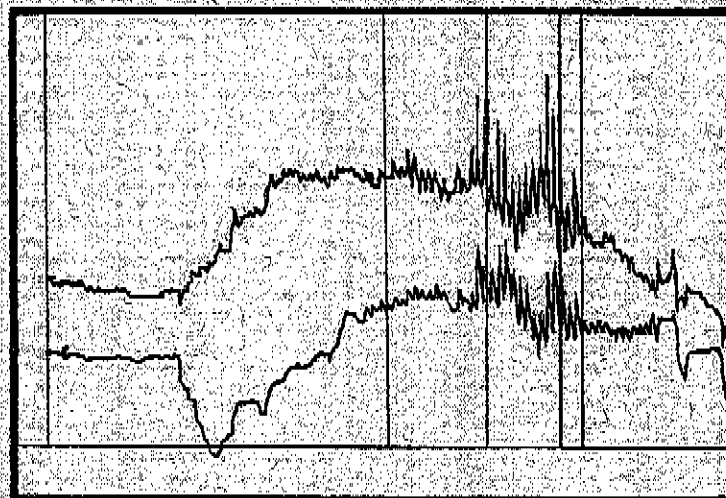


34580  
WHO/DAP/91.1  
Distr.: limited

# WHO / UNICEF study on the stability of drugs during international transport



H.V. Hogerzeil (1), A. Battersby (1),  
V. Srdanovic (2), L.V. Hansen (2), O.Boye (2),  
B. Lindgren (3), G. Everitt (3), N.E. Stjernstrom (3)

(1) WHO Action Programme on Essential Drugs, 1211 Geneva, Switzerland; (2) UNICEF Supply Division, Freeport, 2100 Copenhagen, Denmark; (3) Medical Products Agency, Husargatan 8, S-75125 Uppsala, Sweden

## LIST OF CONTENTS

<b>Summary</b>	4
<b>Introduction</b>	5
<b>Materials and methods</b>	
Selection of the drugs	7
Comments on the selection of drugs	9
Selection of routes	10
AUTOLOG equipment	10
Packing locations and routing of the kits	11
Sampling procedures and test methods	11
<b>Results</b>	
<i>Time in transportation</i>	13
<i>Temperature</i>	14
Temperature during international transport	14
Differences between temperature in the kits and mean ambient temperature	14
Differences between night and day	17
Differences between locations in the ship and within the container	18
<i>Relative humidity</i>	19
Relative humidity during international transport	19
Differences between night and day	19
Differences between locations in the ship and within the container	20
<i>Quality analysis of the drugs</i>	19
Loss of potency during international transport	21
Decomposition products	23
Other quality tests	23
<b>Discussion</b>	
Climatic conditions	25
Potency and quality of the drugs	26
<b>Conclusion</b>	30
<b>References</b>	31
<b>Annotated Bibliography</b>	33
<b>Annex 1</b> Temperature and humidity recordings	
<b>Annex 2</b> Quality analyses of the drugs	

## SUMMARY

The objective of this study was to determine whether the present method of international shipment of essential drugs by sea has any adverse effect on their quality and potency. The study was designed as a controlled longitudinal study of three shipments of 11 essential drug products each, shipped by international sea transport from the UNICEF warehouse in Copenhagen (Denmark) to Lagos (Nigeria), to Kampala (Uganda, by sea to Mombasa and then overland) and to Bangkok (Thailand), with three-hourly monitoring of temperature and humidity within the test kits. Potency and quality of the drugs were measured before and after shipment. Drugs were selected on the basis of a suspicion of instability, high turnover with UNICEF and medical relevance.

The three journeys to Lagos, Mombasa-Kampala and Bangkok took up to 52 days, of which 5-10% was spent in European ports, 45-75% at sea and 10-30% in the port of destination before customs clearance. Recorded temperatures within the test kits ranged from -3.5 to 42.4 °C and relative humidity from 20 to 88%. This is much higher than is usually recommended for drug storage. Considerable fluctuations occurred during storage in tropical port areas and during inland transportation. Temperature in the kits was 10-26% higher than the ambient temperature. The accumulated differences in temperature and humidity between the various locations within the ship or within the container were usually less than 5% and never more than 11%.

Three drug products showed a loss of potency that is statistically significant: ergometrine injection (5.8%), methylergometrine injection (1.7%) and retinol (1.5%). The latter is of little therapeutic significance but the instability of (methyl)ergometrine injection when stored unrefrigerated has serious practical consequences and merits further study. There are no indications that the other drugs are unstable during international transport. This is especially important for the antibiotics (ampicillin, benzylpenicillin, phenoxymethylpenicillin and tetracycline).

We conclude that the present method of international shipment of essential drugs has no significant effect on their potency and quality, with the exception of (methyl)ergometrine injection. More recordings should be made of the climatic pattern on other representative sea routes. Longitudinal studies within tropical countries and studies on brand-to-brand variation in stability are also needed.

## INTRODUCTION

For industrially manufactured pharmaceutical products distributed and used in tropical climates stability may pose serious problems. According to WHO the manufacturer and the distributor should be responsible for the quality of the products they manufacture or distribute (1). It is acknowledged, however, that stability studies conducted for temperate climates may not be fully relevant to storage and distribution in countries with extreme climatic conditions (2).

Elevated temperatures may accelerate drug decomposition (3). However, only one study has been published that describes the real temperatures that drug products may be exposed to in tropical climates. It describes the temperature within a box of emergency drugs stored in the life raft on board a German naval vessel during a voyage from Europe to the Indian ocean and back (4). The maximum recorded temperature inside the box was 40.2 °C. The quality of the products was not tested.

Studies describing the influence of tropical storage conditions on the quality of medicines are rare (5). York describes a simulation study on the stability of three antibiotics in tropical climates, but the drugs were stored under simulated temperature and humidity conditions and out of their original containers. He found a serious loss of potency and dissolution characteristics (6).

Even the possible extent of the problem has rarely been studied. In 1988 a small WHO field survey of 24 samples of ergometrine injection taken from twenty peripheral health facilities in Zimbabwe, Democratic Yemen and Bangladesh showed that only nine (37%) conformed to USP and BP standards with potencies between 450-550 µg/ml while seven (29%) had potencies of 20% or less (7). A longitudinal study on the stability of six drugs during two years of transport and storage in Sudan showed a serious loss in potency of ergometrine injection, lidocaine/epinephrine injection and suxamethonium injection (8).

We may therefore conclude that drug products may be exposed to elevated temperatures and that some drugs pose problems of stability in tropical climates, but that the extent of the problem is not fully known.

In 1987 UNICEF supplied essential drugs and vaccines to developing countries, many of them with tropical climates, for a total value of over US\$ 55 million (9). About half of this amount was spent on drug products. In view of the general lack of field data WHO and UNICEF decided to plan and execute a joint study on the stability of essential drugs in tropical climates. A protocol was finalized in 1988 (10) and the study was carried out in 1988 and 1989.

The objective of the study was to determine whether present methods of international shipment of essential drugs by sea have any adverse effect on their quality and potency. This is a first step in determining the quality of the whole distribution system for essential drugs from manufacturer to patient and it should be regarded as a pilot study.

Its design is a controlled longitudinal study of three shipments of 11 essential drugs products, shipped by international sea transport from the UNICEF warehouse in Copenhagen (Denmark) to Lagos (Nigeria), to Kampala (Uganda, by sea to Mombasa and then overland) and to Bangkok (Thailand), with three-hourly monitoring of temperature and humidity within the test kits. Potency and quality of the drugs were measured before and after shipment.

This report includes a detailed description of the materials and methods, a summary of the climatic recordings within the test kits, the full results of the quality analyses of the drugs and a discussion of the results. A list of references and an annotated bibliography are also included. The complete details of the climatic conditions are contained in a separate report (\*).

The study was financed through grants from UNICEF and SIDA/SAREC, whose support is gratefully acknowledged.

\* Battersby A, Hogerzeil HV. Study on the stability of drugs during international transport. Findings and analysis of climatic conditions. Geneva, WHO, 1990; DAP

## MATERIALS AND METHODS

### Selection of the drugs

The objective of the study was to screen the effect of international shipment on the quality and potency of essential drugs. The three criteria that have been used to select a range of essential drugs for the study are listed in Table 1.

In the WHO accelerated stability study as many as 110 out of 296 substances tested were found to degrade under the conditions employed (11) and this observation was used as the first selection criterion. However, as the number was too large for all drugs to be included in the present study, other criteria were introduced to limit their number, while maintaining the maximum chance that signs of instability in medically and economically important drugs would not remain unnoticed.

For the second criterion figures of the annual turnover in UNICEF were used. The 20 drug products with the highest volume distributed in 1987 were listed, representing about 87% of the total drug volume distributed by UNICEF that year (10). The same was done for drugs with the highest turnover in value; their total value represented about 79% of UNICEF's annual drug turnover. A third criterion of medical relevance was used to ensure that no efforts and funds would be wasted on drugs that were therapeutically less relevant, e.g. vitamins.

A preliminary list of 25 items was identified that satisfied one or more of the criteria. From this initial list a further selection was made during discussions between WHO, UNICEF and the Drug Quality Control Laboratory in Uppsala. The reduction in number was achieved through a rationalization of the list. For example, it is known that several of the antibiotics on the list had similar characteristics, justifying the selection of just one from the group (e.g. benzylpenicillin as a marker for all injectable penicillins). At the same time some drugs were deleted that could not be considered as life-saving, e.g. ascorbic acid tablets and bacitracin/neomycin ointment. The final selection is given in Table 2, with the criteria for their inclusion.

Table 1  
Selection criteria for drugs included in the study

---

1	A suspicion that the drug may decompose or degrade, based on accelerated stability studies carried out by WHO (11) or on other studies (6-8,12).
2	High turnover in UNICEF, either in volume or value
3	Vital or possibly life-saving therapeutic effect of the drug.

---

Drug stability is dependent on many product-related factors, e.g. the active ingredient and the excipients, the dosage form, the manufacturing process and the nature of the packaging (1,2,5,13-15). This implies, of course, that the stability of one brand does not necessarily prove the stability of that drug in general. The logical consequence should be to test drugs from various manufacturers. However, due to financial constraints this was not possible. It was therefore decided to test only those drug products that were actually being stocked and supplied by UNICEF at the time of the study. All of these are produced by well-known suppliers under their generic name and usually supplied to UNICEF on the basis of large tenders, sometimes resulting in long term contracts. Acetylsalicylic acid is the only drug for which two different brands, in different packages, were included. Both types are regularly supplied by UNICEF.

All samples were taken from the normal UNICEF stock available at that time, implying that not all products were necessarily freshly manufactured. Drugs in the control and test kits were all taken from the same batch. Detailed data on each sample, including manufacturing date and expiry date, are given in Annex 2.

Table 2  
Drug products included in the study

Drug	Accel. stability study (11)	Ref. to other stab. studies	High UNICEF turnover*	
			Volume	Value
Acetylsalicylic acid tab. 300 mg	x		4	13
Ampicillin trihydrate cap. 250 mg	x	(8, 16,17)		4
Ampicillin sodium powder for inj. 500 mg	x			15
Benzylpenicillin inj. 1 MU	x			15
Ergometrine maleate inj. 0.2 mg	x	(7,8,12)		
Methylethergometrine maleate inj. 0.2 mg	†			
Ferrous salt/folic acid tab. 60/0.25 mg	x §		2/15	8
Phenoxymethylpenicillin tab. 250 mg	x		11	5
Retinol cap. 60 mg	x		14	6
Tetracycline HCl tab. 250 mg	x	(6)	19	18
(Tetracycline eye ointment, 5 g)	x ¥			10

\* Number indicates ranking order (10)

† Included to test the hypothesis that methylethergometrine is more stable than ergometrine

§ Only ferrous salt was found unstable in the WHO accelerated stability study (11)

¥ Different test protocol

## Comments on the selection of the drugs

### *acetylsalicylic acid*

Acetylsalicylic acid is known to be unstable in humid tropical climates. The drug is included in the study to analyze whether any degradation takes place during international transport if the drug is kept in an appropriate container. For this reason two commonly used brands of the drug, in their original package, were tested.

### *ampicillin*

Ampicillin trihydrate capsules have been found unstable in several studies (8,16,17). This drug is frequently shipped by UNICEF. Ampicillin sodium powder for injection was included for comparison.

### *penicillins*

All commonly used injectable penicillins were found unstable in the WHO study (11) and together they represent 13% of all UNICEF drug expenditure. As their stability profile is likely to be identical it was decided to include only one injectable penicillin. For procain penicillin, which is the drug with the third highest financial turnover in UNICEF, no signs of instability were found in the Sudan study (8) and for this reason benzyl penicillin was chosen this time. Oral phenoxymethylpenicillin was also included.

### *ergometrines*

Three studies are now available that indicate that ergometrine injection is unstable under tropical conditions (7,8,12). As there are few alternatives for this life-saving drug, the most common presentation (ergometrine maleate injection) was tested together with the first alternative, methylergometrine maleate, which was believed to be more stable.

### *ferrous salt and folic acid*

Ferrous sulphate was found liable to oxydization and was therefore considered unstable in the WHO study (11), while folic acid was not. The combination was selected for the study because it is very commonly used by UNICEF. Monocomponent ferrous sulphate tablets were also included in case the analytic tests were affected by the presence of the folic acid.

### *retinol*

Retinol is an important vitamin, found unstable in the WHO study (11) and a high-value item for UNICEF. Quality analysis of the drug is technically complicated as there are many active and inactive degradation products.

### *tetracycline*

Tetracycline is a difficult and expensive drug to test, as there are several degradation products. Whether these are toxic is a matter for discussion. As the drug is suspected to be unstable (11,15) tetracycline tablets were included. Tetracycline eye ointment, a high-value item for UNICEF, was also selected to test the effect of high temperatures on the distribution of the active ingredient within the tube.

### *Drugs not included in the study*

A few drug products with a high turnover by UNICEF, of which the active ingredient was identified as unstable in the WHO study (11) were not included. Sodium lactate solution for infusion was omitted because as a solution this substance is likely to be stable; the same applies for sulfadimidine for which a study in Vietnam found no signs of instability (18). Ascorbic acid tablets and bacitracine/neomycin ointment were considered to be of insufficient medical relevance.

### Selection of routes

Eight different sea routes from Copenhagen were identified to represent global shipping, and these are listed in Table 3. For each route an indicative climatic profile was prepared, showing the average daily maxima and minima for relative humidity and temperature taken from general meteorological data for locations close to the sea (10). Three routes (West Africa, East Africa and Far East) represent over 35 (45%) of the 77 countries served by UNICEF, or nearly 40% of the total volume despatched in 1987, and these routes were selected for the study. To select the actual destination on these routes an assessment was made of the drugs sent out in 1987 (10). Ten countries account for over 60% of total shipment volume (19).

For the West Africa route, which represents the largest number of UNICEF countries, Nigeria was chosen because it receives the largest single volume in that area. Uganda was chosen to represent East Africa, being the land-locked country receiving the highest volume in 1987. Bangkok was selected as a nodal point for Far East bound shipping. All three destinations have local UNICEF offices which assisted in returning the test kits.

*Table 3*  
Representative sea-routes from Copenhagen.

---

West Africa
Southern Africa
East Africa
Middle East, including all countries bordering the Red Sea
West Asia (Iran to Myanmar)
Far East and Pacific Islands
Central America and countries reached through the Panama canal
South America

---

### AUTOLOG® equipment

For the recording of temperature and relative humidity "AUTOLOG®" devices were used, produced by REMONSYS Ltd, Bristol, UK. In a simple version such devices are used to record temperature in international shipments of meat and vegetable products. For the present study a modified AUTOLOG was developed which could measure and record the relative humidity as well as the temperature. Each device was fixed in a small wooden box of about 20 x 15 x 10 cm with large holes for the free circulation of air.

Both measurement and recording of the data were done electronically. The frequency was set at one measurement every three hours, and at that frequency the battery lasted for over 100 days. The data were stored in a micro chip and were later down-loaded into a computer programme run on a personal computer. The temperature

sensor had an accuracy of approximately 1% and the humidity sensor about 3%. The humidity readings were slightly affected by changes in barometric pressure.

#### **Packing locations and routing of the kits**

The test kits consisted of a triple wall cardboard box, manufactured to the UNICEF standard for international shipping and similar to the boxes used for regular drug shipments. Each kit contained the selected drugs and the AUTOLOG recording equipment. Within the box the drugs were packed around the AUTOLOG, ensuring that sufficient air could circulate around the device. Polystyrene chips were used for filling. The cartons were closed, sealed and labeled in bright orange as a sample for study purposes that should be returned unopened.

Four test kits were prepared for each of the three routes, for two reasons. The first was to reduce the risk that the AUTOLOG recorders would fail. Secondly, this would make it possible to test different locations in the container and on the ship. Three control kits were prepared without AUTOLOGs. The test kits were placed in two different locations in the containers (20 or 30 feet steel boxes used for international shipping) that were filled with regular essential drugs shipments: one kit in the middle of the container, and one in the top corner near the ceiling and the door. Two of such containers were packed and shipped simultaneously to the same destination, with one container stowed in the hold of the ship and one on deck. This resulted in four different locations of the kit on board for each sea-route.

At the time of despatch one control kit was sent to the laboratory in Uppsala and kept under refrigeration; the other control kits were kept in normal storage at the UNICEF warehouse. On 16 November 1988 four test kits left for Lagos, where they arrived on 6 January 1989; four other kits were sent to Mombasa by ship and from there overland to Kampala, where they arrived on 13 January 1989. Both in Lagos and in Kampala the test kits were identified by local UNICEF staff and returned immediately to the laboratory in Uppsala, by air. There the kits were stored under refrigeration until the time of analytical testing. The information from the AUTOLOGS was downloaded and analyzed.

Although all eight test kits returned safely from Lagos and Kampala, unfortunately one of the four AUTOLOGs sent to Lagos and two of the four to Kampala did not function. For this reason the despatch to Bangkok, which was already late because no regular shipment was due, was postponed to check and adapt the devices before sending them off. After the necessary repairs and test runs the four kits for Bangkok were sent on 25 October 1989; they arrived in Bangkok on 21 November 1989. There they were not cleared through customs but kept in bonded storage in the port until 18 January 1990 on which date they were sent to Uppsala, but, regrettably, by sea again rather than by air as requested. As a consequence they arrived only on 12 February 1990 in Uppsala, unrefrigerated. Since the results could not be interpreted as the effect of a one-way journey by sea, only the climatological data of these four kits were analyzed and no analytical testing on the drugs was performed.

#### **Sampling procedures and test methods**

Analytic tests were carried out by the Drug Quality Laboratory of the Department of Drugs of the Ministry of Health and Social Welfare in Uppsala, Sweden (now called the Medical Products Agency). A summary of the sampling methods is given in Table 4

and the nature of the tests performed is summarized in Table 5. The analyses concentrated on the level of active ingredient, the presence of degradation products and, if indicated, any other tests that would indicate a serious loss of quality. A detailed description of the analytical methods used for each of the drugs is given in Annex 2.

Table 4  
Summary of sampling methods, per kit

Drug	Kit content	No. of samples control	test	Sample size	No. of analyses per sample
Acetylsalicylic acid tab A	2000	2	1	10	1
Acetylsalicylic acid tab B	2000	2	1	10	1
Ampicillin trihydrate cap.	1000	2	1	10	2
Ampicillin sodium pow. inj.	25	2	1	9	3
Benzylpenicillin pow. inj.	50	2	1	10	2
Ergometrine maleate inj.	100	10	10	1	1
Methylergometrine mal. inj.	100	10	10	1	1
Ferrous salt/folic acid tab.	1000	2	1	10	2
Phenoxymethylpenicillin tab.	200	2	1	10	2
Retinol cap.	200	2	1	10	2
Tetracycline HCl tab.	1000	1	1	30	2

Table 5  
Summary of analytic methods

Drug	Active ingredient	Degradation products	Other tests
Acetylsalicylic acid tab. A	HPLC		Weight variation
Acetylsalicylic acid tab. B	HPLC		Weight variation
Ampicillin trihydrate cap.	Pot.titr.	Pot.titr.	Dissolution
Ampicillin sodium pow. inj.	Pot.titr.	Pot.titr.	
Benzylpenicillin pow. inj.	HPLC	Pot.titr.	
Ergometrine maleate inj.	HPLC		
Methylergometrine mal. inj.	HPLC		
Ferrous sulphate	Pot.titr.		Weight variation,
folic acid	HPLC		disintegration, hardness
Phenoxymethylpenicillin tab.	HPLC	Pot.titr.	Disintegration
Retinol cap.	HPLC	HPLC	Weight variation
Tetracycline HCl tab.	HPLC	HPLC	Weight variation

## RESULTS

### TIME IN TRANSPORTATION

All routes started at the UNICEF warehouse in Copenhagen where the AUTOLOGS were activated. Table 6 summarizes the three routes and the time in transportation. The dates are taken from the captain's logbook and the form attached to the test kits.

Table 6  
Time in transportation

Route	Copenhagen to Lagos via Aarhus	Copenhagen to Kampala via Mombasa	Copenhagen to Bangkok via Hamburg and Singapore
AUTOLOG activation	28.10.88	28.10.88	23.10.89
Dispatch by UNICEF	16.11.88	16.11.88	25.10.89
Loading first ship	17.11.89	22.11.88	26.10.89
Loading second ship	27.11.88		16.11.89
Off-loaded in port	23.12.88	17.12.89	21.11.89
Start overland transport		30.12.88	
Arrival overland transport		10.01.89	
Cleared and receipt by UNICEF	06.01.89	13.01.89	*
Total journey (in days)	51	52	27
% time in loading port	10		7
% time at sea	57	46	93
% time in port of destination	33	27	*
% time overland		21	
% time in bond on land		6	

\* After arrival in Bangkok on 21.11.89 the consignment was never delivered to UNICEF and was returned by ship leaving Bangkok on 18.01.90, arriving at Uppsala on 12.02.90

## TEMPERATURE

### Temperature during international transport

A sample climatic recording from the trip to Lagos is shown in Figure 1 and a similar recording for the journey to Kampala is shown in Figure 2. Such graphs are a complete representation of the three-hourly temperature and relative humidity recordings made by one AUTOLOG device.

Annex 1 presents a summary of all data available per journey. These graphs contain, for every five-day period, the maximum temperature as measured by each AUTOLOG, the minimum temperature from one AUTOLOG, and the mean ambient temperature taken from the ship's logbook or from data from the meteorological office (10). Minimum and maximum temperatures recorded on each journey are summarized in Table 7.

Table 7.  
Minimum and maximum temperatures recorded (in °C)

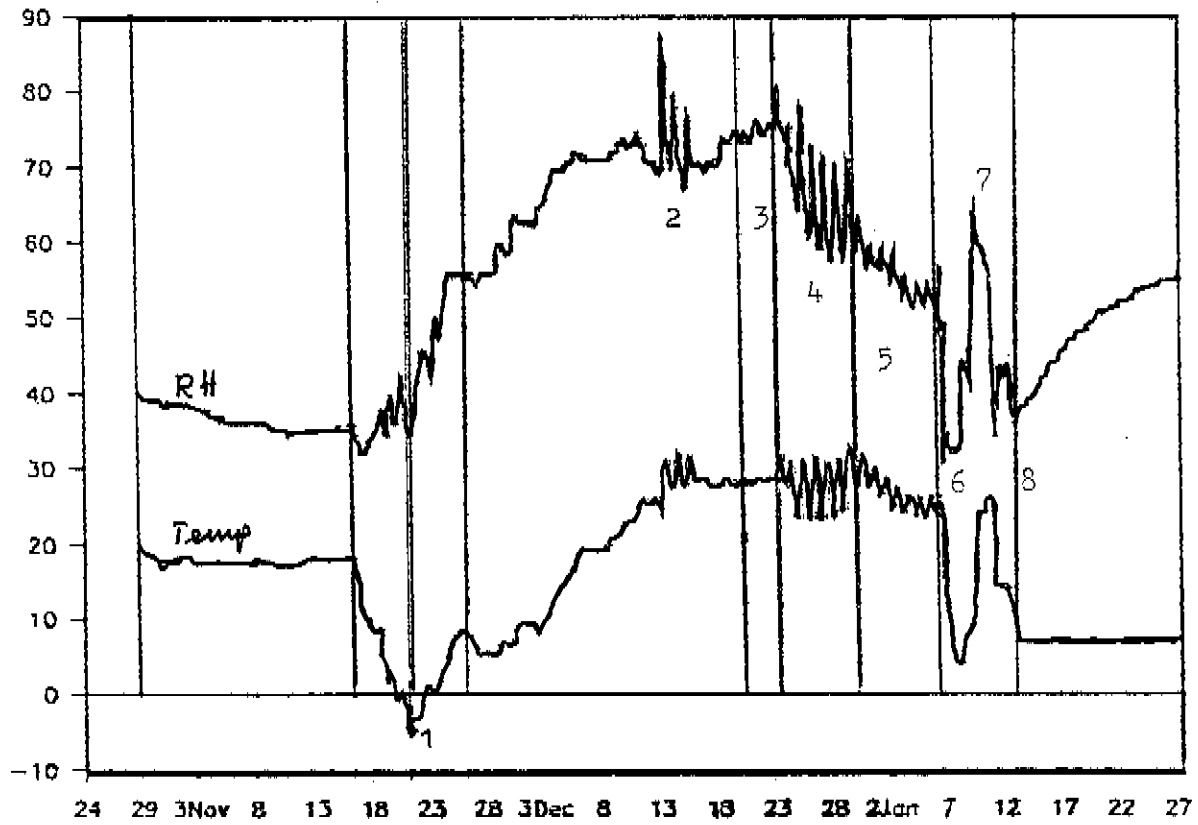
	Lagos	Kampala	Bangkok
Minimum temperature	- 3.5	- 2.3	1.9
Maximum temperature	33.6	42.4	37.5

### Differences between temperature in the kits and mean ambient temperatures

In Table 8 a summary is presented of the difference between the mean ambient temperature and the maximum temperature recorded in the test kits. For the journeys to Lagos and Bangkok ambient temperature was recorded in the captain's logbook; for the journey to Kampala actual ambient temperatures were not available and the estimate was made from recorded temperature data collected from land stations along the route.

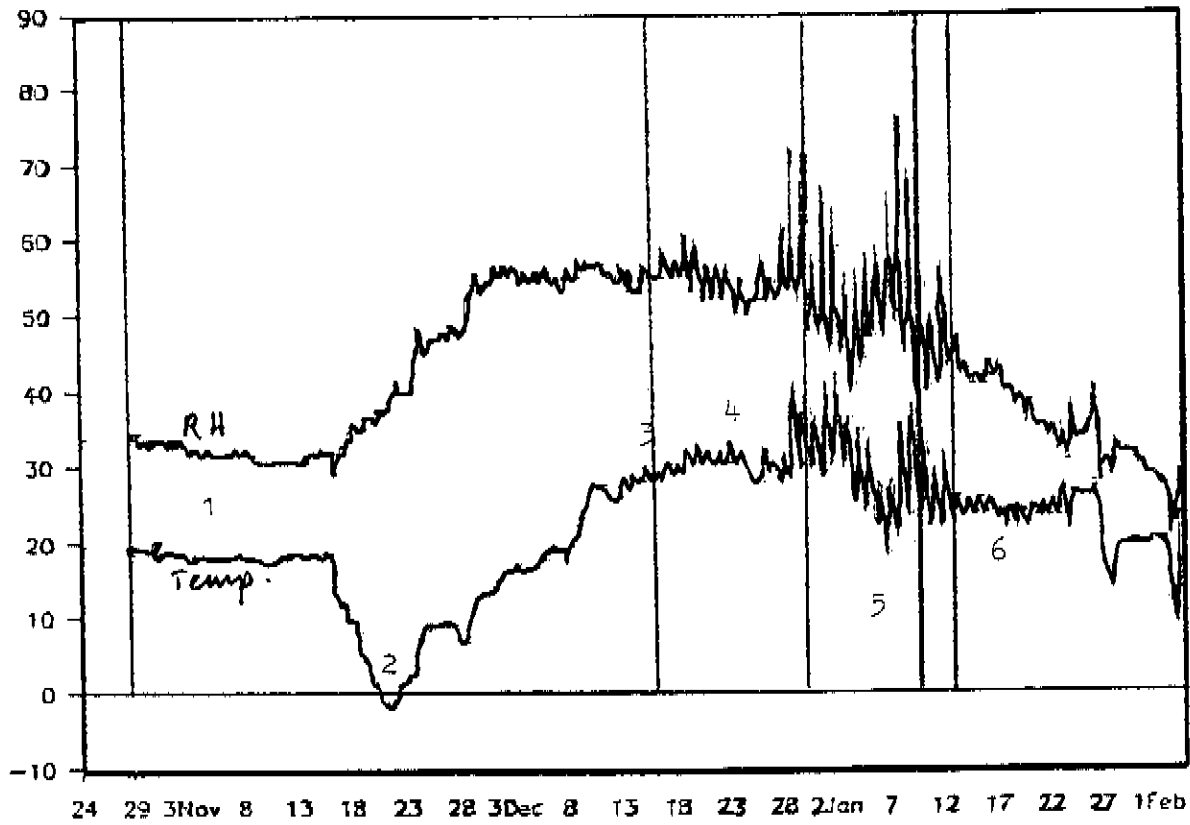
From the Lagos and Bangkok recordings it is clear that the maximum temperature inside the containers was considerably higher than the outside temperature as recorded by the captain. The recordings from Kampala show the same picture but are less reliable as they refer to the average rather than the actual outside temperature. For the Bangkok journey the temperature in the deck container was higher than the hold container, probably because the latter was slower in warming up.

Figure 1  
Sample temperature and relative humidity recording (Lagos)



- 1 Aarhus
- 2 Other W-African port?
- 3 Waiting outside Lagos harbour
- 4 In customs bondage
- 5 In UNICEF warehouse
- 6 In the refrigerator in Lagos
- 7 Sent to Uppsala
- 8 Uppsala arrival and storage

Figure 2  
 Sample temperature and relative humidity recording (Kampala)



- 1 In UNICEF warehouse in Copenhagen
- 2 In Aarhus port
- 3 Arrival in Mombasa
- 4 Period in port area
- 5 Overland transport to Kampala
- 6 In UNICEF warehouse in Kampala

*Table 8*  
Difference between maximum internal and outside temperature (\*)

Route	Sector	Location § DT	DC	HT	HC
Lagos	at sea	+23%	+26%	n.a.	+26%
Kampala †	at sea	+32%	+35%	n.a.	n.a.
Bangkok	at sea	+20%	+20%	+10%	+10%

\* positive values indicate that temperature in the kit was higher than ambient temperature

§ D=deck container; H=hold container; T=top of the container; C=centre of the container

† Comparison with average ambient temperature only

#### Differences between night and day

For each journey the difference between the daily maximum and minimum temperature has been calculated and compared. The results are summarized in Table 9. Days were not always hotter than nights. On the Lagos journey the greatest fluctuations occurred on board the feeding vessel between Copenhagen and Aarhus were the maximal diurnal range was  $\pm 4^{\circ}\text{C}$ ; for the rest of the journey the range was about  $\pm 1^{\circ}\text{C}$ . On the Kampala trip the maximum diurnal range was about  $\pm 14^{\circ}\text{C}$  during the journey overland. This picture is also visible on Figures 1 and 2. At sea en route to Bangkok the maximum range was  $\pm 4^{\circ}\text{C}$  while in the harbour a maximum of  $\pm 10^{\circ}\text{C}$  was recorded.

The accumulated day and night temperatures were calculated and the results are shown in Table 10. They show that, due to the effects of the thermal lag, the overall difference between night and day is very slight. However, the effect of expansion and contraction caused by the considerable changes in diurnal temperatures could have an effect on the seals of drug packages.

*Table 9*  
Diurnal fluctuations in temperature, in  $^{\circ}\text{C}$ .

	Lagos	Kampala	Bangkok
At sea	4	3.5	5
In port	2	4	0.4*
Inland transport	14		

\* Once a fluctuation of  $\pm 10^{\circ}\text{C}$  occurred

Table 10  
Accumulated temperature differences between night and day, in % \*

	Lagos	Kampala	Bangkok
At sea	+ 3%	+ 1%	+ 9% §
In port	- 11%	+ 4%	+ 3%
Inland transport		+ 9%	
Total journey	+ 2%	+ 2%	+ 2%

\* positive values indicate that day temperature is higher than night

§ + 2% for the return journey

#### Differences between locations in the ship and within the container

For the Lagos and Bangkok journey the differences in temperature between the container in hold and the one on deck have been analyzed. No data are available from the Kampala journey due to AUTOLOG failure. For the Lagos journey the accumulated temperature in the hold of the ship was about 5% higher than on deck. For the Bangkok journey the situation was reversed, with the hold about 2% lower than the deck.

Although the accumulated differences are slight, individual differences can be considerable. For example on 4 November 1989, en route to Bangkok, the deck container was 18 °C warmer than the hold container. This happened when the ship entered tropical waters.

With regard to the location of the kit in the container there is little difference between the accumulated temperatures of the centre as compared to the top. For the Lagos trip as a whole, temperature in the centre was 0.2% higher. On the Kampala route the accumulated difference was 5%, while on the Bangkok route the centre was 0.1% lower. However, individual differences at a given time can be considerable. During the period in Lagos port the centre was often 5-8 degrees warmer than the top and on 3 January 1989 there was a 19 °C difference. On the inland leg of the Kampala trip differences of 6-16 °C occurred. On the Bangkok trip the differences were usually 4-6 °C, with once a difference of 16 °C while in the port at Bangkok.

Although there are considerable fluctuations between deck and hold recorded temperatures and also between the temperatures recorded in the centre and the top of the container, the overall effect is slight, because many of the differences cancel each other. This is due to the effect of thermal lag.

## RELATIVE HUMIDITY

### Relative humidity during international transport

Figures 1 and 2 show one AUTOLOG recording from the Lagos and Kampala trips, which also includes the pattern of the relative humidity (RH). Annex 1 shows the full recordings of all AUTOLOGS for each journey, with all maximum values and one minimum value per five-day period. Absolute minimum and maximum values recorded are summarized in Table 11.

*Table 11*  
Minimum and maximum values of relative humidity

	Lagos	Kampala	Bangkok
Minimum	29 %	20 %	46 %
Maximum	88 %	77 %	79 %

### Differences between night and day

For each journey the differences between the daily minimum and maximum RH have been calculated and compared. The results are summarized in Table 12. On the Lagos journey the greatest fluctuations occurred in Lagos port, with a maximum of  $\pm 30\%$  in one kit. During the sea voyage fluctuations were very small ( $\pm 0-3\%$ ). For the Kampala trip fluctuations of 10-30% occurred during the period of overland transport. During the Bangkok journey very few fluctuations occurred, and also in Bangkok port storage they were usually between 0-4% with a maximum of 12%. The accumulated differences between day and night are summarized in Table 13 and are rather small.

*Table 12*  
Diurnal fluctuations in relative humidity

	Lagos	Kampala	Bangkok
At sea	17 %	4 %	3 %
In port	30 %	22 %	11 %
Inland transport		30 %	

Table 13

Accumulated difference in relative humidity between day and night \*

	Lagos	Kampala	Bangkok
At sea	-0.1 %	2 %	0.5 % §
In port	4 %	3 %	- 3 %
Inland transport		4 %	
Total journey	0.3 %	2 %	1 %

\* positive values indicate higher day values

§ 2% for the return journey

#### Differences between locations in the ship and within the container

In spite of some temporary fluctuations the difference in RH between containers located in the hold and those on deck were generally small. The accumulated difference for the Lagos journey is 0.7% lower in the hold than on deck; for the Bangkok journey the situation is reversed, with the hold 2% higher than the deck. No data from Kampala are available because of AUTOLOG failure.

The differences within the container are slightly larger. Temporary differences of 10-30% RH occurred between the centre and the top of the container in Lagos harbour and during inland transport to Kampala. Nevertheless the total accumulated differences over the journey as a whole were rather small. For the Lagos and Kampala routes the accumulated RH was 2% higher in the centre of the container; for the Bangkok route this figure was 5%.

## QUALITY ANALYSIS OF THE DRUGS

Only for those drugs that were transported to Lagos and Kampala the potency and quality were studied. The full analytical results are given in Annex 2. For each drug the first of the two pages in this annex contains the administrative data, the sampling methods, the assay method, the summary results and the conclusions. The second page contains the detailed test results of all analyses. The results of the potency tests of all drugs have been summarized in Table 14. Tetracycline ointment, which was studied with a different protocol, did not show any signs of degradation (see Annex 2, p 25).

Table 14

Potency of drugs before and after international shipment, expressed as percentage of stated content

Drug	Control kit		Test kits		Difference *	
	Mean (%)	95% CL (%)	Mean (%)	95% CL (%)	(%)	p
Acetylsal.tab(A)	101.0	99.7-102.2	100.7	99.9-101.4	-0.3	n.s.
Acetylsal.tab(B)	100.0	99.9-100.2	100.2	99.7-100.8	+0.2	n.s.
Ampicillin cap.	96.6	95.0-98.3	96.1	95.8-96.4	-0.2	n.s.
Ampicillin inj.	84.1	83.4-84.8	83.7	82.6-84.9	-0.4	n.s.
Benzylpenicillin inj.	96.6	92.8-100.5	96.2	95.6-96.8	-0.5	n.s.
Ergometrine inj.	87.1	86.0-88.1	82.0	80.3-83.8	-5.8	< 0.001
Methylethergometrine inj.	100.7	100.0-101.4	99.0	98.6-99.5	-1.7	< 0.001
Ferrous salt tab.	100.0	98.5-101.4	100.1	99.2-101.0	+0.2	n.s.
Folic acid tab. †	108.6	91.2-125.9	106.6	103.1-110.0	-2.0	n.s.
Phenoxym.pen. tab.	96.3	94.1-98.5	96.0	95.6-96.4	-0.3	n.s.
Retinol cap.	120.8	120.2-121.4	119.0	118.1-119.9	-1.5	< 0.001
Tetracycline tab.	101.8	n.a.	101.5	99.5-103.4	-0.3	n.s.

\* Expressed as percentage of control value

† Combined with ferrous salt in one tablet

### Loss of potency during international transport

As can be seen from table 14 all but two of the drugs seem to have lost some potency during international transport. However, the decrease is usually less than 2% and most of the differences are statistically insignificant. For some drugs the differences are more pronounced and these will be discussed in more detail.

#### *ergometrine injection*

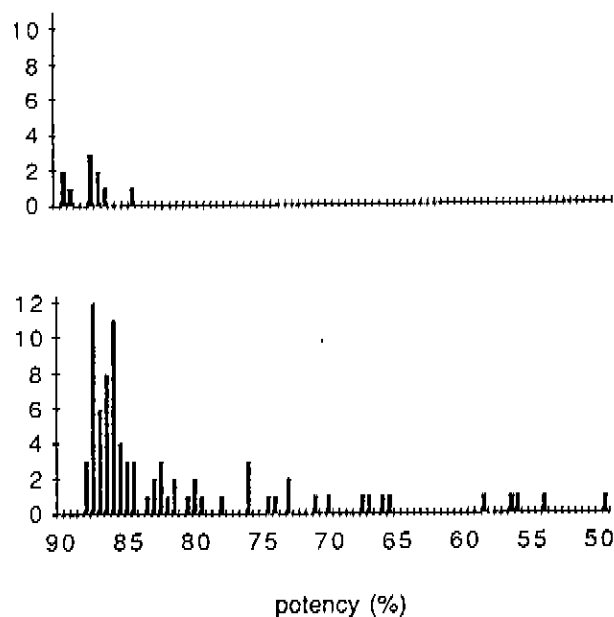
For ergometrine injection the average loss of potency during international transport

was about 5.8% ( $p < 0.001$ ). Moreover, the 80 test samples show much more variation in potency than those of the 10 controls, with 18/80 samples measuring less than 80% potency and 3/80 less than 60% (see Annex 2, pp.11-12). One sample was even below 50% potency. This increased variation is visualized in Figure 3.

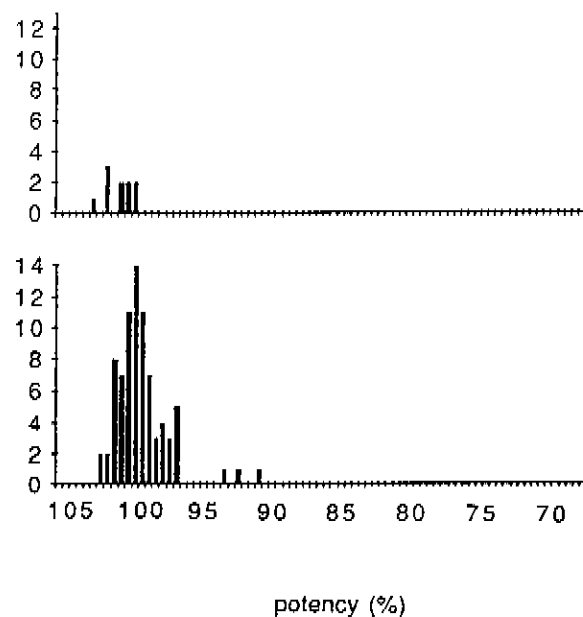
*methylergometrine injection*

For methylergometrine the same picture emerges as for ergometrine, but less extreme. The average loss of potency is about 1.7% ( $p < 0.001$ ) and the test samples show more variation than the controls (see Figure 4).

*Figure 3*  
Potency of ergometrine injection before and after international shipment. Top: before (n=10); bottom: after (n=80)



*Figure 4*  
Potency of methylergometrine injection before and after international shipment. Top: before (n=10); bottom: after (n=80)



*retinol*

For retinol the average loss of potency is 1.5% ( $p < 0.001$ ). The results show very little variation.

*folic acid*

The folic acid component of the ferrous salt/folic acid tablets shows an average loss of potency of 2%. This difference is statistically not significant because of a rather large variation in the results which is caused by the fact that the analytical method was rather difficult.

### Decomposition products

For five drugs the content of decomposition products before and after international transport was tested. The detailed analytical results are given in Annex 2 and summarized in Table 15. As can be seen from the table, ampicillin capsules and benzylpenicillin injection show an increase which is statistically significant.

Table 15

Decomposition products before and after international transport

Drug	Control kit *		Test kits *		Difference †	
	(%)	95%CL	(%)	95%CL	(%)	p
Ampicillin cap.	2.36	2.20-2.53	2.70	2.60-2.80	+14%	< 0.001
Ampicillin inj.	9.51	8.74-10.27	9.58	9.22-9.94	+ 1%	n.s.
Benzylpenicillin inj.	0.94	0.92-0.96	1.00	0.97-1.03	+ 6%	< 0.001
Phenoxyrn.pen. tab.	0.95	0.53-1.38	0.92	0.89-0.94	- 4%	n.s.
Tetracycline tab.						
epi-	2.16	n.a.	2.27	2.08-2.47	+ 5%	n.s.
anhydro-	0.55	n.a.	0.45	0.33-0.57	- 18%	n.s.

\* Expressed as percentage of active ingredient

† Expressed as percentage of the amount in the control sample

### Other quality tests

For some of the drugs other quality tests were carried out; most of these refer to physicochemical properties (weight, hardness and dissolution). The results are summarized in Table 16; detailed results are given in Annex 2. All tests gave satisfactory results and none showed a difference between the control and test kits.

Table 16  
Results of other quality tests

---

<i>Acetylsalicylic acid tablets</i>	
Mean weight (A)	363.8 mg/tablet (variation -2.45%, +3.3%)
Mean weight (B)	335.6 mg/tablet (variation -1.37%, +1.34%)
<i>Ampicillin capsules</i>	
Dissolution	>80% after 20 minutes in all samples
<i>Ferrous sulphate/folic acid tablets</i>	
Mean weight	228.9 mg/tablet
Disintegration	All samples disintegrated within 18 minutes
Hardness	Control: 47.1 N; test: 49.6 N
<i>Phenoxymethylpenicillin tablets</i>	
Disintegration test	All samples disintegrated within 7 minutes
<i>Retinol capsules</i>	
Mean weight	202 mg/capsule (variation -3.5%, +8.4%)
<i>Tetracycline tablets</i>	
Mean weight	305.0 mg/tablet (variation -1.1% and +4.5%)

---

## DISCUSSION

### Climatic conditions

The three journeys to Lagos, Mombasa-Kampala and Bangkok took up to 52 days, of which 5-10% was spent in European ports, 45-75% on sea and 10-30% in the port of destination before customs clearance. This implies that up to one third of the total travel time was spent in the port of destination.

The minimum temperature in any of the kits was  $-3.5^{\circ}\text{C}$ , recorded in the kits to Lagos, on board the feeder vessel in the port of Aarhus; the temperature was below zero for about 54 hours during three days. In the same period the kits to Kampala reached a minimum of  $-2.3^{\circ}\text{C}$ . The maximum temperature was  $42.4^{\circ}\text{C}$ , recorded in Mombasa harbour. Maximum temperatures on the other journeys were  $33.6^{\circ}\text{C}$  in Lagos and  $37.5^{\circ}\text{C}$  in Bangkok. On average, temperature in the kits was 10-26% higher than the ambient temperature.

Although temperature fluctuations occurred of up to  $16^{\circ}\text{C}$  within one day, there was no real accumulating difference between night and day temperatures. Most fluctuations occurred during the period of inland transport between Mombasa and Kampala.

The location of the container in hold or on deck showed an accumulated temperature difference of 2-5% with the centre recording a higher temperature on the Lagos journey, but a lower one on the one to Bangkok. The location of the kit within the container (centre or top) showed a maximum difference of 5%, especially in the port of Lagos and during inland transport to Kampala, with higher temperatures recorded in the centre. While the accumulated temperature differences are small the fluctuations are considerable.

The relative humidity (RH) ranged between 20 and 88%. The RH was above 70% for about 67% of the time of the Lagos journey; for the Kampala route it was 17% and for Bangkok 29% of the time. Fluctuations between night and day of 15-30% RH occurred especially in Lagos harbour and during the overland trip to Kampala; the accumulated differences were 4% and 9% respectively, the RH being higher during the day. The differences between the container in hold or on deck were never more than 2%; the centre of the container had a 2-5% higher RH than the top.

In general the temperature and the relative humidity show an identical pattern of a steady rise on approaching tropical waters, followed by periods of high values and moderate fluctuation in tropical harbours, and periods of high values and strong fluctuations during storage and transport on land. Temporary differences may occur between the various locations of the kit, especially within the container, probably because of the thermal lag. However, the accumulated differences in temperature or relative humidity were negligible.

WHO defines normal storage conditions as storage in dry, well-ventilated premises at temperatures of  $15-25^{\circ}\text{C}$  or, depending on climatic conditions, up to  $30^{\circ}\text{C}$  (20). In the present study the temperature and the relative humidity in the test kits were

considerably higher than that. An other important finding is that the temperature in the kits was 10-26% higher than the ambient temperature (see Table 8). The results of this study therefore indicate that the temperature and relative humidity during international transport are often much higher than is recommended for drug storage. They may also show considerable fluctuation, which could have a detrimental effect on the seals to drug packages.

Very few studies have been published on the climatic pattern during transport and storage in tropical climates. One study describes the temperature in a box of emergency drugs kept in a life raft on board a German naval vessel during a voyage from Kiel through the Suez canal to Karachi, Colombo, Mombasa and back (4). The highest temperature recorded in the box was 40.2 °C; during the passage through the Suez canal and the Red Sea the average temperature was between 30 and 35 °C; in the Indian Ocean temperatures were around 25 °C. Humidity was not recorded. A Japanese study (21) measured the annual temperature in a workshop in Osaka (range 7-37 °C) and concluded that such aggregated data can be used to predict stability in the domestic market, as the annual average atmospheric temperature in Osaka is the highest of the major cities in Japan.

From our study we can conclude that the temperature and relative humidity experienced by the drugs while at sea were less of a problem than during the rest of the journey. However, during the periods spent on board in the harbour, in customs bondage in the port area and during transport over land extreme climatic conditions did occur. For the Lagos trip this was 17 days (33% of the total time) and for the trip to Kampala 26 days (54%). Most of the time spent in a tropical port area will expose the drugs to a combination of high temperature and high relative humidity, which is the most likely condition to cause a loss of potency and quality. For this reason the period in customs bondage and in warehousing close to the port area should be reduced to the minimum. The same applies for transport overland.

#### **Potency and quality of the drugs**

Three of the eleven drugs included in this study showed a loss of potency which is statistically significant (ergometrine injection, methylethergometrine injection and retinol). Statistical significance does not necessarily mean medical significance and the operational implications of this observation should be discussed.

In the case of retinol the loss of potency has no medical and practical implications. The loss is very limited (1.5%), this particular brand of the drug contained about 20% extra of the active ingredient and the therapeutic margin of the drug is rather wide.

The case of ergometrine and methylethergometrine injection is different. In a previous study on the potency of ergometrine injection samples taken from 24 health units in Zimbabwe, Democratic Yemen and Bangladesh, only nine (37%) were within BP requirements, eight had potencies between 80-90% and the rest were below 80% (7). Recent data from Malawi confirm this picture (22). Nine different samples were taken from the field, from five different manufacturers and all within their expiry date, and none complied with BP (mean potency 66%, range 34-88%). In a longitudinal study in Sudan ergometrine injection lost 10% of its potency during the first few months in Port Sudan and was found to be only 53% potent after 25 months within the country (8).

In this light the average loss of 5.8% for ergometrine injection and 1.7% for methylethergometrine during international transport should be seen. The drugs are

classified as vital and life-saving and although medically speaking a loss of a few percent is not dramatic, this loss occurred in less than two months. The results from Sudan suggest that a considerable further loss is to be expected during inland transport and storage and it is obvious that for this drug a potency of less than 90% will have serious if not fatal consequences. An additional problem is that there is no obvious alternative for the drug. A recent WHO meeting concluded that oxytocin would be the second best choice (23) but its stability in tropical climates is not known and may pose similar problems.

Storage guidelines for ergometrine are far from consistent and stability data from the literature are often contradictory and confusing (see Table 17). The WHO accelerated stability study (11) based its conclusion that ergometrine is unstable on tests on the raw material. One manufacturer indicated that the stability of ergometrine is very much dependent on the manufacturing and filling process and mentions that a better stability is achieved with filling under protection from light and oxygen, with a pH between 2.7-3.5.

From our results it cannot be concluded whether or not methylegometrine will always be more stable than ergometrine injection, because only one brand of each was studied. Two manufacturers guarantee a shelflife of three years if the product is stored below 25 °C and protected from light. One literature survey (30) quotes five publications on the subject (31-35) and concludes that methylegometrine seems to be more stable than ergometrine injection. Our study could support this conclusion but it is not clear whether the manufacturing process or the chemical composition is responsible for any difference in stability. We must therefore conclude that more specific studies are needed in which the stability of several brands of both drugs are compared.

Table 17  
Storage guidelines and stability data on ergometrine injection

<i>Storage guidelines</i>	
Goodman and Gillman, 1980 (24)	0-12 °C, protect from light
USPDI, 1986 (26)	Below 40 °C, preferably 15-30 °C, protect from light and freezing
Martindale, 1989 (25)	2- 8 °C, protect from light
<i>Manufacturers information</i>	
Vitarine, 1975 (27)	If stored below 17 °C: 3 yr
Lily, 1975 (27), 1983 (28)	If stored between 15-30 °C: 2 m
South Tees Health Authority, 1985 (29)	If stored between 10-15 °C and protected from light, as long as no discoloration has occurred
Antigen, 1987 (12)	If kept at room temperature: 13 m
Gideon Richter, 1988	If kept below 15 °C and protected from light: 2 yr
Paris Chemical, 1988	If stored between 2-8 °C: 2 yr
Medisca, 1989	If stored below 25 °C and protected from light: 3 yr
<i>Stability studies</i>	
WHO Accelerated stability studies, 1986 (11)	Substance subject to degradation
Zimbabwe, Yemen, Bangladesh, 1988 (7)	Complete loss of potency in 7/24 unrefrigerated field samples
Sudan, 1990 (8)	53% potency after 24 months unrefrigerated storage
Malawi, 1990 (21)	9 unrefrigerated field samples showed 34-88 % potency

The increased variation of the potency within the same batch of ergometrine and methylegometrine after international transport (see figures 3 and 4) has also been observed in the Sudan study (18) and may be interpreted as a first sign of loss in potency. This phenomenon is a cause for concern as it implies that the results of quality tests on samples of the drug already in the field can probably not be extrapolated to the batch as a whole. It has been suggested that a discoloration of the solution in an individual ampoule indicates a loss of potency (8,29,30). This potentially useful observation should first be verified and quantified in a separate study before practical guidelines could be issued.

There are no indications that any of the other drugs included in this study are unstable during international transport. From a medical point of view this is particularly important for the antibiotics, none of which showed a significant decrease in potency. This conclusion does not imply that they will remain potent in tropical climates, and the small loss of potency and the slight increase in decomposition products could be the start of a further loss during inland transport and storage.

Table 18  
Stability under tropical conditions of some common antibiotics

Ampicillin	<p>A.sodium substance strongly degradable (11)  A.trihydrate substance subject to decomposition (11)  Humidity is more damaging than high temperature (16)  Anhydrous form more stable than trihydrate (16,17)  Field study: ampicillin trihydrate powder for injection in Sudan showed &lt;10% hydrolytic degradation (8)</p>
Benzylpenicillin	<p>Both -Na and -K substance subject to decomposition (11)  Dry powder is stable if stored dry (16)  Absorbed water increases decomposition rate (37)  Stable in solid phase when kept dry, even at elevated temperatures; at 75% RH and 20 °C. it lost 50% in 6m (36)</p>
Chloramphenicol	<p>Substance subject to decomposition (11)  Substance very stable when kept in the dark; some indications for photochemical decomposition (16)  Shelf-life of unprotected capsules reduced to 9.2 and 5.7 months under hot-humid conditions (6)</p>
Procaine benzylpenicillin	<p>Slight decomposition of the substance (11)  Field study: no instability observed in Sudan (8)</p>
Tetracycline	<p>Substance subject to decomposition (11)  Shelf-life of unprotected capsules reduced to 4.6 and 5.5 months under hot-humid conditions (6)  Field study: no instability observed in Sudan (8)</p>

The few published studies on the stability of antibiotics in tropical climates are summarized in Table 18. The results are all based on accelerated stability studies. The only field study under real-life conditions is the longitudinal study in Sudan which included procaine benzylpenicillin, ampicillin and tetracycline (8).

Procaine benzylpenicillin seems to be the most stable of the antibiotics. Although the substance showed some signs of decomposition in the WHO accelerated stability tests (11), the Sudan study found no signs of instability in the field (8). Benzylpenicillin powder showed more decomposition during the accelerated tests (11) but the powder is stable when stored dry (16), even at elevated temperatures (36). No signs of instability were found in our study and it seems likely that the glass vial offers adequate protection from humidity.

Ampicillin sodium and ampicillin trihydrate powder are unstable under accelerated stability tests (11). As with benzylpenicillin, humidity is more harmful than elevated temperatures (16). For this reason it is understandable that the anhydrous form is more stable than the trihydrate (8,17,18). The ampicilline trihydrate capsules in the Sudan study showed initial hydrolytic degradation which continued only as long as the water content was sufficient (8); the loss on drying remained within the specified limits. In our study the ampicillin trihydrate in the capsules and the ampicillin sodium powder for injection did not show signs of instability.

Tetracycline as a substance is subject to degradation under accelerated stability tests (11); in one study the shelf-life of capsules of two different brands outside their packing was reduced to less than six months under tropical conditions (6). In our study there were no signs of instability of the drug within the packing material.

There is a pattern in the results of these different studies. For most antibiotics the accelerated stability studies on the unprotected substance show signs of degradation, and so do tests on the unprotected tablets or capsules. For most substances the humidity is more harmful than the elevated temperature. This implies that the stability in the field is very much dependent on the level of protection against humidity and that the actual product, when adequately packed in glass vials or humidity resistant containers, is likely to be stable. This is confirmed in the Sudan study and in the results of our study, and reconfirms the need for stability studies to be performed within the original package of the product (38,39).

A separate finding of the present study was that two drugs were already of low potency before international transport. In the case of ampicillin the use of inferior raw materials is likely to be the cause rather than instability; this view is supported by the relatively high level of decomposition products in the control samples and by the facts that the drug had been produced only six months prior to the test and that the problem was partially corrected by the manufacturer by overfilling the vials. In the case of ergometrine the test was carried out 15 months after manufacture and the low potency is likely to be due to instability.

Another observation that can be made is that the potency of the more expensive drugs included in this study (mostly antibiotics) is closer to the lower than to the upper end of the pharmacopoeal limits, implying that the margins in case of instability in tropical climates are relatively small. Both observations underscore the need for a careful evaluation of potential suppliers and for a constant check on the quality of sensitive products.

## CONCLUSION

This study was intended to document the climatic conditions during international transport and to measure the effect of these conditions on a number of frequently used essential drugs for which a suspicion of instability existed.

The temperature and relative humidity within the test kits during international transport proved to be much higher than is generally recommended for drug storage. No significant differences were found between the various locations on board or within the container. Apart from (methyl)ergometrine injection no significant loss of potency or quality could be found in the 11 essential drugs that were included in the study. This is especially reassuring with regard to the antibiotics that were included (ampicillin, benzylpenicillin, phenoxymethylpenicillin and tetracycline). The result is in line with the only other longitudinal study on drug stability in the tropics, carried out in Sudan, in which most of the loss of potency observed occurred within the country rather than during international transport (8).

Our results should be interpreted within the limits of any screening exercise and keeping in mind the inherent difficulties in any attempt to prove that something does *not* exist. The study could never be comprehensive and was never intended to be. It is a first attempt to gain some insight into possible stability problems of essential drugs in tropical climates, and it was clear from the beginning that more work would be necessary to complete the picture. We therefore recommend to carry out several other types of studies.

First, more recordings should be made of the climatic pattern on other representative sea routes; these are being carried out in a second phase of the present study. Secondly, more longitudinal stability studies *within* tropical countries are needed, as the climatic patterns observed during storage in port areas and inland transport by truck are not reassuring. High values and strong fluctuations in temperature and relative humidity have been found and these are exactly the conditions that are known to be most detrimental to drug quality. Keeping in mind the results of the Sudan study, more loss of potency and quality is to be expected during inland transport and storage.

Thirdly, the instability of (methyl)ergometrine, which is reconfirmed in this study, underscores the need for more work in this field. In view of the fact that the manufacturing process seems to be all important for the stability of the individual product, more brands of the drugs should be examined. The climatic pattern known through this study and through existing literature on the kinetic average temperature (14,40) make it possible to design simple simulation studies to define the specific storage instructions needed for this vital and life-saving drug. Lastly, studies should be undertaken to compare brand-to-brand differences in other drug products.

## REFERENCES

- 1 WHO Expert Committee on specifications for pharmaceutical preparations. Geneva, World Health Organization, 1980: Technical Report Series, 645
- 2 WHO Expert Committee on specifications for pharmaceutical preparations. Geneva, World Health Organization, 1990. Technical Report Series 790:25
- 3 Grimm, W von. Stabilitätsprüfung pharmazeutischer Zubereitungen. Teil 2: Durchführung von Langzeittests (in German). 1975; 12: 1075-84
- 4 Becker C, Fritz HE, Mennicke W, Möbers F and Witt M. Temperaturbelastung von Arzneimitteln an Bord (Temperature of medicines on board). *Pharmazeutische Zeitung* 1983; 15: 794-7
- 5 Smallenbroek, H. Stability of drugs in the tropics. Groningen, The Netherlands. Wetenschapswinkel voor Geneesmiddelen, 1983
- 6 York, P. The shelf-life of some antibiotic preparations stored under tropical conditions. *Pharmazie* 1977; 32: 101-4
- 7 Walker GJA, Hogerzeil HV, Hillgren U. Potency of ergometrine in tropical countries (letter). *Lancet* 1988 (ii); 393
- 8 Abu-Reid IO, El-Samani SA, Hag Omer AI, Khalil NY, Mahgoub KM, Everitt G, Grundstrom K, Lindgren B and Stjernstrom NE. Stability of drugs in the tropics. A study in Sudan. *Int Pharm J* 1990; 4: 6-10.
- 9 Essential Drugs Price List July-December 1990. Copenhagen, UNICEF Supply Division, 1990
- 10 Battersby A, Hogerzeil HV. WHO/UNICEF Study on the stability of drugs during international shipment (protocol). Geneva, World Health Organization, 1988; DAP
- 11 Accelerated stability studies of widely used pharmaceutical substances under simulated tropical conditions. Geneva, World Health Organisation, 1986; Doc WHO/PHARM/86.529
- 12 Longland PW, Rowbotham PC. Stability at room temperature of medicines normally recommended for cold storage. *Pharm J* 1987 (Jan); 147-151
- 13 Mollica JA, Ahuja S, Cohen J. Stability of pharmaceuticals. Review article. *J Pharm Sci* 1978; 67: 443-65.
- 14 Grimm W. Stability testing in industry for worldwide marketing. *Drug Dev Ind Pharm* 1986; 12:1259-92
- 15 Stability of drug dosage forms. Geneva, World Health Organization, 1988. Doc.PHA/EC/SPP/88.6
- 16 Vos GI. Houdbaarheid van antibiotica (Stability of antibiotics, in Dutch). Groningen, The Netherlands. Wetenschapswinkel voor Geneesmiddelen, 1982
- 17 Pawelczyk E, Hermann T, Knitter B, Smilowski B. Kinetics of drug decomposition Part 61. Kinetics of various ampicillin forms degradation in solid phase. *Pol J Pharmacol Pharm* 1980; 32:47-54
- 18 Stjernstrom, N. Personal communication
- 19 Battersby A, Hogerzeil HV. WHO/UNICEF Study on the stability of drugs during international shipment (protocol). Geneva, World Health Organization, DAP, 1988; Appendix 3
- 20 WHO Expert Committee on specifications for pharmaceutical preparations. Geneva, World Health Organisation, 1990. Technical Report Series 790:30-31
- 21 Terao M, Aoki K, Ueki Y. A proposed method for the prediction of stability based on actual field temperatures. *Chem Pharm Bull* 1982; 30:2971-9
- 22 Hogerzeil, HV. Personal communication
- 23 The prevention and management of postpartum haemorrhage. Report of a technical working group. Geneva, World Health Organization, 1990. Document WHO/MCH/90.7
- 24 Goodman and Gillman. *The pharmacological basis of therapeutics*, 6th Ed. New York, MacMillan, 1980; 946
- 25 Martindale. *The Extra Pharmacopoea*, 29th Ed. London, The Pharmaceutical Press, 1989
- 26 Drug Information for the Health Care Provider (USPDI). Rockville, MD, USA; The US Pharmacopoeial Convention, Inc, 1986
- 27 Wolfert RR, Cox MR. Room temperature stability of drug products labeled for refrigerated storage. *Am.J.Hosp.Pharm.* 1975; 32: 585-7
- 28 Vogenberg FR, Souney PF. Stability guidelines for routinely refrigerated drug products. *Am J Hosp Pharm* 1983; 40: 101-2

- 29 South Tees Health Authority Pharmaceutical Service. The storage of drugs under controlled temperature conditions. Middlesbrough, Cleveland. South Cleveland Hospital, department of pharmacy, 2nd ed., 1985.
- 30 Van Dokkumburg AW. Stabiliteit van ergometrine injecties (Stability of ergometrine injections, in Dutch). Groningen, The Netherlands. Wetenschapswinkel voor Geneesmiddelen, 1989
- 31 Frandsen P. The stability of ergometrine injection Ph Nord '63 with some remarks on the biological assay. Dansk Tidsskr.Farm, 1966;40:19-31
- 32 El Masry. Testing the stability of ergometrine dosage forms. Manufacturing Chemist and Aerosol News, September 1978; p 53
- 33 Tokunaga H, Kimura T, Kawamura J, Yamaha T. Stability of ergometrine maleate in aqueous solutions. Iyakuhin Kenkyu 1985;16, ISS 1:130-135
- 34 Smith HT, Molinaro NC. High-performance liquid chromatographic method for the determination of methysergide and methylergonovine in human plasma. J Chromatogr 1988;424(2):416-23
- 35 Krugers Dagneaux PGLC, Klein Elhorst JT, Knuif AJ. Bereiding en analyse van ergometrine injectie vloeistof (preparation and analysis of ergometrine injection, in Dutch). Ziekenhuis Pharmacie, 1987;3:116-8
- 36 Pawelczyk E, Plotkowiak Z, Knitter K, Kozakiewicz-Wegner B. Kinetics of drug decomposition, Part 62. Kinetics of penicillin G potassium salt (PGP) thermal degradation in solid phase. Pol J Pharmacol Pharm 1980;32:55-62
- 37 Pikal MJ, Lukes AL, Lang JE. Thermal decomposition of amorphous B-lactam antibacterials. J Pharm Sc 1977;66:1312-6
- 38 Industrial Pharmacists Group and Joint Pharmaceutical Analysis Group. Standardising stability tests. Pharm J 1981 (Jul); 82-4.
- 39 Taborsky-Urdinola CJ, Gray VA and Grady LT. Effects of packaging and storage on the dissolution of model prednisolone tablets. Am J Hosp Pharm 1981; 38: 1322-7
- 40 Haynes JD. Worldwide virtual temperatures for product stability testing. J Pharm Sc 1971;60:927-9

## ANNOTATED BIBLIOGRAPHY

### General

WHO Expert Committee on specifications for pharmaceutical preparations. Geneva, World Health Organisation, 1990. Technical Report Series 790.

Contains a short chapter on stability of drugs, a list of less stable drug substances based on the WHO report on accelerated stability studies, and a glossary of terms.

Stability of drug dosage forms. Geneva, World Health Organization, 1988. Doc.PHA/EC/SPP/88.6

General overview on the problem of drug stability. Lists factors that may influence stability. Contains a glossary of terms, a list of more easily degradable drug substances from the WHO Model List and a list of selected references. Reproduced in abridged form in TRS 790

Grimm W. Stability testing in industry for worldwide marketing. *Drug Dev Ind Pharm* 1986;12:1259-92

Good overview of requirements and practices of stability testing for worldwide marketing, with a section on kinetic temperatures in four climatic zones. The paper gives good advice in simple wording.

Smallembroek, H. Stability of drugs in the tropics. Groningen, The Netherlands. Wetenschapswinkel voor Geneesmiddelen, 1983

Literature study on the stability of drugs in the tropics, with some consideration of the question as to whether expired drugs can be used and other practical problems. Contains useful definitions and many literature references.

Mollica JA, Ahuja S, Cohen J. Stability of pharmaceuticals. *J Pharm Sci* 1978; 67: 443-65.

A very detailed review article on the stability of drugs, with 432 references. Mentions the effects of environmental factors on drugs. Large section on accelerated stability tests. Very detailed paper, but not completely up-to-date.

### Theoretical aspects

Newton DW, Miller KW. Estimating shelf-life of drugs in solution. *Am J Hosp Pharm* 1987; 44:1633-40

Rather technical paper describing the use of pseudo-first order chemical reaction kinetics and Arrhenius thermodynamic principles in estimating the effect of temperature on shelf-life of drug solutions.

Stewart PJ, Tucker IG. Prediction of Drug stability - Part 1: Mechanisms of drug degradation and basic rate laws. *Aust J Hosp Pharm* 1984; 14: 165-70

Describes the common mechanisms of drug degradation in solution including hydrolysis, oxidation, isomerisation, photolysis and polymerisation. Concept of reaction order and shelflife are defined and the influence of temperature on reaction rate (Arrhenius equation).

Stewart PJ, Tucker IG. Prediction of Drug stability - Part 2: Hydrolysis. *Aust J Hosp Pharm* 1985; 15: 11-6

Stewart PJ, Tucker IG. Prediction of Drug stability - Part 3: Oxydation and photolytic degradation. *Aust J Hosp Pharm* 1985; 15: 111-117

Stewart PJ, Tucker IG. Prediction of Drug stability - Part 4: Isomerisation. *Aust J Hosp Pharm* 1985; 15: 181-188

Stewart PJ, Tucker IG. Prediction of Drug stability - Part 5: Physical stability. *Aust J Hosp Pharm* 1985; 15: 236-246

Stewart PJ, Tucker IG. Prediction of Drug stability - Part 6: Stability trials. *Aust J Hosp Pharm* 1986; 16: 35-43

Reviews the various aspects of different types of stability trials, including accelerated stability tests and stability trials for extemporaneous products. Includes a list of common deficiencies in stability data and trial design.

Amirjahed AK. Simplified method to study stability of pharmaceutical preparations. *J Pharm Sc* 1977;66:785-9

Describes a model study establishing a linear relationship between the logarithm of  $t(0.9)$  and the reciprocal of the corresponding temperature in absolute degrees, to predict shelf-life of dosage forms. Very technical paper.

Bakar S, Niazi S. Simplified method to study stability of pharmaceutical preparations (letter). *J Pharm Sc* 1978;67:141

Letter to the Editor stating that the conclusions of the original paper are not valid.

Haynes JD. Worldwide virtual temperatures for product stability testing. *J Pharm Sci* 1971;60:927-9

Key article on the use of virtual temperatures to reflect annual temperature fluctuations in various locations in the world as the basis for stability testing.

## Accelerated stability tests

Accelerated stability studies of widely used pharmaceutical substances under simulated tropical conditions. Geneva, World Health Organisation, 1986; Doc WHO/PHARM/86.529

Describes the results of accelerated stability tests on the active substance of 196 drugs on the WHO Model List of Essential Drugs. Classifies 110 substances as degradable.

Stewart PJ, Tucker IG. Prediction of Drug stability - Part 6: Stability trials. *Aust J Hosp Pharm* 1986; 16: 35-43

Reviews the various aspects of different types of stability trials, including accelerated stability tests and stability trials for extemporaneous products. Includes a list of common deficiencies in stability data and trial design.

Smallegenbroek, H. Stability of drugs in the tropics. Groningen, The Netherlands. Wetenschapswinkel voor Geneesmiddelen, 1983

Literature study on the problem of stability of drugs in the tropics, with emphasis on some practical problems. Discusses the limitations of accelerated tests on drug substances alone.

Mollica JA, Ahuja S, Cohen J. Stability of pharmaceuticals. *J Pharm Sci* 1978; 67: 443-65.

A very detailed review article on stability of drugs, with 432 references. Large section on accelerated stability tests. Very detailed paper, but not completely up-to-date.

York, P. The shelf-life of some antibiotic preparations stored under tropical conditions. *Pharmazie* 1977; 32: 101-4

Accelerated stability study of three antibiotics kept at 31% and 75% relative humidity and at 40, 50 and 60 °C. Using the Arrhenius equation the expected shelf-life for each condition was calculated. The drugs were kept outside their package.

## Standardisation of stability testing

WHO Expert Committee on specifications for pharmaceutical preparations. Geneva, World Health Organisation, 1990. Technical Report Series 790.

Contains a short chapter on stability of drugs and a glossary of terms which is intended to standardise stability testing and storage instructions.

Stewart PJ, Tucker IG. Prediction of Drug stability - Part 6: Stability trials. *Aust J Hosp Pharm* 1986; 16: 35-43

Reviews the various aspects of different types of stability trials. Includes a list of common deficiencies in stability data and trial design.

Expiration dating and stability testing for human drug products. Inspection Technical Guide, Food and Drug Administration, ORO/ETSB (HF-133), nr. 41, 1985

FDA technical guide, giving background information on expiry date and stability testing regulations.

Hartmann V, Krummen K, Schnabel G and Bethke H. Techniques of stability testing and shelf-life predictions. *Pharm Ind* 1982; 44, 1: 71-9.

Technical paper describing different stability tests and the ways to predict stability. Statistical simulation proves that a reasonable forecast of the shelf-life is possible often already after one, practically always after two years.

Industrial Pharmacists Group and Joint Pharm. Analysis Group. Standardising stability tests. *Pharm J* 1981 (Jul); 82-4. Report on a meeting on the standardisation of stability tests. Recommends that stability studies test the drug in its marketing closure/container system.

Haines BA. Worldwide regulatory data requirements for expiration dating. *Drug Inf Journal* July-Sep 1979:97-100

Describes the various requirements for stability testing used by different regulatory bodies in the world and some initiatives to come to standardized requirements. Mentions that room temperature in BP is 15-25 °C and 15-30 °C in the USP, a difference which can have important consequences for the shelf-life.

Grimm, W von. Stabilitätsprüfung pharmazeutischer Zubereitungen. Teil 2: Durchführung von Langzeittests (in German). 1975; 12: 1075-84

A rather technical paper on the design of longterm stability studies. Useful for its listing of four climatic zones, and calculations of virtual average temperature for each zone. Tries to standardise stability studies.

## Practical information on the stability of individual drugs

- Longland PW, Rowbotham PC. Stability at room temperature of medicines normally recommended for cold storage. *Pharm J* 1987 (Jan); 147-151  
Lists the shelf-life of 200 drugs recommended for cold storage if stored at room temperature (18-25 °C), based on information supplied by the manufacturers.
- South Tees Health Authority Pharmaceutical Service. The storage of drugs under controlled temperature conditions. Middlesbrough, Cleveland. South Cleveland Hospital, Department of pharmacy, 2nd ed., 1985.  
Contains a summary of storage information on approximately 2000 substances, taken from established pharmacopoeas and standard textbooks.
- Vogenberg FR, Souney PF. Stability guidelines for routinely refrigerated drug products. *Am J Hosp Pharm* 1983; 40: 101-2  
Short paper in which information by suppliers is summarized on the effect of storage other than recommended by the supplier. Contains information on 34 drugs, listed alphabetically under brand name.
- Kirschenbaum BE, Latiolais CJ. Stability of injectable medications after reconstitution. *Am J Hosp Pharm* 1976; 33: 767-91  
Presents a long list of summarized information, obtained from manufacturers, on the stability of injectable drugs after reconstitution. The list contains about 220 drugs, listed alphabetically under brand name.
- Wolfert RR, Cox MR. Room temperature stability of drug products labeled for refrigerated storage. *Am.J.Hosp.Pharm.* 1975; 32: 585-7  
Presents a list of about 50 products that are recommended for refrigerated storage, together with manufacturer's information on the shelf-life if the drugs are kept at room temperature not exceeding 25 °C. The paper concludes that many drugs are more stable than their storage instruction would suggest.
- Bakker P, Gooskens V, Van Doorne H, Wieringa NF. Dermatological preparations for use in the tropics. Groningen, The Netherlands. Wetenschapswinkel voor Geneesmiddelen (address: Antonius Deusinglaan 2, 9713 AW Groningen).  
Thorough study on the selection, preparation and stability of essential dermatological preparations for tropical countries. Contains a chapter on the stability of commonly used substances and preparations, with a summary list of expected shelf-life of various preparations. The book also contains lists of simple formulations for PHC and for hospitals.
- The shelf-life of drug supplies. Geneva, World Council of Churches, Christian Medical Commission. Contact (year unknown)  
Discusses the problems of stability problems in tropical climates with a summary list of maximum storage time and storage conditions of 33 essential drugs on the WHO Model List.

## Field studies

- Abu-Reid IO, El-Samani SA, Hag Omer AI, Khalil NY, Mahgoub KM, Everitt G, Grundstrom K, Lindgren B and Stjernstrom NE. Stability of drugs in the tropics. A study in Sudan. *Int Pharm J* 1990; 4: 6-10.  
Describes a longitudinal study in which six drugs were tested at regular intervals during a two-year flow period in the drug distribution system in Sudan; two drugs showed a considerable loss of potency.
- Stability of drugs in the tropics. A study in Sudan. Hag Omer AI, Stjernstrom NE (letter). *Trop Doct* 1990;20:129  
Gives a summary of the same study
- Walker GJA, Hogerzeil HV, Hillgren U. Potency of ergometrine in tropical countries (letter). *Lancet* 1988 (ii); 393  
Describes a field survey of 24 samples of ergometrine injection taken from rural health clinics in Zimbabwe, Democratic Yemen and Bangladesh. None were kept in the refrigerator. Only 9 confirmed to BP/USP and 7 had potencies below 20%.
- Terao M, Aoki K, Ueki Y. A proposed method for the prediction of stability based on actual field temperatures. *Chem Pharm Bull* 1982;30:2971-9  
Describes the use of actual annual recorded temperatures to be used in studies to predict shelf-life; mentions examples from Bangkok and Osaka. Includes an example on adrenaline, predicting that the drug is unstable in tropical climates.

## Manufacturing process and packaging in tropical climates

Bos, T. Tropical tablets: the development of tablet formulations for use in tropical countries. Groningen, The Netherlands. State University, 1990. Dissertation. Available from: Mrs T.Bos, Fazantenveld 96, Cuijk, The Netherlands.

A detailed study on the use of various types of starch and on the prevention of chemical and microbiological instability in the preparation of tablets for use in tropical climates.

Bos CE, Van Doorne H, Lerk CF. Microbiological stability of tablets stored under tropical conditions. *Int J Pharmaceutics* 1989; 55: 175-83

Several types of tablet excipients were tested for their potential for microbiological contamination in tropical climates. Tablets, when stored at 31.C/95%RH are at risk to microbial spoilage. The addition of a preservative can prolong their microbiological shelf-life. When tablets are stored below 75% RH the addition of preservatives is not necessary.

Smallegenbroek, H. Stability of drugs in the tropics. Groningen, The Netherlands. Wetenschapswinkel voor Geneesmiddelen, 1983

Literature study on the stability of drugs in the tropics, concentrating on practical problems. Contains a survey on the properties of various packing materials.

Taborsky-Urdinola CJ, Gray VA and Grady LT. Effects of packaging and storage on the dissolution of model prednisolone tablets. *Am J Hosp Pharm* 1981; 38: 1322-7.

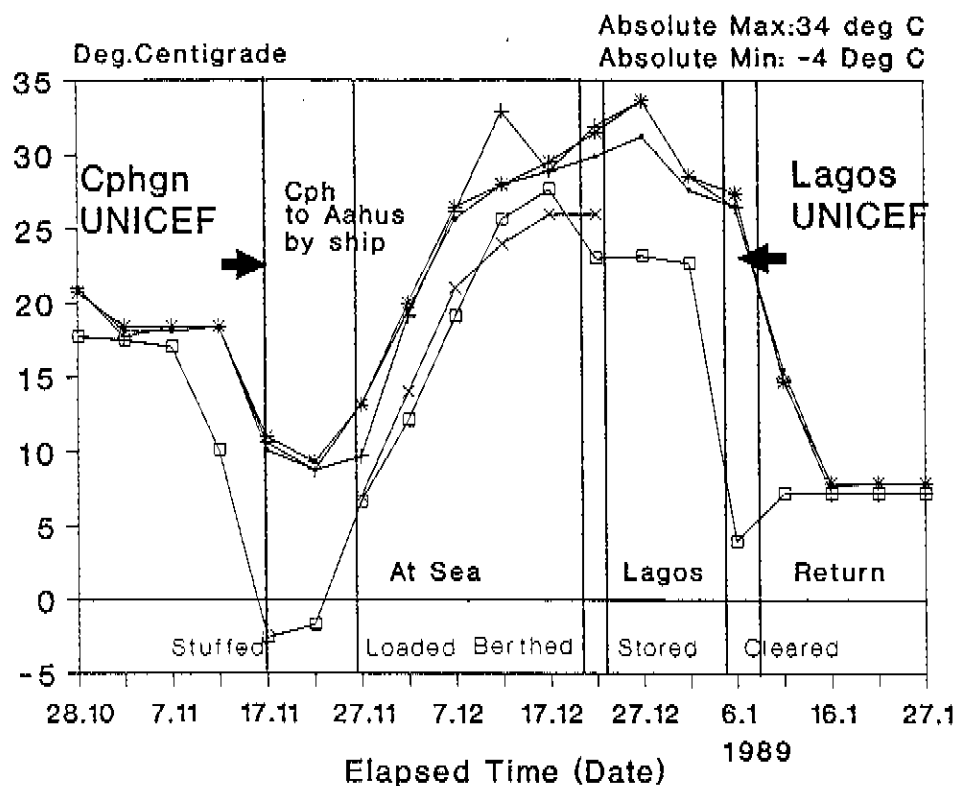
Describes a study of the effect of packaging material on the physical dissolution of (prednisolone) tablets under three climatic conditions. Tablets in the least moisture-permeable container were least affected by storage. Proper package and storage are essential to maintain product integrity; the original expiry date cannot be put on drugs that have been repacked into smaller containers at the pharmacy level.

York, P. A preliminary study of the physical stability of tablets prepared from powders stored under tropical conditions. *Pharmazie* 1976;31:383-6

The effects of storing powders under tropical conditions was studied on the physical stability of tablets as measured by changes in tablet weight, hardness and volume. Differences in stability are related to different degrees of moisture uptake by the powders during storage.

# ANNEXES

## Temperature between Copenhagen and Lagos



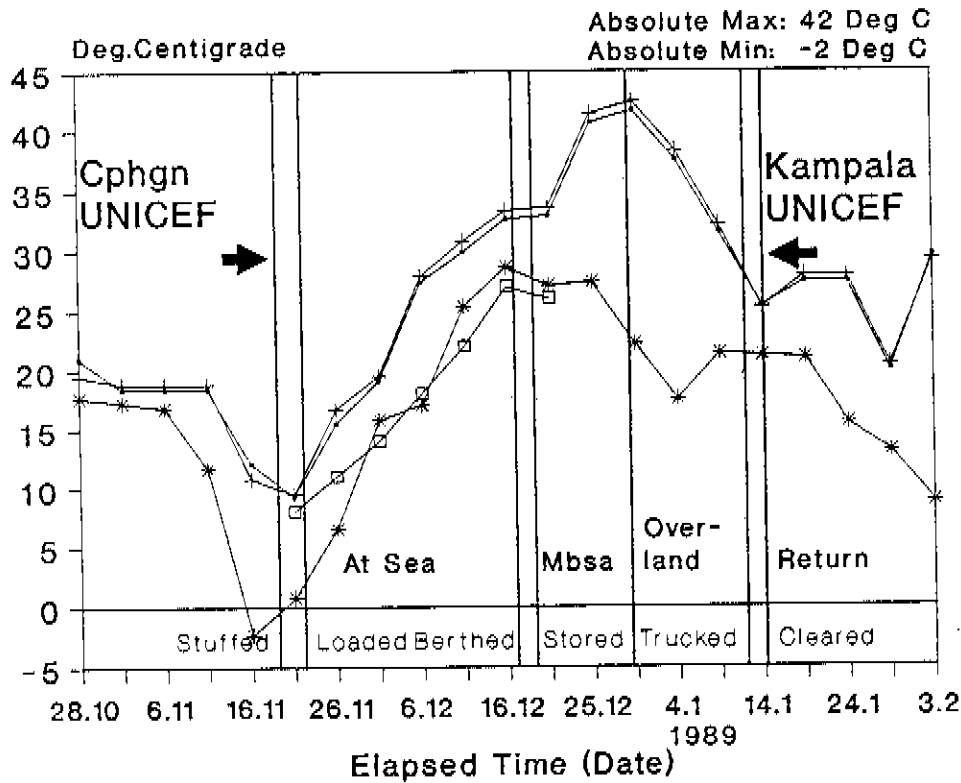
Sensor & Location			
—●—	#1,D,T (max)	—+—	#2,D,C (max)
—*—	#8,H,C (max)	—□—	#1,D,T (min)
—x—	Mean Ambient		

Note: D - Deck T - Top of Container  
H - Hold C - Centre of Container  
Mean Ambient recorded from ship's log

*Summary of the journey*

The containers were packed during cold weather and loaded onto a feeder vessel to take the drugs to Aarhus, from where the ocean going ship departed. During the time it took to reach Aarhus the AUTOLOGs recorded minus 3.5 °C, which was the lowest temperature of the whole journey. The temperature remained below zero for 18 three-hour readings spread over three days. During the voyage to Lagos the temperature rose steadily peaking at 32 °C. The ship's logbook recorded that the weather in Lagos and the vicinity was unusually cool, due to strong Harmattan winds which both lowered the temperature and the humidity. During the time that the containers were in storage at Lagos port the temperature fell from a high of 33.6 °C to a low of 23.0 °C. On 7 January the kits were placed in a refrigerator by UNICEF Lagos.

Temperature between Copenhagen and Kampala



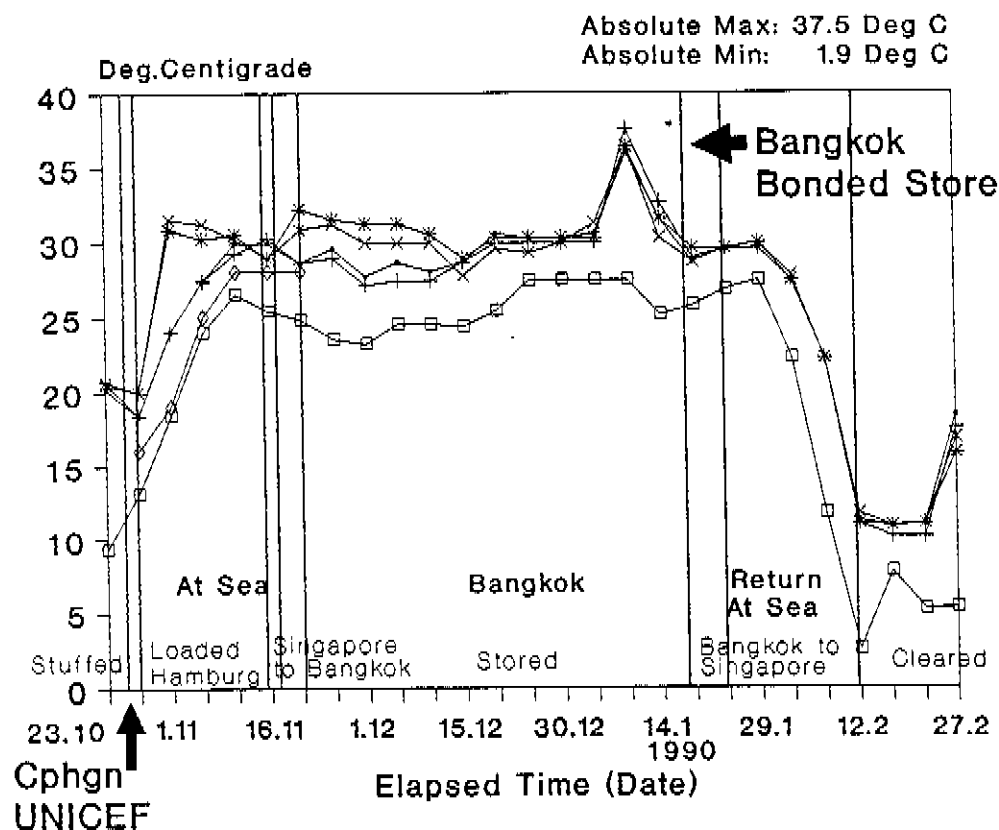
Sensor & Location			
—+—	#3,Deck,Top (max)	—x—	#4,Deck,Ctr (max)
—*—	#3,Deck,Top (min)	—□—	Mean Ambient

Mean Ambient recorded from Met Office data

*Summary of the journey*

As with the Lagos consignment, this consignment was packed at low temperatures, with a minimum of - 2.3 °C. During the voyage the temperature rose to 33 °C. While the containers were in port in Mombasa the temperature fluctuated between 28 °C and 40 °C. During the journey from the coast to Kampala there was considerable fluctuation in temperature. The highest recorded temperature was 42.4 °C while the lowest was 17.5 °C.

Temperature between Copenhagen and Bangkok



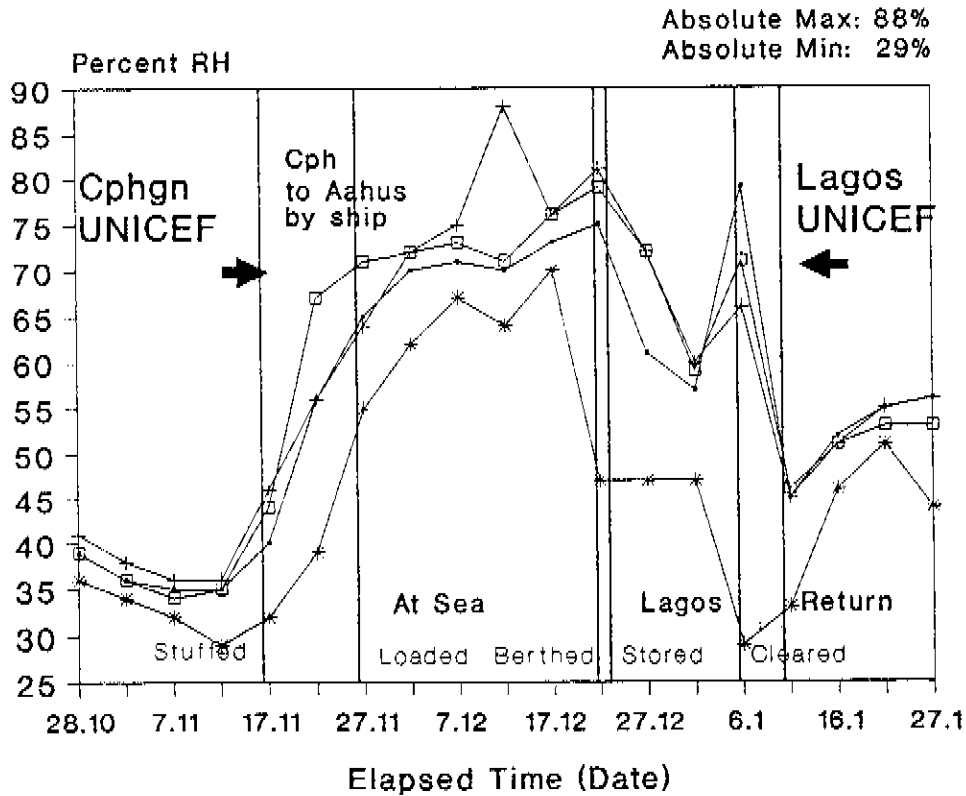
Sensor & Location		
— #11,H,T(max)	+ #12,H,C(max)	* #5,D,T(max)
—□ #11,H,T(min)	* #6,D,C(max)	◇ Mean Ambient

Note: D = Deck, T = Top of Container  
H = Hold, C = Centre of Container  
Mean Ambient recorded from ship's log

*Summary of the journey*

Temperatures during loading were between 10 and 20 °C; they rose to 30.5 °C during the journey by sea. Throughout the time that the drug kits remained in the bonded store in Bangkok the temperature remained fairly constant ranging from 24 to 36 °C. It is unclear why there was an increase in temperature during the period of 12-14 January 1990. Unintentionally, the kits returned by sea. The return journey had characteristics very similar to the outbound one.

Relative humidity between Copenhagen and Lagos

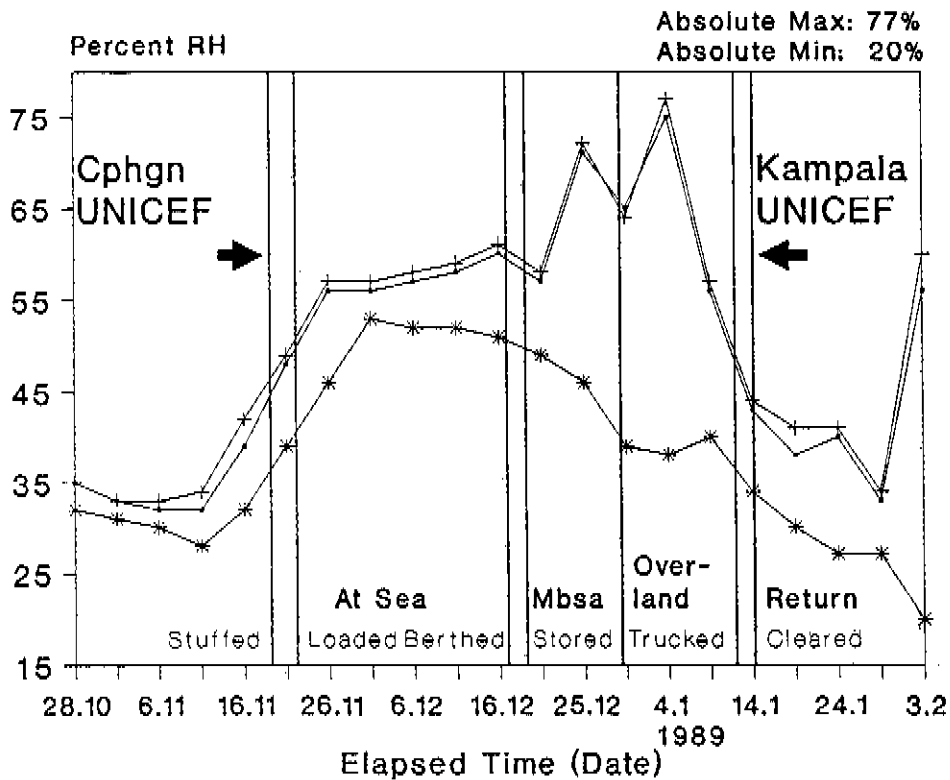


Sensor & Location			
—+—	#1,Deck,Top (max)	—+—	#2,Deck,Ctr (max)
—*—	#1,Deck,Top (min)	—□—	#8,Deck,Ctr (max)

*Summary of the journey*

The containers were packed during cold weather and loaded onto a feeder vessel to take the drugs to Aarhus. During the time it took to reach Aarhus the RH was 30-55%. During the voyage between Aarhus and Lagos the relative humidity rose steadily peaking at over 88% six days before the ship reached Lagos, presumably during a call in another West African port. The ship's logbook recorded that the weather in Lagos was unusually cool and dry, due to strong harmattan winds which both lowered the relative humidity and the temperature. During the time that the containers were in storage in Lagos port the RH fell from a high of 80% to a low of 30%.

Relative humidity between Copenhagen and Kampala

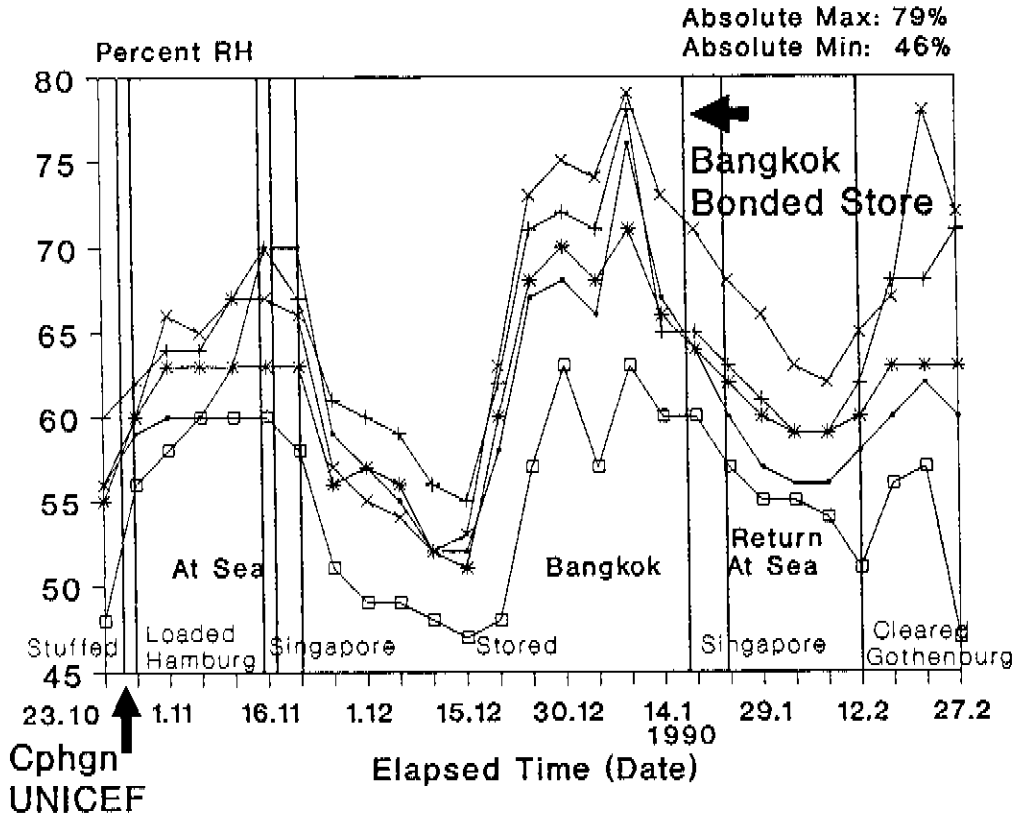


Sensor & Location	
—	#3,Deck,Top (max)
—+	#4,Deck,Ctr (max)
—*	#3,Deck,Top (min)

*Summary of the journey*

As with the Lagos consignment, this container was packed at low RH which remained low throughout the voyage, rising to a maximum of 60%. While the containers were in the port at Mombasa the RH fluctuated between 35-70%. During the journey from the coast to Kampala fluctuation was even greater, ranging from 35-75%.

Relative humidity between Copenhagen and Bangkok



*Summary of the journey*

During packing and loading the RH was between 45-55%, which rose to 70% during the sea voyage. During the time that the kits stayed in bonded storage in Bangkok the RH was between 45-60% during the first month, rising to 60-78% in the second month. The (unintended) return journey by ship shows much the same pattern with RH between 50-65%.

## Acetylsalicylic acid tablets 300 mg (A)

MNF	4/88	DECLARED AMOUNT: 300 mg	BP: 95-105%
EXP	4/93	BATCH NR: 18088	USP: 95-105%

**Sampling** CONTROL KIT: 11/88 TEST KITS: 1/89  
From each kit a sample of 10 tablets was taken; the contents of the 10 tablets were mixed and analyzed. From the control kit, two samples were analyzed.

**Assay method** High Pressure Liquid Chromatography; Column 1: Apex ODS RP18, 30cm; Column 2: Spherisorb ODS RP18 30cm; detection at UV 280 nm; mobile phase: 2g of sodium 1-heptanesulphonate in a mixture of 850 ml water and 150 ml acetonitrile adjusted with glacial acetic acid to pH 3.4

Summary results	CONTROL KIT		TEST KITS	
n	2		8	
Min	302.41	100.8%	296.87	99.0%
Max	303.28	101.1%	305.27	101.8%
Mean	302.85	101.0%	302.05	100.7%
SD	0.43	0.1%	2.71	0.9%
SE	0.304		0.958	
t	12.706		2.365	
95% CL-	298.99	99.7%	299.78	99.9%
95% CL+	306.71	102.2%	304.31	101.4%
	DECREASE FROM CONTROL		0.3%	

**Weight variation** Mean weight 363.8 mg/tablet (+3.3, -2.45%)

### Conclusions

- 1 All samples are within BP/USP requirements.
- 2 Test samples have lost, on average, 0.3% of potency during international transport (n.s.).
- 3 There are no indications that acetylsalicylic acid tablets are unstable during international transport.



## Acetylsalicylic acid BP tablets 300 mg (B)

MNF	3/88	DECLARED AMOUNT:	300 mg	BP: 95-105%
EXP	3/92	BATCH NR:	88038	USP: 95-105%

**Sampling** CONTROL KIT: 11/88 TEST KITS: 1/89  
From each kit a sample of 10 tablets was taken; the contents of the 10 tablets were mixed and analyzed. From the control kit, two samples were analyzed.

**Assay method** High Pressure Liquid Chromatography; column: Spherisorb ODS RP18 30cm; detection UV 280 nm. Mobile phase: 2g of sodium 1-heptanesulphonate in a mixture of 850 ml water and 150 ml acetonitrile adjusted with glacial acetic acid to pH 3.4

Summary results	CONTROL KIT	TEST KITS
n	2	8
Min	300.08 100.0%	298.06 99.4%
Max	300.19 100.1%	302.96 101.0%
Mean	300.14 100.0%	300.62 100.2%
SD	0.05 0.0%	1.96 0.7%
SE	0.035	0.692
t	12.706	2.365
95% CL-	299.69 99.9%	298.98 99.7%
95% CL+	300.59 100.2%	302.25 100.8%
	INCREASE FROM CONTROL	0.2%

**Weight variation** Mean weight 335.6 mg/tablet (+1.34, -1.37%)

### Conclusions

- 1 All samples are within BP/USP requirements.
- 2 Test samples have lost no potency during international transport.
- 3 There are no indications that acetylsalicylic acid tablets are unstable during international transport.



## Ampicilline BP capsules 250 mg

---

MNF	2/88	DECLARED AMOUNT:	250 mg	BP: 92.5-107.5%
EXP	2/91	BATCH NR:	63 149	USP: 90-120%

---

**Sampling** CONTROL KIT: 11/88 TEST KITS: 1/89  
 From each kit, one sample of 10 capsules was taken; the contents of the 10 capsules were mixed and analyzed two or three times. From the control kit, two samples were analyzed.

**Assay method** Potentiometric titration using mercuric nitrate as titrant

Summary results	CONTROL KIT		TEST KITS	
n	2		8	
Min	96.43	96.4%	95.74	95.7%
Max	96.79	96.8%	96.42	96.4%
Mean	96.61	96.6%	96.14	96.1%
SD	0.18	0.2%	0.35	0.4%
SE	0.130		0.125	
t	12.706		2.365	
95% CL-	94.95	95.0%	95.84	95.8%
95% CL+	98.26	98.3%	96.43	96.4%
	DECREASE FROM CONTROL		0.5%	

**Dissolution** Method analogous to the assay method above, and in accordance with USP requirements. Samples were taken after 20 and 45 minutes. In all cases more than 80% was dissolved after 20 minutes (requirement: more than 75% after 45 minutes).

### Conclusions

- 1 All control and test samples are within BP requirements.
- 2 Test samples have lost, on average, 0.5% of potency (n.s.).
- 3 No indications that ampicillin capsules may be instable during international transport.

## Full results of analyses

	CNTROL	H1 LHT	H2 LDC	H3 EDT	H4 EDC	H7 LDT	H8 LHC	H9 EHT	H10 EHC
<b>Assay (mg)</b>									
1	97.12	96.41	95.57	96.49	95.84	95.39	95.96	95.37	96.38
	96.84	96.30	96.88	96.34	95.63	96.05	95.92	95.91	95.35
	96.42	96.62			96.90		96.92	96.63	
2	96.34								
	96.51								
Mean	96.79 96.43	96.36	96.36	96.42	95.74	96.11	95.94	96.07	96.12
<b>Decomposition products (%)</b>									
1	2.26	2.55	3.55	2.69	2.52	3.37	2.56	2.77	2.68
	2.36	2.59	2.55	2.71	2.66	2.62	2.55	2.73	2.88
	2.41	2.58			2.53		2.67	2.62	
2	2.39								
	2.37								
Mean	2.34 2.38	2.57	2.89	2.70	2.59	2.84	2.56	2.72	2.73
<b>Dissolution test (%)</b>									
20 min	96.81 93.72	95.57	94.34	95.57	87.56	87.56	86.32	83.86	91.87
45 min	102.90 102.83	103.48	104.07	103.48	102.07	105.76	101.42	104.44	102.78

## Ampicilline injection BP (500 mg)

MNF	5/88	DECLARED AMOUNT: 250 mg	BP: 95-105%
EXP	5/91	BATCH NR: 7188	USP: 90-115%

**Sampling** CONTROL KIT: 11/88 TEST KITS: 1/89  
From each kit one sample of 9 vials was taken; the contents of the 9 vials were mixed and analyzed three times. From the control kit, two samples were analyzed.

**Assay method** Potentiometric titration with mercuric nitrate as titrant.

Summary results	CONTROL KIT		TEST KITS	
n	2		8	
Min	84.02	84.0%	82.11	82.1%
Max	84.17	84.2%	86.32	86.3%
Mean	84.10	84.1%	83.71	83.7%
SD	0.08	0.1%	1.39	1.4%
SE	0.055		0.490	
t	12.706		2.365	
95% CL-	83.39	83.4%	82.55	82.6%
95% CL+	84.80	84.8%	84.87	84.9%
	DECREASE FROM CONTROL		0.39%	

**Observations** The analyses showed low values for the active component in all control and test samples. This was partly compensated for by 13.8% overfilling to 569 mg per vial. In spite of this the results fall outside BP limits. If judged according to USP requirements the results fall just within the lower limit of 90% of the labelled amount; however, the label refers to BP.

**Conclusions**

- 1 All control and test samples show low values of active ingredient which fall outside BP and USP limits.
- 2 Overfilling with 13.8% has brought all samples just within the USP limits. If judged according to BP, 4/8 test samples are then still below the 95% limit.
- 3 Control samples show 9.42 - 9.59 % decomposition products (mean 9.51). Test samples show 8.84 - 9.98 % decomposition products (mean 9.58).
- 4 Test samples have lost 0.39% of potency during international transport (n.s.).
- 5 There are no indications that ampicillin injection is unstable during international transport.

## Full results of analyses

	CNTROL	H1 LHT	H2 LDC	H3 EDT	H4 EDC	H7 LDT	H8 LHC	H9 EHT	H10 EHC
<b>Assay (%)</b>									
1	84.75	83.64	81.87	82.73	84.79	85.15	84.15	81.78	82.61
	84.02	82.80	82.44	82.07	84.35	86.81	85.37	81.98	82.54
	83.75	84.19	82.95	82.94	85.20	87.00	85.18	82.57	83.92
2	85.10								
	83.97								
	82.98								
Mean	84.17	83.54	82.42	82.58	84.78	86.32	84.90	82.11	83.02
	84.02								
<b>Degradation products (%)</b>									
1	9.38	8.94	9.51	9.77	9.80	8.71	8.92	9.66	9.34
	9.30	9.43	10.20	10.46	10.42	8.93	9.27	10.10	10.15
	10.10	9.23	10.21	9.58	9.70	8.89	9.24	10.19	9.36
2	8.87								
	8.79								
	9.15								
Mean	9.59	9.20	9.97	9.94	9.97	8.84	9.14	9.98	9.62
	9.42								

Ampicillin sodium references substance WHO 27 40 02: Decomposition products 5.16%

## Benzylpenicillin BP (inj 1 MU) (as sodium salt)

MNF	2/88	DECLARED AMOUNT: 1 MU	BP: 95-105%
EXP	2/92	BATCH NR: B 647	USP: 90-120%

**Sampling** CONTROL KIT: 11/88 TEST KITS: 1/89  
From each kit, one sample of 10 vials was taken; the contents of the 10 vials were mixed and analyzed twice. From the control kit, two samples were tested.

**Assay method** High Pressure Liquid Chromatography; column RP18, 5µm; detection at UV 258 nm. Mobile phase: acetonitrile (27%) in phosphate buffer (4.32 g/l potassium hydrogen phosphate; 6.00 g/l sodium heptane-1-sulphonate) adjusted to pH 3.17 with phosphoric acid. Degradation products by potentiometric titration using mercuric nitrate as titrant.

Summary results	CONTROL KIT		TEST KITS	
n	2		8	
Min	96.22	96.2%	95.13	95.1%
Max	97.07	97.1%	97.29	97.3%
Mean	96.65	96.6%	96.19	96.2%
SD	0.43	0.4%	0.71	0.7%
SE	0.301		0.252	
t	12.706		2.365	
95% CL-	92.83	92.8%	95.59	95.6%
95% CL+	100.46	100.5%	96.78	96.8%
	DECREASE FROM CONTROL		0.5%	

### Conclusions

- 1 All mean assay values of control and test samples are within BP requirements.
- 2 Degradation products 0.94% for controls and 0.97 - 1.08% (mean 1.00%) for test samples.
- 3 Test samples have lost, on average, 0.5% of potency during international transport (n.s.).
- 4 There are no indications that benzylpenicillin injection is unstable during international transport.



**Ergometrine injection B.P.**

MNF	6/87	DECLARED AMOUNT: 0.200 mg	BP: 90-110 %
EXP	6/90	BATCH NR: 5287	USP: 90-110 %

**Sampling:** CONTROL KIT: 11/88 TEST KIT: 1/89  
10 boxes of 10 ampoules were tested in every kit (one control kit and 8 testkits). From each box, 3 ampoules were mixed and after dilution injected without any other treatment.

**Assay method** Liquid chromatography; reversed phase. Hypersil ODS 5um, 250x4.6mm  
Mobile phase: 0.5M phosphate buffer pH 2.1 and acetonitrile (75:25) Detection: UV 312 nm

Summary results:	CONTROL KIT	TEST KITS
n	10	80
Min	0.168 84.0%	0.099 49.5%
Max	0.178 89.0%	0.176 88.0%
Mean	0.174 87.1%	0.164 82.0%
SD	0.003 1.4%	0.016 7.9%
SE	0.0009	0.0018
t	2.262	1.995
95% CL-	0.172 86.0%	0.161 80.3%
95% CL+	0.176 88.1%	0.168 83.8%
DECREASE FROM CONTROL		0.010 5.8%
SE difference		0.00198
Difference/SE diff		5.09214
p		< 0.001

**Observations** Ampoules with lower amount of egometrine had yellow-coloured solutions

**Conclusions**

- 1 None of control- or test samples complies with BP.
- 2 All controls have 84-89% potency (mean 87%, SD 1.5%, 95%CL 85.9-88.1)  
Test samples show much more variation in potency  
18/80 of test samples are below 80% potency  
12/80 of test samples are below 70% potency  
3/80 of test samples are below 60% potency (minimum 49.5%)
- 3 Test samples have lost on average 5.8% of potency during international transport (p < 0.001)
- 4 Ergometrine injection is instable during international transport.

## Full results of analyses

	CNTROL	H1 LHT	H2 LDC	H3 EDT	H4 EDC	H7 LDT	H8 LHC	H9 EHT	H10 EHC
Assay (mg)									
1	0.178	0.131	0.142	0.167	0.174	0.171	0.171	0.174	0.156
2	0.172	0.170	0.132	0.172	0.174	0.153	0.171	0.166	0.173
3	0.174	0.174	0.172	0.173	0.173	0.175	0.175	0.161	0.173
4	0.173	0.172	0.165	0.165	0.173	0.173	0.175	0.153	0.170
5	0.174	0.175	0.172	0.176	0.175	0.172	0.160	0.169	0.159
6	0.173	0.140	0.176	0.135	0.150	0.163	0.163	0.169	0.170
7	0.178	0.149	0.175	0.113	0.174	0.171	0.173	0.175	0.175
8	0.174	0.160	0.173	0.166	0.175	0.175	0.146	0.172	0.172
9	0.168	0.165	0.175	0.164	0.117	0.175	0.169	0.134	0.174
10	0.177	0.172	0.176	0.153	0.172	0.172	0.099	0.146	0.172
Mean	0.174	0.161	0.166	0.158	0.166	0.170	0.160	0.162	0.169
SD	0.003	0.015	0.015	0.019	0.018	0.007	0.022	0.013	0.006
Min	0.168	0.131	0.132	0.113	0.117	0.153	0.099	0.134	0.156
Max	0.178	0.175	0.176	0.176	0.175	0.175	0.175	0.175	0.175

## Methylergometrine inj 0.2 mg/ 1 ml

MNF	3/88	DECLARED AMOUNT:	0.200 mg	BP: 90-110 %
EXP	3/91	BATCH NR:	392MF0388	USP: 90-110 %

**Sampling:** CONTROL KIT: 11/88 TEST KIT: 1/89  
10 boxes of 10 ampoules were tested in every kit (one control kit and 8 testkits). From each box, 3 ampoules were mixed and after dilution injected without any other treatment.

**Assay method** Liquid chromatography; reversed phase Hypersil ODS 5um, 250x4.6mm. Mobile phase: 0.5M phosphate buffer pH 2.1 and acetonitrile (75:25). Detection: UV 312 nm

Summary results:	CONTROL KIT	TEST KITS
n	10	80
Min	0.199 99.5%	0.181 90.5%
Max	0.205 102.5%	0.204 102.0%
Mean	0.201 100.7%	0.198 99.0%
SD	0.002 1.0%	0.004 2.0%
SE	0.0006	0.0004
t	2.262	1.995
95% CL-	0.2000 100.0%	0.1972 98.6%
95% CL+	0.2028 101.4%	0.1989 99.5%
DECREASE FROM CONTROL		0.0033 1.7%
SE difference		0.0007
Difference/SE diff		4.4599
p		< 0.001

### Conclusions

- 1 All control samples and all test samples comply with BP/USP
- 2 Test samples have lost on average 1.7% of potency during international transport (p < 0.001).
- 3 Methylergometrine inj seems a bit more stable than ergometrine inj.

## Full results of analyses

	CNTROL	H1 LHT	H2 LDC	H3 EDT	H4 EDC	H7 LDT	H8 LHC	H9 EHT	H10 EHC
<b>Assay (mg)</b>									
1	0.199	0.196	0.200	0.198	0.199	0.193	0.198	0.201	0.199
2	0.200	0.199	0.200	0.195	0.197	0.201	0.198	0.202	0.201
3	0.199	0.197	0.201	0.193	0.199	0.195	0.200	0.202	0.198
4	0.203	0.194	0.203	0.193	0.196	0.184	0.198	0.198	0.200
5	0.205	0.195	0.204	0.199	0.193	0.198	0.202	0.203	0.198
6	0.203	0.198	0.201	0.199	0.199	0.197	0.199	0.202	0.198
7	0.201	0.194	0.200	0.199	0.197	0.200	0.197	0.200	0.196
8	0.200	0.202	0.199	0.181	0.201	0.195	0.198	0.200	0.202
9	0.201	0.202	0.200	0.201	0.193	0.197	0.202	0.204	0.200
10	0.203	0.199	0.200	0.186	0.194	0.197	0.199	0.199	0.199
Mean	0.201	0.198	0.201	0.194	0.197	0.196	0.199	0.201	0.199
SD	0.002	0.003	0.001	0.006	0.003	0.004	0.002	0.002	0.002
Min	0.199	0.194	0.199	0.181	0.193	0.184	0.197	0.198	0.196
Max	0.205	0.202	0.204	0.201	0.201	0.201	0.202	0.204	0.202

**Ferrous salt/folic acid tabs 200/.25 mg**

(ferrous sulphate component)

MNF	4/88	DECLARED AMOUNT:	170 mg (*)	BP: 90-110%
EXP	4/91	BATCH NR:	80415007	USP: 95-110%

**Sampling**

CONTROL KIT: 11/88 TEST KITS: 1/89

From each kit one sample of 10 tablets was taken; the contents of the 10 tablets were mixed and analyzed twice. From the control kit, two samples were analyzed.

**Assay method**

Potentiometric titration with ammonium cerium (IV) sulphate (ferrous sulphate-anhydrous measured). Disintegration: 6 tablets from every sample were tested.

**Summary results**

	CONTROL KIT		TEST KITS	
n	2		8	
Min	169.7	99.8%	168.8	99.3%
Max	170.3	100.1%	174.7	102.7%
MEAN	170.0	100.0%	170.1	100.1%
SD	0.28	0.2%	1.80	1.1%
SE	0.19445		0.637	
t	12.706		2.365	
95% CL-	167.5	98.5%	168.6	99.2%
95% CL+	172.4	101.4%	171.6	101.0%
INCREASE FROM CONTROL			0.17%	

] **Conclusions**

- 1 Active ingredient in all samples varied between 99.3 - 102.7 % of declared amount.
- 2 Hardness (mean value from ten tablets) varied from 42.8 - 54.3 N (mean 49.59 N). Hardness of the control sample was 47.1 N.
- 3 Disintegration of all tablets was within the USP limit of 30 minutes.
- 4 Test samples have not lost potency during international transport.
- 5 There are no indications that ferrous sulphate / folic acid tablets are unstable during international transport.

\* 200 mg dried ferrous sulphate equals 170 mg FeSO<sub>4</sub> equals 60 mg iron

## Full results of analyses

	CNTROL	H1 LHT	H2 LDC	H3 EDT	H4 EDC	H7 LDT	H8 LHC	H9 EHT	H10 EHC
<b>Assay (mg)</b>									
1	170.9	170.7	171.3	169.9	169.9	169.9	170.2	179.1	169.1
	168.5	168.8	170.3	168.2	168.9	167.7	169.2	170.2	168.9
2	170.6								
	169.9								
Mean	169.7	169.8	170.8	169.1	169.4	168.8	169.7	174.7	169.0
	170.3								
<b>Mean weight</b> 228.9 mg per tablet									
<b>Disintegration</b> In the control sample all tablets were disintegrated in 18 minutes. In the test sample all tablets were disintegrated within 13-15 minutes.									
<b>Hardness (Newton)</b>									
1	56	28	52	45	50	37	28	50	69
2	33	62	32	34	48	62	50	37	52
3	56	40	44	52	50	52	37	63	60
4	46	54	54	44	48	54	35	61	56
5	56	61	52	49	55	58	53	52	52
6	54	54	52	39	47	46	24	48	48
7	49	56	48	53	60	43	49	52	60
8	48	45	50	66	47	48	34	60	56
9	29	58	62	58	40	56	58	52	40
10	44	31	50	55	27	58	60	55	50
Mean	47.1	48.9	49.6	49.5	47.2	51.4	42.8	53	54.3
SD	9.09	11.64	7.31	8.91	8.38	7.39	12.11	7.14	7.48

## Ferrous salt/folic acid tabs 200/.25 mg

(folic acid component)

MNF	4/88	DECLARED AMOUNT:	250 ug	BP: 90-110
EXP	4/91	BATCH NR:	804150 07	USP: 90-115%

**Sampling** CONTROL KIT: 11/88 TEST KITS: 1/89  
From each kit one sample of 10 tablets was taken; the contents of the 10 tablets were mixed and analyzed twice. From the control kit, two samples were analyzed.

**Assay method** Reversed phase liquid chromatography. It was not an easy method and it was destructive to the chromatographic system. For that reason the results fluctuated more than usually.

Summary result	CONTROL KIT		TEST KITS	
n	2		8	
Min	266.6	106.6%	241.6	96.6%
Max	276.3	110.5%	279.0	111.6%
Mean	271.4	108.6%	266.4	106.6%
SD	4.82	1.9%	10.37	4.1%
SE	3.412		3.668	
t	12.706		2.365	
95% CL-	228.1	91.2%	257.7	103.1%
95% CL+	314.8	125.9%	275.1	110.0%
	DECREASE FROM CONTROL			2.0%

**Conclusions**

- 1 Active ingredient in control samples varied between 106.6 - 110.5 % of declared amount. Active ingredient in test samples varied between 96.6 - 111.6 %.
- 2 Hardness (mean value from ten tablets) varied from 42.8 - 54.3 N.  
Hardness of the control sample was 47.1 N.
- 3 Disintegration of all tablets was within USP limit of 30 minutes.
- 4 Test samples have, on average, lost 2.0% potency during international transport (n.s.).
- 5 There are no indications that ferrous sulphate / folic acid tablets are unstable during international transport.

## Full results of analyses

	CNTROL	H1 LHT	H2 LDC	H3 EDT	H4 EDC	H7 LDT	H8 LHC	H9 EHT	H10 EHC
<b>Assay (ug)</b>									
1	271.4 261.8	275.8 259.4	291.6 256.8	279.5 262.6	262.4 267.3	281.3 250.2	263.7 270.6	299.4 258.6	246.7 236.5
2	284.7 267.8								
Mean	266.6 276.3	267.6	274.2	271.1	264.9	265.8	267.2	279.0	241.6
(%)	106.6 110.5	107.0	109.7	108.4	105.9	106.3	106.9	111.6	96.6

## Phenoxyethylpenicillin BP tabs 250 mg (as potassium salt)

MNF	5/87	DECLARED AMOUNT: 250 mg	BP: 92.5-107.5%
EXP	5/92	BATCH NR: 219 B005	USP: 90-120%

**Sampling** CONTROL KIT: 11/88 TEST KITS: 1/89  
From each kit, one sample of 10 tablets was taken; the contents of the 10 tablets were mixed and analyzed twice. From the control kit, two samples were analyzed.

**Assay method** High Pressure Liquid Chromatography; Lichrosorb RP18, 10µm; 250 x 4.6 mm; detection at UV 266 nm. Mobile phase: acetonitrile : MeOH : 0.01M Potassium Dihydrogen Phosphate; 19:11:70. Degradation products by potentiometric titration using mercuric nitrate as titrant. Disintegration in water 37 degrees, six tablets from each kit.

Summary results	CONTROL KIT		TEST KITS	
n	2		8	
Min	96.01	96.0%	95.12	95.1%
Max	96.50	96.5%	96.84	96.8%
Mean	96.26	96.3%	96.00	96.0%
SD	0.25	0.2%	0.50	0.5%
SE	0.173		0.175	
t	12.706		2.365	
95% CL-	94.05	94.1%	95.58	95.6%
95% CL+	98.46	98.5%	96.41	96.4%
	DECREASE FROM CONTROL			0.3%

### Conclusions

- 1 All samples fall within BP limits.
- 2 Control samples show 0.89 - 1.07 % degradation products (mean 0.95 %).  
Test samples show 0.77 - 1.21 % degradation products (mean 0.92)
- 3 All samples were disintegrated within 7 minutes.
- 4 Test samples have lost, on average, 0.3% of potency during international transport (n.s.).
- 5 There are no indications that phenoxyethylpenicillin tablets are unstable during international transport.

## Full results of analyses

	CNTROL	H1 LHT	H2 LDC	H3 EDT	H4 EDC	H7 LDT	H8 LHC	H9 EHT	H10 EHC
<b>Assay (%)</b>									
1	96.01								
2	96.50								
Mean	96.26	96.04	96.06	96.24	95.95	96.84	95.12	96.31	95.43
<b>Degradation products (%)</b>									
1	0.93	0.90	1.21	0.92	0.92	0.89	0.91	0.91	0.90
	1.07	0.92	0.77	0.91	0.90	0.90	0.91	0.90	0.90
2	0.89								
	0.92								
Mean	1.00	0.91	0.99	0.92	0.91	0.90	0.91	0.91	0.90
	0.91								
<b>Disintegration test</b>									
(min)	6	7	7	6	6	7	7	7	7

## Vitamin A (retinol) BP capsules

MNF	12/87	DECLARED AMOUNT: 60 mg	BP: > 97%
EXP	12/90	BATCH NR: 59018	USP: 95-120%

**Sampling** CONTROL KIT: 11/88 TEST KITS: 1/89  
From each kit one sample of 10 capsules was taken; the contents of the 10 capsules were mixed and analyzed twice. From the control kit, two samples were analyzed.

**Assay method** Liquid Chromatography, normal phase. Column: Lichrosorb Si-60, 5  $\mu$ m, 150 x 4.6 mm; detection UV 326 nm. Mobile phase: 10% dioxan in heptan + 50  $\mu$ l water/100 ml. 0.1 g of mixed content from ten capsules was solved in 25 ml 9% KOH in ethanol in a 100 ml round bottle. The standards were treated in the same way. It was boiled for 30 min. After cooling it was transferred to a 250 ml separator funnel. The bottle was rinsed with 3 x 10 ml water, which was added to the separator funnel. Extracted with 80 ml heptan for 3 min. The waterphase was extracted with another 2 x 20 ml heptan for 3 min each. The heptan-phases were collected and extracted with 50 ml water until the water was not colored by phenolphthalein. Filtered through sodium sulphate and diluted to 150 ml. 400  $\mu$ l was diluted to 25 ml and injected.

Summary results	CONTROL KIT		TEST KITS	
n	2		8	
Min	72.44	120.7%	70.54	117.6%
Max	72.52	120.9%	72.49	120.8%
Mean	72.48	120.8%	71.41	119.0%
SD	0.04	0.1%	0.65	1.1%
SE	0.027		0.232	
t	12.706		2.365	
95% CL-	72.14	120.2%	70.86	118.1%
95% CL+	72.81	121.4%	71.95	119.9%
DECREASE FROM CONTROL			1.071	1.5%
SE difference			0.23302	
Difference/SE diff.			4.59458	
P			< 0.001	

**Weight variation** Mean weight 202 mg of content/capsule (+8.4, -3.5%)

### Conclusions

- 1 All samples are within BP requirements.
- 2 Test samples have lost 1.5% potency during international transport ( $p < 0.001$ ).
- 3 There are indications that retinol capsules are somewhat unstable during international transport.

## Full results of analyses

---

	CNTROL	H1 LHT	H2 LDC	H3 EDT	H4 EDC	H7 LDT	H8 LHC	H9 EHT	H10 EHC
Assay (mg)									
1	72.62 72.26	72.51 70.17	72.51 70.59	72.65 70.60	72.56 72.41	70.77 70.31	72.41 70.31	71.23 70.28	72.84 70.36
2	72.62 72.41								
Mean	72.44 72.52	71.34	71.55	71.63	72.49	70.54	71.36	70.76	71.60

---

## Tetracycline HCl BP 250 mg tablets

MNF	6/88	DECLARED AMOUNT:	250 mg	BP: 97-110%
EXP	6/91	BATCH NR:	88F07	USP: 90-125%

**Sampling** CONTROL KIT: 11/88 TEST KITS: 1/89  
From each kit (including control kit) one sample of 30 tablets was taken; the contents of the 30 tablets were mixed; the sample was analyzed twice. Samples were dissolved in methanol by ultrasonic bath. One part of the solution was evaporated and dissolved in mobile phase just before injection.

**Assay method** Liquid chromatography; reversed phase; Lichrosorb RP-18, 5µm, 200x4.6 mm. Mobile phase: 0.1M phosphate buffer incl 0.1% DMOA, pH 8.2 and acetonitrile (73:27). Detection: UV 280 nm

Summary results:	CONTROL KIT	TEST KITS
n	1	8
Min		244.91 98.0%
Max		262.68 105.1%
Mean	254.51 101.8%	253.69 101.5%
SD		5.78 2.3%
SE		2.044
t		2.365
95% CL-		248.86 99.5%
95% CL+		258.52 103.4%
	DECREASE FROM CONTROL	0.33%

**Average weight** 305.0 mg/tab  
**Weight variation** -1.1 - +4.5% of average weight

**Impurities**  
Epi-TC 1.9 - 2.7%  
Anhydro-TC 0.3 - 0.9%  
Epianhydro-TC < 0.5% in all samples

### Conclusions

- 1 All control and test samples comply with BP standards.
- 2 Test samples have, on average, 0.3% less potency than the control (n.s.).
- 3 There are no indications that tetracycline HCl tablets are unstable during international transport.

## Full results of analyses

	CNTROL	H1 LHT	H2 LDC	H3 EDT	H4 EDC	H7 LDT	H8 LHC	H9 EHT	H10 EHC
<b>Assay (mg)</b>									
1	255.84	265.51	258.39	265.60	247.53	249.09	263.88	263.85	252.46
2	253.18	259.85	251.54	239.07	242.29	246.94	256.82	249.99	246.21
Mean	254.51	262.68	254.97	252.34	244.91	248.02	260.35	256.92	249.34
<b>Impurities (% of tetracycline)</b>									
Epi-	2.16	2.16	1.88	2.48	2.26	2.35	2.14	2.20	2.71
Anhydro-	0.55	0.44	0.43	0.81	0.45	0.29	0.34	0.43	0.44
Epi-anhydro-	All samples < 0.5%								

**Tetracycline HCl , ophthalmic ointment (USP)**

---

MNF	6/88	DECLARED AMOUNT:	1%
EXP	6/92	BATCH NR:	806302

---

**Appearance**                      Smooth, yellow ointment. Ointment spread out on a plate of glass and examined through a microscope were all similar to each other. No changes of colour or consistency within the whole tube could be noticed for all of the nine packages of the ointment.

---

**LEGENDA**

L	LAGOS
E	ENTEBBE/KAMPALA
D	DECK
H	HOLD
C	CENTRE
T	TOP