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Actual versus recommended storage temperatures of oral anticancer medicines at patients' homes

ND Vlieland[1], BJF van den Bemt[2,3,4], DA van Riet-Nales[5], ML Bouvy[6], ACG Egberts[1,6] and H Gardarsdottir[1,6]

Abstract

Background: Substantial quantities of unused medicines are returned by patients to the pharmacy each year. Redispensing these medicines would reduce medicinal waste and health care costs. However, it is not known if medicines are stored by patients as recommended in the product label. Inadequate storage may negatively affect the medicine and reduce clinical efficacy whilst increasing the risk for side effects.

Objective: To investigate the proportion of patients storing oral anticancer medicines according to the temperature instructions in the product label.

Methods: Consenting adult patients from six Dutch outpatient hospital pharmacies were included in this study if they used an oral anticancer medicine during February 2014 – January 2015. Home storage temperatures were assessed by inclusion of a temperature logger in the original cancer medicines packaging. The primary outcome was the proportion of patients storing oral anticancer medicines as specified in the Summary of Product Characteristics, either by recalculating the observed temperature fluctuations to a single mean kinetic temperature or by following the temperature instructions taking into account a consecutive 24-h tolerance period.

Results: Ninety (81.1%) of the 111 included patients (47.8% female, mean age 65.2 (SD: 11.1)) returned their temperature loggers to the pharmacy. None of the patients stored oral anticancer medicines at a mean kinetic temperature above 25°C, one patient stored a medicine requiring storage below 25°C longer than 24 h above 25°C. None of the patients using medicines requiring storage below 30°C kept their medicine above 30°C for a consecutive period of 24 h or longer.

Conclusion: The majority of patients using oral anticancer medicines store their medicines according to the temperature requirements on the product label claim. Based on our results, most oral anticancer medicines will not be negatively affected by temperature conditions at patients' homes for a maximum of three months and are likely to be suitable for redispensing.

Keywords

Oral anticancer drugs, home storage conditions, temperature, redispensing

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[1]Department of Clinical Pharmacy, Division of Laboratory and Pharmacy, University Medical Center Utrecht, Utrecht, the Netherlands
[2]Department of Pharmacy, Sint Maartenskliniek, Nijmegen, the Netherlands
[3]Department of Pharmacy, Radboud Medical Center, Nijmegen, the Netherlands
[4]Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Center, Maastricht, the Netherlands
[5]Quality Department, Medicines Evaluation Board, Utrecht, the Netherlands
[6]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands

Corresponding author:
H Gardarsdottir, Department of Clinical Pharmacy, Division of Laboratory and Pharmacy, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, the Netherlands.
Email: H.Gardarsdottir@umcutrecht.nl

Introduction

The increased availability of anticancer medicines allowing for oral administration to treat different types of cancer puts a growing burden on national health care budgets. The costs of oral anticancer medicines were estimated at 173 million Euros in 2015 in the Netherlands, which is approximately one fourth of total expenditure on anticancer medicines.[1] To make better use of current health resources, several suggestions have been made to minimize medicine waste leading to reduced costs and contributing to a sustainable health care for patients with cancer. These include prescribing smaller quantities[2] and redispensing unused medicines.[3] However, for the latter, the quality of medicines needs to be guaranteed and the storage conditions at patients' homes remain a concern. Inadequate storage may negatively affect the medicine and reduce clinical efficacy whilst increasing the risk for side effects.

Some oral anticancer medicines should be dispensed in their original packaging to keep them protected from light and moisture, and require temperature conditions below 25°C or 30°C. Storage claims are defined by the drug companies and based on standardized drug stability test conditions that are outlined in the Q1A International Conference on Harmonisation (ICH) guideline for new drug products.[4] Stability test conditions established by the ICH for climate zone I and II (all European countries) are based on ambient temperature and relative humidity measurements performed in the 1980s.[5,6] Stability indicating parameters include appearance, assay (potency), impurities, water content, dissolution, particle size and/or other parameters that may be required by the authorities. Stability tests are normally performed at long term, intermediate and accelerated conditions (Table 1). At the time of submission to the regulatory authorities, medicines which fulfil all criteria when tested at long-term and accelerated conditions receive no special storage conditions towards temperature. If a medicine fails to meet the specification after six months accelerated testing, it should be tested at intermediate conditions (30°C/65%RH) as well. When test outcomes at intermediate and accelerated conditions are out of specification, the corresponding storage claims will be to store below 25°C.[7] All product label storage claims should be described in the European Summary of Product Characteristics (SmPC) or United States Product Insert and correspond with the product labels informing distributors, pharmacies, and patients about the required storage conditions.

Table 1. Stability studies and storage conditions for new and existing drug products. (4,12)

Stability study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH[a]	6[b]/12 months
Intermediate	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

RH: relative humidity.
[a]The drug company decides whether long-term studies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.
[b]For existing active substances and related finished products.

Few studies have investigated home storage conditions of medicines. Two studies suggest that medicines are often not adequately stored at home,[8,9] but the studies did not investigate storage temperatures of specific medicines at home over a longer period of time or the influence of ambient temperature. In this study, we investigate the proportion of patients storing oral anticancer medicines according to the temperature instruction in the product label. Furthermore, we investigate the influence of the ambient temperature on the actual storage temperature of oral oncolytics in patient homes.

Methods

Setting and study population

This multicenter observational study was conducted in six outpatient pharmacies in the Netherlands between February 2014 and January 2015. Adult patients (≥18 years) were eligible for inclusion if they were receiving one of the following oral anticancer medicines: imatinib, gefitinib, erlotinib, sunitinib, sorafenib, dasatinib, lapatinib, nilotinib, pazopanib, vandetanib, dabrafenib, everolimus, axitinib, vemurafenib, abiraterone, enzalutamide, and lenalidomide. Patients with obvious cognitive impairments and non-Dutch-speaking patients were excluded. Eligible patients received both written and oral information and were asked for a written informed consent. The study protocol was reviewed and approved by the Medical Ethics Review Board of the University Medical Center Utrecht (protocol reference number 14-628/C).

Study procedure

Patients received their oral anticancer medicine in the original company's primary (e.g. bottles, blisters) and secondary (e.g. cardboard boxes) packaging including a Safe-Rx temperature logger, which was attached to the outer packaging and put in a closed polyethylene seal bag. The Safe-Rx temperature logger is a small

(18 mm × 32 mm × 2 mm) temperature measurement device that has been validated according to international standards.[10] The logger was activated upon medicine dispense and device settings were adjusted to have a temperature measurement every 2 min. Patients received standard instructions on adequate storage upon dispensing by the pharmacy's personnel. No extra information was given to those participating in the study. Patients were asked to keep the temperature logger and package in the seal bag and to return the temperature logger(s) when the dispensed medicine had been used. In case the temperature loggers were not returned within four months, a reminder was sent by post including a pre-stamped envelope to return the temperature logger(s). If needed, second and third reminders were given by telephone.

Outcomes

The primary outcome was the proportion of patients storing oral anticancer medicines as specified in the SmPC within the storage tolerances as specified below. We investigated if oral anticancer medicines were stored in accordance with the conditions specified in the SmPC and were not exposed to a mean kinetic temperature (MKT) above 25°C (sorafenib and everolimus) or above 30°C (imatinib, lapatinib, nilotinib, vandetanib and abiraterone). The MKT is described in the ICH Q1A guideline as follows:

> A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period.[4]

The MKT was calculated for each patient and package over the complete storage period and is generally higher than the mean temperature and takes into account temperature variations and their influence on the medicine based on the Arrhenius equation. Furthermore, we investigated if medicines were stored above 25°C or 30°C for a consecutive period of at least 24 h.[11,12] Other oral anticancer medicines (gefitinib, erlotinib, sunitinib, dasatinib, pazopanib, dabrafenib, enzalutamide, lenalidomide, vemurafenib and axitinib) do not require special temperature storage conditions. We investigated whether oral anticancer medicines in this group were stored at an MKT above 40°C or temperatures that exceeded 40°C for at least 24 h. The maximum storage temperature of 40°C was based on accelerated stability test conditions medicines were exposed to.[4] Information on storage temperature requirements were retrieved from the SmPC of each medicine (consulted on 19 October 2015).[13] We also set the maximum storage period at three months, which corresponds with the maximum dispensing period in the Netherlands. Secondary outcomes were defined as the total storage time for all patients of oral anticancer medicines according to the product label and the relation between storage temperatures and ambient temperature values obtained from hourly measurements from the Royal Netherlands Meteorological Institute in De Bilt, the Netherlands.[14]

Data analysis

Demographic data were presented using descriptive statistics. Characteristics (gender and age) of patients lost to follow-up were compared with patient characteristics of those who returned temperature loggers to the pharmacies using *t* test for normally distributed continuous variables and Pearson chi-square test for differences in proportions. A two-sided p value less than 0.05 was considered to indicate a significant difference. The proportion of storage time at or above 25°C or at or above 30°C and the proportion of patients that stored oral anticancer medicines according to the product label were calculated. The mean and 97.5 percentile of daily storage temperatures and mean daily ambient temperatures were calculated and plotted in a line chart. Hourly storage and ambient temperature data were used to visualize individual patient data. The effect of ambient temperatures on daily storage temperatures was investigated in spring (1 March 2014–31 May 2014), summer (1 June 2014–31 August 2014), autumn (1 September 2014–30 November 2014) and winter (1 December 2014–31 January 2015) and analyzed following a linear mixed effects model. All calculations were made with the statistical package from SAS version 9.2.

Results

Study population

A total of 111 patients were included in the study of which 81.1% (n = 90) returned their temperature loggers to the pharmacy. 'Temperature logger lost or discarded' (n = 3) and 'patient deceased' (n = 4) were reasons for not returning the temperature logger to the pharmacy. Fourteen patients did not respond after the third reminder to return their temperature logger and were considered lost to follow-up. Of our study population, 47.8% (n = 43) was female and the mean age was 65.2 (SD: 11.1) years (Table 2). Male patients were more likely not to return the temperature logger to the pharmacy ($p < 0.001$). Most patients who returned the temperature loggers received imatinib (20.0%) followed by everolimus (13.3%) and

nilotinib (11.1%). Thirteen patients (14.5%) used oral anticancer medicines that required storage below 25°C, 37 patients (41.1%) used products that required storage below 30°C and 40 patients (44.4%) used products that required no special temperature conditions. The mean total measured storage time per patient was 64.0 days (SD: 25.3).

Table 2. Patient characteristics (N = 111).

	Patients included in analysis (N = 90)		Patients lost to Follow-up (N = 21)	
Age (mean, SD)	65.2 (11.1)		65.1 (13.5)	
Gender	N	%	N	%
Female	43	47.8	6	28.6[a]
Type of oral anticancer medicine				
Everolimus	12	13.3	3	14.3
Sorafenib	1	1.1	1	4.8
Abiraterone	9	10.0	2	9.5
Imatinib	18	20.0	2	9.5
Nilotinib	10	11.1	0	0.0
Axitinib	0	0.0	1	4.8
Dabrafenib	1	1.1	0	0.0
Dasatinib	6	6.7	1	4.8
Enzalutamide	3	3.3	3	14.3
Erlotinib	2	2.2	0	0.0
Gefitinib	3	3.3	2	9.5
Lenalidomide	7	7.8	3	14.3
Pazopanib	4	4.4	1	4.8
Sunitinib	8	8.9	1	4.8
Vemurafenib	6	6.7	1	4.8

[a] $p < 0.001$

Primary outcome

Eighty-nine patients (98.9%) met the criteria of the primary endpoint and stored their oral anticancer medicines according to the storage temperature defined in the SmPC (Table 3). One patient stored a medicine that requires storage below 25°C for a consecutive period longer than 24 h above 25°C. None of the patients stored their medicine at an MKT above 25°C or above 30°C and most medicines were stored between 15°C and 25°C. None of the patients using medicines requiring storage below 30°C kept their medication above 30°C for a consecutive period of 24 h or longer.

Secondary outcomes

The proportion of measured storage time per temperature for patients using oral anticancer medicines that require storage below 25°C (Figure 1(a)), below 30°C (Figure 1(b)) and those that require no special storage temperature conditions (Figure 1(c)) are presented in Figure 1(a) to (c). The proportion of total storage time below 25°C (Figure 1(a)) for patients using oral anticancer medicines that require storage below 25°C (sorafenib, everolimus) was 642.0 days (71.3%). For patients using oral anticancer medicines that require storage below 30°C (Figure 1(b)), the proportion of storage time below 30°C was 1143.3 days (93.4%). There was no storage time above 40°C for patients using oral anticancer medicines that required no special temperature conditions (Figure 1(c)). Mean storage temperatures per day based on all patient measurements are presented in Figure 2 and ranged from 17.4°C (SD: 0.56) on 20 February, 2014 to 25.6°C (SD: 1.59) on 20 July 2014. Mean daily storage temperature in patients using oral anticancer medicines that require storage below 25°C, below 30°C or no special temperature storage conditions were 20.6°C (SD: 4.1), 20.7°C (SD: 3.0) and 21.6°C (SD: 3.1),

Table 3. Compliance to drug storage temperature criteria for oral anticancer medicines.

	Sorafenib, everolimus (T = 25)	Imatinib/lapatinib/nilotinib/ vandetanib/abiraterone (T = 30)	Gefitinib/erlotinib/sunitinib/ dasatinib/pazopanib/dabrafenib/ enzalutamide/lenalidomide/ vemurafenib/axitinib (T = 40)
Patients, n(%)	13 (14.4)	37 (41.1)	40 (44.5)
Patients with at least one package where MKT ≥ T	0 (0.0)	0 (0.0)	0 (0.0)
Patient with at least on package where storage temperature were 24 h or longer ≥ T	1 (7.7)	0 (0.0)	0 (0.0)

MKT: mean kinetic temperature.

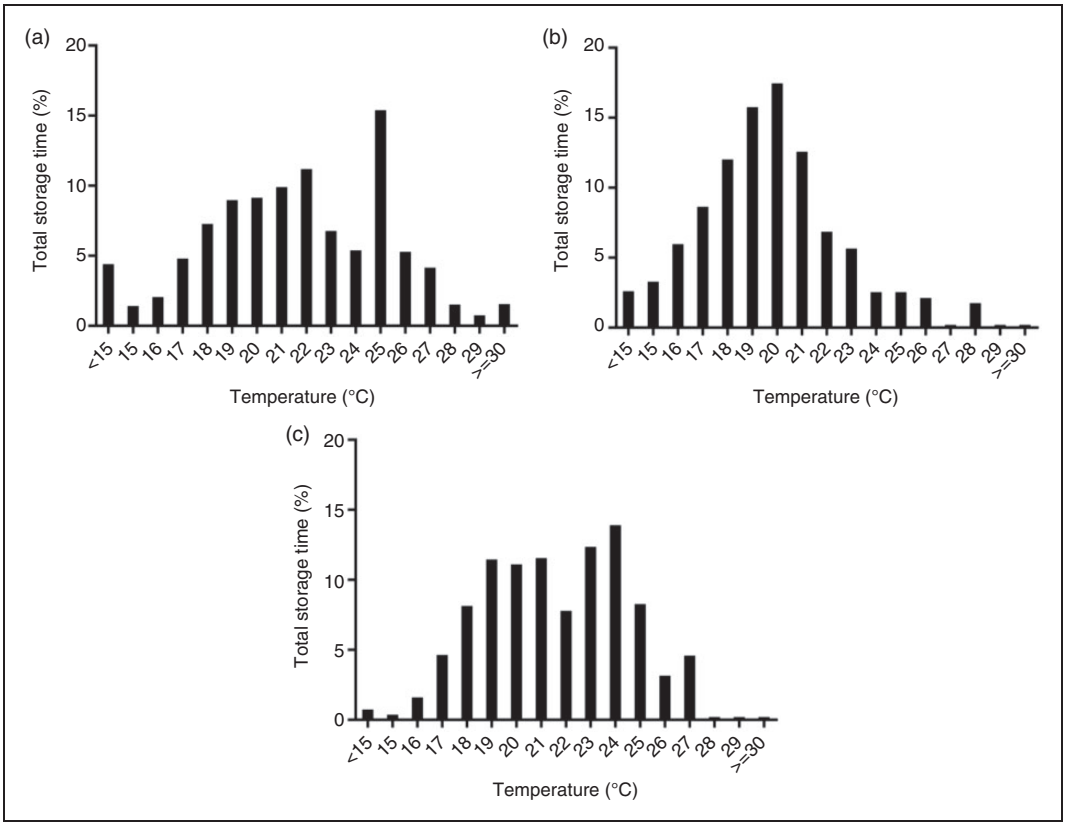

Figure 1. (a) proportion of total storage time per temperature for oral anticancer medicines requiring storage below 25°C, (b) proportion of total storage time per temperature for oral anticancer medicines requiring storage below 30°C and (c) proportion of total storage time per temperature for oral anticancer medicines requiring no special temperature conditions.

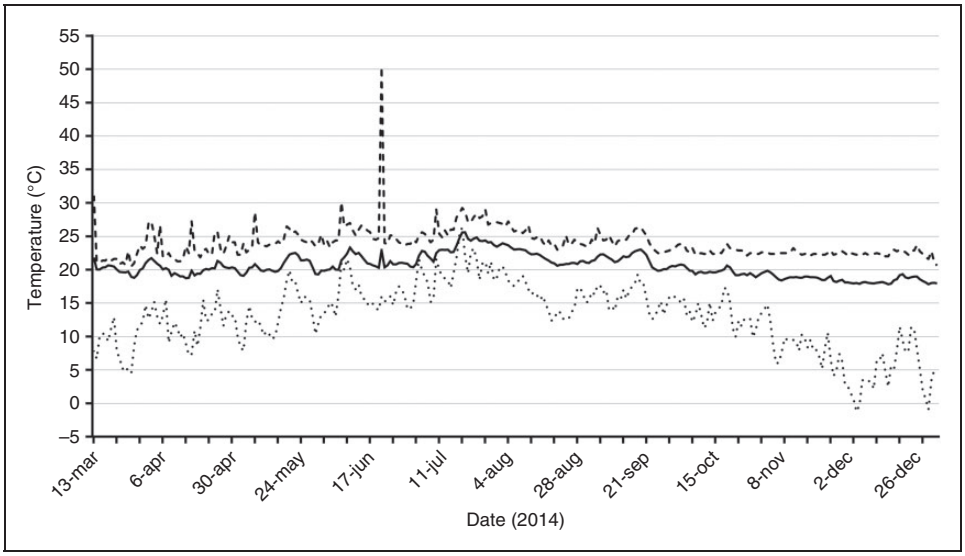

Figure 2. Daily mean (solid line) and 97.5th percentile (dashed line) of storage temperatures from all patients versus daily mean ambient temperatures (dotted line) from 13 March 2014 until 31 January 2015.

respectively. Maximum and minimum storage temperatures of 58.0°C (21 June 2014) and 1.9°C (19 January 2015) were measured. In summer months, an increase of 1°C ambient temperature resulted in an increase of 0.30°C storage temperature. This effect was less in the spring (increase of 0.20°C/1°C ambient temperature), autumn (increase of 0.20°C/1°C ambient temperature) and winter (increase of 0.06°C/1°C ambient temperature) period.

Discussion

The majority of patients using oral anticancer medicines store their medicines according to temperature conditions stated on the product label. Most oral anticancer medicines are, therefore, likely to be suitable for redispensing if returned unused to the pharmacy, although for some oral anticancer medicines sensitive to humidity and light, these storage conditions should also be assessed. In the Netherlands, a relationship between actual storage temperature at patient' homes and ambient temperature has been identified, which is the most significant during summer.

Our temperature measurements are in line with what Hewson et al.[15] reported on home storage conditions in New Zealand (climate zone I/II) which showed mean storage temperatures from 18.4°C to 23.6°C with maximum storage temperatures above 25°C. Oral anticancer medicines may be stored at temperatures above 25°C in daily practice, but it is unclear if excursions up to several days above 25°C will affect medicine quality. ICH stability test requirements for authorization of new medicines and existing active substances and their related medicines are based on the MKT, and were investigated by Wolfgang Grimm in 1985 and 1986.[5,6] As the MKT value expresses the cumulative thermal stress, it is assumed that temperature excursions (up to 40°C) above 25°C or 30°C induce no significant changes in the medicines' chemical stability.[16] None of the medicines we investigated were stored at MKTs above 25°C, which makes it unlikely that significant chemical degradation of the medicines occurred in our study. For climate zone I in Europe (the Netherlands, Amsterdam), an MKT of 19.3°C and mean temperature of the four hottest months of 20.6°C were measured.[6] These temperatures are slightly lower than mean storage temperatures that we measured in our study (20.6°C–21.6°C). In comparison with the Netherlands, storage conditions in patient homes in climate zone II southern European countries such as Greece and Italy (where mean ambient temperatures in the hottest four months are over 30°C) are likely to be higher and might result in more frequent and longer periods of storage time above 25°C.[5,6] Furthermore, if patients travel to countries classified as climate zone III or IV, such as India, Israel or Brazil, storage claims based on climate zones I/II stability tests do not longer apply. It is considered that product stability testing in climate zone III and IV would require at least 12 months 30°C/65%RH (long-term conditions) and 6 months 40°C/75%RH (accelerated conditions).[17,18] Patients are often not aware of different climate zones and might risk medicine exposure to high temperatures at a specific place at home (e.g. near the heating or window) or abroad.

According to the Public Assessment Report (PAR) documentation, all oral anticancer medicines in our study were tested, according to the ICH Q1A guideline for new medicines, at 25°C/60%RH or 30°C/65%RH long-term/intermediate conditions and at accelerated conditions 40°C/75%RH. The majority of oral anticancer medicines in our study were stable within product specifications at long-term and accelerated conditions. The documentation for two oral anticancer medicines that require storage below 25°C – everolimus and sorafenib – describe a slight increase in impurities at accelerated test conditions.[19,20] No information is available in the PAR documentation about the possible consequences of inadequate storage.

Unused medicines are returned to pharmacies every day.[21] The possibility of redispensing expensive unused medicines has been discussed in the Netherlands to reduce health care costs and the ambition to create a more sustainable pharmaceutical supply chain.[3] This study investigated important requirements for redispensing and identified medicine quality as one of the main concerns and temperature monitoring as a critical quality parameter. The majority of patients in our study stored oral anticancer medicines according to the storage temperature on the product label. Most medicines were stored at MKTs below 25°C or 30°C and without spikes of 24 h or longer above the defined tolerances. Only for the patients using medicines that require storage below 25°C, storage temperatures are often above 25°C for shorter periods less than 24 h. Although the quality of most oral anticancer medicines can be guaranteed by measuring storage temperatures at home, other storage requirements, such as the ability and willingness of patients keeping the medicine in the original container to protect against moisture and light if stated in the product label are needed to guarantee the medicine quality. If implementing a redispensing system, it should be legally possible, cost beneficial, patients should be willing to participate and accept medicines that have been stored, quality should be assured and there should be clear guidelines (e.g. party responsible for quality of redispensed medicines).[3]

As far as we know, this is the first study that measures home storage temperatures of oral anticancer medicines. Although our sample size was small and

there were only six outpatient pharmacies that recruited patients in the study, this study suggests that a large majority of patients store oral anticancer medicines according to recommended storage temperatures. The moment of medicine administration by the patient was unknown and some patients may have started weeks later after the dispensing date or left some of the medicines unused. Therefore, we do not know the exact period of time oral anticancer medicines were exposed to the temperatures measured. We minimized the possible time temperature loggers were not measuring temperature storage data by having a maximum measurement period of three months. By setting the measurement period at three months according to the maximum prescription period, we could have excluded actual storage time. In addition, patients were aware of the study and might have changed their storage practices and locations before starting the measurement period, which might have resulted in an overestimation of the number of patients that store medicines according to the recommended storage temperature on the product label. Ambient temperature measurements were performed at one location only, whereas patients on locations elsewhere might have been exposed to different ambient temperatures which could have influenced the relation between storage temperatures and ambient temperatures. Our results are restricted to climate zone I and II countries, as countries in other climate zones require other test conditions and storage conditions for medicines. Finally, no measurements were performed to assess the relative humidity or light exposure at patient homes. Most oral anticancer medicines are, according to the SmPC, not sensitive to light or moisture and if they are, packages should protect medicines from light exposure and moisture. However, for some oral anticancer medicines that are sensitive to moisture and light, these conditions should be assessed.

Conclusion

The majority of patients using oral anticancer medicines store their medicines according to the temperature conditions stated on the product label. However, if storage below 25°C is required, patients may need additional advice as where to store their medicines at home or when travelling. Before medicines would be suitable for redispensing from a quality perspective, other criteria including light and humidity should be assessed for medicines sensitive to light or moisture. Especially, in warmer periods, there is a correlation between ambient temperature and storage temperature. As temperatures in the Netherlands rarely are above 25°C, this is not a major issue in the Netherlands. We suggest, however, that this correlation should be further investigated for other climate zone I/II countries with higher daily ambient temperatures.

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Declaration of Conflicting Interest

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