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What is the point of "heating" medicinal products to 15–25 °C?

A case study challenging conventional limits

Excerpt from the GMP Compliance Adviser Chapter 16.F and the GMP Series e-book Storage of Medicinal Products

by Christoph Frick, PhD

There is no legal, ecological or pharmaceutical reason why a preparation should be heated from 12 °C (the outside temperature), for example, to a constant temperature of 20 °C (i.e. the mean of 15–25 °C) and stored at this temperature. This is not required to ensure the quality or safety of the medicinal product. It is a waste of time and energy and the environment is unnecessarily burdened.

If a preparation has proven stable for 3 years at 25°C in accordance with ICH Q1A(R2), it will also be stable at lower temperatures such as 15, 12 or 10 °C. This results from the scientific fact that the degradation of active ingredients and excipients is slower at these temperatures than at 25 °C. These are known aspects of chemical reaction kinetics, which can be calculated using the Van't Hoff equation or the Arrhenius equation.

There is therefore no reason at this point to retain the random lower temperature limit of 15 °C: 2–25 °C in accordance with the WHO-GSP is acceptable and should be used as long as nothing else is specified. There is no plausible reason for "heating" medicinal products to a temperature in the 15–25 °C range during storage or transportation.

However, a risk analysis should be carried out to question whether there are reasons that justify or necessitate storage at 15–25 °C and whether reducing the lower temperature to below 15 °C would represent an unacceptable risk.

Risk assessment: What are the risks of storage at xx°C–25°C instead of 15–25°C?

The expression "xx °C" refers to a temperature in degrees Celsius below 15 °C to be determined during the risk analysis.

Products with the storage statement "Do not refrigerate or freeze"

In the interests of protection and safety, the secondary packaging of preparations that are sensitive to refrigeration are labelled "Do not refrigerate or freeze", i.e. these products may not be stored at 2–8 °C. Even though the effects of exposure to a cold-storage temperature are reversible in many of these preparations, this can result in the

quality of the product being negatively affected. One way of reducing this risk is to use a lower temperature limit of 9 °C instead of 15 °C. 9 °C guarantees a significant distance to the critical cold-storage temperature of 8 °C. If preparations that are sensitive to refrigeration were stored at a temperature between 9 °C and 25 °C, they would be protected against storage temperatures that are too low (2–8 °C). A warning limit of 10 °C can be used as an additional safety measure.

Temperature mapping/monitoring is carried out to monitor and document the constant and uniform temperature in the different storage areas.

Products with the storage statement "Store at 15–25 °C"

There are already medicinal products on the German market that contain the storage statement "Store at 15–25 °C" or "Store at 15–30 °C" on their outer packaging. This also applies to more and more preparations in Belgium and Austria. Based on the comments above, there is no plausible reason for using this type of labelling. In fact, a preparation that is stable when stored at 15 °C remains stable when stored at 12 °C or 11 °C, for example, and the quality is not impacted.

For the purpose of this case study, 16 therapeutically identical medicinal products and 3 medical devices were identified and examined whose primary packaging is identical but has different storage statements in different EU states.

All of the data available for the selected medicinal products underwent a comparative examination. The storage statements in the various countries, information about the manufacturers in the respective countries and the composition of the excipients were included in the documentation. Pharmaceutical aspects were also discussed.

The result of the evaluation of the data contained in the table was as follows:

- 10 of the 16 preparations are identical, i.e. they have identical compositions and identical manufacturers. The specification of different storage conditions is therefore incomprehensible. The 15–25 °C requirement is not plausible and cannot be inferred from pharmaceutical requirements.
- The remaining preparations are identical products that were manufactured by

different companies within the EU. This is however not deemed to be a justification for different storage statements.

Conclusion and outlook

The temperature range of 15–25 °C that has established itself in recent years for the storage of standard medicinal products cannot be inferred from the regulations nor is it required for ensuring the pharmaceutical quality of products.

The reduction of the lower temperature limit from 15 °C to 9 °C (warning limit of 10 °C) makes pharmaceutical and economic sense and does not contradict the regulatory specifications. The quality and safety of the medicinal product is also ensured in this temperature range. Storage at 9–25 °C saves energy and resources and helps protect the environment. The positive effects outlined here have an even stronger impact in free-standing warehouses.

Transportation is mobile storage, therefore a new way of thinking is also required with regard to the transportation of medicinal products. A temperature range of 9–25 °C should be seen as an improved alternative to the current 15–25 °C. Air-conditioning aggregates in motor vehicles can be left off for longer periods of time, reducing the cost of logistics and avoiding unnecessary environmental damage.

It should also be considered whether a temperature range of 2–25 °C should be defined for transportation as it can be taken for granted that a brief exposure to lower temperatures will not affect the quality of products even if they are sensitive to refrigeration. The "Codex for the Transportation of Medicinal Products in Austria" already confirms this idea.

> "For transportation on the micro-logistics level in Austria, short-term deviations (up to 12 hours) in a temperature range of 2–30 °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."
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> Extract from the Codex for the Transportation of Medicinal Products in Austria, 2014, Chapter 1

Source:

This text is a shortened excerpt from the GMP Compliance Adviser Chapter 16.F and the GMP Series e-book Storage of Medicinal Products. Here you will find the complete case study, including all data and results.

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E-Book

Storage of Medicinal Products

This pharma guide explains the current regulatory requirements for storage of medicinal products and describes their implementation in practice. You will learn which requirements the premises must meet and how you can ensure the required storage conditions.

A detailed case study provides risk-based concepts for storage at room temperature and challenges conventional limits.

The e-book also addresses:

- Storage organisation, areas and conditions
- Incoming goods
- Standard storage at 15–25 °C?

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