Codex for the Transportation of Medicinal Products in Austria

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Version 1: June 2007
Revision 1: October 2007
Revision 2: March 2009
Revision 3: June 2014

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Introduction

The following Codex constitutes a policy for the transportation of medicinal products by pharmaceutical operators (manufacturers/distributors/wholesalers) in accordance with the Medicinal Products Site Regulation (AMBO) as amended. The main focus of this document is on local transportation of finished medicinal products. This Codex does not govern any commercial aspects of transportation.

The Codex was prepared by members of PHAGO (formerly ARGE Pharmazeutika) and PHARMIG and applies to all transports coming within the scope of AMBO. In preparing this document, the Guidelines of 7 March 2013 on Good Distribution Practice of Medicinal Products for Human Use (GDP) were used as reference.

This version of the Codex Transportation has been completely revised so as to take due account of the experience gathered over the past few years in Austria in implementing European-level regulations.[1]

Pursuant to GDP, temperature conditions have to be maintained within acceptable limits during transport. A risk-based approach should be applied when planning transportation.

The required storage conditions for medicinal products should be maintained during transportation within the defined temperature limits as described by the manufacturers or on the outer packaging.

Compliance with these conditions to ensure the safety of medicinal products is a key requirement everybody involved in the supply chain has to meet.

As per AMBO, the means of transport and the transport packaging shall be qualified, and the transportation process shall be validated on the basis of quality risk management (QRM). The scope and depth of the validation and qualification shall be defined in QRM.

Given the diversity of ways to achieve the quality standards required under AMBO, this Codex has to be understood as a guidance for interpreting AMBO that has been harmonised with the respective authorities. It does, however, not relieve the persons responsible of the obligation to study AMBO in detail.

[1] In June 2007, industry experts and pharmaceutical wholesalers drew up the first version of the Codex Transportation with a view to offering support to entities active in the pharmaceutical distribution chain in regarding the transportation of medicinal products, which involves a variety of organisational measures and technical complexities, in line with the requirements set out in AMBO 2005 and AMBO 2009.

Following publication of the “Guidelines of 7 March 2013 on Good Distribution Practice of Medicinal Products for Human Use” in the Official Journal of the European Union (2013/C 68/01), the GDP now largely encompasses the same requirements on the European level as were already contained in the Austrian AMBO 2009.

Since the first introduction of the Codex Transportation, transportation of medicinal products in Austria has seen a major step forward in terms of quality. As for micro-logistics, a technical standard applicable to the vehicles being used has become established. Where necessary, palette shipments are transported using temperature-controlled box bodies or equivalent solutions. Improved active and passive cooling systems have been established for refrigerated shipments.

Whenever measures other than those described in this Codex are chosen, we urgently recommend to adequately document such measures.

The following areas will be described in more detail below:

1. Global risk assessment and definition of acceptability criteria
2. Procedure for the qualification of equipment and validation of transport processes
3. Quality review
4. Picking and handover of goods
5. Transportation of goods at room temperature / cold chain products
6. Duty to exercise due care when taking delivery
7. Vehicles
8. Personnel
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1. Global risk assessment and definition of acceptability criteria

AMBO stipulates that all pharmaceutical companies have to subject any processes relevant for quality, which includes transportation processes, to a risk analysis. The depth of validation and, consequently, the depth of qualification, depends on the risk inherent in the process in question.

In a general risk analysis on finished medicinal products, the following potential risks have to be taken into account above all others:

- Cross-contamination
- Harmful effects of temperature (e.g. direct sunlight, danger of frost)
- Humidity
- Improper handling (breakage, etc.)
- Misdirected items, improper transit storage over the weekend and on public holidays

When looking at probability in combination with potential consequences, the greatest risks are the ones posed by humidity and, in particular, by harmful effects of temperature. Consequently, these risks deserve the most attention. The handling of misdirected items or improper transit storage (e.g. on weekends/public holidays) should likewise be analysed primarily with a view to these risks.

When it comes to storing medicinal products, a general distinction is made between goods stored at room temperature and refrigerated goods. Storage facilities shall therefore be qualified for these temperature ranges. Pursuant to GDP, products have to be ‘maintained within acceptable limits during transport’. This wording takes into account that the distribution of medicinal products involves so many individual

process steps (loading, unloading, etc.) that it is impossible, when using qualified standard transportation systems at economically reasonable cost, to maintain the defined storage temperatures at all times and without any interruption throughout all stages of the transportation process.

For this reason, it is justified to define risk-based acceptability criteria for short-term interruptions (up to 12 hours) in local transportation.[2]

For transportation on the micro-logistics level in Austria, short-term deviations (up to 12 hours) in a temperature range of 2°C – 30°C are deemed acceptable for goods that have to be stored at room temperature. A risk assessment has to be carried out to establish that the impact of such short-term (up to 12 hours), transportation-induced deviations on stability and preservability is negligible in terms of the maximum admissible depletion of the active substance over the entire shelf-life of the products.[3]

Exceptions, such as products that have to be transported within mandatory temperature limits of 15°C to 25°C without any deviations, shall be labeled accordingly, and such special requirements shall be explicitly communicated to the carrier.

Refrigerated products with a mandatory storage temperature between 2°C and 8°C shall be subject to stricter acceptability criteria during transport, which implies that the relevant processes must be able to accommodate both passive and active cooling solutions. See Chapter 5.2.

It is an undisputed fact that, in our geographical region, transportation at room temperature conditions is not possible without technical aids, even if the acceptability range of 2°C - 30°C is applied. See Chapter 5.

In practice, it is recommendable to form risk clusters for defined product groups based on a risk assessment.

[2] The initial requirement put forward in the consultation on GDP of 15 July 2011 was as follows: “The required storage condition for medicinal products should be maintained during transportation within defined limits as described on the packaging information.” However, the final GDP guidelines of 7 March 2013 stipulate the following: “The required storage conditions for medicinal products should be maintained during transportation within the defined limits as described by the manufacturers or on the outer packaging.”

It is also stated that “the temperature conditions are maintained within acceptable limits during transport” and that a risk-based approach should be utilised to ensure that “medicines have not been exposed to conditions that may compromise their quality and integrity”.

On page 136, the WHO Technical Report contains the following definition: “Drug products that must be stored under defined conditions require appropriate storage instructions. Unless otherwise specifically stated (e.g. continuous maintenance of cold storage) deviation may be tolerated only during short-term interruptions, for example, during local transportation.“

[3] Cf. „Einfluss von Transporttemperaturen zwischen 2-30°C auf die Stabilität von Arzneimitteln“, Bernkop-Schnürch, 2014, http://www.phago.at/en/legal-framework/

2. Procedure for the qualification of equipment and validation of transport processes

In line with quality risk management (QRM), medicinal products shall be transported and stored in such a manner that no damage occurs during transport or storage. The means of transport and the transport packaging shall be qualified, and the transport process be validated on the basis of QRM (§ 30 paras 9 and 10 AMBO).

Transport processes shall be documented and categorised. The goal of qualification and validation is to provide proof that the defined temperature limits for the goods to be transported are observed under the given environmental and ambient conditions.

This involves the following steps:

- Define processes and equipment used (e.g. packaging)
- Define transport categories (e.g. delivery to urban or countryside destination, daytime or nighttime, season of the year)
- Define critical parameters
- Define parameter limit values and worst-case scenarios
- Define criteria according to which deviations will be accepted (acceptability criteria)
- Define the measurement method
- Define the measurement instruments
- Document the results
- Ensure reproducibility of results
- Establish documented standard operating procedures to ensure that the parameter limit values established upon qualification are complied with
- Periodically evaluate critical influencing factors and limit values

Measurements shall be taken using calibrated temperature loggers. If no calibration certificate is available for a logger or a temperature indicator built into the motor vehicle, these measurement devices shall be calibrated by comparison and documented at least once per year. Any temperature deviations as compared to calibrated temperature loggers shall be documented.

Proof shall be provided by measuring temperatures inside the transport container and/or packaging, and by adequately positioning the temperature logger in the cargo compartment, covering representative scenarios during qualification. Transport duration is defined as loading time, travel time, any relocation at the carrier’s transshipment points as well as unloading up to taking delivery by the customer/recipient (passing of risk).

Proof shall be provided and documented separately for each relevant configuration. In order to ensure reproducibility, all results shall be verified by several separate and independent measurements.

Standard operating procedures shall be drawn up on the basis of the data obtained from qualification and validation in order to ensure by organisational means that the defined parameters are actually complied with.

3. Quality review

Transport routes shall be periodically checked with a view to the defined transport categories. The evaluation of such check results shall be documented and stored. If a certain route cannot be assigned to any of the available categories, it shall be validated and documented separately.

It shall be checked at appropriate and defined intervals whether the proof for the underlying influence factors is still valid.

In addition, random checks shall be performed regularly to ensure that defined processes, defined temperature ranges and transport periods are adhered to. The results shall be documented.

Deviations from the defined temperature ranges shall be justified in line with the procedures described in the company quality assurance system and/or as part of the continuous improvement process, and appropriate countermeasures shall be taken where necessary.

The quality agreement concluded with the carrier shall include an obligation to provide information on any deviations.

Regular internal quality audits (self-inspections) during the year shall ensure that procedures and processes are actually complied with. Internal audits shall be recorded accordingly. The results and any possible subsequent measures will thus ensure a continuous improvement process.

4. Picking and handover of goods

The picking process is defined as including all activities from removing the goods from the storage rack to making them available for dispatch, including packaging.

If, in cases where the products are collected, handover does not take place at controlled room temperature, the consignor shall ensure that the goods remain within the defined temperature range until the defined passing of risk, and shall validate this process. Upon handover, the products shall be made available in a manner to ensure that the loading time will be as short as possible.

If a product cannot be transported within the acceptable temperature range of 2°C - 30°C, the consignor shall be obliged to inform the recipient. The qualified means of

transport appropriate for meeting the product-related temperature requirements shall be specified by mutual consent between consignor and recipient.

As stated in the preamble, this Codex does not govern any commercial aspects between the contracting parties.

Where the products are delivered, the period of time between picking and departure shall also be part of the validation process of the delivery agent.

If the goods are handed over to an Austrian pharmaceutical operator that is subject to the Medicinal Products Act and thus to AMBO, it can be assumed that it will carry out transportation in compliance with AMBO standards and is inspected by the Federal Agency for Safety in Health Care (BASG).

The responsibility to ensure that the transport complies with AMBO standards shall lie with the party commissioning such transport.

If transports are conducted with third party carriers, such transports shall likewise be subject to the QRM of the party commissioning the transfer, and the goods shall be handed over in accordance with the operator's individual SOPs (Standard Operating Procedures).

In the case of cold chain goods, special aspects need to be taken into account during picking and handover. See Chapter 5.2.

5. Transportation

5.1 Products requiring to be stored at room temperature

The transportation of medicinal products shall be validated as set out in Chapter 2, with the relevant equipment being qualified accordingly. For this reason, it is necessary to classify the individual transport processes and to define measures to ensure that the required temperature conditions can be met throughout the year and at different ambient temperatures so to comply with the acceptability criteria.

Such a specification shall also include activities such as loading and unloading as well as transshipment at transshipment points or intermediate storage facilities. Please note that, when relying on conventional conditions of transportation and, in particular, standard parcel services providers, compliance with the acceptability criteria cannot be guaranteed without adjustments to processes or without technical aids.

It is therefore recommended to resort to the acceptable limits of 2°C - 30°C only under defined conditions.

In the course of validation and qualification, either the transport service provider or in-house transport operations shall conduct temperature measurements in cargo

compartments and transshipment areas that are sufficiently representative in statistical terms. Measurement equipment shall be calibrated or calibrated by comparison. Evaluation of transport temperatures shall be documented for each means of transport and transshipment point.

Below is a non-exhaustive list of useful measures which are not mandatory, however, depending on the logistics available in each case:

- When taking delivery, the temperature of the cargo compartment should already have reached the required level so that the temperature can be maintained during a short loading period.

- Loading/unloading of the means of transport carrying the goods shall take place as quickly as possible. The cargo compartment shall not be open longer than absolutely necessary, especially in cases where there is no loading bay with lateral weather protection or strip curtains. This shall be specified and documented in writing in standard operating procedures.

- If, prior to loading, the cargo compartment does not feature the required temperature, hot/cold air shall be supplied in sufficient amounts and at sufficient speed.

- Goods shall not be stored out in the open, not even for a short time. This shall be specified and documented in writing in standard operating procedures. Where intermediate storage is necessary, the products shall not be sorted into or stored in stationary swap bodies that are exposed to ambient temperature without air conditioning.

- Transport vehicles shall have adequate insulation in the cargo compartment, shall not have any windows in the back, and shall have an active heating system as well as adequate active air conditioning, where this appears to be necessary based on the validation of delivery in terms of transport temperature (long delivery trips, etc.).

- During the trip, the current cargo compartment temperature shall be displayed to the driver on the dashboard. The sensors and their functioning shall be calibrated at least once a year through a reference measurement and be documented.

- A standard operating procedure shall be in place describing how compliance with the requirements is ensured. Random checks using loggers shall be carried out and documented. The carrier’s quality assurance system shall describe how regular monitoring is ensured.

- The duration of temporary storage at transshipment points shall be kept as short as possible. The temperatures specified shall be complied with also during transshipment.

Wholesalers largely deliver the transport boxes from a wholesale warehouse directly to the authorised buyer. This means that the products are not forwarded via several transshipment points and are therefore not exposed to changing climatic conditions.

Where sorting is necessary, the products shall not be sorted into stationary swap bodies that are exposed to ambient temperature without air conditioning.

Under AMBO, pharmaceutical wholesalers are obliged to set up a quality assurance system so that distribution will take place in accordance with unchanging quality standards, ensuring that the quality and integrity of the medicinal products have not been compromised during transport and storage.

Carriers shall likewise set up a quality assurance system for the activities conferred upon them. This especially includes the following:

- Product/transport unit labeling must not be lost.
- No contamination of or by other products or materials may occur.
- Adequate precautions must be taken against leakage, damage or theft.
- A preventive pest control programme should be in place to afford protection against the entry of insects, rodents or other animals.
- The cleaning of means of transport and transshipment areas must be documented.
- Goods must be protected against unauthorised access.

All employees involved in the transportation of pharmaceutical products shall be instructed as to the specifics of the transportation of medicinal products and the transportation of hazardous goods. Such training shall be documented in writing. In this context, please note the details set out in Chapter 10.

The transport company and the drivers shall be familiar with the classes of goods and/or the goods to be transported. Loading shall be permitted only with the consent of an authorised and trained person.

Pursuant to AMBO, training documents, quality assurance documents and any other documentation shall be stored for five years.

The following shall be recorded, legibly, on the shipping documents:

- Time of pickup
- Time of delivery at recipient
- License plate of vehicle
- Name of driver for pickup and delivery

Other types of logistics arrangements shall be separately agreed upon between consignor and recipient and shall be qualified and validated as well as documented.

It must be ensured that the products are transported in suitable shipment containers or transport packaging during shipping which provide adequate protection against mechanical forces during transportation and transshipment.

For each trip, the transport service provider shall document the following:

- Trip (designation, number or the like for identification)
- Date of the trip
- Time of pickup and handover of the goods
- Driver
- Vehicle license plate
- Unloading/loading places

This documentation must be archived accordingly.

In order to minimise potential risks during transport, an easy-to-understand manual should be available in the vehicle, describing what to do in cases of technical defects, accidents, absence of recipient, breakage of goods, etc. and offering the driver a standardised course of action, based on a risk analysis of the delivery process.

5.2 Cold chain products

This Chapter details the logistics required for products that have to be kept refrigerated, i.e. at a temperature between 2°C – 8°C, during transport and storage.

Apart from the narrower temperature range, the same requirements for transportation apply as for products stored at room temperature.

If the products are picked and packed at standard storage temperatures (15°C – 25°C), these processes have to take place immediately after their removal from the refrigeration area.

If passive cooling, i.e. special transport containers and cool packs, is used for transportation, the consignor shall provide proof that, given defined ambient conditions, the packaging used ensures that the temperature in the refrigeration container neither exceeds nor falls below the required temperature range during the time of transport.

As to qualifying refrigeration containers, it may be assumed that, in Austria, as a rule no more than 26 hours (24 hours for transport + 2 hours for taking delivery by the recipient) will pass between dispatch and receipt of goods and that the ambient temperature for qualification will be between 2°C – 30°C.

Compliance with the maximum time limit of two hours for taking the products into storage shall be ensured by the recipient by means of standard operating procedures.

Where products are delivered in a temperature-controlled vehicle without separate refrigerated transport packaging and within a temperature range of 2°C – 8°C, the recipient shall be given the time needed to take delivery of the goods as quickly as

possible in compliance with quality assurance rules, to check them for completeness and finally take them to the designated storage spaces (refrigerated warehouse).

In the shipping documents, cold chain goods shall be labelled as such so that the recipient will be able to immediately take the necessary steps when taking delivery. Pallets or transport units with cold chain goods shall be clearly and conspicuously labelled.

Weekends and public holidays shall be given special consideration when it comes to organ sing cold chain transportation.

6. Duty to exercise due care when taking delivery

In general, it is the party commissioning the transport that shall be responsible for choosing a suitable transport method. Such transport shall comply with the basis for the qualification of packaging and the validation of the transport temperature range. In exercising due care, the recipient shall be obliged to notify the party commissioning the transport of any obvious deviations from the transport conditions.

When taking delivery it needs to be controlled that the arriving consignment is correct, that the medicinal products originate from authorised suppliers and that they have not been visibly damaged during transport.

7. Vehicles

Pursuant to GDP, dedicated vehicles should be used, where possible, for transporting medicinal products. Should this be impossible, there must be procedures in place to ensure that the quality of the medicinal products is not compromised.

It is recommended to conduct risk analyses for this purpose and then define adequate procedures based on the results.

Procedures for vehicle operation shall be in place that also address cleaning and safety precautions.

8. Personnel

Well-trained personnel is an important quality factor in the pharmaceutical business. By extension, this also applies to the personnel of subcontractors or transport companies.

Each and every employee shall be made aware that he or she is personally responsible for being familiar with, and adhering to, standard operating procedures and applicable rules and regulations. Regardless of who caused them, employees shall document deviations, defects or other observed shortcomings and report them to their supervisors (e.g. remark in a blank field on the transport list / trip list, report to the transport manager).

The pharmaceutical trade and the companies commissioned for transportation shall therefore use only trained personnel for deliveries. The only exception shall be emergency shipments for defined medicinal products.

During a transport, drivers must be contactable by telephone and be able to inform their supervisors immediately about any problems or deviations.

9. Hygiene

Vehicles shall be kept clean and tidy. A cleaning plan setting out mandatory cleaning intervals shall be available.

Reusable transport containers shall also be cleaned at regular intervals.

This fact shall be documented accordingly in a cleaning list available for each and every vehicle. The use of suitable cleaning agents shall be ensured.

Natural wear and cosmetic defects shall be acceptable, however.

10. Training on transport matters

Below is a list of key areas where standardised training is to be provided.

The training programmes shall be designed so as to take account of specific in-house conditions. Training shall be provided once when an employee starts working for a company and subsequently at annual intervals.

Training documentation shall be stored for a period of five years.

Participants shall be provided with hard-copy documents on the training programmes.

Participation in training programmes shall be confirmed by the participating employee (‘I have read, I have understood, I will follow the instructions’)

Key areas for training:

- General instructions

- Loading
- Temperature
- Deviations
- Handover

10.1 General instructions

10.1.1 Product information:

General instructions on hazards and precautionary measures when dealing with medicinal products, and special transportation conditions for specific products.

10.1.2 How to proceed when transporting medicinal products:

General instructions on how to proceed when transporting medicinal products. This comprises, for example, handling medicinal products in such a way as to avoid damage and adverse effects, precautionary measures for unforeseen occurrences with medicinal products, etc.

10.1.3 Vehicle security:

Measures to protect products against unauthorised access during loading and unloading and during transport.

10.1.4 Hygiene:

Issues to be addressed include the cleaning of the vehicle, the cargo compartment, cleaning intervals and the methods and procedures used.

10.2 Loading

10.2.1 Loading:

Instructions for loading in areas protected from the weather and not accessible to the public.

10.2.2 Securing of loads:

Properly securing loads is an important factor in avoiding damage to products. It is just as important for the safety of the carrier and other road users. Hazardous goods, in particular, must be properly secured.

10.3 Temperature

10.3.1 Temperature range:

It has to be ensured that the acceptability range defined in validation is adhered to. Responsibility for compliance lies with the carrier. Where transports are outsourced or taken over, the provisions of Part 8 AMBO (Operations performed under contract) must be complied with.

10.3.2 Cold chain products:

Special handling steps required for transporting cold chain products need to be specified.

10.4 Deviations

10.4.1 Flow of information:

It needs to be specified who is to be informed of deviations and who is to document deviations and in what manner so to ensure that they can be analyzed at a later stage.

10.4.2 How to proceed in case of disruptions to climate control:

Drivers have to be trained so that, in the event of a disruption to climate control, they know what to do and what measures to take to re-establish the required temperature range as quickly as possible.

10.4.3 How to proceed in case of traffic congestion or accident:

Includes precautionary measures, safeguards, onward transport, etc.

10.5 Handover

The address stated on the delivery note must coincide with the delivery address stated on the labels or on the trip list. The products must not be delivered to any address other than the one stated on the labels or trip list.

11. Returned goods

All Parts of this Codex shall apply mutatis mutandis to returned goods.

12. List of abbreviations

AMBO	Medicinal Products Site Regulation
BASG	Federal Agency for Safety in Health Care
GDP	Good Distribution Practice
QMS	Quality Management System
QRM	Quality Risk Management
QA	Quality Assurance
SOP	Standard Operation Procedure
WHO	World Health Organization