnage:* Loose packing material used to protect TTSPs from damage during
13 transport.

14 *External distribution:* Transport of TTSPs through various steps in the customer's
15 supply chain (i.e. transport from a pharmaceutical manufacturer's distribution centre,
16 to commercial customers (including wholesalers, retailers, buying groups, etc), to
17 clinical facilities or direct to the patient).

18 *Internal distribution:* Transport of a TTSP within a pharmaceutical manufacturer's
19 internal supply chain (i.e. all internal transports from manufacturing facility to
20 packaging facility to warehouse to distribution centre).

21 *Net storage capacity:* The total volume available for storing TTSPs, taking account
22 of the type of load support system employed (floor standing pallets, adjustable pallet
23 racking, shelving units, etc.), as modified by the utilization factor that can be achieved
24 in the store.

25 *Passive systems:* Systems which maintain a temperature-controlled environment
26 inside an insulated enclosure, with or without thermostatic regulation, using a finite
27 amount of pre-conditioned coolant in the form of chilled or frozen gel packs, phase
28 change materials, dry ice or others.

29 *Pharmaceutical product:* Any product intended for human use or veterinary product
30 intended for administration to food producing animals, presented in its finished
31 dosage form, that is subject to control by pharmaceutical legislation in either the

- 1 exporting or the importing state and includes products for which a prescription is
2 required, products which may be sold to patients without a prescription, biologicals
3 and vaccines. It does not, however, include medical devices¹.
- 4 *Pests*: Includes birds, bats, rodents and insects whose uncontrolled presence affects
5 hygiene and cleanliness.
- 6 *Qualification*: Documented testing that demonstrates with a high degree of assurance
7 that a specific process will meet its pre-determined acceptance criteria².
- 8 *Refrigeration equipment*: The term 'refrigeration' or 'refrigeration equipment' means
9 any equipment whose purpose is to lower air and product temperatures and/or to
10 control relative humidity.
- 11 *Service Level Agreement (SLA)*: A service level agreement or contract (commonly
12 referred to as a Quality Agreement), is a negotiated agreement between the
13 customer and service provider that defines the common understanding about
14 materials or service quality specifications, responsibilities, guarantees and
15 communication mechanisms. It can either be legally binding, or an information
16 agreement. The SLA may also specify the target and minimum level performance,
17 operation or other service attributes³.
- 18 *Standard Operating Procedure (SOP)*: A set of instructions having the force of a
19 directive, covering those features of operations that lend themselves to a definite or
20 standardized procedure without loss of effectiveness. Standard operating policies
21 and procedures can be effective catalysts to drive performance improvement and
22 improve organizational results.
- 23 *Storage temperature*: The temperature range listed on the TTSP label, and within
24 the regulatory filings, for long-term storage.
- 25 *Storage unit temperature/humidity distribution*: The range and pattern of
26 temperatures and/or humidity within a temperature-controlled storage unit during
27 normal operation.
- 28 *Temperature-controlled*: Includes any environment in which the temperature is
29 actively or passively controlled at a level different from that of the surrounding
30 environment within precise pre-defined limits.
- 31 *Temperature-modified*: Includes any environment in which the temperature is
32 predictably maintained at a level different from that of the surrounding environment,
33 but is not actively or passively controlled within precise pre-defined limits.
- 34 *Temperature excursion*: An excursion event in which a TTSP is exposed to
35 temperatures outside the range(s) prescribed for storage and/or transport.
36 Temperature ranges for storage and transport may be the same or different; they are
37 determined by the product manufacturer, based on stability data.
- 38 *Time and temperature sensitive pharmaceutical product (TTSP)*: Any
39 pharmaceutical good or product which, when not stored or transported within pre-
40 defined environmental conditions and/or within pre-defined time limits, is degraded to
41 the extent that it no longer performs as originally intended.
- 42 *Transport temperature profile*: Anticipated ambient temperature variation and
43 duration to which a TTSP may be exposed during transport.

¹ Definition from WHO/QAS/08.252 Rev 1 Sept 2009. *Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments.*

² Definition from PDA Technical Report No. 39, 2007.

³ Definition from IATA, Chapter 17, 9th Edition, June 2009.

- 1 *Utilization factor:* The percentage of the total volume available for storing TTSPPs
2 that can reliably be achieved in practice, taking account of the types of SKU, the
3 types of load support system and the stock management systems used in the store.
4 *Validation:* Documented testing performed under highly controlled conditions,
5 demonstrating that processes, methods, and systems consistently produce results
6 meeting pre-determined acceptance criteria⁴.

7 **Introduction**

8 This guideline sets out the principal requirements for the safe storage and distribution
9 of time and temperature-sensitive pharmaceutical products (TTSPPs). It is based
10 upon existing regulations and best practice guidance from a wide range of
11 international sources (see Annex 1), whilst accepting that local legislation and
12 regulations will continue to take precedence. The target audience includes
13 regulators, logisticians and pharmaceutical professionals in industry, government and
14 the international agencies.

15 The document has been prepared in close consultation with the *WHO Task Force on*
16 *Regulatory Oversight on Pharmaceutical Cold Chain Management* which has been
17 central to the review process. A full list of members is given in Annex 3.

18 The intention is that the listed requirements should be directly applicable in less
19 developed countries as well as in the industrialized world. To this end,
20 supplementary materials will be developed to show how the requirements can
21 practicably be achieved, particularly in resource-constrained settings.

22 The document is designed to give a balanced overview of the major aspects of good
23 storage and distribution practice for TTSPPs. As such it deliberately includes
24 references to requirements which can be found in general guides to Good
25 Manufacturing Practice (GMP), Good Storage Practice (GSP) and Good Distribution
26 Practice (GDP). The purpose is not to supplant these source materials, but to ensure
27 that the reader is aware of the relevant GMP, GSP and GDP implications when seen
28 from the particular and specialized perspective of TTSPP management.

29 **Key to conventions used**

30 The following conventions are used in the requirements clauses:

- 31 • The imperative voice is used to denote a mandatory or highly desirable
32 requirement. For example: '**Ensure that**, '**Provide**....., etc.
- 33 • The phrase '**where possible**' is used to denote an optional but desirable
34 requirement.
- 35 • Many clauses are followed by a brief explanation setting out the underlying
36 **reason** for including the clause.

37

⁴ Definition from PDA Technical Report No. 39, 2007.

1 **1. Importation**

2 **1.1 Port handling and customs clearance**

3 *1.1.1 Port of entry*

4 Where possible, import TTSPPs through a port of entry that is equipped to handle
5 such products.

6
7 Reason: To minimize the risk of damage.
8

9 *1.1.2 Offloading*

10 As soon as possible after arrival, remove TTSPP shipments from the wharf or airport
11 apron to a safe and suitable temperature-controlled storage location.

12
13 Reason: To minimize the risk of theft and to avoid exposure to adverse ambient
14 conditions.
15

16 *1.1.3 Temporary storage at port of entry*

17 Store TTSPP shipments in a secure warehouse under the conditions recommended
18 by the product manufacturer, until the shipment has been authorised for removal by
19 customs⁵.

20
21 Reason: To avoid risk of theft or damage during temporary storage.
22

23 *1.1.4 Customs clearance*

24 Draw up procedures and memoranda of understanding to ensure that TTSPP
25 shipments are cleared through customs as rapidly as possible. Where possible,
26 customs staff should be supported and assisted during the clearance process by
27 personnel with suitable pharmaceutical training, especially when clearance involves
28 the opening and re-sealing of temperature-controlled packaging.

29
30 Reason: To avoid delays during customs clearance that may cause temperature
31 excursions and place TTSPPs at risk.
32

33 **2. Warehousing sites**

34 **2.1 Site layout**

35 *2.1.1 Natural hazards*

36 Select and/or develop storage sites to minimize risks associated with flooding,
37 hurricanes, tornados, landslides, earthquakes and other extreme weather conditions
38 and natural hazards.
39

⁵ In some situations, arrangements can be made for formal customs clearance to take place away from the port of entry – for example, at a national vaccine store. In situations where the port of entry is not equipped with suitable cold storage facilities, this can reduce the risk of temperature excursions.

1 Reason: To protect against loss of valuable pharmaceutical products, to ensure
2 continued supply to patients in the market and to protect personnel working in the
3 store.

4 **2.1.2 Site access**

5 Provide vehicular access to storage buildings sufficient to accommodate the largest
6 vehicles visiting the site, including emergency vehicles.

7
8 Reason: To ensure convenient operation of the facility.
9

10 **2.2 Site security**

11 Provide perimeter protection to ensure security of the grounds and storage buildings
12 against anticipated risks.

13
14 Reason: To protect against vandalism, theft and other illegal incursions. Security
15 arrangements should be appropriate to the site location and the value of goods
16 stored there.
17

18 **2.3 Site cleanliness**

19 Keep the site free of accumulated dust, dirt, waste and debris. Ensure that pests are
20 kept under control within the site area. Collect waste in designated closed containers
21 and arrange for safe disposal at frequent intervals.

22
23 Reason: To help protect storage buildings against ingress by dust, dirt and pests
24 such as rodents, bats, birds and insects.
25
26

27 **3. Storage buildings**

28 **3.1 Construction standards**

29 Construct or procure storage buildings that are:

- 30 • purpose-designed for the storage of TTSPPs, or adapted for this purpose;
 - 31 • suited to the climate, and designed to minimize energy consumption;
 - 32 • built to minimize hiding and nesting places for pests;
 - 33 • constructed using materials and finishes that are robust and easy to clean.
- 34

35 Reason: Storage in unsuitable buildings places TTSPPs at risk.
36

37 **3.2 Accommodation and layout**

38 Ensure that the storage buildings are well laid out and contain all the necessary
39 storage areas, goods assembly, receiving and dispatch bays and office
40 accommodation needed for efficient operation of the TTSPP store.
41

1 **3.3 Goods assembly and quarantine areas**

2 **3.3.1 Goods assembly areas**

3 Provide sufficient space to receive, assemble and pack TTSPPs for dispatch under
4 temperature-modified conditions. Preferably these areas should be physically close
5 to the temperature-controlled storage area.

6
7 Reason: Protection of TTSPPs during arrival, order assembly and dispatch.

8 **3.3.2 Quarantine area**

9 Provide a quarantine area for the isolation of returned, faulty, recalled and otherwise
10 withdrawn goods pending decision on disposal or re-stocking by the qualified person
11 or department. Materials within quarantine areas must be clearly identified with their
12 status.

- 13 • With temperature control, for items returned for re-stocking.
- 14 • With temperature control, for items recalled for testing.
- 15 • Without temperature control, for items awaiting disposal.

16 The quarantine area may be a physically separated zone, or it may be defined using
17 a suitable stock control information system, or by a combination arrangement.

18
19 Reason: Items for re-stocking, testing and disposal should be kept separate to avoid
20 the risk of inappropriate use.

21

22 **3.4 Loading bays**

23 **3.4.1 Loading bays**

24 Ensure that receiving and dispatch bays are protected from dust, dirt, rain and snow
25 and wind, and from extremes of heat, cold and solar radiation that could damage
26 TTSPPs.

27
28 Reason: Protection against damage and maintenance of product quality.

29

30 **3.4.2 Receiving bays**

31 Provide receiving areas with suitable equipment to clean containers of incoming
32 materials and pharmaceutical products before the containers are stored.

33
34 Reason: Protection against contamination of TTSPPs.

35

36 **3.5 Environmental control of ancillary areas**

37 Ensure, where possible, that ancillary areas where TTSPPs are temporarily held
38 during arrival, order assembly or dispatch are:

- 39 • maintained at temperature and humidity levels appropriate to the goods being
40 handled⁶;
- 41 • monitored during the times when TTSPPs are handled;
- 42 • protected from undue exposure to direct sunlight;
- 43 • protected from the weather;

⁶ Active environmental control of ancillary areas may not be needed if all TTSPPs are kept in temperature-controlled packaging and/or humidity-protective packaging when passing through these areas.

- 1 • protected against dust, dirt, and waste accumulation;
- 2 • adequately ventilated;
- 3 • adequately lit to enable operations to be carried out accurately and safely.

4
5 Reason: Protection of TTSP quality during arrival, order assembly or dispatch.
6

7 **3.6 Building security**

8 *3.6.1 General building security*

9 Ensure that buildings used to store TTSPs have sufficient security to prevent
10 unauthorized access and to prevent misappropriation of goods.
11

12 Reason: To protect against vandalism, theft and other illegal incursions. Security
13 arrangements should be appropriate to the site location and the value of goods
14 stored there.

15 *3.6.2 Controlled and hazardous substances areas*

16 Ensure that all areas that are used to store controlled or hazardous TTSPs are:
17 • dedicated securely locked facilities that comply fully with all legislative and
18 regulatory requirements applicable in the country where the store is located;
19 • only accessible to authorized staff;
20 • protected by automatic intruder and/or fire and smoke, and/or chemical and/or
21 radiological sensor alarm systems appropriate to the type(s) of product being
22 stored⁷;
23 • designed to be explosion-proof, where explosive TTSPs are stored;
24 • continuously monitored by security staff.

25
26 Reason: Protection of property and life.
27

28 **3.7 Fire protection**

29 *3.7.1 Fire protection equipment*

30 Provide suitable fire detection and fire-fighting equipment in all TTSP storage areas
31 and ensure that equipment is regularly serviced in accordance with the equipment
32 manufacturers' recommendations and local regulations.
33

34 Reason: Protection of property and life.
35

36 *3.7.2 Fire-fighting prevention, detection and control procedures*

37 Follow standard operating procedures for fire prevention, detection and control.
38 Train staff and carry out regular fire drills. Prohibit smoking in all areas.
39

40 Reason: Protection of property and life.
41

⁷ Zoned sprinkler systems are recommended to control fires and to localize product damage in the event of system activation.

1 **3.8 Building cleanliness**

2 **3.8.1 Building cleanliness**

3 Implement a cleaning programme for all receiving areas, storage areas, goods
4 assembly areas and loading bays:

- 5 • Do not allow the accumulation of dust, dirt and waste, including packaging
6 waste.
- 7 • Take precautions against spillage or breakage, and cross-contamination.
- 8 • Collect waste in designated closed containers and arrange for safe disposal
9 at frequent intervals.
- 10 • Do not permit consumption of food or beverages in receiving areas, storage
11 areas, goods assembly areas or loading and dispatch bays.
- 12 • Maintain cleaning records to demonstrate compliance.

13
14 Reason: Protection against damage and contamination of TTSPPs and to minimize
15 the risk of pest infestation.

16 **3.8.2 Pest control**

17 Implement a programme to keep storage buildings, receiving bays, goods assembly
18 and loading bays free of pests, including enclosed receiving and loading bays.
19 Maintain records to demonstrate compliance with a robust pest control programme.

20
21 Reason: Protection against damage and contamination of TTSPPs.
22

23 **3.9 Uninterrupted power supply**

24 **3.9.1 Uninterrupted power supply**

25 Where possible, and where necessary⁸, ensure that all temperature controlling
26 equipment for TTSP storage (i.e. refrigerators, freezers, building management
27 systems, HVACs, compressors, air handling units, monitoring systems, alarms and
28 related computer equipment are connected to a UPS system. Generators, where
29 used should:

- 30 • be able to start all connected temperature controlling and temperature-
31 monitoring equipment⁹;
- 32 • be equipped with automatic mains failure start-up and automatic shut down
33 when power is restored;
- 34 • have fuel tank capacity sufficient to cover a prolonged power outage.

35 Regularly test and service UPS equipment and generators. Maintain records to
36 demonstrate compliance.

37
38 Reason: Loss prevention.
39

⁸ UPS systems may be unnecessary in countries with a very reliable electricity supply. In smaller stores in countries where electricity is only available for a limited period each day, or is entirely absent, an alternative approach to UPS is to use refrigeration equipment with extended holdover capacity; for example, ice-lined refrigerators, or gas, kerosene or solar-powered refrigerators.

⁹ The installed capacity of the UPS system can be minimized by fitting electronic controls which reduce compressor start-up loads.

1 **3.9.2 Power failure contingency plan**

2 Develop and maintain a contingency plan to protect TTSPPs in the event of a serious
3 power failure. Alternative emergency cooling systems (e.g. liquid nitrogen or dry ice)
4 are acceptable.

5

6 Reason: Loss prevention.

7

8 **3.10 Building maintenance**

9 Implement a planned preventive maintenance programme to ensure that storage
10 buildings and building systems are well maintained. Keep records to demonstrate
11 compliance with the programme.

12

13 Reason: To ensure that storage buildings continue to protect stored products against
14 damage.

15

16 **4. Temperature-controlled storage**

17 **4.1 Normative references**

- 18 • EN 60068-3 parts 5, 6, 7 and 11: *Environmental testing. Guidance.*
- 19 *Confirmation of the performance of temperature chambers*
- 20 • IATA *Perishable Cargo Regulations Chapter 17*. 9th Edition, July 2009.
- 21 • USP <1079> *Good storage and shipping practices*.
- 22 • USP <1118> *Monitoring devices – time, temperature and humidity*.

23

24 **4.2 Storage capacity of temperature-controlled stores**

25 Ensure that the net storage capacity of the temperature-controlled stores is sufficient
26 to accommodate peak TTSPP stock levels and their associated transit temperature
27 protection components (i.e. freezer blocks, flexible ice blankets, refrigerated gel
28 packs, phase change materials, etc), under correct temperature conditions and in a
29 manner which enables efficient and correct stock management operations to take
30 place.

31

32 Reason: To avoid the risks associated with over-stocking and to ensure that good
33 warehousing practices can be adopted (i.e. EEFO). Overstocking makes EEFO
34 handling difficult or impossible and inhibits accurate physical stock counts.

35

36 **4.3 Temperature-controlled storage**

37 Ensure that TTSPPs are stored in temperature-controlled rooms, cold rooms, freezer
38 rooms, refrigerators and freezers which comply with the following requirements:

39

40 *Temperature-controlled rooms, cold rooms and freezer rooms*

- 41 • capable of maintaining the temperature range defined by the system set
42 points over the full annual ambient temperature range experienced at the
43 store location;
- 44 • preferably equipped with an auto-defrost circuit which has a minimal effect on
45 temperature within the unit during the defrost cycle;
- 46 • equipped with a low temperature protection circuit in cold climates where
47 there is a risk of breaching the low temperature set point for TTSPPs that are
48 damaged by exposure to low temperatures;
- 49 • connected to an uninterrupted power supply as described in clause 3.9.1;

- 1 • equipped with calibrated continuous temperature monitoring system with
- 2 sensors located at points representing greatest temperature variability and
- 3 temperature extremes;
- 4 • preferably equipped with continuous humidity monitoring devices with sensors
- 5 located at points representing humidity extremes;
- 6 • equipped with alarms to indicate temperature excursions and/or refrigeration
- 7 failure;
- 8 • fitted with lockable doors, or access control system, as necessary;
- 9 • qualified as defined in clause 4.7.

10 *Refrigerators and freezers*

- 11 • purpose-designed for the storage of TTSPPs; household-style units are only
- 12 acceptable for products that are unaffected by the temperature excursions
- 13 which occur in such units;
- 14 • capable of maintaining the temperature range specified by the TTSPP
- 15 manufacturer over the full annual ambient temperature range experienced at
- 16 the storage site;
- 17 • equipped with calibrated temperature monitoring devices appropriate to the
- 18 level of risk but preferably capable of continuous recording and with sensor(s)
- 19 located at a point or points within the cabinet which most accurately
- 20 represents the temperature profile of the equipment during normal operation;
- 21 • preferably equipped with alarms to indicate temperature excursions and/or
- 22 refrigeration failure;
- 23 • fitted with lockable doors or lids, or access control system, as necessary;
- 24 • qualified and/or tested as defined in clause 4.7.

25 Reason: To maintain labelled TTSPP storage temperatures during long-term storage.

26 **4.4 Temperature-controlled storage for controlled and hazardous products**

27 Ensure that controlled and hazardous TTSPPs are securely stored:

- 28 • Provide dedicated temperature-controlled rooms, cold rooms, freezer rooms,
- 29 refrigerators and freezers for these TTSPPs, in separate secure areas, as
- 30 described in clause 3.6.2.
- 31 • Alternatively, but only if acceptable to the regulatory authority, bulk stocks of
- 32 TTSPPs with high illicit-value may be stored in a securely locked section of a
- 33 general temperature-controlled storage area.

34 Reason: To protect this category of TTSPPs against theft and misuse and to

35 safeguard workers and general storage areas in the event of an accident involving

36 hazardous substances.

37 **4.5 Temperature and humidity control and monitoring in storage**

38 *4.5.1 Temperature control*

39 Provide thermostatic temperature control systems for all temperature-controlled

40 rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPPs.

41 Comply with the following minimum requirements:

- 42 • system able continuously to maintain air temperatures within the set point
- 43 limits throughout the validated storage volume;
- 44 • sensors accurate to $\pm 0.5^{\circ}\text{C}$ or better;
- 45 • sensors calibrated as described in clause 4.10.1;
- 46 • sensors located in areas where greatest variability in temperature is expected
- 47 to occur in order to maximize available safe storage volume;

- 1 • sensors positioned at the hot and cold spots determined by temperature
- 2 mapping, even if affected by door opening, unless recommendations are
- 3 being made not to store products in such areas.
- 4 • sensors independent of the temperature monitoring system.

5 *4.5.2 Temperature monitoring*

6 Provide air temperature monitoring systems and devices for all temperature-
7 controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store
8 TTSPPs. Systems and devices should comply with the following minimum
9 requirements:

10 *General requirements:*

- 11 • sensors accurate to $\pm 0.5^{\circ}\text{C}$ or better;
- 12 • sensors calibrated as described in clause 4.10.1;
- 13 • sensors located in areas where greatest variability in temperature is expected
- 14 to occur within the qualified and/or tested storage volume as defined in clause
- 15 4.7.
- 16 • sensors positioned so as to be minimally affected by transient events such as
- 17 door opening;
- 18 • thermometers, temperature traces or electronic temperature records manually
- 19 checked at least twice a day, in the morning and evening, seven days a week.

20 *Temperature-controlled rooms, cold rooms and freezer rooms*

- 21 • provides a temperature record with a minimum recording frequency of six
- 22 times per hour for each sensor position;
- 23 • provides documentation for each sensor position which can be stored and
- 24 accessed;
- 25 • continues to operate independently in the event of a power failure¹⁰.

26 *Refrigerators and freezers*

- 27 • as a minimum, provide a thermometer or maximum/minimum thermometer;
- 28 • preferably connect refrigerators and freezers to a multi-point monitoring
- 29 system with a minimum recording frequency of six times per hour for each
- 30 sensor position which can operate independently in the event of a power
- 31 failure¹¹;
- 32 • alternatively use battery-powered portable temperature monitoring devices
- 33 with a minimum recording frequency of six times per hour;
- 34 • provide documentation for each appliance which can be stored and accessed.

35 Reason: To maintain labelled TTSPP temperatures during long-term storage.

36 *4.5.3 Humidity control*

37 Provide humidity control in temperature-controlled rooms that are used to store
38 TTSPPs which are adversely affected by high relative humidity and are not
39 sufficiently protected by packaging.

40 *4.5.4 Humidity monitoring*

41 Provide humidity monitoring systems and devices in temperature-controlled rooms
42 that are used to store TTSPPs which are adversely affected by high relative humidity
43

¹⁰ Where there is no UPS, the autonomy period for the device should be matched to the maximum length of anticipated power outages.

¹¹ *Ibid.*

1 and are not sufficiently protected by packaging. Systems and devices should comply
2 with the following minimum requirements:

- 3 • sensors accurate to $\pm 5\%$ RH;
- 4 • sensors calibrated as clause 4.10.2;
- 5 • sensors located to monitor worst-case humidity levels within the qualified
6 storage volume defined in clause 4.7;
- 7 • sensors positioned so as to be minimally affected by transient events such as
8 door opening.
- 9 • provides a humidity record with a minimum recording frequency of six times
10 per hour for each sensor position;
- 11 • provides documentation for each sensor position which can be stored and
12 accessed.
- 13 • continues to operate independently in the event of a power failure¹².

14 .
15 Reason: To maintain labelled TTSPP humidity conditions during long-term storage.
16

17 **4.6 Alarm systems**

18 **4.6.1 Temperature alarms**

19 Provide temperature alarm systems for temperature-controlled rooms, cold rooms,
20 freezer rooms, refrigerators and freezers, used to store TTSPPs. Systems should
21 comply with the following minimum requirements:

22 *General requirements:*

- 23 • sensors accurate to $\pm 0.5^\circ\text{C}$;
- 24 • sensors calibrated as described in clause 4.10.1;
- 25 • sensors located to monitor worst-case temperatures within the validated
26 storage volume defined in clause 4.7; where the alarm system is not
27 integrated with the temperature monitoring system, sensors should be located
28 close to the temperature monitoring sensors;
- 29 • sensors positioned so as to be minimally affected by transient events such as
30 door opening;

31 *Temperature-controlled rooms, cold rooms and freezer rooms:*

- 32 • high/low alarms set points to trigger appropriately located visual alarm(s).
- 33 • preferably there should also be appropriately located audible alarm(s) in
34 addition to the visual alarm(s);
- 35 • preferably there should be an automatic telephone dial-up or SMS text
36 warning system to alert on-call personnel when an alarm is triggered outside
37 working hours.

38 *Refrigerators and freezers:*

- 39 • preferably there should be a visual and/or audible alarm system; this may be
40 integrated with a portable continuous temperature monitoring device.

41 Ensure that alarm sensors monitor the same medium (air or product) as the
42 temperature alarm system.

43
44 Reason: Loss prevention.

45 **4.6.2 Humidity alarms**

46 Provide humidity alarm systems for temperature-controlled rooms, used to store
47 TTSPPs that are sensitive to moisture and are not sufficiently protected by

¹² Where there is no UPS, the autonomy period for the device should be matched to the maximum length of anticipated power outages.

- 1 packaging. Systems and devices should comply with the following minimum
2 requirements:
- 3 • sensors accurate to $\pm 5\%$ RH;
 - 4 • sensors calibrated as described in clause 4.10.2;
 - 5 • sensors located to monitor worst-case humidity levels within the validated
6 storage volume defined in clause 4.7; where the alarm system is not
7 integrated with the humidity monitoring system, sensors should be located
8 close to the humidity monitoring sensors;
 - 9 • sensors positioned so as to be minimally affected by transient events such as
10 door opening.
 - 11 • high/low alarms set points to trigger appropriately located visual alarm(s);
 - 12 • preferably there should also be appropriately located audible alarm(s) in
13 addition to the visual alarm(s);
 - 14 • preferably there should be an automatic telephone dial-up or SMS text
15 warning system to alert on-call personnel when an alarm is triggered outside
16 working hours.

17
18 Reason: Loss prevention.
19

20 **4.7 Qualification of temperature-controlled stores**

- 21 Qualify new temperature-controlled storage areas and new refrigeration equipment
22 before it becomes operational. The qualification procedure should:
- 23 • demonstrate the air temperature profile throughout the storage area or
24 equipment cabinet, when empty and when fully loaded;
 - 25 • define zones which should not be used for storage of TTSPPs (for example
26 areas in close proximity to cooling coils, cold air streams or heat sources);
 - 27 • demonstrate the time taken for temperatures to exceed the designated limits
28 in the event of power failure;

29 Fully document the initial qualification. Carry out additional qualification exercises
30 whenever modifications are made to the storage area that may increase loading or
31 affect air circulation, or when changes are made to the refrigeration equipment.
32 Consider the need for re-qualification whenever temperature and/or humidity
33 monitoring shows unexplained variability that is greater than normal.

34
35 Qualification may not be required for off-the-shelf equipment that has been
36 independently tested and found suitable for the storage of TTSPPs. Independent
37 testing must be carried out between the chosen set points and under the ambient
38 temperature conditions to which the equipment will be exposed during operation.

39
40 Reason: To ensure that labelled TTSPP temperatures can be maintained during
41 long-term storage and that the facility can demonstrate to the regulatory authorities
42 and other interested parties that due diligence has been carried out.
43

44 **4.8 Cleanliness of temperature-controlled stores**

- 45 Implement a cleaning and decontamination programme for all temperature-controlled
46 rooms:
- 47 • Ensure that floor areas are fully accessible for cleaning. Do not store goods
48 directly on the floor.
 - 49 • Do not permit storage of any non-pharmaceutical products except transport-
50 related items such as icepacks, gel packs and the like.
 - 51 • Do not allow the accumulation of dust, dirt and waste, including packaging
52 waste.
 - 53 • Take precautions against spillage or breakage, and cross-contamination.

- 1 • Do not allow accumulation of frost and ice, particularly ice contaminated by
2 spillages.
3 • Collect waste in designated closed containers and arrange for safe disposal
4 at frequent intervals.

5 Maintain cleaning records to demonstrate compliance.

6

7 Reason: Protection against damage and contamination of TTSPPs and hazards to
8 workers arising from spillage or breakage.

9

10 **4.9 Refrigeration equipment maintenance**

11 Implement a maintenance programme for all temperature-controlled rooms, cold
12 rooms, freezer rooms, refrigerators and freezers:

- 13 • Carry out regular planned preventive maintenance on all temperature
14 controlling equipment.
15 • Make arrangements to ensure that emergency maintenance is carried out
16 within a time period that does not place TTSPPs at risk of damage.
17 • Ensure that there is a contingency plan to move products stored in non-
18 functioning equipment to a safe location before damage to the product occurs
19 in the event that equipment cannot be repaired in a timely manner.

20 Maintain records to demonstrate compliance.

21

22 Reason: Loss prevention.

23

24 **4.10 Calibration and verification of control and monitoring devices**

25 *4.10.1 Calibration of temperature control and monitoring devices*

26 Calibrate devices at least once a year against a certified, traceable reference
27 standard. Single-use devices that are supplied with a manufacturer's calibration
28 certificate do not need to be calibrated.

29 *4.10.2 Calibration of humidity control and monitoring devices*

30 Calibrate devices at least once a year against a certified, traceable reference
31 standard. Single-use devices that are supplied with a manufacturer's calibration
32 certificate do not need to be calibrated.

33 *4.10.3 Alarm equipment verification*

34 Check functionality of temperature and humidity alarms at least once a year at the
35 designated set points.

36

37 Maintain records to demonstrate compliance.

38

39 Reason: To ensure that labelled TTSPP storage temperatures and humidity control
40 can be maintained during long-term storage and that the store can demonstrate to
41 the regulatory authorities and other interested parties that due diligence has been
42 carried out.

43

1 **5. Materials handling**

2 **5.1 Materials handling equipment**

3 Where powered materials handling equipment is used in temperature-controlled
4 rooms, cold rooms or freezer rooms, select equipment which is certified for safe use
5 in confined spaces.

6
7 Reason: Protection of the workforce.
8

9 **6. Transport and delivery**

10 **6.1 Normative references**

- 11 • Directive 94/62/EC. *European Parliament and Council Directive of 20*
12 *December 1994 on packaging and packaging waste.*1994.
- 13 • EN 13428:2004. *Packaging. Requirements specific to manufacturing and*
14 *composition. Prevention by source reduction.*
- 15 • EN 13430:2004. *Packaging. Requirements for packaging recoverable by*
16 *material recycling.*
- 17 • EN 13431:2004. *Packaging. Requirements for packaging recoverable in the*
18 *form of energy recovery, including specification of minimum inferior calorific*
19 *value.*
- 20 • EN 13432:2000. *Packaging. Requirements for packaging recoverable through*
21 *composting and biodegradation. Test scheme and evaluation criteria for the*
22 *final acceptance of packaging.*
- 23 • IATA *Perishable Cargo Regulations Chapter 17*, 9th Edition, July 2009.
- 24 • *Isothermal and refrigerating containers for health products – Thermal*
25 *performance qualification method.*
- 26 • *Practical guide – Cold chain for drugs.*
- 27 • ISTA – 5B: *Focused Simulation Guide for Thermal Performance Testing of*
28 *Temperature Controlled Transport Packaging.*
- 29 • ISTA – 7D: *Thermal Controlled Transport Packaging for Parcel Delivery*
30 *System Shipment. Basic Requirements: atmospheric conditioning, vibration*
31 *and shock testing.*
- 32 • WHO Technical Report Series, No. 937, 2006. Annex 5: *Good distribution*
33 *practices for pharmaceutical products.*

34 **6.2 Product stability profiles**

35 Transport TTSPPs in such a manner that transport temperatures meet local
36 regulatory requirements at the sending and receiving sites and/or so that temperature
37 excursions above or below the manufacturer's labelled storage temperature range do
38 not adversely affect product quality.

39
40 Reason: Protection of TTSPPs against damage.
41

42 **6.3 Transport route profiling and qualification**

43 Profile and qualify transport routes:

- 44 • Select the most suitable methods for protecting TTSPPs against anticipated
45 ambient temperature and humidity conditions encountered throughout the
46 year.

- 1 • Use suitable methods, including published standards, weather data,
2 laboratory tests and field tests to select suitable transport equipment and
3 shipping containers.
4

5 Reason: To ensure that TTSPPs can safely be transported within the transport
6 temperature profile defined for each product and that compliance can be
7 demonstrated to the regulatory authorities and other interested parties.
8

9 **6.4 Temperature-controlled transport**

10 **6.4.1 Air and sea transport**

11 Ensure that any carrier contracted to transport TTSPPs by air or by sea operates
12 under the terms of a formal Service Level Agreement drawn up between the parties.

13 Reason: To ensure that the carrier is made responsible for maintaining load
14 temperatures within the transport temperature profile defined for each product and
15 that compliance can be demonstrated to the contracting organization, the regulatory
16 authorities and other interested parties.
17

18 **6.4.2 Temperature-controlled road vehicles operated by common carriers**

19 Temperature-control in vehicles operated by a common carrier must be qualified and
20 the details and responsibilities for this process should be set out in a formal Service
21 Level Agreement drawn up between the parties.

22 Reason: To ensure that the carrier is made responsible for maintaining load
23 temperatures within the transport temperature profile defined for each product and
24 that compliance can be demonstrated to the contracting organization, the regulatory
25 authorities and other interested parties.
26

27 **6.4.3 Temperature-controlled road vehicles generally**

28 Ensure that temperature-controlled road vehicles used for the transport of TTSPPs
29 are:

- 30 • capable of maintaining the temperature range defined by the system set
31 points over the full annual ambient temperature range experienced over
32 known distribution routes and when the vehicle is in motion, or parked with
33 the main engine stopped;
34 • equipped with a low temperature protection circuit in cold climates where
35 there is a risk of breaching the low temperature set point for TTSPPs that are
36 damaged by exposure to low temperatures;
37 • equipped with calibrated temperature monitoring devices with sensors located
38 at points representing temperature extremes;
39 • equipped with alarms to alert the driver in the event of temperature
40 excursions and/or refrigeration unit failure;
41 • fitted with lockable doors.
42 • qualified as defined in clauses 6.6.1 and 6.6.2;

43 Carry out regular calibration and maintenance and keep records to demonstrate
44 compliance.
45

46 Reason: To ensure that TTSPPs can safely be transported within the transport
47 temperature profile defined for each product and that compliance can be
48 demonstrated to the regulatory authorities and other interested parties.
49

1 **6.4.4** *Transport of controlled TTSPPs and TTSPPs with high illicit value*

2 Ensure that controlled TTSPPs and TTSPPs with high illicit value are transported in
3 the following manner:

- 4 • Transport practices comply with all relevant local legislation and regulations.
- 5 • Vehicles are equipped with lockable doors and an intruder alarm.
- 6 • Vehicles use unique seal lock indicating devices such as cable seal locks with
7 unique identifiers.
- 8 • Contents are not indicated on outer packaging.
- 9 • Security-cleared delivery drivers are employed.
- 10 • All deliveries are documented and tracked.
- 11 • Signed dispatch and arrival records are kept.
- 12 • Shipments are fitted with security equipment appropriate to the product being
13 transported and the assessed security risk, such as GPS devices located in
14 the vehicle and/or hidden in the product.

15
16 *Reason:* To prevent theft and misappropriation of this category of TTSPP and to
17 ensure the security and safety of the driver.
18
19

20 **6.5** **Temperature and humidity control and monitoring during transit**

21 **6.5.1** *Temperature control in temperature-controlled road vehicles*

22 Provide thermostatic temperature control systems for all temperature-controlled
23 vehicles used to transport TTSPPs. Comply with the following minimum
24 requirements:

- 25 • system able continuously to maintain air temperatures within the set point
26 limits throughout the validated storage volume defined in clause 8.6;
- 27 • sensors accurate to $\pm 0.5^{\circ}\text{C}$;
- 28 • sensors calibrated as section 6.7.1;
- 29 • sensors located to control worst-case temperatures in order to maximize
30 available safe storage volume;
- 31 • sensors positioned so as to be minimally affected by transient events such as
32 door opening;
- 33 • sensors independent of the temperature monitoring system.

34
35 **6.5.2** *Temperature monitoring in temperature-controlled road vehicles*

36 Provide air and/or load temperature monitoring systems and devices for vehicles
37 used to transport TTSPPs. Systems and devices should comply with the following
38 minimum requirements:

- 39 • sensors accurate to $\pm 0.5^{\circ}\text{C}$;
- 40 • sensors calibrated as clause 6.7.2;
- 41 • sensors located to monitor worst-case temperatures within the qualified
42 storage zone defined in clause 6.6;
- 43 • sensors positioned so as to be minimally affected by transient events such as
44 door opening;
- 45 • provide a temperature record with a minimum recording frequency of six
46 times per hour for each sensor position¹³;
- 47 • provides documentation which can be stored and accessed.

¹³ Recording frequency should take account of the storage capacity of the data logger and the expected transport period.

1 Establish transit temperature specifications and document transit temperatures for
2 every internal and external shipment.

3 **6.5.3 Humidity monitoring in temperature-controlled road vehicles**

4 Preferably provide humidity monitoring systems and devices for temperature-
5 controlled vehicles which are used to transport TTSPPs that are sensitive to moisture
6 and are not sufficiently protected by packaging. Systems and devices should comply
7 with the following minimum requirements:

- 8 • sensors accurate to $\pm 5\%$ RH;
- 9 • sensors calibrated as clause 6.7.3;
- 10 • sensors located to monitor worst-case humidity levels within the qualified
11 storage zone defined in clause 6.6;
- 12 • sensors positioned so as to be minimally affected by transient events such as
13 door opening.
- 14 • provides a humidity record with a minimum recording frequency of six times
15 per hour for each sensor position;
- 16 • provides documentation which can be stored and accessed.

17 Establish transit humidity specifications and document transit humidity conditions for
18 internal and external shipments where required.

19 **6.5.4 Temperature monitoring in passive and active shipping containers**

20 Use chemical or electronic freeze indicators, electronic loggers (with or without
21 alarms), and/or other suitable indicators to monitor temperature and/or humidity
22 exposure during internal distribution. Preferably use these devices for external
23 distribution. Monitor and document indicator status upon arrival.

24
25 Reason: To ensure that TTSPPs can safely be transported within the transport
26 temperature profile defined for each product and that compliance can be
27 demonstrated to the regulatory authorities and other interested parties.
28

29 **6.6 Qualification of temperature-controlled road vehicles**

30 Where temperature-controlled vehicles are directly owned and/or operated, qualify
31 each vehicle before it becomes operational. The qualification procedure should:

- 32 • demonstrate the air temperature distribution throughout the temperature-
33 controlled compartment for both air and product temperatures for commonly
34 used load layouts and at the ambient temperature extremes anticipated
35 during normal operation over known routes;
- 36 • where products are being transported that are sensitive to moisture and are
37 not sufficiently protected by packaging, demonstrate the humidity distribution
38 throughout the temperature-controlled compartment for commonly used load
39 layouts;
- 40 • define zones within the vehicle's payload area which should not be packed
41 with TTSPPs (for example areas in close proximity to cooling coils or cold air
42 streams);
- 43 • demonstrate the time taken for temperatures to exceed the designated
44 maximum in the event that the temperature controlling unit fails;
- 45 • document the qualification exercise.

46
47 Carry out additional qualification exercises whenever significant modifications are
48 made to the vehicle. Consider the need for re-qualification whenever temperature
49 and/or humidity monitoring shows unexplained variability that is greater than normal.
50

1 Reason: To ensure that TTSPPs can safely be transported within the transport
2 temperature profile defined for each product and that compliance can be
3 demonstrated to the regulatory authorities and other interested parties.
4

5 **6.7 Calibration and verification of transport monitoring devices**

6 *6.7.1 Calibration of transport temperature control devices*

7 Calibrate devices against a certified, traceable, reference standard at least once a
8 year, unless otherwise justified.

9 *6.7.2 Calibration of transport temperature monitoring devices*

10 Calibrate devices against a certified, traceable, reference standard at least once a
11 year, unless otherwise justified.

12 *6.7.3 Calibration of transport humidity monitoring devices*

13 Calibrate devices against a certified, traceable, reference standard at least once a
14 year, unless otherwise justified.

15 *6.7.4 Verification of transport alarm equipment*

16 Check functionality of temperature and humidity alarms at the designated set points.
17 Check functionality of security alarm systems. Carry out these checks at least once
18 a year, unless otherwise justified.

19
20 Maintain records to demonstrate compliance.

21
22 Reason: To ensure that TTSPPs can safely be transported within the transport
23 temperature profile defined for each product and that compliance can be
24 demonstrated to the regulatory authorities and other interested parties.
25

26 **6.8 Shipping containers**

27 *6.8.1 Container selection generally*

28 Select shipping containers that:

- 29 • comply with applicable national and international standards relevant to the
- 30 product type and the chosen transport route and mode(s);
- 31 • protect personnel and the general public from hazards arising from spillage
- 32 leakage or excessive internal pressure;
- 33 • protect the product being transported against mechanical damage and the
- 34 anticipated ambient temperature range that will be encountered in transit;
- 35 • can be closed in a manner that allows the recipient of the consignment to
- 36 establish that the boxes have not been tampered with during transport.

37
38 Reason: Quality assurance and safety.

39 *6.8.2 Un-insulated containers*

40 Ensure that un-insulated containers are correctly used in a manner which protects
41 their contents:

- 42 • Transport un-insulated containers in a qualified temperature-controlled
- 43 environment such as an actively or passively temperature-controlled vehicle.
- 44 • Ensure that the transport system is able to maintain the temperature of the
- 45 TTSPP within the product's stability profile as stated by the product
- 46 manufacturer and/or to maintain the TTSPP within the transit temperature

1 specification requirements specified by the regulatory authorities at both the
2 sending and receiving locations.

3

4 Reason: Quality assurance and safety.

5 **6.8.3 Qualification of insulated passive containers**

6 Qualify insulated passive containers, including any and all necessary ancillary
7 packaging such as temperature stabilising medium, dry-ice, ice or gel packs, cool
8 water packs or warm packs, phase change materials, partitions, bubble wrap and
9 dunnage:

- 10 • Ensure that the qualified packaging system is capable of maintaining the
11 TTSP within the temperature range needed to meet the product stability
12 profile as stated by the product manufacturer. Container qualification should
13 include full details of the packaging assembly, the thermal conditioning
14 regime and the minimum and maximum shipping volume, weight and thermal
15 mass that can safely be accommodated in the container. Qualification should
16 also include the correct placement of temperature monitors where these are
17 used.
- 18 • Take account of the transport route and of the anticipated ambient
19 temperature profile over the duration of transport, measured from the point of
20 departure to the point of arrival in the recipient's temperature-controlled store.

21

22 Reason: To ensure that TTSPs can safely be transported within the transport
23 temperature profile defined for each product and that compliance can be
24 demonstrated to the regulatory authorities and other interested parties.

25 **6.8.4 Qualification of active containers**

26 Qualify active containers:

- 27 • Ensure that the container is capable of maintaining the TTSP within the
28 temperature range needed to meet the product stability profile as stated by
29 the product manufacturer.
- 30 • Take account of the transport route and of the anticipated ambient
31 temperature profile over the duration of transport, measured from the point of
32 departure to the point of arrival in the recipient's temperature-controlled store.

33

34 Reason: To ensure that TTSPs can safely be transported within the transport
35 temperature profile defined for each product and that compliance can be
36 demonstrated to the regulatory authorities and other interested parties.

37

38

39 **6.9 Shipping container packing**

40 Pack TTSP shipping containers to:

- 41 • the exact specified configuration to ensure that the correct TTSP
42 temperature range is maintained;
- 43 • minimize the risk of theft and fraud and assure the recipient that the goods
44 have not been tampered with whilst in transit– for example by using locked
45 containers or shrink-wrapped pallets;
- 46 • minimize the risk of mechanical damage during transport;
- 47 • protect freeze-sensitive products against temperatures below 0°C when
48 frozen packs are used;
- 49 • protect products against light, moisture and contamination or attack by micro-
50 organisms and pests.
- 51 • protect products against adverse effects when dry ice is used as a coolant;

- 1 • clearly label containers to identify the correct transport temperature range and
2 to show correct orientation for handling;
3 • ensure that packages containing dangerous goods (including dry ice) are
4 labelled in compliance with relevant transport regulations and requirements.
5

6 Reason: To ensure that shipping containers are systematically used in the manner
7 defined during the container qualification process and that this can be demonstrated
8 to the regulatory authorities and other interested parties.
9

10 **6.10 Product handling during packing and transport**

11 Handle TTSPPs correctly during packing and transport:

- 12 • Pack TTSPPs in an area set aside for the assembly and packaging of these
13 products as clause 3.3.1.
14 • Take precautions against spillage or breakage, contamination and cross-
15 contamination.
16 • Deliver TTSPPs to outside recipients by the most suitable mode(s) of
17 transport available in order to minimize delivery time.
18 • Ensure that patients receiving TTSPP deliveries are given clear advice on
19 correct product storage before use.
20

21 Reason: To maintain TTSPP quality during transport.
22
23

24 **6.11 Cleaning road vehicles and transport containers**

25 Implement a cleaning and decontamination programme for all road vehicles and
26 reusable shipping containers used to transport TTSPPs:

- 27 • Ensure that all internal surfaces of load compartments are regularly cleaned.
28 • Do not allow the accumulation of dust, dirt and waste, including packaging
29 waste in load compartments, or in reusable shipping containers.
30 • Take precautions against spillage or breakage, and cross-contamination.
31 • Do not allow accumulation of frost and ice in refrigerated vehicles, particularly
32 ice contaminated by spillages.
33 • Collect waste in designated closed containers and arrange for safe disposal
34 at frequent intervals.

35 Maintain cleaning records for vehicles and reusable shipping containers to
36 demonstrate compliance.
37

38 Reason: Protection against damage and contamination of TTSPPs and hazards to
39 workers arising from spillage or breakage.
40

41 **6.12 Transport of returned and recalled TTSPPs**

42 *6.12.1 Transport of returned TTSPPs*

43 Ensure that that returned TTSPPs are transported under the same conditions as
44 those used for the initial delivery:

- 45 • The sender and recipient must work together so that that the product is
46 maintained within the temperature range needed to meet the manufacturer's
47 stated product stability profile
48 • Take account of the anticipated ambient temperature profile over the duration
49 of transport, measured from the point of departure to the point of return.

- 1 • Quarantine returned TTSPPs in temperature-controlled storage pending a
2 decision by the quality control department or qualified person to dispose of
3 the product or to return it to stock.
4

5 Reason: To ensure that returned and recalled TTSPPs are maintained within the
6 correct transport temperature profile so that they can safely be re-stocked if a
7 decision to do so is made.

8 6.12.2 *Transport recalled TTSPPs*

9 Ensure that recalled TTSPPs are:

- 10 • Marked for disposal as either 'recalled' or 'withdrawn'.
11 • Transported back from the recipient and quarantined under secure conditions
12 pending a final decision on disposal as clause 7.5.3.
13

14 7. **Labelling**

15 7.1 **Normative references**

- 16 • *IATA Perishable Cargo Regulations Chapter 17 9th Edition, July 2009.*
17 *Clauses 17.10.5 and 17.10.6.*
18

19 7.2 **Labelling**

20 7.2.1 *Labelling generally*

21 Label internal shipping and external distribution containers containing TTSPPs as
22 follows:

- 23 • identify the product in accordance with all national and international labelling
24 requirements relevant to the container content, transport route and mode(s);
25 • identify hazardous products in accordance with relevant national and
26 international labelling conventions.
27 • indicate the appropriate temperature and humidity ranges within which the
28 product is to be transported and/or stored.

29 7.2.2 *Labelling air-freighted shipments*

30 In cases where TTSPPs are to be air-freighted, label packaging using the standard
31 IATA *Time and Temperature-sensitive* symbol. Apply the label to the outer surface of
32 individual shipping packages, overpacks or bulk containers.
33

34 Reason: To ensure that products are correctly and safely handled at all points in the
35 supply chain.
36

37 8. **Stock management**

38 8.1 **Stock control systems**

39 8.1.1 *General stock control systems and procedures*

40 TTSPP stock control systems and procedures should meet the following minimum
41 requirements:

- 42 • Provide security-enabled access control designed to ensure that the system
43 cannot be accessed by unauthorized persons.
44 • Record all receipts and dispatches.
45 • Record batch numbers and expiry dates.

- 1 • Record short-dated and expired products.
- 2 • Record product status (e.g. released, quarantined, hold, reject, etc.).
- 3 • Record all product returns, recalls, withdrawals, damage and disposals.
- 4 • Manage the issue of products in EEFO order.
- 5 • Take regularly physical inventories and reconcile stock records with the actual
- 6 physical count. Investigate and report on stock discrepancies in accordance
- 7 with agreed procedures. Preferably physical counts should be conducted at
- 8 least twice a year.

9
10 Reason: To ensure that accurate and complete stock records are kept at all times.

11 12 **8.1.2 Stock control procedures for controlled and hazardous TTSPPs**

13 In addition to the requirements set out in clause 7.1.1, implement the following
14 procedures:

- 15 • Institute a customer verification process to ensure that all recipients of these
- 16 products are authorized to receive them.
- 17 • Maintain stock records which specifically identify products in these categories.
- 18 • Carry out regular audits and make audit reports available to the responsible
- 19 authorities.
- 20 • Comply with all record-keeping procedures specified in local legislation and
- 21 regulations. Retain product transaction/delivery records for at least the
- 22 minimum time period required by local regulations.

23
24 Reason: To ensure that accurate and complete stock records are kept at all times
25 and to satisfy the requirements of the regulatory authorities.

26 27 **8.2 Goods incoming**

28 **8.2.1 Product arrival checks**

29 Check and record the following for all incoming TTSPPs:

- 30 • product name, item code (identifier), strength, and batch/lot number;
- 31 • quantity received against order;
- 32 • name and address of the supplying site;
- 33 • examine containers for tampering, damage or contamination;
- 34 • examine expiry dates – accept short-dated products only if prior agreement
- 35 has been reached with the supplier; do not accept products that have expired
- 36 or which are so close to their expiry date that this date is likely to occur before
- 37 use by the consumer;
- 38 • delays encountered during transport;
- 39 • status of any attached temperature recording device(s) and/or
- 40 time/temperature indicators;
- 41 • verify that required storage and transport conditions have been maintained.

42 **8.2.2 Actions following arrival checks**

- 43 • Enter product details, including product name/number, strength, batch
- 44 numbers, quantities received, expiry dates, and acceptance status into the
- 45 stock recording system.
- 46 • Store checked goods under the correct temperature and security regime
- 47 immediately upon receipt.
- 48 • Quarantine defective or potentially defective products, products with
- 49 incomplete or missing paperwork, products that experienced unacceptable
- 50 temperature excursions during transport, or products suspected to be
- 51 counterfeit. Do not release until checks have been completed satisfactorily.

- 1 • Report any defects to the supplying store or holder of the marketing
2 authorization.
3 • Do not transfer to saleable stock until all relevant disposition procedures have
4 been completed.

5
6 Reason: To ensure that incoming TTSPPs are in acceptable condition, accurately
7 recorded and correctly stored and that defective and/or incorrect shipments are
8 followed up with the supplier.
9

10 **8.3 Goods outgoing (external deliveries)**

11 **8.3.1 Management of outgoing goods**

- 12 Implement outgoing goods procedures to ensure that:
- 13 • Transport vehicle conformity, including conformity with SLA or QA
14 agreements, is checked before loading goods.
 - 15 • Expired products are never issued.
 - 16 • Products with short expiry dates are not issued unless the recipient accepts
17 that they can be consumed before the expiry date is reached.
 - 18 • Products are distributed in strict EEFO order unless product-based time-
19 temperature exposure indicators demonstrate that a batch should be
20 distributed ahead of its EEFO order.
 - 21 • Details of any temperature monitoring devices packed with the external
22 distributions are recorded.
 - 23 • Details of outgoing products, including product name/number, strength, batch
24 numbers, expiry dates and quantities distributed, are entered into the stock
25 recording system.

26 **8.3.2 Actions following dispatch**

- 27 Monitor TTSPPs following dispatch in order to:
- 28 • Trace products to their intended destination.
 - 29 • Record and retain records to provide assurance of goods arrival status. A
30 suitable delivery report from the carrier is an acceptable alternative.
 - 31 • Take appropriate action in the event of returns, recalls or complaints.

32
33 Reason: To ensure that outgoing TTSPPs are in acceptable condition, that short-
34 dated stock does not accumulate in the store and that evidence is kept to
35 demonstrate that correct quantities are distributed and received in good condition.
36

37 **8.4 Product complaint procedures**

- 38 Manage product complaints as follows:
- 39 • If a product defect is discovered or suspected in a batch of TTSPPs,
40 determine whether other batches are affected and whether a product recall is
41 required.
 - 42 • Where complaints or defects relate to a product or its packaging, immediately
43 notify the holder of the marketing authorisation for the product.
 - 44 • Where complaints or defects arise as a result of errors or omissions within the
45 organization, immediately evaluate the causes and take remedial measure to
46 prevent a recurrence.
 - 47 • Record all complaints and the remedial actions taken. Monitor and analyse
48 trends in the complaint records.

49
50 Reason: Protection of the public and the reputation of the supplying organization.

1

2 **8.5 Product return, recall, withdrawal, and disposal procedures**

3 *8.5.1 Return procedures*

4 Manage product returns as follows:

- 5 • Quarantine returned TTSPPs in a suitable temperature-controlled area and
6 under the security conditions applicable to the product type.
- 7 • Do not return to saleable stock unless storage and transport temperature
8 conditions after dispatch from the distribution site have been fully verified and
9 documented, including the return leg to the distribution site.
- 10 • Where appropriate, obtain written advice from the holder of the marketing
11 authorisation regarding handling and/or disposal of the returned TTSPP.
- 12 • If returned stock is re-issued, distribute in EEFO order or in accordance with
13 the exposure status of any product-mounted time-temperature indicator
14 device.
- 15 • Quarantine returned TTSPPs that have been exposed to incorrect storage
16 and/or transport temperatures and mark for disposal.
- 17 • Maintain records of all returned TTSPPs.

18

19 Reason: Protection of the public.

20 *8.5.2 Recall procedures*

21 Manage product recalls as follows:

- 22 • Conduct urgent and non-urgent TTSPP recalls in accordance with an agreed
23 emergency plan.
- 24 • Notify the local regulatory authority(ies).
- 25 • Notify overseas regulatory counterparts where the product has been
26 exported.
- 27 • Notify all affected customers as applicable.
- 28 • Quarantine any remaining inventory of recalled TTSPPs and mark for
29 disposal.
- 30 • Maintain records of all TTSPP recalls, including reconciliation of quantity sold,
31 quantity returned, quantity remaining, quantity consumed, etc).

32

33 Reason: Protection of the public and conformity with regulatory requirements.

34 *8.5.3 Disposal procedures*

35 Manage product disposals as follows:

- 36 • Ensure that rejected and/or recalled/withdrawn TTSPPs cannot be used,
37 released or cause contamination to other products. Store separately from
38 other products until they are destroyed or returned to the supplier.
- 39 • Safely dispose of rejected and/or recalled/withdrawn products in accordance
40 with local regulations, including where relevant, regulations covering the
41 disposal of hazardous and controlled drugs.
- 42 • Maintain disposal records.

43

44 Reason: Protection of the public and the environment.

45

1 **8.6 Counterfeit product procedures**

2 **8.6.1 Counterfeit products**

3 Implement systems for identifying and managing counterfeit products found in the
4 supply chain as follows:

- 5 • Physically segregate any counterfeit TTSPPs found in the supply chain and
6 store securely until legal investigations are complete.
- 7 • Label them clearly as 'Not for sale' or other similar phrase.
- 8 • Immediately notify the regulatory authority(ies), the police, and the holder of
9 the marketing authorisation of the original product.
- 10 • Cooperate with regulatory authorities to assist with investigating the source of
11 counterfeit products and implement appropriate remedial action(s).
- 12 • Document the decision-making process for disposal of counterfeit TTSPPs
13 and make these records available to the relevant authorities.

14
15 Reason: Protection of the public, protection of legitimate suppliers and manufacturers
16 and conformity with regulatory requirements.
17

18 **8.7 Traceability/ stock tracking**

19 **8.7.1 Traceability**

20 Ensure that stock and distribution records enable traceability of TTSPPs from the
21 point of supply to the end user/patient. Traceability should include records of the
22 temperature exposure of the product during internal shipping and storage. Monitor,
23 record, and investigate discrepancies.
24

25 Reason: To demonstrate that TTSPPs have been correctly distributed and to
26 facilitate product recalls and detect theft and fraud.
27

28 **9. General procedures and record keeping**

29 **9.1 Emergencies and contingency planning**

30 Make contingency arrangements for the safe storage of TTSPPs in the event of
31 emergencies, including, but not confined to:

- 32 • extended power supply outages;
- 33 • equipment failure;
- 34 • vehicle breakdown during transport of TTSPPs.

35 Prepare action plans to deal with products subjected to temperature excursions.

36 Ensure that responsible staff know, and have rehearsed, the appropriate actions to
37 be taken in the event of the identified emergency scenarios.
38

39 Reason: Loss prevention.
40

41 **9.2 General record keeping**

42 **9.2.1 Record keeping**

43 Maintain comprehensive records and ensure that they are laid out in an orderly
44 fashion and are easy to check.
45

46 Paper records must be:

- 47 • stored and maintained so that they are accessible and easily retrievable;

- 1 • labelled, dated and filed for easy identification;
- 2 • protected against deterioration and loss due to fire, flood or other hazards;
- 3 • kept secure and protected against unauthorised access;
- 4 • signed and dated by authorised persons and not changed without due
- 5 authorisation;
- 6

7 Computer records must be:

- 8 • logically filed for easy identification and retrieval;
- 9 • kept secure and protected against unauthorised access;
- 10 • manually signed, dated and scanned or electronically signed and dated by
- 11 authorised persons and not changed without due authorisation;
- 12 • regularly backed up and archived on a secure server.

13 9.2.2 *Content of records*

14 Ensure that the following traceability data is recorded for each TTSP batch number,
15 as applicable:

- 16 • Product arrival status.
- 17 • Temperature and humidity records including records of excursions outside
- 18 labelled storage and/or transit temperature specification conditions.
- 19 • General TTSP stock transactions, including purchase and sale records.
- 20 • Controlled drug audits.
- 21 • Audits for products with high illicit-value.
- 22 • Audits for hazardous products.
- 23 • Stock tracking.
- 24 • Return, recall, withdrawal, and disposal reports, where relevant.
- 25 • Product complaint reports, where relevant.
- 26 • Counterfeit product reports, where relevant.

27 Maintain all records in accordance with local legislation and regulations..

28 9.2.3 *Record review and retention*

29 Ensure that records are reviewed and approved on a regular basis by a designated
30 member of the quality management team. Ensure that records are accessible for
31 review by end-users, the regulatory authority and other interested parties. Retain
32 records for the minimum period required under local legislation, but for not less than
33 three years.

34 Reason: Internal quality control, transparency and external inspection by the
35 regulatory authorities and other interested parties.

36

37 9.3 **Temperature and humidity records**

38 9.3.1 *Temperature records*

39 Monitor and record storage temperatures in all temperature-controlled rooms, cold
40 rooms, freezer rooms, refrigerators and freezers, as follows:

- 41 • Check and record temperatures at least twice daily – in the morning and
- 42 evening – and preferably continuously.
- 43 • Review temperature records monthly and take action to rectify systematic
- 44 excursions.
- 45 • Systematically file temperature records for each storage environment or piece
- 46 of equipment to ensure traceability. Keep records for at least one year after
- 47 the end of the shelf-life of the stored material or product, or as long as
- 48 required by national legislation.
- 49

1 **9.3.2 Humidity records**

2 Where applicable, monitor and record humidity levels in all temperature-controlled
3 rooms as follows:

- 4 • Record humidity at least twice every 24 hours and preferably continuously.
- 5 • Check humidity records daily.
- 6 • Review humidity records monthly and take action to rectify systematic
7 excursions.
- 8 • Systematically file humidity records for each temperature-controlled room to
9 ensure traceability. Keep records for at least one year after the end of the
10 shelf-life of the stored material or product, or as long as required by national
11 legislation.

12
13 Reason: Internal quality assurance and availability of records for review by the
14 regulatory authorities and other interested parties.
15

16 **10. Environmental management**

17 **10.1 Normative references**

- 18 • ISO 14001: 2004. *Environmental management systems – Requirements with*
19 *guidance for use.*
- 20 • *The Montreal Protocol on Substances that Deplete the Ozone Layer.* UNEP,
21 2000.
22

23 **10.2 Environmental management of refrigeration equipment**

24 Ensure that all new refrigeration equipment for temperature-controlled storage and
25 transport is specified to:

- 26 • use refrigerants that comply with the Montreal Protocol;
- 27 • minimize or eliminate the use of refrigerants with high Global Warming
28 Potential (GWP);
- 29 • minimize CO₂ emissions during operation.

30 Select equipment to minimize whole-life environmental impact and employ best
31 practice to eliminate leakage of refrigerant into the environment during installation,
32 maintenance and decommissioning of refrigeration equipment.
33

34 Reason: Compliance with international protocols and accords on climate change and
35 environmental protection.
36

37 **11. Quality management**

38 **11.1 Normative references**

- 39
- 40 • ICH, 2005: *ICH Harmonised Tripartite Guideline: Quality Risk Management*
41 *Q9.*
- 42 • ISO 9000:2005. *Quality management systems -- Fundamentals and*
43 *vocabulary*
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46 *improvements*
- 47 • ISO 10005:2005. *Quality management systems -- Guidelines for quality plans*

- 1 • ISO 19011:2002. *Guidelines for quality and/or environmental management*
2 *systems auditing*
3

4 **11.2 Organizational structure**

5 Establish, document and maintain an organizational structure for the TTSP storage
6 and shipping and distribution operations which clearly identifies all key management
7 responsibilities, and the individuals accountable.

8
9 Reason: Quality management.
10

11 **11.3 Quality systems**

12 *11.3.1 Quality system*

13 Establish, document and maintain a quality system for the management of TTSPs
14 including, the following, as applicable:

- 15 • standard quality system(s) and associated auditing procedures;
- 16 • written procedures and specifications;
- 17 • record storage, record retention and record destruction programme;
- 18 • risk management;
- 19 • calibration programme;
- 20 • stability programme;
- 21 • qualification and validation programme;
- 22 • deviation and root cause investigation programme;
- 23 • corrective and preventive action (CAPA) programme;
- 24 • training programme;
- 25 • periodic temperature-controlled process assessment;
- 26 • change control programme;
- 27 • maintenance programme;
- 28 • management controls;
- 29 • product return and recall/withdrawal policies, including emergency recalls;
- 30 • product complaint policies;
- 31 • material destruction programme;
- 32 • warehouse and storage programme;
- 33 • shipping and distribution programme;
- 34 • notification systems for regulatory agencies; Boards of Health and Ministries
35 of Health;
- 36 • self-inspection programme;

37 Carry out periodic reviews of the quality management system to ensure that it
38 remains appropriate, relevant, and effective.

39
40 Reason: Quality assurance.

41 *11.3.2 Self inspections*

42 Conduct regular self-inspections to ensure continuing compliance with quality
43 management standards Good Storage Practice (GSP) and Good Distribution
44 Practices (GDP); record results.

45
46 Reason: To demonstrate compliance with adopted quality management standards.
47
48

1 **11.4 Management of documents and SOPs**

2 *11.4.1 Standard operating procedures (SOPs)*

3 Develop and maintain SOPs covering correct storage, internal shipping and external
4 distribution of TTSPPs, including, but not limited to, the following topics:

- 5 • Security, including management of controlled and hazardous TTSPPs.
- 6 • Safe handling of TTSPPs.
- 7 • Temperature monitoring.
- 8 • Calibration of temperature and humidity monitoring devices and alarm
9 systems.
- 10 • Qualification and validation procedures, including temperature mapping.
- 11 • Maintenance of controlled-temperature equipment.
- 12 • Facility cleaning and pest control.
- 13 • Facility maintenance.
- 14 • Product arrival (receiving) procedures and records.
- 15 • Stock storage and warehousing procedures (put away, replenishment, order
16 fulfilment, packing, etc.).
- 17 • Stock control procedures and records.
- 18 • Distribution procedures and records.
- 19 • Management of temperature excursions.
- 20 • Product return and recall/withdrawal procedures and records.
- 21 • Product complaint procedures and records.
- 22 • Safe disposal of damaged, expired and quarantined products and records.
- 23 • Temperature-controlled packaging and route qualification.
- 24 • Temperature-controlled vehicle operation.
- 25 • Emergency response procedures.
- 26 • Environmental management.

27 Ensure that all documents are clear and unambiguous and that document change
28 control procedures are in place as clause 11.5.

29
30 Reason: Quality management and staff training.

31
32

33 **11.5 Document change control**

34 Ensure that all quality manuals, standard operating procedures and the like are:

- 35 • authorized by an appropriate person;
- 36 • recorded in a document register;
- 37 • regularly reviewed and kept up-to-date, with all changes recorded and
38 authorized;
- 39 • version controlled;
- 40 • issued to all relevant personnel;
- 41 • withdrawn when superseded.

42 Withdraw superseded documents and retain record copies for document history files.

43
44 Reason: Good quality management practice.

45
46

47 **12. Personnel/ training**

48 **12.1 Normative references**

- 49 • IATA *Perishable Cargo Regulations Chapter 17*. 9th Edition, July 2009

50

1 **12.2 Training**

2 *12.2.1 General training*

3 Provide regular and systematic training for all relevant personnel responsible for
4 storage, loading and unloading areas used for non-hazardous TTSPPs, covering the
5 following:

- 6 • applicable pharmaceutical legislation and regulations;
- 7 • standard operating procedures and safety issues;
- 8 • response to emergencies.

9 Ensure that each employee understands his or her specific responsibilities. Maintain
10 individual training records to demonstrate compliance and perform effectiveness
11 checks on training. Provide similar training for drivers who are responsible for
12 transporting these substances. Maintain individual training records to demonstrate
13 compliance.

14
15 Reason: To ensure that all relevant personnel are competent to carry out their duties.

16 *12.2.2 Specialist training*

17 In addition to the training described in clause 12.2.1, provide regular and systematic
18 additional training for relevant personnel responsible for storage, loading and
19 unloading used for controlled or hazardous TTSPPs. Training should cover the
20 following:

- 21 • applicable legislation and regulations;
- 22 • security and safety risks;
- 23 • response to emergencies.

24 Ensure that each employee understands his or her specific responsibilities. Maintain
25 training records to demonstrate compliance and perform effectiveness checks on
26 training. Provide similar training for drivers who are responsible for transporting
27 these substances. Maintain individual training records to demonstrate compliance.

28
29 Reason: To ensure that all relevant personnel are competent to handle controlled or
30 hazardous TTSPPs.

31

1 **Annex 1 – Key references**

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3 WHO/PSM/PAR/2007.3
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5 2006.
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- 17 EU Regulation 4/2007. [Good distribution practices for pharmaceutical wholesalers.](#)
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3

4 **Annex 2 – Other references consulted**

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7 Directive 94/62/EC. *European Parliament and Council Directive of 20 December*
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28

1 **Annex 3 – Task force membership**

| Name | Organization | Category | Country |
|-------------------|---|------------------------|-----------------|
| Henry Ames | Sensitech | Temperature monitoring | USA |
| Claude Ammann | Topotarget Switzerland SA Avenue de Sévelin 20 CH-1004 Lausanne | Manufacturer | Switzerland |
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| Richard Brown | TGA | Regulatory | Australia |
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| Michael Eakins | USP Packaging and Storage Expert Committee, USP, USA | Regulatory | USA |
| Juliman Fuad | Bio Farma / Indonesia | Manufacturer | Indonesia |
| Andreas Giger | Berlinger | Temperature monitoring | Switzerland |
| Jochen Heinzl | Representative Narcotics Supply Chain, Quality Management Distribution, F. Hoffmann-La Roche AG, PTGS-Q3, Building 238/2.19, 4070 Basel | IFPMA | Switzerland |
| Laila Jarrar | Director of Drug department in Jordan Food & Drug Administration | NRA | Jordan |
| Santosh Kutty | CDL Kasauli | Regulatory | India |
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| Adrien Lehideux | ColdPack | Passive cooling | France |
| Zhang Lei | China National Biotec Group (Chengdu Institute) / China | Manufacturer | China |
| Eric Lindquist | Entropy Solutions | Passive cooling | USA |
| Kåre Lindroos | Huure | Active cooling | Finland |

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| | | | |
|---------------------------|---|------------------------|------------|
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| Cristiane Frensch Pereira | Bio-Manguinhos / Brazil | Manufacturer | Brazil |
| Thadeus Prusik | TempTime | Temperature monitoring | USA |
| Eric Raemdonk | International Air Transport Association | IATA | Canada |
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| Sarah Skuce | Health Canada | Regulatory | Canada |
| Engko Sosialine M | National Agency of Drug and Food Control Republic of Indonesia | Regulatory | Indonesia |
| John Taylor | MHRA | Regulatory | UK |
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| Denis Maire | FCH/QSS | WHO | Switzerland |
| World Health Organization | | | |
| Lahouari Belgharbi | FCH/QSS | WHO | Switzerland |
| Ivana Knezevic | FCH/QSS | WHO | Switzerland |
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| Revision history | | | |
|-------------------------|---|-------------------|----------|
| Date | Change summary | Reason for change | Approved |
| 01.10.2009 | V1b: Note on document status added | ECBS requirement | |
| 28.04.2010 | V2: Incorporating further review comments | | |
| 11.05.2010 | V2b: Further revisions and reorganization | | |

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