NATIONAL PHARMACEUTICAL REGULATORY DIVISION
MINISTRY OF HEALTH MALAYSIA

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SUPPLEMENTARY NOTES ON ANNEX 1: MANAGEMENT OF TIME AND TEMPERATURE SENSITIVE PRODUCTS (TTSP) OF GUIDELINE ON GOOD DISTRIBUTION PRACTICE

(These notes are to be read alongside with the Guideline)

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GLOSSARY OF TERMS

Active Systems	Actively powered systems using electricity or other fuel source to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulation (e.g. cold rooms, refrigerators, temperature-controlled trucks, refrigerated ocean and air container)
Cold Chain	The process used to maintain optimal conditions during the transport, storage, and handling of cold chain products, from the point of manufacturer to the point of use
Passive Systems	Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of pre-conditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others
Qualification	Documented testing that demonstrates, with a high degree of assurance, that an equipment/ facility will meet its predetermined acceptance criteria
Temperature-controlled	Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits
Temperature Excursion	An excursion event in which a time and temperature sensitive products is exposed to temperatures outside the range(s) prescribed for storage and/or transport. These temperature range may be the same or different which are determined by the manufacturer, based on stability data
Temperature Monitoring Device	This includes temperature indicators such as data-loggers, cold chain monitors (CCM), vaccine vial monitors (VVM) and freeze watch indicator.
Time and Temperature Sensitive Products	Any good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.
Validation	Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria

Paragraph	Explanation
PRINCIPLE	
Policies and procedures should be available to ensure that the activities of receipt, storage and distribution are done without compromising on the safety, identity, strength, purity and quality of time and temperature sensitive products (TTSP) according to the manufacturer's recommended conditions as per the approved product's label by the authority as well as the product stability data.	➢ Written procedures on the handling of time and temperature sensitive products should be available to ensure that the quality, efficacy and safety of the products are not compromised. ➢ All policies and procedures should be made aware to all personnel concerned. ➢ All policies and procedures should be available in writing and situated in accessible area for easy reference by the personnel.
PERSONNEL	
1. List of products including the cold chain storage temperature specifications should be provided for reference to personnel who handle the receipt of TTSP. 2. Regular and appropriate training should be provided for all personnel (including drivers) involved in the handling of TTSP to ensure the quality of TTSP are maintained. The training should also cover on applicable pharmaceutical legislations and regulations; SOPs and safety issues and response to emergencies. Training records and effectiveness checks on training provided should be available upon request.	➢ List of all time and temperature sensitive products and its storage requirement should be available for reference to all warehouse personnel who handle the receipt of products. ➢ Training schedule, continuous training and assessment to ensure personnel are equipped with specific knowledge and skills to handle time and temperature sensitive products should be provided. Training record and effectiveness checks on training should be recorded and available upon request.
FACILITIES AND EQUIPMENTS	
3. Net storage capacity of the storage facilities should be sufficient to accommodate peak TTSP stock levels under correct temperature conditions and in a manner which enables efficient and correct stock management operations to take place.	➢ Storage facilities should be of sufficient capacity to avoid the risks associated with overstocking and to ensure that good warehousing practices can be adopted. (First In-First Out (FIFO) or First Expired-First Out (FEFO). Overstocking makes FIFO or FEFO handling difficult or impossible and hinders accurate physical stock counts.

4. TTSP storage facilities should be qualified prior to prevail that it is capable of storing the product in accordance with the specifications given situation. Qualification and validation records must be kept and TTSP storage facilities must be able to operate at all time in accordance to the qualifying conditions.	➢ Storage facilities should be qualified to ensure that labelled TTSP temperatures can be maintained during long-term storage and that the facility can be demonstrated to the authority and other interested parties that due diligence has been observed. ➢ Storage facilities should be able to operate as per validated condition. ➢ Qualification documents of the storage facilities should be readily available upon request.
5. Household-style unit refrigerators and freezers are only acceptable if they have been independently tested and found to comply with the temperature control requirements of a recognized standard for pharmaceutical refrigerators or freezers.	➢ Household-style unit refrigerators and freezers should be purpose-designed for the storage of time and temperature sensitive products.
6. Controlled or hazardous TTSP should be stored in dedicated, separated and securely locked facilities/areas that comply fully with all legislative and regulatory requirements.	➢ To protect this category of products against theft and misuse and to safeguard personnel in the event of an accident involving hazardous substances.
7. Cold room, freezer room, refrigerator and freezer must be fitted with an alarm system to alert personnel if any occurrence of temperature beyond specifications. Action and warning limits should be established. Periodic testing program on the alarm system should be established to ensure the alarm system is functioning.	➢ Alarm systems should include visual and audible alarms. ➢ Alarm systems should be able to alert personnel during emergencies (including after working hours).
8. Alternative power systems should be established to ensure temperature remained and the temperature/humidity detector will continue functioning in the event of power failure. Periodic testing program on alternative power systems should be established to ensure that it works. Alternative plan to provide alternative areas where storage temperature equivalent should be provided if no alternative power systems can be	➢ Company should provide back-up power supply (e.g. uninterrupted power supply (UPS) system). ➢ Company to develop and maintain a contingency plan in the event of power failure or any other unforeseen situation that may cause products to be at risk.

provided.	
9. Calibration and temperature monitoring functions of all equipment, including alarms and other related equipment, must be inspected at least annually.	➢ No clarifying remarks.
10. Periodic maintenance program for all temperature controlled rooms, cold rooms, freezer rooms, refrigerators and freezers must be established and implemented.	➢ Refer Chapter 3 for more information on temperature mapping study. ➢ Company should provide validation reports for temperature mapping of the facilities. ➢ Location of temperature logger should be identified.
13. Maximum and minimum temperature and humidity (if needed) for all temperature controlled rooms, cold rooms, freezer rooms, refrigerators and freezers must be monitored and recorded continuously using temperature and humidity monitoring devices.	➢ Temperature and humidity (if needed) monitoring should be recorded to ensure that products are stored according to their temperature specifications. ➢ Continuous recording devices are preferable as thermometers provide only limited and discontinuous temperature information.
14. Suitability of locations for placing temperature sensors in all temperature controlled rooms, cold rooms, freezer rooms, refrigerators and freezers used for storage of TTSP should be subjected to temperature mapping study. Mapping studies should be conducted in accordance with written procedures and storage conditions determined before operation.	➢ Validation reports for temperature mapping of storage facilities should be available. ➢ Location of temperature logger should be identified.
STOCK RECEIVING AND HANDLING	
11. Verification upon receipt of products should be done to ensure there are no signs of tampering and non-conformance (such as deviation of temperature profile from the manufacturer's recommendation as per the approved product's label by the authority, physical damage to products, packaging materials, etc.).	➢ Verification of products upon receipt should be conducted by personnel to ensure no signs of tampering to container systems used for delivery of products as well as other non-conformity such as deviation of temperature profile from the manufacturer's recommendation as per the approved product's label; physical damage to the products, packaging

	materials, label defects, etc.
12. All TTSP (e.g. rejected, quarantined) must be stored under the storage conditions stated on the label other than the product which will be disposed off. If the storage temperature is found to have deviated from the storage specifications, manufacturer for the products should be contacted to confirm the suitability of the use of products and the decision recorded.	➢ No clarifying remarks.
15. Container systems used for delivery of TTSP should be fully qualified to show that it is 'fit for purpose' and capable of maintaining the temperature profile defined for each product during transportation/distribution, can minimize product degradation due to temperature sensitivity and can meet the product stability profile requirements stated by the pharmaceutical manufacturer. Documented evidence of such assurance and compliance should be demonstrated and available upon request.	➢ To ensure that products can safely be transported within the temperature profile defined for each product and that compliance should be able to be demonstrated to authority and other interested parties. ➢ Qualification and validation reports for container systems used in delivery of products should be available.
16. Packaging operations for TTSP should be verified in accordance with written procedures. Packaging for TTSP should be mapped and continuously monitored.	➢ The packaging operations should be verified by a second person to ensure that the packaging operations are carried out in accordance with written procedures. ➢ Packaging for products should be mapped and continuously monitored by temperature indicator / calibrated temperature monitoring device.
17. There should be a system in place to control the reuse of temperature protection components (e.g. ice/water blankets, water/gel packs, phase change materials, insulated packaging, etc.) to ensure that incomplete components are not used in error.	➢ There should be procedure and associated records in place if cool packs are to be reused, in order to prevent the use of incompletely cooled packs, expired cool packs as well as physical segregation between frozen and cool packs.
18. Necessary precaution steps should be implemented when using dry ice during transportation in order to avoid a direct contact with the product and consequently	➢ No clarifying remarks.

caused coagulation of products.	
19. TTSP should be clearly labelled and identifiable from other products in the same delivery. In cases where TTSP are to be air freighted, the package(s) should be labelled according to the International Air Transport Association (IATA) regulations.	➢ To ensure that products are correctly and safely handled at all points in the supply chain.
20. Procedures must be implemented to handle the returned products and also the products that have been stored under out of the specified storage condition during the reception, storage and distribution of products.	➢ No clarifying remarks.
TRANSPORTATION	
21. TTSP should be transported under validated conditions to ensure that the relevant temperature range is maintained according to the directions on the label of the products. In addition, simulation studies can be conducted to validate the delivery conditions, taking into account the possibility of the worst situation.	➢ Any temperature excursions outside of the labeled storage conditions, for brief period, may be acceptable provided stability data and scientific/technical justification is available to ensure that product quality is not affected. ➢ To ensure that products can safely be transported within the temperature profile defined for each product and that compliance should be able to be demonstrated to authority and other interested parties. ➢ Validation reports for transportation should be available. ➢ Temperature monitoring devices or indicators should be used when appropriate (based on validation study done).
22. Refrigerated vehicles or containers to transport TTSP should be mapped and continuously monitored.	➢ Transportation of time and temperature sensitive products should be continuously monitored by calibrated temperature monitoring device.
23. Delivery route planning for TTSP should be created to prevent the risk of exposure to the products beyond the control of the ambient temperature. TTSP should be	➢ No clarifying remarks.

clearly identified from other items in the same distribution activities.	
24. Products labelled "Keep Frozen" should be transported in such a manner to ensure that it remains frozen.	➢ No clarifying remarks.

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