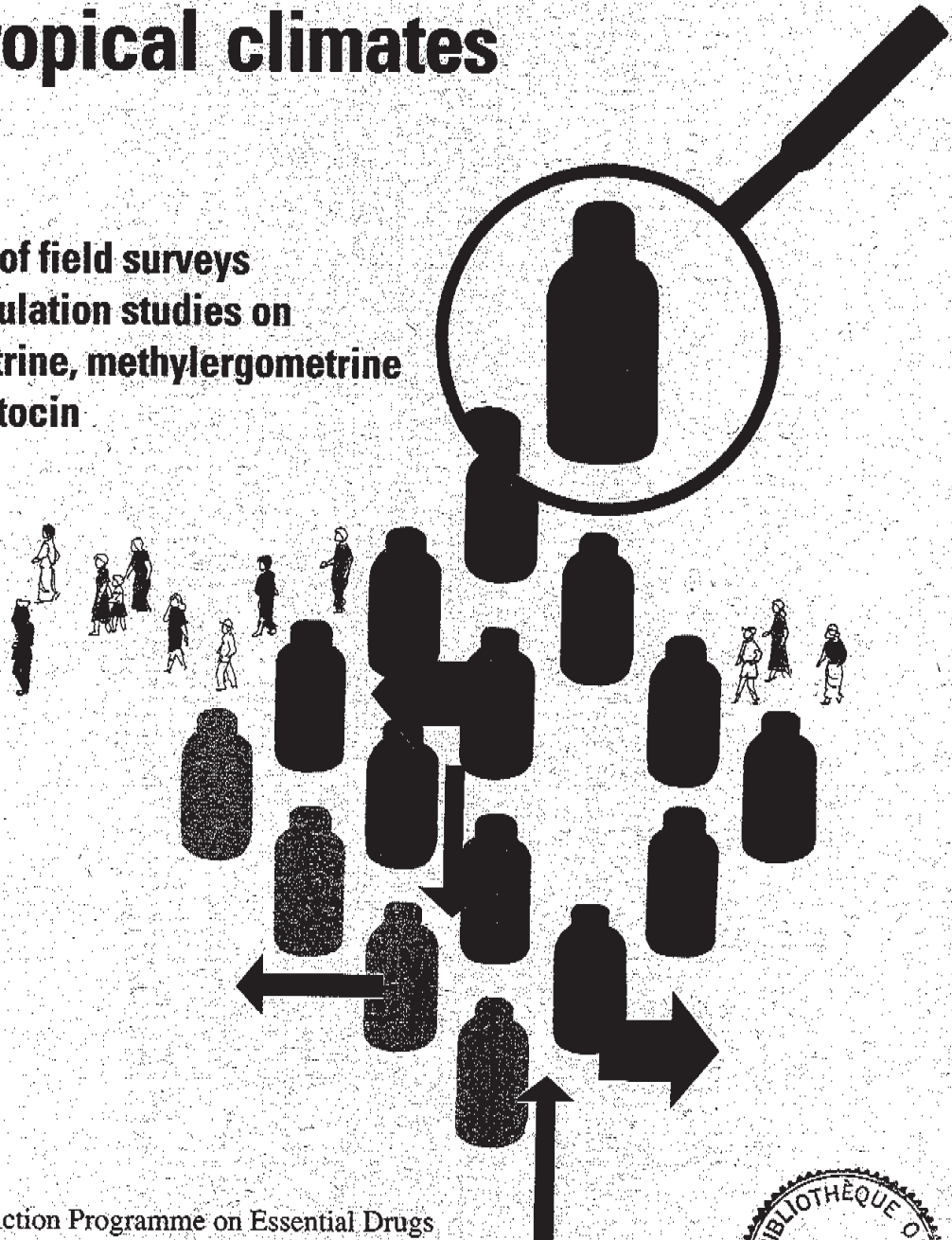


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ergometrine, methylergometrine  
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Action Programme on Essential Drugs



Safe Motherhood Research Programme



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# Stability of injectable oxytocics in tropical climates

Results of field surveys and simulation studies on  
ergometrine, methylegometrine and oxytocin



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## Summary

Post-partum haemorrhage is a major cause of direct maternal death, especially in developing countries. Parenteral ergometrine and methylergometrine are invaluable drugs in the treatment and prevention of excessive uterine bleeding following obstetric delivery; oxytocin is sometimes used as an alternative. Storage guidelines for injectable oxytocics are often contradictory and stability data from manufacturers are far from consistent. However, most reference books note that parenteral ergometrine should be stored at a temperature not exceeding 8°C and be protected from light, but these requirements are very often not followed. Several studies have reported that ergometrine injection is unstable under tropical conditions and in earlier studies a very low level of active ingredient has been found in many field samples.

The research questions for this study are as follows:

- 1 What is the pattern of stability of common injectable oxytocics (ergometrine, methylergometrine and oxytocin)?
- 2 What is the effect of long-term dark storage at 25 and 30°C, and of short-term exposure to higher temperatures and to light?
- 3 Can guidelines be developed for the selection and storage of injectable oxytocics in tropical climates?
- 4 Is there a correlation between the colour of the solution and its level of active ingredient?
- 5 Is there a correlation between the pH of the product and its stability under tropical conditions?

The study consists of two components. The first is a series of field surveys in Gambia, Malawi, Sudan and Zimbabwe, covering 29 samples of ergometrine injection taken from medical stores and rural health facilities, produced by 10 manufacturers from 6 countries. In the discussion the results are combined with those of earlier field surveys.

The second and largest component is a laboratory study on the stability of injectable oxytocic drugs under simulated tropical conditions, measuring the level of active ingredient at various temperature and light conditions at regular intervals over a period of up to two years. This part of the study is limited to 11 brands of ergometrine, methylergometrine and oxytocin injection that are most commonly supplied to developing countries by IDA and UNICEF. The main outcome measure is the amount of active ingredient in the sample, expressed as percentage of the stated amount; the colour of the solution, expressed on a dilution scale of brown; and oxygen content and pH of the solution.

## Conclusions

There is a widespread problem with the stability of injectable ergometrine. In only 31% of field samples taken from six tropical countries the level of active ingredient complied with USP/BP limits of 90-110% of the stated content, while 31% of samples contained less than 60%. No field data on methylegometrine are available. The few field data on oxytocin suggest that the average quality at the level of the end user is acceptable, mainly because many products contain more active ingredient than the stated amount.

Simulation studies on eleven brands of injectable ergometrine, methylegometrine and oxytocin under different conditions of temperature and light show that there is no difference in stability between ergometrine and methylegometrine other than differences between brands, which however can be considerable. When kept under refrigeration for twelve months, the eight brands of ergometrine and methylegometrine lost, on average, about 4-5% of their active ingredient (range 0-14%). When kept at 30°C in the dark the products lost on average about 25% after twelve months (range 2-57%). When kept at 21-25°C under exposure of light, as so often happens in tropical countries, 21-27% of the active ingredient was lost after one month, and over 90% after one year. Two months exposure to 40°C in the dark led to a loss of potency of about 5%.

For oxytocin the pattern is different. There was, on average, no loss of potency after twelve months refrigerated storage, and about 14% loss after one year at 30°C in the dark (range 9-19%). No destabilizing effect of light was found.

We conclude that the stability of oxytocin is better than that of ergometrine and methylegometrine, mainly because it lacks the adverse effects of exposure to light but also because it is probably more stable when kept in the dark with or without refrigeration.

There is a strong correlation between the colour of the solution of (methyl)ergometrine and its level of active ingredient ( $r=0.8487$  for ergometrine,  $r=0.8730$  for methylegometrine). We conclude that any discolouration of (methyl)ergometrine of good initial quality which makes the solution different from water implies, with a sensitivity of 97-100%, that the level of active ingredient is below USP/BP standards of 90% of the stated content, and should not be used. When this rule is applied, about 15% of colour failures are false-positives. The comparison should be made in identical clear glass tubes against a well-lit white background.

Instability of some of the samples could not be related to an abnormal pH or oxygen content of the initial solution.

## Recommendations

### *Selection of injectable oxytocic for tropical climates*

There is no difference between the stability of ergometrine and methylergometrine *per se*, other than differences between brands. Oxytocin is more stable than (methyl)ergometrine, certainly under exposure of light and probably also when kept in the dark with or without refrigeration.

In view of the observed differences between brands, ergometrine and methylergometrine should only be procured from a reputable supplier who submits all necessary documents in accordance with the WHO Certification Scheme, and whose product is of proven quality and stability. Upon arrival in the country, or upon delivery to Central Medical Stores, every batch should at least be tested for colour of the solution, and, if possible, for level of active ingredient. Ergometrine and methylergometrine delivered in clear glass ampoules should be rejected.

### *Storage*

Injectable ergometrine, methylergometrine and oxytocin should be stored under refrigeration as much as possible. All products should clearly be marked with "keep under refrigeration" and ergometrine and methylergometrine should additionally be marked with "protect from light". For most products short periods of unrefrigerated transport are acceptable (not exceeding one month at 30°C or 2 weeks at 40°C).

In dispensaries and labour wards ampoules of ergometrine, methylergometrine and oxytocin should be kept under refrigeration, and should only be taken from their box when actually used. Especially ampoules of ergometrine and methylergometrine should *not* be kept ready in open trays, as this would reduce the level of active ingredient by about 21-27% per month. In case refrigerated storage is not available temporary storage outside the refrigerator at a maximum of 30°C is acceptable for most products for a period not exceeding 3 months. The actual recommended storage conditions for a particular brand may differ from the above recommendations, due to the differences in stability between brands.

### *Identification of ampoules with low level of (methyl)ergometrine*

Before being administered to the patient, every injection of (methyl)ergometrine should be visually checked by the health worker, and any product for which the colour is different from clear water should not be used. In addition, staff responsible for the quality of drugs (e.g. hospital pharmacists) should regularly check on the colour of the injectable (methyl)ergometrines in stock, by means of a careful comparison in glass tubes between the product and clear water.

## Introduction

Post-partum haemorrhage is a major cause of direct maternal death, causing around 33% of such deaths where maternal mortality is high,<sup>1</sup> 21% in countries with lower rates,<sup>2</sup> and 8% in England and Wales.<sup>3</sup> An estimated 125,000 women, mainly living in developing countries, die every year from this cause. Parenteral ergometrine and methylergometrine are invaluable drugs in the treatment and prevention of excessive uterine bleeding following obstetric delivery.<sup>4</sup>

Occasional ineffectiveness of ergometrine has been reported by obstetricians and others working in developing countries. Most reference books note that parenteral ergometrine should be stored at a temperature not exceeding 8°C and be protected from light. These requirements are either not known by most people involved in drug supply in tropical countries or are not followed. In a field survey carried out in Bangladesh, Democratic Yemen and Zimbabwe none of the 24 samples of ergometrine injection taken from 20 different rural health facilities was kept in a refrigerator, and 5 had passed the manufacturer's expiry date by up to 12 months<sup>5</sup>. Only 9 (37%) conformed to USP and BP standards with levels of active ingredient between 90 and 110% of the stated amount; 8 (33%) had potencies of 80-89% and the remaining 7 (29%) had potencies of 20% or less. Several samples were presented in unstained glass.

In a longitudinal study in Sudan ergometrine lost 10% of its active ingredient during the first few months in Port Sudan and was found to be only 53% potent after 25 months within the country.<sup>6</sup> In another longitudinal study, carried out by WHO and UNICEF on two series of essential drug kits shipped by container from Copenhagen to Lagos and Entebbe, ergometrine injection lost 6% of its active ingredient during 8 weeks in transport.<sup>7,8</sup> Under similar circumstances methylergometrine injection lost 2% of its potency. During transport the temperature within the container had been as high as 42.4°C.

All studies, including some early field results of the present study which have been published elsewhere,<sup>9,10,11,12</sup> indicate that ergometrine injection is not stable in developing countries, where the drug is rarely kept under refrigeration, resulting in a decreased level of active ingredient in many samples taken from the field. A reduced potency of this vital and life-saving drug will have serious if not fatal consequences.

An additional problem is that there is no obvious alternative for the drug. In a literature review,<sup>13</sup> quoting several other studies,<sup>14,15,16,17</sup> it has been suggested that methylergometrine maleate injection would be more stable than ergometrine maleate. However, this conclusion could not be confirmed in the WHO/UNICEF study as only one brand of each was included and as it was not clear whether the manufacturing process or the chemical composition were responsible for the observed difference in stability.<sup>18</sup> A WHO technical working group in 1990<sup>19</sup> and a literature review published in 1991<sup>20</sup>

Table 1

Storage guidelines and manufacturer's stability information on injectable oxytocics

**Ergometrine injection**

Goodman and Gillman, 1980 <sup>21</sup>	Store at 0-12 °C, protect from light
USPDI, 1986 <sup>22</sup>	Store <40°C, pref. 15-30 °C, protect from light and freezing
BP, 1988 <sup>23</sup>	Store at 2-8°C
Martindale, 1989 <sup>24</sup>	Store at 2-8 °C, protect from light
Vitarine, 1975 <sup>25</sup>	If stored <17 °C: 3 yr
Lily, 1975 <sup>25</sup> , 1983 <sup>26</sup>	If stored at 15-30 °C: 2 m
Sth Tees Hlth Authority, 1985 <sup>27</sup>	If stored at 10-15 °C and protected from light, as long as no discolouration has occurred
Antigen, 1987 <sup>28</sup>	If kept at room temperature: 13m
Gedeon Richter, 1988	If kept <15 °C and protected from light: 2 yr
Paris Chemical, 1988	If stored at 2-8°C: 2 yr
Scanpharm, 1988	After 1yr at 23°C: 23% loss of potency observed
Medisca, 1989	If stored <25°C and protected from light: 3 yr Filling under N2 and protected from light, adding antioxidants, improves stability

**Methylergometrine injection**

Martindale, 1989 <sup>29</sup>	Store <8°C, fill under N2, protect from light
USPDI-6 <sup>30</sup>	Store <40°C, preferably between 15-30°C, protect from light and freezing
Sandoz Netherlands	If stored <25°C: 3y
Medisca	If stored <30°C, 18m no loss of potency If stored <25°C, protected from light: 3y

**Oxytocin injection**

Martindale, 1989 <sup>31</sup>	Store at 2-8°C; expiry 3y
BP, 1988 <sup>32</sup>	If stored <25°C: 2y
Sandoz Australia, 1989	Store at 2-15°C, pH between 3.5-4.5 If stored <25°C, protected from light: 3y If stored at 30°C. 50% loss of potency after 4y 5000k, 150W light: stable for 96h
Sandoz UK, 1989	If stored at 8-22°C, protected from light: 3y
Medisca, 1989	If stored <25°C, pH 3.1-4.9: no change
Scanpharm, 1988	Short period of >25°C is possibly harmful Stored at 23°C: no change observed after 10m

**Ergometrine/oxytocin injection**

BP, 1988 <sup>33</sup>	Store <25°C; expiry at least 2y
Sandoz UK, 1989	If stored at 8-22°C, protected from light: 2y If stored at 25°C in pack: 3m shelf life Any light causes rapid degradation.
Sandoz Australia, 1989	If stored at 25°C: stable for 4-5 days 5000k, 150W light, at 25°C: after 4-5 days 50% potency loss observed for ergometrine If stored >25°C: great loss of stability

## Stability of injectable oxytocics

concluded that, in view of its fewer side effects, oxytocin rather than ergometrine is to be preferred for use in routine active management of the third stage of labour. However, there is insufficient information on the relative efficacy of these drugs, as on their stability in tropical climates.

Storage guidelines for injectable oxytocics are often contradictory and stability data from the manufacturers are far from consistent (see Table 1). One manufacturer indicated that the stability of ergometrine is very dependent on the manufacturing and filling process.

### Outline of the study

In view of the apparent problems associated with the stability of oxytocic drugs and the lack of practical and consistent guidelines on their storage under tropical conditions, this study was designed to address the following questions:

- (1) What is the pattern of stability of the common injectable oxytocics (ergometrine maleate, methylergometrine maleate and oxytocin) regularly supplied to tropical countries by the main international non-profit suppliers? Are there significant differences between the drugs and between brands of the same drug?
- (2) What is the effect of long-term dark storage at 25 and 30°C on the amount of active ingredient?
- (3) What is the effect of short-term exposure to 30 and 40°C and of short-term exposure to light?
- (4) Can guidelines for the selection and storage of oxytocic drugs in tropical climates be developed?

In addition, the following questions with regard to (methyl)ergometrine were formulated in the course of the study:

- (5) Is there a correlation between the colour of the solution and its level of active ingredient?
- (6) Can an observed loss of active ingredient be (partially) explained by a different pH or oxygen content of the product?

The study consists of two components. The first is a series of small field surveys on the level of active ingredient in samples of oxytocic drugs taken from health facilities in Gambia, Malawi, Sudan and Zimbabwe. The second and largest component is a study on the stability of injectable oxytocic drugs under simulated tropical conditions, measuring the level of active ingredient at various temperature and light conditions over time. This part of the study covers all brands of (methyl)ergometrine and oxytocin injection that are most commonly supplied by the two largest non-profit drug suppliers IDA (Amsterdam) and UNICEF (Copenhagen).

The main outcome measure is the amount of active ingredient in the sample, expressed as percentage of the stated amount. Additional outcome measures are the colour of the solution, pH and oxygen content.

### **Acknowledgments**

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The research project was planned and conducted jointly by the WHO Action Programme on Essential Drugs, the WHO Maternal Health and Safe Motherhood Research and the International Dispensary Association. The chemical analyses were carried out at the Laboratory of the Royal Dutch Association for the Advancement of Pharmacy in The Hague (O.S.N.M. Smeets, pharmacist, Mrs A.E.E.M. van de Langerijt and Mrs H. Rosing, technicians), whose active and creative collaboration is very much appreciated.

Statistical advice was given by Mrs M. Anker of the Epidemiological and Statistical Methodology unit of WHO. Comments on the draft were made by Mr O.S.N.M. Smeets of the Laboratory of the Royal Dutch Association for the Advancement of Pharmacy in The Hague, Dr A. Mechkovski of the WHO Quality Assurance unit in Geneva, Mrs P. Brudon-Jakobowicz and Ms D.A. Fresle of the WHO Action Programme on Essential Drugs and Dr N. Stjernstrom of the Swedish Medical Products Agency in Uppsala. Their support is gratefully acknowledged.

## Materials and methods

### Sampling methods

#### *Field research*

Seven samples of ergometrine maleate injection were taken from current stock in Central Medical Stores in Banjul (Gambia), Khartoum (Sudan) and Harare (Zimbabwe). 22 samples were taken from 13 different district hospitals in Malawi, Sudan and Zimbabwe. The 29 samples were produced by 10 different manufacturers from 6 countries; 25 samples were imported. Full details of all samples are given in Annex 1. Six samples of oxytocin injection, all imported from the same manufacturer, were taken from five district hospitals in Zimbabwe.

#### *Simulation study*

Two batches each of three brands of ergometrine maleate injection were included in the simulation study. This selection covers all major suppliers of UNICEF and IDA. In addition, two batches of specially produced ergometrine maleate injection were included for a controlled comparison of their stability with similar solutions of methylergometrine injection. A total of 392 samples were analyzed. Two batches each of three brands of methylergometrine maleate injection, representing the major suppliers to UNICEF and IDA, were included plus two batches specially produced for a controlled comparison with ergometrine. A total of 392 samples were analyzed. Two batches each of three brands of oxytocin injection, representing the major suppliers of UNICEF and IDA, were included in the study. A total of 180 samples were analyzed.

### Temperature and light conditions, time interval

In the first phase of the study, which included only two brands of ergometrine and two brands of methylergometrine plus the prepared solutions, samples were kept in the dark at 4-8°C, 21°C, room temperature, 25°C, 30°C, 40°C and 50°C and in daylight at room temperature (but protected from direct sunshine). In the second phase of the study, in which one more brand each of ergometrine and methylergometrine plus three brands of oxytocin were included, dark storage at 21°C and at room temperature were omitted from the schedule.

In the first phase of the study, samples were tested after 0, 0.5, 1, 2, 3, 6 and 12 months. In the second phase this was simplified to 0, 2, 6 and 12 months. The most stable brand of ergometrine and methylergometrine, the special solutions, and all three brands of oxytocin were kept for another year and studied over a total period of two years.

### Laboratory analysis

All analyses were carried out in the laboratory of the Royal Dutch Association for the Advancement of Pharmacy, in The Hague. The amount of active ingredient of ergometrine and methylergometrine was measured by HPLC, following the USP method as modified by Krugers Dagneaux<sup>34</sup> with the following specifications: Column nucleosil 120, C18 (100x3 mm). Mobile phase: acetonitril R 15% - 0.01M potassium dihydrogen phosphate, with phosphoric acid to pH 2.5 85%; flow 0,8 ml/min; injection volume 20 ul; detection 313 nm; sample injected undiluted; run time 5 minutes. USP reference standards were used. For each sample the mean value was taken of separate measurements on two ampoules. In case of very divergent results (especially ergometrine E1 at 12 months) four separate ampoules were measured and the two extreme values excluded from the mean.

Results are expressed as a percentage of the stated amount (the amount stated on the label of the product). This expression is appropriate, as the absolute content may be different between products (e.g. ergometrine injection is presented as 0.15, 0.2 and 0.5 mg/ml). Although expressed as a percentage, the results should be interpreted as an absolute value as they reflect the actual amount of active ingredient in the sample. In some cases the levels of active ingredient are also expressed as a percentage of the initial amount. This is necessary when the level of active ingredient is followed over time in samples of which the initial amount is not 100% of the stated amount. These figures should be interpreted as true percentages - they express the loss of active ingredient over time, in relation to the level of active ingredient in the initial sample.

Oxytocin was measured with HPLC in accordance with the concept monograph for the European pharmacopoeia<sup>35</sup>. This implies a stainless steel column, 4.6 x 150 mm, packed with octadecylsilyl silica, particle size 5µm (Hypersil ODS). Mobile phase: gradient elution from 30% to 60% A in 30 minutes. Mobile phase: solvent A 50% (v/v) acetonitril in water, solvent B 0.1M sodium dihydrogen phosphate. Injection volume 50ul for injection of 10 IU/ml, and 100ul for injection of 5 IU/ml solution. Detection at 220 nm. Retention time oxytocin about 13.7 minutes; retention time chlorbutanol (preservative) 25 min. Results are expressed as percentage of the stated amount.

For all (methyl)ergometrine samples the colour of the solution was measured against a dilution scale of brown in accordance with the European Pharmacopoeia<sup>36</sup>. In this scale 1 is the undiluted colour and 9 can not be distinguished from water. For each sample the colour of two ampoules was measured separately and the mean value reported.

The comparison between the colour of the solution and the level of active ingredient was made in two ways. For each level on the dilution scale the mean potency and 95% confidence limits were calculated; for this purpose any value between two colour levels was rounded off downwards (i.e. towards the darker brown). In addition, a regression analysis was carried out on the full values (i.e. including the half values).

Oxygen content and pH of the (methyl)ergometrine samples were measured in all initial samples of the simulation study.

## Results

### Field research

The results of the analyses on the 29 ergometrine samples from Malawi, Gambia, Sudan and Zimbabwe are given in Annex 1 and summarized in Table 2. As can be seen from the table, 4 (14%) field samples were expired. Only 6 (21%) conformed to USP/BP standards with a level of active ingredient of 90-110% of the stated amount. 8 (28%) samples had less than 60% active ingredient. Defective products were found in all four countries.

Levels of active ingredient in the six samples of oxytocin injection taken from district hospitals in Zimbabwe are given in Annex 2. One sample was expired. Of the remaining five samples one was within USP/BP limits and four were above, with values between 104-142% of the stated amount.

*Table 2*  
Active ingredient of ergometrine maleate injection in five countries

	No.	Expired	Level of active ingredient*			
			90-110%	80-89%	60-79%	<60%
Malawi, 1990	9	2		1	3	3
Gambia, 1990	4	2	1		1	
Sudan, 1990	5				1	4
Zimbabwe, 1991	11		5	3	2	1
Total	29	4	6	4	7	8
%	100%	14%	21%	14%	24%	28%

\* as percentage of stated content

### Simulation study

The results of the simulation study are given in Annex 3. For each brand the analytical results of the two batches are reported separately. For each batch the main findings are visualized in a graph, showing the level of active ingredient over time at various storage conditions. Colour of the solution and pH and oxygen are reported in separate tables. A summary of the results is given below.

#### Active ingredient

The stability results per batch, as shown in Annex 3, give a consistent pattern. An example is given in Figure 1. From this example of ergometrine injection it can be seen that the level of active ingredient in this product remains fairly constant when it is stored at 4-8°C in the dark; stability declines with increasing storage temperature. At 50°C in the dark the product is very unstable, with only 26% of the stated amount of active ingredient left after 12 months. When stored in the dark at 21-25°C, potency remains between 93-100% of the stated amount for 12 months. However, if kept in the light at the same temperature, potency decreases to 16% after 12 months. Storage for 24 months at 4-8°C and 21°C in the dark result in potencies of 103 and 86% respectively.

For practical purposes the stability of each product can be characterized by looking at the level of active ingredient after 12 months storage at 4-8°C and at 30°C in the dark, and at 21-25°C in the light. These data are presented in Annex 4. Data referring specifically to the influence of light are summarized separately in Annex 5. The mean values per drug, as listed in Annex 4, are summarized in Table 3. The results are expressed both as percentage of the stated amount and as percentage of the initial amount, with 95% confidence limits.

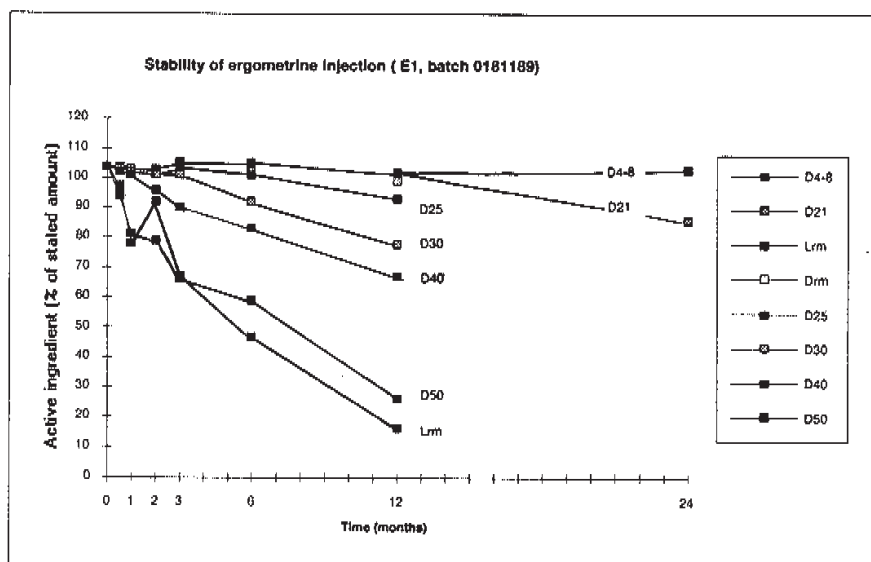


Figure 1

## Stability of injectable oxytocics

Table 3  
Stability of injectable oxytocics

Time Storage	t=0	t=12m Dark, 4-8°C	Dark, 30°C	Light, 21-25°C
<i>% of stated amount*</i>				
Ergometrine	100 (96-104)	95 (88-102)	70 (55-84)	9 (3-16)
Methylethergometrine	87 (68-106)	84 (65-103)	73 (56-95)	8 (0-19)
Oxytocin	105 (83-127)	105 (83-128)	90 (71-109)	97 (78-118)
<i>% of initial amount*</i>				
Ergometrine	100	95 (90-100)	69 (56-83)	9 (2-15)
Methylethergometrine	100	96 (92-100)	82 (69-94)	9 (0-22)
Oxytocin	100	101 (99-102)	86 (83-90)	93 (91-95)

\* Mean values (95% confidence limits)

#### Colour

For each sample of (methyl)ergometrine the colour of the solution on the dilution scale is given in Annex 3. The mean levels of active ingredient per degree of discolouration are summarized in Tables 4 and 5 and visualized in Figures 2 and 3. Maximum discolouration is represented by 1 on the dilution scale.

The correlation coefficient ( $r$ ) between discolouration and level of active ingredient is 0.8487 for ergometrine ( $t=31.69$ ,  $p<0.001$ ) and 0.8730 for methylethergometrine ( $t=35.35$ ,  $p<0.001$ ). The regression equation is  $y=15.54+(9.35)x$  for ergometrine and  $y=3.60+(10.35)x$  for methylethergometrine. These lines have been included in Figures 2 and 3.

#### Oxygen content and pH

Oxygen content of the samples varied from 2.7-19.6 KPs for ergometrine and 2.9-13.6 KPs for methylethergometrine. In five samples of ergometrine and two of methylethergometrine the oxygen content exceeded the usual industrial standard of 4.7 KPs for products which are easily oxidizable.

The pH of the samples varied from 3.0-3.6. All samples complied with BP limits of pH 2.7-3.5 except two batches from one and the same manufacturer.

Stability of injectable oxytocics

*Table 4*  
Mean level of ergometrine per degree of discolouration

Discolouration (max = 1)	n	Mean level of active ingredient* (95%CL)
9	224	100 (99-100)
8	22	83 (76-90)
7	15	76 (60-92)
6	32	83 (80-86)
5	46	61 (53-70)
4	16	61 (54-69)
3	11	48 (43-52)
2	7	42 (22-63)
1	19	20 (12-27)

\* As percentage of stated amount

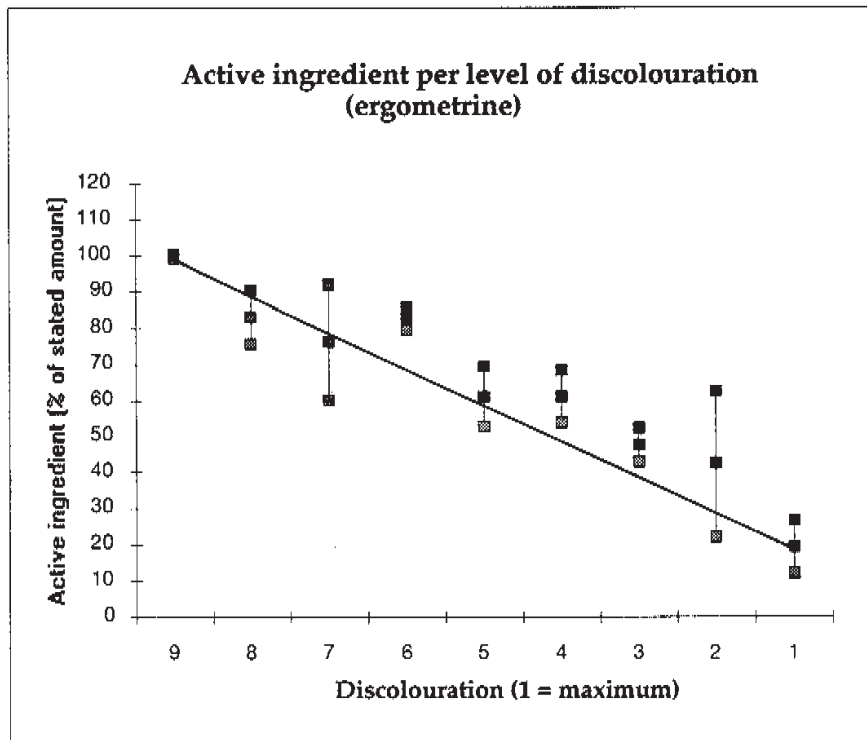


Figure 2

Stability of injectable oxytocics

**Table 5**  
Mean level of methylethergometrine per degree of discolouration

Discolouration (max = 1)	n	Mean level of active ingredient* (95%CL)
9	212	98 (97-99)
8	10	84 (78-91)
7	17	69 (60-79)
6	22	53 (36-70)
5	44	57 (49-65)
4	18	51 (45-56)
3	47	37 (34-40)
2	10	24 (19-29)
1	12	14 (7-20)

\* As percentage of stated amount

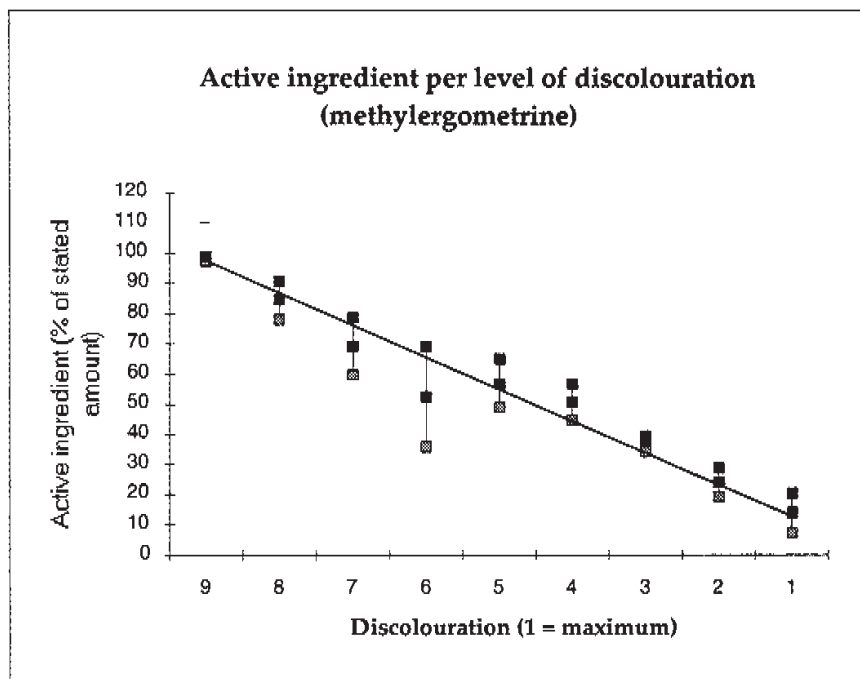


Figure 3

## Discussion

### Field research

The results of 29 ergometrine samples from Gambia, Malawi, Sudan and Zimbabwe (Table 2) confirm the picture from earlier field studies from Bangladesh, Yemen and Zimbabwe<sup>5</sup> in which only 9/24 (37%) samples complied with the USP/BP levels of active ingredient at 90-110% of the stated content. In the present series only 6/25 (24%) samples comply to USP/BP limits.

The combined data of both series therefore refer to 49 unexpired samples from 34 different facilities in 6 countries. Of these, only 15 (31%) complied with USP/BP limits; 12 (24%) had an 80-89% level of active ingredient, and as much as 15 (31%) samples had less than 60% potency.

These data indicate that there is a real field problem with the potency of ergometrine injection at the level of the end-user. The fact that over 70% of all non-expired samples do not comply to USP/BP standards strongly suggests that there is a stability problem.

Informal observations from the Royal Dutch Association for the Advancement of Pharmacy of the Netherlands suggests that the problem is not limited to developing countries. For example, one of four samples of locally formulated ergometrine injection taken from different large hospital pharmacies in the Netherlands did not comply to USP/BP standards, with a level of active ingredient of 84% of the stated amount<sup>37</sup>. Further study seems justified.

The 15 (31%) unexpired ergometrine samples in the two studies with potencies less than 60% were taken from five developing countries and concerned six different manufacturers. This shows that some products are of very bad quality at the level of the end-user, and that the problem is a real and not an academic one.

With oxytocin injection there seems to be less of a problem, but field data are too few to draw definitive conclusions (see Annex 2). One of the 6 samples from Zimbabwe was expired. Of the remaining 5 samples one was within the pharmacopoeial limits, and the other four were over the limit of 110%. There seems to be a pattern in which the products contain over 140% of the stated amount one year after manufacture, decreasing to 104-123% after about two years. If this overdose would be intentional this practice is not recommended. However, the results should be interpreted with caution as the official analysis method of oxytocin is still a biological method on rat uterus, which is prone to inaccuracy.

### Pattern of stability of common injectable oxytocics

#### *Ergometrine*

When ergometrine was stored at 4-8°C in the dark, the mean loss of active ingredient amounted to 5% (95%CL 0-10%, range 0-14%) per year. At 30°C in the dark the mean loss was 31% (95%CL 17-44%, range 15-57%) per year and when kept at 21-25°C in the light the drug lost over 90% of its potency (Table 3). Short-term exposure to heat did not have an immediate adverse effect. After two weeks at 40°C (storage temperature that may occasionally occur in tropical climates<sup>7,8</sup> the mean loss was 2% (range 0-7%).

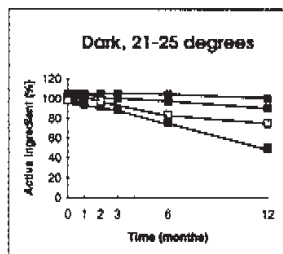
Although the general pattern of stability is rather similar, there are differences between the various brands which only become visible after long term storage. Figure 4, taken from Annex 5/1, shows the stability of each of the four products when kept at 21-25°C in the dark. The losses after one year are 5%, 10%, 23% and 49%. In fact the first two products would still give an acceptable potency after 12 months, while the latter two would definitely not. Similar differences occur under the influence of light.

The results concur with those of two longitudinal studies from developing countries. In a study in Sudan ergometrine lost 10% of its active ingredient during the first few months in Port Sudan and was found to be only 53% potent after 25 months within the country<sup>6</sup>. In a WHO/UNICEF study ergometrine injection lost 6% of its active ingredient during 8 weeks in transport to Lagos and Entebbe. During transport the temperature within the container had been as high as 42.4°C.

The data from the simulation study suggest that ergometrine injection loses, on average, about 5% (range 0-14%) active ingredient per year at 4-8°C in the dark. When shipped or stored at 30°C in unopened packages the drug may lose about 30% (range 15-57%) of its potency per year, while the influence of light results in an even faster deterioration (see below). However, it should be stressed that some products are more stable than others and that the average value can not be used to predict the stability of individual products.

Figure 4

Stability of four brands of ergometrine injection at 21-25°C in the dark



*Methylergometrine*

The mean levels of active ingredient, stated in the left half of Annex 4, are distorted by the fact that three of the eight batches were already far below USP/BP standards at the start of the study, with values of 38-82% of the stated content. To overcome this problem the level of active ingredient over time has been expressed as a percentage of the initial content (right half of Annex 4).

When stored for one year at 4-8°C in the dark, the mean loss of potency of methylergometrine is 4% of the initial content (95%CL 0-8%, range 0-13%). At 30°C in the dark it is 18% (95%CL 6-31%, range 2-45%) and at 21-25°C in the light the loss is over 90%. Two weeks at 40°C resulted in a mean loss of 3% (range 0-11%). As with ergometrine, there are considerable differences in stability between the four brands, as already illustrated by the presence of one defective product. However, at 21-25°C in the dark the other three show a similar pattern of stability (see Annex 5/2).

In the only field study that included methylergometrine, the WHO/UNICEF transport study<sup>7,8</sup>, the drug lost 2% of its active ingredient during 8 weeks of transport from Copenhagen to Lagos and Entebbe. This study included only one brand and the result is in line with that of the same brand in the present study.

The results of the simulation study suggest that methylergometrine may lose, on average, about 4% potency (range 0-13%) per year when stored at 4-8°C in the dark, and about 18% (range 2-45%) at 30°C. The influence of light at room temperature results in a rapid loss of active ingredient. Some products are more stable than others and the average value should be interpreted with caution.

*Oxytocin*

One product was defective from the start, with initial levels at 75-87% of the stated content (see Annex 4). When the results of all three products are expressed as a percentage of the initial amount, there is no loss of potency at 4-8°C in the dark, and 14% loss (95%CL 10-17%, range 9-19%) at 30°C. There is no influence of light.

A great similarity in behaviour exists between the three brands, when expressed as a percentage of the initial amount. However, the initial level of active ingredient varied between 75-133% of the stated amount. This considerable variation between the products should be seen in the light of the observed variation of 104-142% in the field samples (Annex 2). Some variation may be due to the fact that the level of oxytocin is difficult to measure with the official biological method based on rat uterus. Some of the overfill may also have been intentional, anticipating a certain loss of active ingredient over time. This practice is not recommended.

The conclusion is therefore that a wide variation exists in the level of active ingredient in the initial samples of oxytocin injection. Some of the higher values may be intentional. On average there is no loss of potency at 4-8°C, 3-7% per year at 21-25°C and 9-19% per year at 30°C. No destabilizing effect of light was found.

*Figure 5*  
Ergometrine in an open tray in a district pharmacy in Africa



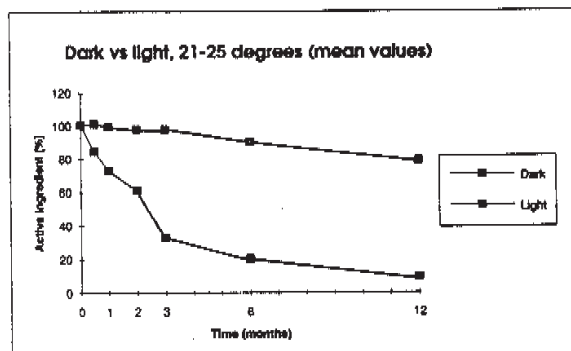
#### *Influence of light*

Most storage guidelines mention that ergometrine and methylergometrine should be protected from light (Table 1). However, it is widespread practice in African countries and probably also in other developing countries to take the ampoules from their boxes and keep them in trays in the dispensary or in open kidney dishes in the labour ward (Figure 5). Apart from elevated temperatures, the drugs may then be exposed to the influence of light for weeks or possibly months.

The effects of light on ergometrine are summarized in Annex 5/1 and visualized in Figure 6. When stored at 21-25°C in the dark the mean loss of potency is about 21% after one year. At the same temperature but subjected to indirect light, on average 27% potency is lost in one month and over 90% within a year. Results for methylergometrine are very similar, with 21% loss after one month exposure to light and 90% after one year (see Annex 5/2).

Although there are gradual differences, all products show a similar effect. One brand of ergometrine is considerably worse than the other three. This was the only product that was delivered in transparent rather than brown ampoules and the result shows that the brown glass prevents some, but by far not all harmful effects of light. Methylergometrine shows the same picture, with the same brand in transparent ampoules showing the strongest effect.

Figure 6  
Stability of ergometrine at 21-25°C with and without exposure to light



For oxytocin no effect of light could be found (Annex 3). This is in line with the information supplied by manufacturers and storage guidelines from the textbooks. However, it contradicts the information supplied by Sandoz and their warning to protect the product from light (Table 1).

The conclusion is that for ergometrine and methylethergometrine exposure to indirect light results in a rapid loss of active ingredient. In the worst case, in transparent ampoules, ergometrine lost 57% potency in one month and methylethergometrine 61%. On average the loss in one month was 21% and 27% respectively. No such effect was found with oxytocin.

#### Short exposure to high temperature

During earlier studies on the temperature pattern of international and inland transport<sup>7,8</sup> the maximum temperature the drugs were exposed to was 42.4°C; similar temperatures were measured within a box of emergency drugs in a life-raft in tropical waters<sup>38</sup>. During the transport study such temperatures occurred intermittently during a few weeks only.

For all three types of injectable oxytocics short-term exposure to high temperatures has a considerable but not excessive effect on the level of active ingredient (see Annex 3); the loss of potency is in line with the pattern at lower temperatures (see Figure 1). For the brand of ergometrine in Figure 1 the loss was 3% after one month at 40°C. The loss of 21% after one month at 50°C seems less relevant as such temperatures are unlikely to occur.

On average, the four brands of ergometrine lost 6% after one month at 40°C (range 3-15%); for methylethergometrine this was 5% (range 1-15%) and for oxytocin 6% (range 5-7%). There were no significant differences between the three substances, but there were differences between brands.

## Stability of injectable oxytocics

*Hypothetical loss of active ingredient in tropical climates*

We can now compare the average loss of active ingredient for a hypothetical pattern of climatic conditions during shipment and storage in tropical climates, which could include 12 months at 30°C, one month at 40°C and one month at 25°C in the light (see Table 6).

From this table it can be seen that the short-term exposure to higher temperatures is much less harmful than the exposure to light which, for ergometrine and methylergometrine, results in 21-27% loss after one month. It is evident that longer exposure to light would result in further loss of potency. These results tally very well with the results of the field research (Table 2 and Annex 1) where 28% of all samples had a potency below 60% of the stated amount, with some samples measuring as low as 21 and 34%.

Table 6

Estimated loss of active ingredient of injectable oxytocics during transport and storage in tropical climates\*

Climatic condition	12 m at 30°C (dark)	1 m at 40°C (dark)	1 m at 25°C (light)
Ergometrine	-30%	-6%	-27%
Methylergometrine	-18%	-5%	-21%
Oxytocin	-14%	-6%	- 1%

\* Expressed as percentage of initial amount

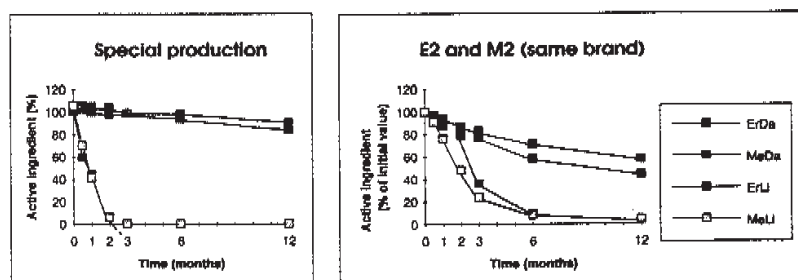
**Selection of the most stable injectable oxytocic**

Differences between brands occur for all three injectable oxytocics and complicate a comparison between the substances. For example, one of the methylergometrines was of lower quality than the other three with initial levels of active ingredient of 75% and 38% for the two batches (see Annex 4); the same applies for certain brands of ergometrine and oxytocin. This effect has to be taken into account when comparisons are made.

Is there a difference between the stability of ergometrine and methylergometrine? First, when the mean level of active ingredient is expressed as a percentage of the initial amount, no significant difference in stability under different temperature conditions can be found between the two (see Table 3). Secondly, in two cases the stability of products from the same manufacturer can be compared at 30°C in the dark and at 21-25°C in the

light, and no difference is found (Figure 7 and Annex 6). The result of the special production is very convincing, as the products were specifically made for this purpose with exactly the same manufacturing and filling process, the only difference being in the active ingredient. The comparison between E2 and M2 from the same manufacturer is confounded by the low initial level of active ingredient of M2, but gives nevertheless the same result.

Figure 7  
Comparison between stability of ergometrine and methylergometrine



LEGEND  
Er = ergometrine; Me = methylergometrine; Da = dark, 30C; Li = light, 21-25C

We conclude that whatever difference may occur in the mean values of the different brands of ergometrine and methylergometrine is only due to the differences between products and not to the active substance *per se*. In other words, a certain brand of methylergometrine may be more stable than a brand of ergometrine (and vice-versa) but this is due to the formulation and/or manufacturing process and not to the difference in active ingredient.

This leaves us with the question whether the stability of oxytocin injection is any better or worse than that of ergometrine and methylergometrine. With regard to exposure to light the difference is very important, with a nearly complete loss of potency for ergometrine and methylergometrine after one year (21-27% per month), and no such effect with oxytocin. However, also under dark storage at 4-8°C and at 30°C the average stability of oxytocin seems to be better than each of the other two, although in both cases the difference is not enough to reach statistical significance.

In conclusion, no difference in stability could be found between ergometrine and methylergometrine, other than differences between brands which are probably due to the production process. The stability of oxytocin is better than that of (methyl)ergometrine, mainly because it lacks the adverse effects of exposure to light but also because it is probably more stable when kept in the dark with or without refrigeration.

### Relation between colour and level of (methyl)ergometrine

The darker the colour of the solution of (methyl)ergometrine, the greater the loss of active ingredient. This relation, which is highly significant ( $r=0.8487$  for ergometrine and  $r=0.8730$  for methylergometrine), may have great practical implications in the field. It may constitute a very simple method to identify, with the naked eye, those products with low levels of active ingredient.

We therefore tested the hypothesis that any ergometrine solution for which the colour is different from that of water has a level of active ingredient below 90% of the stated content. In the dilution scale of brown, 9 cannot be distinguished from clear water, but 8 can; with decreasing numbers the colour intensifies. Of the 392 samples tested, 168 were classified as colour 1-8 (that is, colour of the solution is different from clear water). Of these 168 "colour failed" samples, 24 (14%) can be classified as false-positive with over 90% active ingredient (range 90-95%). This implies a specificity of 86%: in 14% of cases the drug would fail while the level of active ingredient is still acceptable. None of the 224 "colour acceptable" samples had a level of less than 90% active ingredient, implying a sensitivity of 100%: all defective samples would have been identified with this method.

Similarly impressive results were obtained for methylergometrine. Of 180 "colour failed" samples, 9 (5%) were false-positive (range 90-97% active ingredient), indicating a 95% specificity. Of 212 "colour-acceptable" samples, 20 (9.4%) actually had potencies below 90%, implying a sensitivity of 90.6%. It should however be noted that 15 of these 20 false-negatives occurred in one batch only, of a product with a 82% initial content of active ingredient only. It seems likely that no colour-producing metabolites had yet been formed in this batch. If the three batches with such low initial content are excluded from the analysis, only 5/197 of the "colour-acceptable" samples are false negatives, implying 97.5% sensitivity. Specificity is then 85%.

On the basis of these results we conclude that, both for ergometrine and methylergometrine of good initial quality, any discolouration which makes the solution different from water implies with a sensitivity of 97-100% that the product is below USP/BP standards of 90% of the stated content and should not be used. When this rule is applied, about 15% of colour failures are false-positive.

Injectable ergometrine and methylergometrine are usually presented in brown ampoules. In practice this implies therefore that the solution should be tested in a clear glass vial or test tube, comparing it with water in a similar tube under clear light against a white background.

When the solution is drawn in a syringe for injection and discolouration is visible with the naked eye, the level of active ingredient is probably very low and the product should not be used. However, this way a moderate discolouration (scale 7-8) with expected levels of 60-90% active ingredient is likely to be missed as no good comparison with clear water is possible. The method is therefore much less sensitive and would only identify the most serious cases.

One observation from this and earlier studies<sup>7,8,39</sup> may disturb this apparently elegant method to identify deficient products. That is that individual ampoules from the same box from the same batch kept under the same conditions, may behave differently. The most complete proof emerges from the WHO/UNICEF study<sup>7</sup>, in which all ampoules from the same box of ten from the same batch from the same trip were always individually tested. In one box eight ampoules measured 80-88% active ingredient while one measured 63% and one only 49%. A similar pattern, although less extreme, was observed with methylergometrine. This observation was confirmed in the present study, where sometimes two ampoules from the same batch after the same period under similar climatic exposure showed widely different results in colour and level of active ingredient.

We have no explanation for this phenomenon. If proved true, it would imply that "colour acceptable" for one or more sample ampoules from a box or batch may not necessarily mean that all ampoules in that lot are acceptable. This would of course also apply for analytical testing.

#### Oxygen content and pH

Oxygen content and pH of the solutions of ergometrine and methylergometrine were measured for each batch at the start of the simulation study. This was done to check whether any observed instability could be related to or explained by an abnormal acidity or oxygen content of the product. The pH of the solution is specified in the BP as between 2.7-3.5, and ampoules are usually filled under nitrogen to exclude oxygen and prevent subsequent oxidization.

Two samples did not comply with the pH limits and in five the oxygen content was higher than normal. However, these values could not be related to a lower level of active ingredient or instability of the product. It should be mentioned that the simulation study was not specifically planned to analyze the relation between pH or oxygen content and stability. The level of active ingredient is probably dependent on many different factors and this negative outcome does not imply that the existing guidelines for oxygen content and pH are unjustified.

## Conclusions and recommendations

There is a widespread problem with the stability of injectable ergometrine. In only 31% of field samples taken from six tropical countries the level of active ingredient complied with USP/BP limits of 90-110% of the stated content, while 31% of samples contained less than 60%. No field data on methylergometrine are available. The few field data on oxytocin suggest that the average quality at the level of the end user is acceptable, mainly because many products contain more active ingredient than the stated amount.

Simulation studies on eleven brands of injectable ergometrine, methylergometrine and oxytocin under different conditions of temperature and light show that there is no difference in stability between ergometrine and methylergometrine other than differences between brands, which however can be considerable. When kept under refrigeration for twelve months, the eight brands of ergometrine and methylergometrine lost, on average, about 4-5% of their active ingredient (range 0-14%). When kept at 30°C in the dark the products lost on average about 25% after twelve months (range 2-57%). When kept at 21-25°C under exposure of light, as so often happens in tropical countries, 21-27% of the active ingredient was lost after one month, and over 90% after one year. Two month exposure to 40°C in the dark lead to a loss of potency of about 5%.

For oxytocin the pattern is different. There was, on average, no loss of potency after twelve months refrigerated storage, and about 14% loss after one year at 30°C in the dark (range 9-19%). No destabilizing effect of light was found.

We conclude that the stability of oxytocin is better than that of ergometrine and methylergometrine, mainly because it lacks the adverse effects of exposure to light but also because it is probably more stable when kept in the dark with or without refrigeration.

There is a strong correlation between the colour of the solution of (methyl)ergometrine and its level of active ingredient ( $r=0.8487$  for ergometrine,  $r=0.8730$  for methylergometrine). We conclude that any discolouration of (methyl)ergometrine of good initial quality which makes the solution different from water implies, with a sensitivity of 97-100%, that the level of active ingredient is below USP/BP standards of 90% of the stated content, and should not be used. When this rule is applied, about 15% of colour failures are false-positives. The comparison should be made in identical clear glass tubes against a well-lit white background.

Instability of some of the samples could not be related to an abnormal pH or oxygen content of the initial solution.

## Recommendations

### *Selection of injectable oxytocic for tropical climates*

There is no difference between the stability of ergometrine and methylergometrine *per se*, other than differences between brands. Oxytocin is more stable than (methyl)ergometrine, certainly under exposure of light and probably also when kept in the dark with or without refrigeration.

In view of the observed differences between brands, ergometrine and methylergometrine should only be procured from a reputable supplier who submits all necessary documents in accordance with the WHO Certification Scheme, and whose product is of proven quality and stability. Upon arrival in the country, or upon delivery to Central Medical Stores, every batch should at least be tested for colour of the solution, and, if possible, for level of active ingredient. Ergometrine and methylergometrine delivered in clear glass ampoules should be rejected.

### *Storage*

Injectable ergometrine, methylergometrine and oxytocin should be stored under refrigeration as much as possible. All products should clearly be marked with "keep under refrigeration" and ergometrine and methylergometrine should additionally be marked with "protect from light". For most products short periods of unrefrigerated transport are permissible (not exceeding one month at 30°C or 2 weeks at 40°C).

In dispensaries and labour wards ampoules of ergometrine, methylergometrine and oxytocin should be kept under refrigeration, and should only be taken from their box when actually used. Especially ampoules of ergometrine and methylergometrine should *not* be kept ready in open trays, as this would reduce the level of active ingredient with about 21-27% per month. In case refrigerated storage is not available temporary storage outside the refrigerator at a maximum of 30°C is acceptable for most products for a period not exceeding 3 months. The actual recommended storage conditions for a particular brand may differ from the above recommendations, due to the differences in stability between brands.

### *Identification of ampoules with low level of (methyl)ergometrine*

Before being administered to the patient, every injection of (methyl)ergometrine should be visually checked by the health worker, and any product for which the colour is different from clear water should not be used. In addition, staff responsible for the quality of drugs (e.g. hospital pharmacists) should regularly check on the colour of the injectable (methyl)ergometrines in stock, by means of a careful comparison in glass tubes between the product and clear water.

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# ANNEXES

## Results of field studies on ergometrine injection

Level of active ingredient in field samples, expressed as percentage of stated amount

Country	Facility	Manuf	Country of origin	Time since manuf (m)	Expired	Active ingredient (%)			
						90-110	80-89	60-79	<60
Malawi	MA-QEH	E5	India	36				66	
	MA-QEH	E6	Germany	22				74	
	MA-QEH	E1	Hungary	26	yes				
	MA-QEH	E7	Germany	10				61	
	MA-MAW	E7	Germany	10					42
	MA-MAS	E7	Germany	10					34
	MA-CHI	E7	Germany	10					56
	MA-CHI	E1	Hungary	26	yes				
Gambia	MA-CHI	E8	Italy	33			86		
	GA-CMS	E8	Italy	31	yes				
	GA-CMS	E9	Italy	36	yes				
	GA-CMS	E10	unknown	?		92			
Sudan	GA-CMS	E11	unknown	30				76	
	SUD-IDA	E2	France	17				62	
	SUD-B	E2	France	17					52
	SUD-B	E2	France	17					43
	SUD-AH	E2	France	17					44
Zimbabwe	SUD-WH	E2	France	17					44
	ZI-CMS	E12	Zimbab	3		98			
	ZI-CMS	E12	Zimbab	4				77	
	ZI-BB	E12	Zimbab	4			80		
	ZI-BB	E12	Zimbab	24					21
	ZI-ZE	E1	Hungary	17		99			
	ZI-SM	E1	Hungary	17		95			
	ZI-HA	E1	Hungary	17			87		
	ZI-GU	E1	Hungary	17			86		
	ZI-NY	E1	Hungary	17				69	
ZI-BIN	E1	Hungary	17		98				
ZI-BB	E1	Hungary	17		98				
<b>Total</b>	n=29				4	6	4	7	8
<b>%</b>	100%				14%	21%	14%	24%	28%

### LEGEND

MA-QEH	Queen Elisabeth Hospital, Blantyre, Malawi	ZI-CMS	Central Medical Stores, Harare, Zimbabwe
MA-MAW	Machinga Distr Hospital, Malawi (in window)	ZI-BB	Beit Bridge Hospital, Zimbabwe
MA-MAS	Machinga Distr Hospital, Malawi (in store)	ZI-BIN	Binga Hospital, Zimbabwe
MA-CHI	Chikwawa District Hospital, Malawi	ZI-ZE	Zenka Hospital, Zimbabwe
GA-CMS	Central Medical Stores, Banjul, Gambia	ZI-SM	St Michael Hospital, Zimbabwe
SUD-IDA	Reference sample, IDA, Amsterdam	ZI-HA	Hanna Hospital, Zimbabwe
SUD-B	Berber hospital, Nile Province, Sudan	ZI-GU	Gumira Hospital, Zimbabwe
SUD-AH	Abu Hamed Hospital, Nile Province, Sudan	ZI-NY	Nyamatawa Hospital, Zimbabwe
SUD-WH	Wad Hamid Hospital, Nile Province, Sudan		

## Annex 2

## Results of field study on oxytocin injection

Level of active ingredient in field samples from district hospitals in Zimbabwe

Location	Manuf.	Batch no.	Time since manuf (m)	Level of active ingredient*		
				>110%	90-110%	<90%
Lupani Mission hospital	OL	511289	21		107	
					107	
Kariba hospital	O1	430990	12	140		
				142		
Murambinda hospital	O1	430990	12	141		
				142		
Beit Bridge hospital	O1	511289	21	104		
				123		
Selinda hospital	O1	250389	30	112		
				112		
	O1	968400986	60 (expired)			

\* As percentage of stated amount. Separate values are given for two ampoules of every sample.

# Simulation study

E1

Ergometrine maleate injection, 0.5 mg/ml

Level of active ingredient expressed as percentage of stated amount

Batch 0181189

Batch 0201189

Storage condition \*

Time	D4-8	D21	Lrm	Drn	D25	D30	D40	D50
0	104	104	104	104	104	104	104	104
0.5	103	103	97	104	104	103	102	94
1	103	103	78	103	102	102	101	81
2	103	103	92	102	102	101	96	79
3	105	103	67	104	103	101	90	66
6	105	103	47	102	101	92	83	59
12	102	100	16	99	93	78	67	26
24	103	86						

Time	D4-8	D21	Lrm	Drn	D25	D30	D40	D50
0	105	105	105	105	105	105	105	105
0.5	105	106	103	105	106	106	104	100
1	105	105	102	105	105	104	101	85
2	105	104	91	105	104	103	95	69
3	106	106	61	106	105	102	78	56
6	107	105	19	104	99	96	65	50
12	104	99	18	94	83	78	45	24
24	104	81						

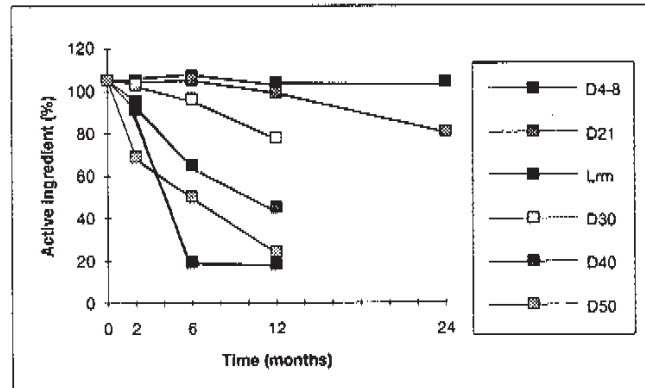
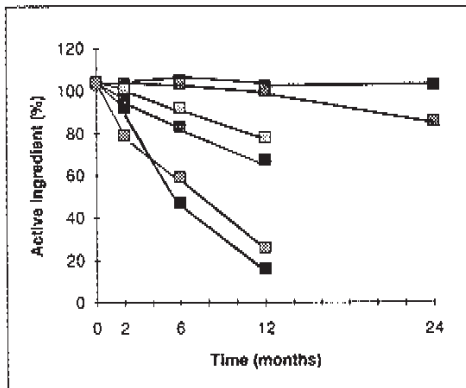
Colour \*\*

Time	D4-8	D21	Lrm	Drn	D25	D30	D40	D50
0	9	9	9	9	9	9	9	9
0.5	9	9	9	9	9	9	9	9
1	9	9	6	9	9	9	9	8
2	9	9	6	9	9	9	9	6
3	9	9	7.5	9	9	9	6.5	5
6	9	9	6	9	9	5.5	5.5	5.5
12	9	9	5.5	9	7	6.5	5.5	2.5
24	9	5						

Time	D4-8	D21	Lrm	Drn	D25	D30	D40	D50
0	9	9	9	9	9	9	9	9
0.5	9	9	9	9	9	9	9	9
1	9	9	9	9	9	9	9	7
2	9	9	6	9	9	9	8	5
3	9	9	2.5	9	9	9	2.5	2.5
6	9	9	1	9	9	9	3.5	1
12	9	9	2	5.5	4.5	4	1	2.5
24	9	4.5						

\* D=Dark, L=Light, rm = roomtemperature; temperature in centigrade

\*\* Colour coding in accordance with European Pharmacopoea, 2nd Ed.



Annex 3/2

Simulation study

E2

Ergometrine malcate injection, 0.2 ml/ml

Level of active ingredient expressed as percentage of stated amount

Batch 92957

Batch 95039

Storage condition \*

Time	D4-8	D21	Lrm	Drm	D25	D30	D40	D50
0	96	96	96	96	96	96	96	96
0.5	96	94	92	95	95	92	89	92
1	94	92	82	93	92	90	80	82
2	95	90	75	90	85	78	74	72
3	93	87	40	87	76	74	64	58
6	91	71	9	70	61	54	51	34
12	83	47	4	49	44	42	33	7
24								

D4-8	D21	Lrm	Drm	D25	D30	D40	D50
99	99	99	99	99	99	99	99
97	98	96	97	97	97	94	92
97	96	89	96	95	93	86	82
97	94	79	94	91	86	79	73
96	91	30	90	82	77	71	60
94	80	8	73	65	59	53	37
86	53	3	51	45	43	36	18

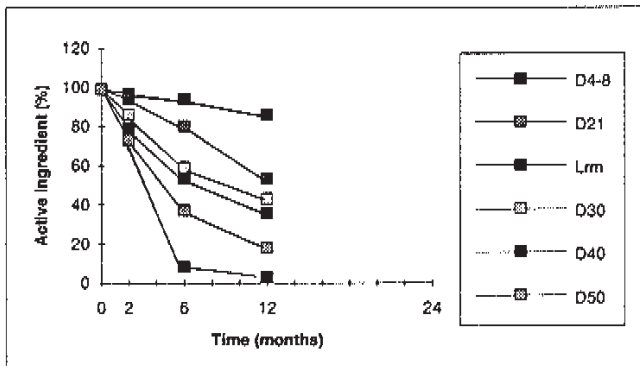
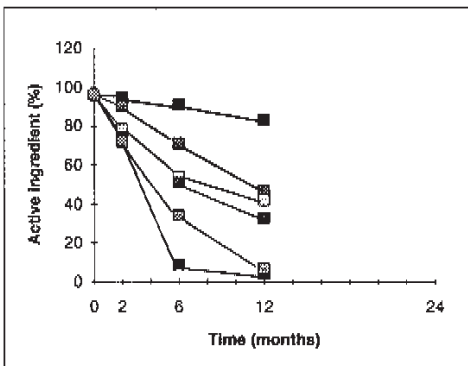
Colour \*\*

0	9	9	9	9	9	9	9	9
0.5	9	9	8	9	9	9	8	8
1	9	9	8	9	8	7	6	6
2	9	9	6	9	7	5.5	5	5
3	9	6.5	4	6.5	5	5	4	4
6	6.5	5	1	4.5	4	4	3	1
12	6	3.5	1	3.5	3	3	1.5	1
24								

9	9	9	9	9	9	9	9	9
9	9	9	9	9	9	9	8	8
9	9	8	9	9	8	7	6	6
9	9	6	9	8	8	6	5.5	5
9	9	4	9	6	5	4.5	4	4
9	5	1	5	4.5	4	3	1	1
6.5	4.5	1	4	3	3	1.5	1	1

\* D=Dark, L=Light, rm = roomtemperature; temperature in centigrade

\*\* Colour coding in accordance with European Pharmacopoea, 2nd Ed.



## Simulation study

E3

Special production of ergometrine maleate injection, 0.15 mg/ml  
Level of active ingredient expressed as percentage of stated amount

Batch 891117A

Batch 891123B

Storage condition \*

Time	D4-8	D21	Lrm	Drm	D25	D30	D40	D50
0	100	100	100	100	100	100	100	100
0.5	103	103	68	103	103	103	101	100
1	101	100	35	100	101	100	98	93
2	100	99	11	100	98	97	94	83
3	102	99	0	100	100	99	91	75
6	99	97	0	95	97	94	79	57
12	96	92	0	90	89	85	63	42
24	86	86						

Time	D4-8	D21	Lrm	Drm	D25	D30	D40	D50
0	101	101	101	101	101	101	101	101
0.5	102	100	51	102	103	103	102	100
1	100	100	52	100	100	100	98	93
2	100	99	1	99	98	98	93	84
3	101	99	0	100	99	98	90	74
6	99	96	0	93	94	93	78	61
12	94	89	0	88	86	83	65	42
24	83	82						

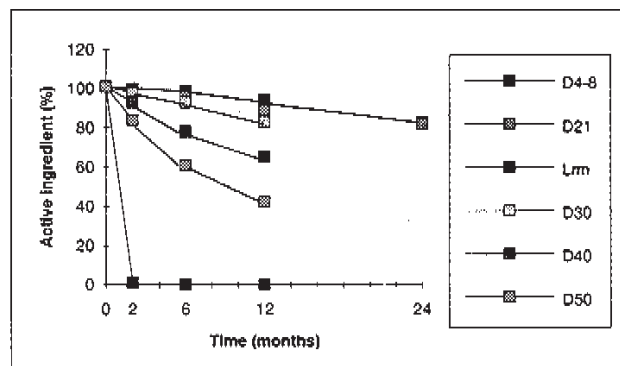
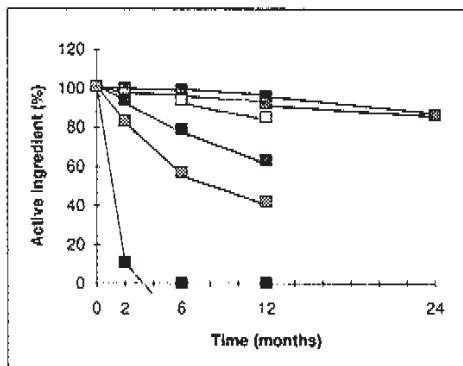
Colour \*\*

Time	D4-8	D21	Lrm	Drm	D25	D30	D40	D50
0	9	9	9	9	9	9	9	9
0.5	9	9	8	9	9	9	9	9
1	9	9	8	9	9	9	9	9
2	9	9	7	9	9	9	9	8
3	9	9	5	9	9	9	6	5
6	9	9	5	9	9	9	6	5
12	9	7	5	7	7	6	5	5
24	6.5	6.5						

Time	D4-8	D21	Lrm	Drm	D25	D30	D40	D50
0	9	9	9	9	9	9	9	9
0.5	9	9	8	9	9	9	9	9
1	9	9	8	9	9	9	9	9
2	9	9	7	9	9	9	9	8
3	9	9	5.5	9	9	9	9	5
6	9	9	5	9	9	9	6	5
12	8	7	5	7	6	6	5	5
24	6	6						

\* D=Dark, L=Light, rm = roomtemperature; temperature in centigrade

\*\* Colour coding in accordance with European Pharmacopoeia, 2nd Ed.



Annex 3/4

# Simulation study

# E4

Ergometrine maleate injection, 0.2 mg/ml  
 Level of active ingredient expressed as percentage of stated amount

Batch 0922

Batch 1207

Storage condition \*

Time	D4-8	D25	Lrm	D30	D40	D50
0	104	104	104	104	104	104
2	104	102	73	90	95	87
6	101	89	34	93	78	20
12	104	84	18	81	42	3
24						

D4-8	D25	Lrm	D30	D40	D50
91	91	91	91	91	91
92	91	66	89	86	78
90	78	41	78	64	13
91	65	13	67	38	0

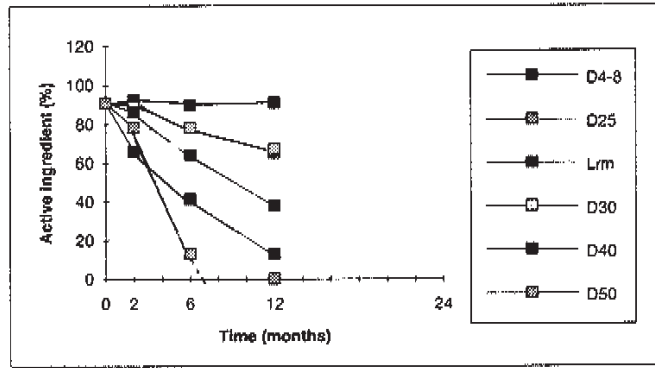
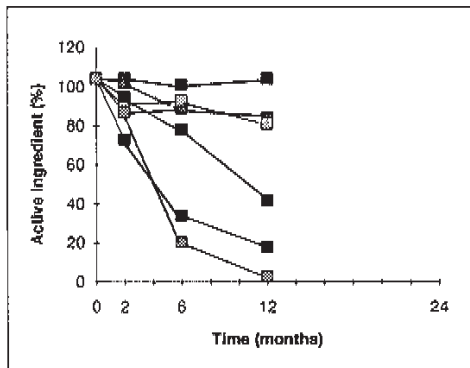
Colour \*\*

0	9	9	9	9	9	9
2	9	8.5	5	7	6.5	5.5
6	9	5.5	2	5.5	5	1
12	9	1	1	6	3	1
24						

9	9	9	9	9	9
9	8	5	8	7.5	6.5
9	5.5	3	5.5	5	1
9	5	1	5	3.5	1

\* D=Dark, L=Light, rm = roomtemperature; temperature in centigrade

\*\* Colour coding in accordance with European Pharmacopoea, 2nd Ed.



## Simulation study

M1

Methylethergometrine maleate injection, 0.2 mg/ml

Level of active ingredient expressed as percentage of stated amount

Batch 89B28

Batch 427MFD0789

		Storage condition *							
Time		D4-8	D21	Lrm	Drm	D25	D30	D40	D50
0		98	98	98	98	98	98	98	98
0.5		99	98	92	99	99	97	97	96
1		98	98	50	98	98	98	97	94
2		98	97	42	97	97	97	95	87
3		98	97	4	98	98	98	93	81
6		97	97	0	96	96	95	84	70
12		95	95	0	94	92	87	76	60
24		97	95						

	D4-8	D21	Lrm	Drm	D25	D30	D40	D50
0	99	99	99	99	99	99	99	99
0.5	99	98	81	99	99	99	98	96
1	98	98	73	98	98	98	97	94
2	98	97	28	97	97	97	94	86
3	98	98	0	98	98	97	93	81
6	97	96	0	96	96	94	84	70
12	96	95	0	94	92	88	75	59
24	98	94						

m

Colour \*\*

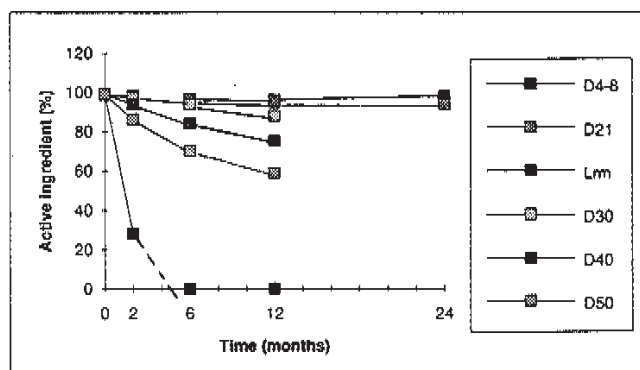
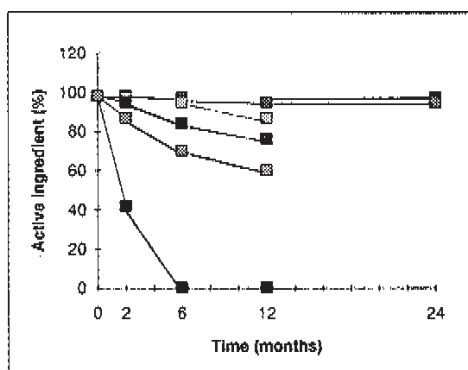
0	9	9	9	9	9	9	9	9
0.5	9	9	9	9	9	9	9	9
1	9	9	7	9	9	9	9	9
2	9	9	7	9	9	9	9	9
3	9	9	6	9	9	9	9	9
6	9	9	6	9	9	9	7	7
12	9	9	6	9	9	9	8	7
24	9	9						

0	9	9	9	9	9	9	9	9
0.5	9	9	8	9	9	9	9	9
1	9	9	8	9	9	9	9	9
2	9	9	6	9	9	9	9	9
3	9	9	6	9	9	9	9	9
6	9	9	6	9	9	9	7	7
12	9	9	5.5	9	9	8	7	7
24	9	9						

m

\* D=Dark, L=Light, rm = roomtemperature; temperature in centigrade

\*\* Colour coding in accordance with European Pharmacopoea, 2nd Ed.



Annex 3/6

# Simulation study

M2

Methylethergometrine maleate injection, 0.2 mg/ml  
 Level of active ingredient expressed as percentage of stated amount

Batch 92254

Time	Storage condition *							
	D4-8	D21	Lrm	Drmm	D25	D30	D40	D50
0	75	75	75	75	75	75	75	75
0.5	71	72	67	70	73	69	67	68
1	73	71	59	71	67	65	61	59
2	72	68	37	69	61	63	58	53
3	67	66	14	65	60	58	55	45
6	65	55	5	57	54	51	44	27
12	65	48	3	47	43	41	30	10
24								
m								

Batch 82247

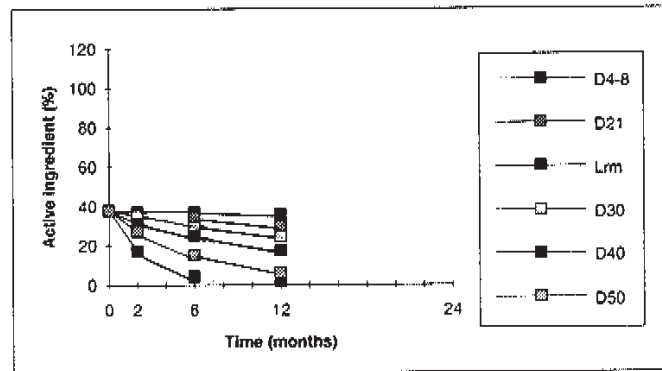
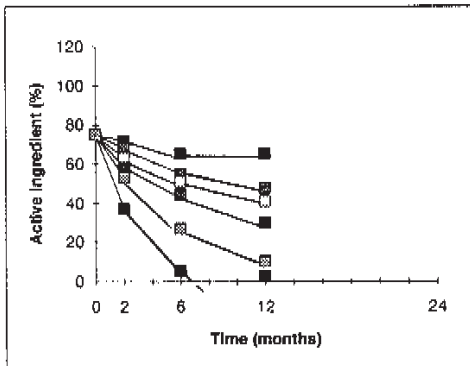
D4-8	D21	Lrm	Drmm	D25	D30	D40	D50
38	38	38	38	38	38	38	38
38	37	36	38	38	37	35	34
37	36	27	37	38	37	34	32
37	37	17	36	36	35	31	27
37	36	13	36	34	36	30	23
37	34	4	34	32	29	25	15
36	30	2	29	26	24	17	6

Colour \*\*

0	5	5	5	5	5	5	5	5
0.5	5	5	5	5	5	5	5	5
1	5	5	5	5	5	5	4	4
2	5	5	3	5	4	4	4	4
3	5	5	2	5	5	4	4	3
6	5	4	1	4	4	4	3	1
12	5	4	1	3.5	3.5	3	1	1
24								
m								

3	3	3	3	3	3	3	3	3
3	3	3	3	3	3	3	3	3
3	3	3	3	3	3	3	3	3
3	3	2	3	3	3	3	2	2
3	3	2	3	3	3	2	1	1
3	3	1	3	3	2	2	1	1
3	2	1	2.5	2	1.5	1	1	1

\* D=Dark, L=Light, rm = roomtemperature; temperature in centigrade  
 \*\* Colour coding in accordance with European Pharmacopoea, 2nd Ed.



## Simulation study

M3

Methylergometrine maleate injection, 0.2 mg/ml

Level of active ingredient expressed as percentage of stated amount

Batch N052

Time	Storage condition *					
	D4-8	D25	Lrm	D30	D40	D50
0	93	93	93	93	93	93
2	94	94	76	94	92	88
6	95	94	61	93	86	69
12	95	92	24	91	78	42
24						

m

Colour \*\*

0	9	9	9	9	9	9
2	9	9	8	9	9	9
6	9	9	6	9	9	7.5
12	9	9	4.5	9	9	5.5
24						

m

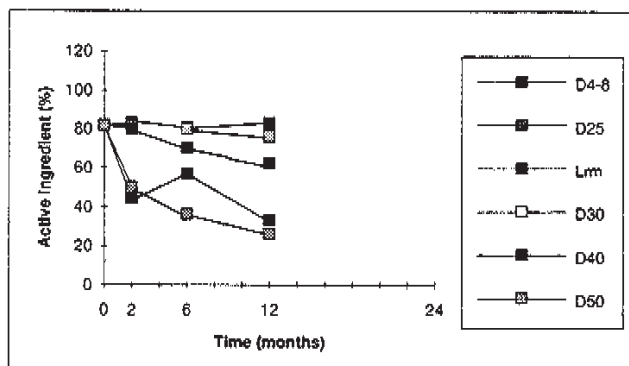
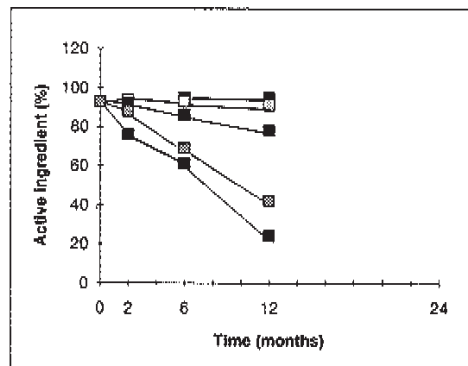
Batch M607

D4-8	D25	Lrm	D30	D40	D50
82	82	82	82	82	82
83	82	44	80	80	50
81	80	57	80	70	36
83	77	33	76	62	26

9	9	9	9	9	9
9	9	4	8.5	9	4
9	9	5	9	6.5	3
9	9	4	9	6.5	4.5

\* D=Dark, L=Light, rm = roomtemperature; temperature in centigrade

\*\* Colour coding in accordance with European Pharmacopoea, 2nd Ed.



Annex 3/8

# Simulation study

M4

Special production methylergometrine maleate injection, 0.2 mg/ml  
 Level of active ingredient expressed as percentage of stated amount

Batch 891120A

Batch 891122B

Storage condition \*

Time	D4-8	D21	Lrm	Drum	D25	D30	D40	D50
0	106	106	106	106	106	106	106	106
0.5	108	108	59	107	107	107	106	103
1	106	106	40	106	106	105	103	99
2	107	106	0	105	104	104	100	90
3	107	106	0	106	105	97	96	81
6	104	103	0	103	101	98	86	68
12	102	97	0	95	93	91	69	50
24	102	91						

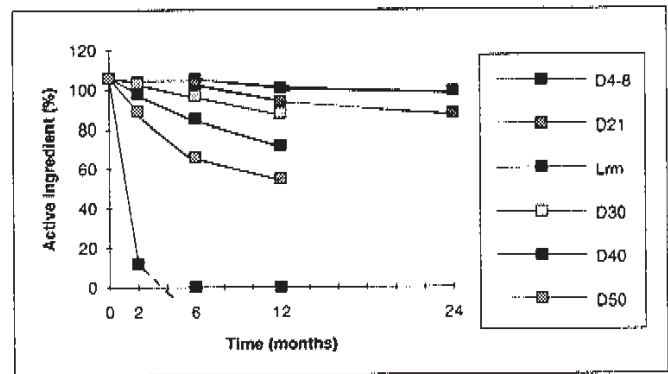
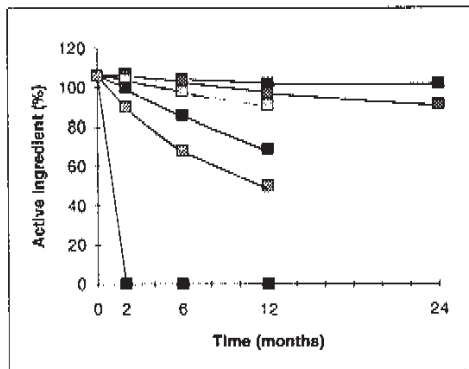
D4-8	D21	Lrm	Drum	D25	D30	D40	D50
106	106	106	106	106	106	106	106
107	107	80	106	105	105	105	106
106	105	42	106	106	105	104	99
104	103	12	105	104	103	98	89
105	105	0	105	102	100	97	79
105	103	0	100	100	97	85	66
101	94	0	97	95	88	72	55
99	88						

Colour \*\*

Time	D4-8	D21	Lrm	Drum	D25	D30	D40	D50
0	9	9	9	9	9	9	9	9
0.5	9	9	7	9	9	9	9	9
1	9	9	7	9	9	9	9	9
2	9	9	6.5	9	9	9	9	9
3	9	9	5	9	9	9	6	6
6	9	9	5	9	9	9	6	6
12	9	9	5	8	7	6	5	5
24	9	6.5						

D4-8	D21	Lrm	Drum	D25	D30	D40	D50
9	9	9	9	9	9	9	9
9	9	8	9	9	9	9	9
9	9	7	9	9	9	9	9
9	9	6	9	9	9	9	7
9	9	5	9	9	9	8	6
9	9	5	9	9	9	6	6
9	7	5	8	7	6	5	5
9	6.5						

\* D=Dark, L=Light, rm = roomtemperature; temperature in centigrade  
 \*\* Colour coding in accordance with European Pharmacopoea, 2nd Ed.



# Simulation study

O1

Oxytocin injection, 5 and 10 IU/ml

Level of active ingredient expressed as percentage of stated amount

10 IU/ml  
Batch 5410690

5 IU/ml  
Batch 0050290

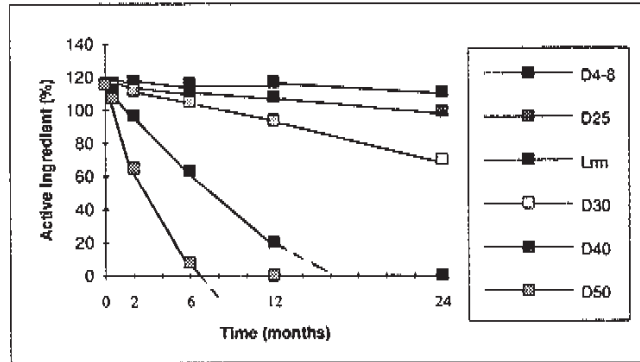
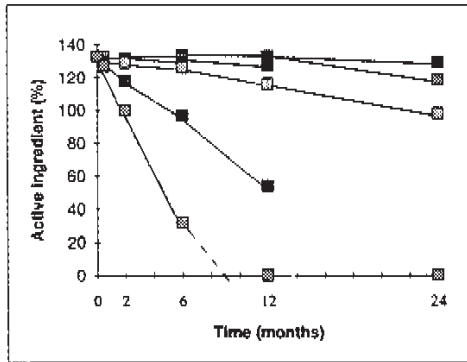
**Storage condition \***

Time	D4-8	D21	Lrm	D30	D40	D50
0	133	133	133	133	133	133
0.5	133	132	132	132	130	127
2	132	132	131	129	118	100
6	134	131	129	126	97	32
12	133	128	127	116	54	0
24	129	119		98		

D4-8	D21	Lrm	D30	D40	D50
116	116	116	116	116	116
116	117	116	115	112	107
118	115	114	112	97	65
116	111	112	105	63	8
117	108	108	94	20	0
111	99		70		

m

\* D=Dark, L=Light, rm = roomtemperature; temperature in centigrade



Annex 3/10

# Simulation study

O2

Oxytocin injection, 10 IU/ml  
Level of active ingredient expressed as percentage of stated amount

Batch 00/2125/103

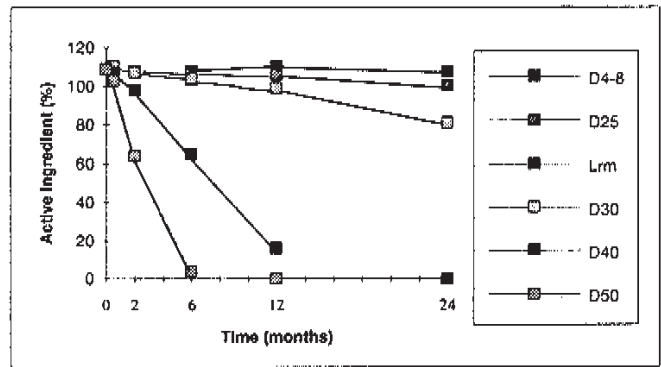
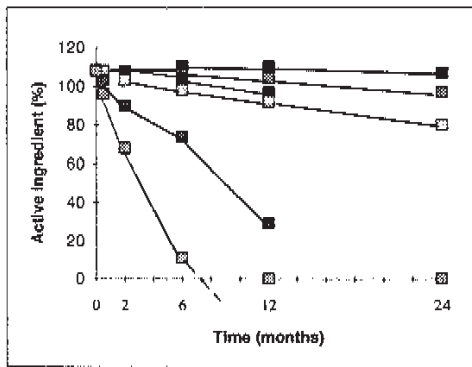
Batch 00/2257/103

Storage condition \*

Time	D4-8	D21	Lrm	D30	D40	D50
0	108	108	108	108	108	108
0.5	108	108	108	107	103	96
2	107	107	108	103	90	68
6	110	106	104	98	74	11
12	110	104	97	92	29	0
24	107	97		80		

D4-8	D21	Lrm	D30	D40	D50
109	109	109	109	109	109
108	110	109	110	107	103
108	107	107	107	98	64
108	106	103	104	65	4
110	106	99	99	16	0
107	100		81		

\* D=Dark, L=Light, rm = roomtemperature; temperature in centigrade



## Simulation study

O3

Oxytocin injection, 5 and 10 IU/ml

Level of active ingredient expressed as percentage of stated amount

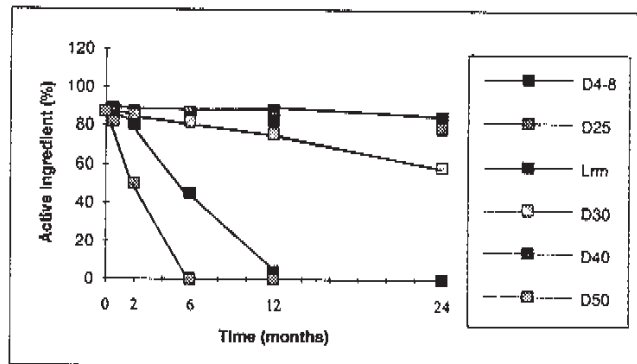
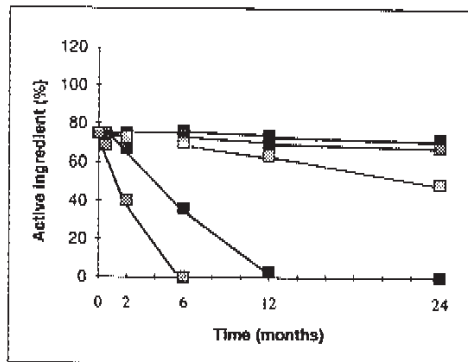
10 IU/ml  
Batch M 0995 IU/ml  
Batch M 473

Storage condition \*

Time	D4-8	D21	Lrm	D30	D40	D50
0	75	75	75	75	75	75
0.5	75	75	74	74	73	69
2	74	75	74	73	67	40
6	76	74	73	70	36	0
12	74	72	70	64	3	0
24	72	68		49		

D4-8	D21	Lrm	D30	D40	D50
87	87	87	87	87	87
87	87	89	86	85	82
87	87	86	85	80	50
87	86	84	82	45	0
88	84	83	76	4	0
85	79		59		

\* D=Dark, L=Light, rm = roomtemperature; temperature in centigrade



## Summary results of simulation studies

% of stated amount			
t=0	t=12m		
	D 4-8	D 30	L 21-25

% of initial amount			
t=0	t=12m		
	D 4-8	D 30	L 21-25

### Ergometrine

E1	104	102	78	16
E1	105	104	78	18
E2	96	83	42	4
E2	99	86	43	3
E3	100	96	85	0
E3	101	94	83	0
E4	104	104	81	18
E4	91	91	67	13
Mean	100.00	95.00	69.63	9.00
95%CL	96.05	88.27	54.92	2.46
	103.95	101.73	84.33	15.54

	100%	98%	75%	15%
	100%	99%	74%	17%
	100%	86%	44%	4%
	100%	87%	43%	3%
	100%	96%	85%	0%
	100%	93%	82%	0%
	100%	100%	78%	17%
	100%	100%	74%	14%
	100%	94.94%	69.39%	8.91%
		90.26%	55.68%	2.40%
		99.62%	83.11%	15.43%

### Methylergometrine

M1	98	95	87	0
M1	99	96	88	0
M2	75	65	41	3
M2	38	36	24	2
M3	93	95	91	24
M3	82	83	76	33
M4	106	102	91	0
M4	106	101	88	0
Mean	87.13	84.13	73.25	7.75
95%CL	68.18	64.99	51.52	-3.19
	106.07	103.26	94.98	18.69

	100%	97%	89%	0%
	100%	97%	89%	0%
	100%	87%	55%	4%
	100%	95%	63%	5%
	100%	102%	98%	26%
	100%	101%	93%	40%
	100%	96%	86%	0%
	100%	95%	83%	0%
	100%	96.27%	81.86%	9.41%
		92.33%	69.31%	-3.31%
		100.22%	94.41%	22.14%

### Oxytocin

O1	133	133	116	127
O1	116	117	94	108
O2	108	110	92	97
O2	109	110	99	99
O3	75	74	64	70
O3	87	88	76	83
Mean	104.67	105.33	90.17	97.33
95%CL	82.88	83.18	71.11	76.61
	126.45	127.49	109.23	118.06

	100%	100%	87%	95%
	100%	101%	81%	93%
	100%	102%	85%	90%
	100%	101%	91%	91%
	100%	99%	85%	93%
	100%	101%	87%	95%
	100%	100.57%	86.16%	92.99%
		99.41%	82.77%	90.56%
		101.74%	89.55%	95.43%

Legenda D= dark, L = light  
Temperature in centigrade

## Stability of ergometrine injection stored at room temperature, dark vs light

Remarks: Value per brand represents mean of two batch values  
Batch value represents mean of two separate ampoule values

Dark				
Time	E1	E2	E3	E4
0	105	98	101	98
0.5	105	96	103	
1	104	94	100	
2	104	92	99	97
3	105	89	99	
6	104	76	97	84
12	100	50	91	75

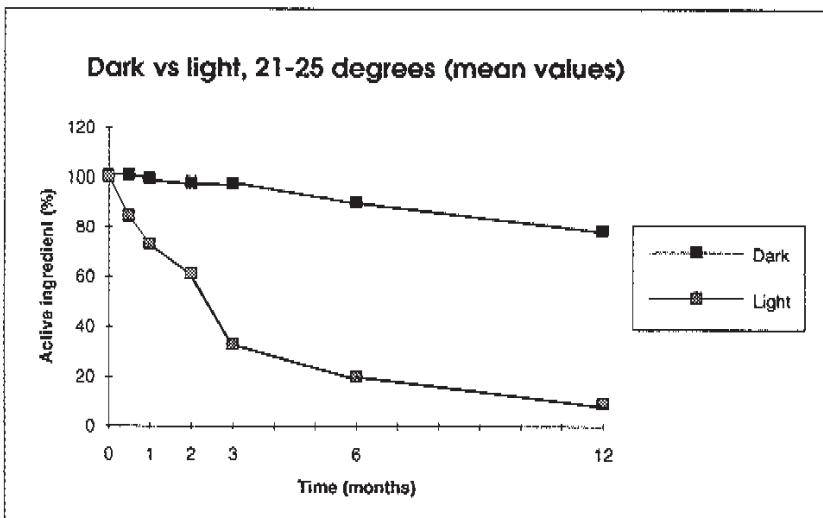
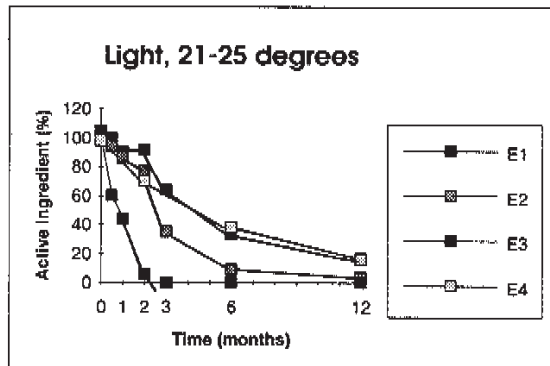
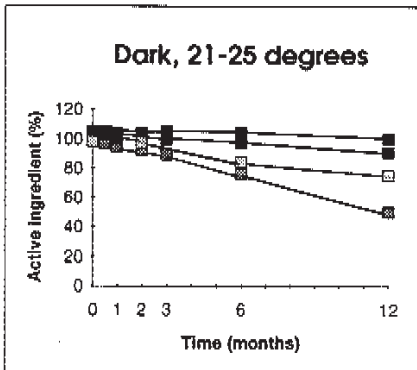
months

Light				
Time	E1	E2	E3	E4
0	105	98	101	98
0.5	100	94	60	
1	90	86	44	
2	92	77	6	70
3	64	35	0	
6	33	9	0	38
12	17	4	0	16

months

Mean		
Time	Dark	Light
0	101	101
0.5	101	85
1	99	73
2	98	61
3	98	33
6	90	20
12	79	16

months



Annex 5/2

## Stability of methylergometrine injection at room temperature, dark vs light

Remarks: Value per brand represents mean of two batch values  
 Batch value represents mean of two separate ampoule values  
 Methylergometrine M2 has been excluded because of low initial values

Dark				
Time	M1	M3	M4	(M2)
0	99	88	106	
0.5	99		107	
1	98		106	
2	97	88	105	
3	98	88	106	
6	96	87	102	
12	94	85	96	

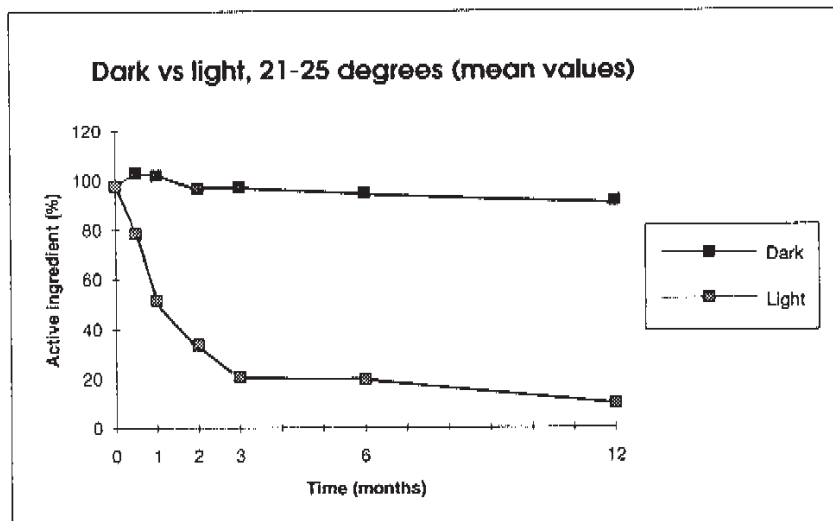
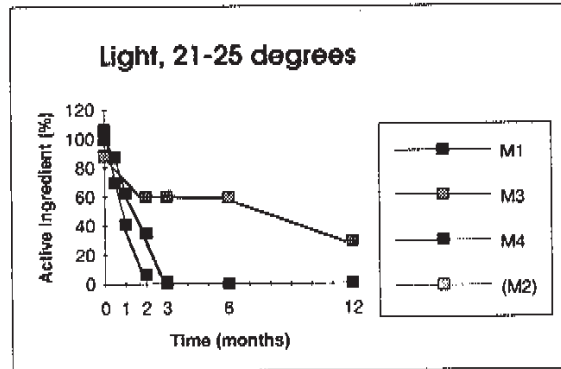
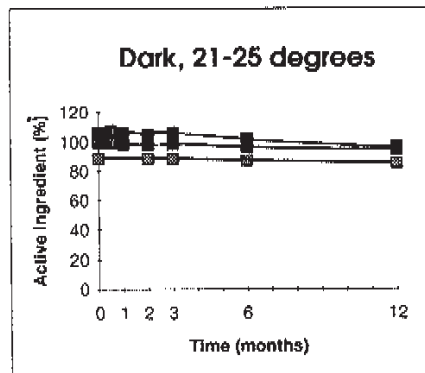
months

Light				
Time	M1	M3	M4	(M2)
0	99	88	106	
0.5	87		70	
1	62		41	
2	35	60	6	
3	2	60	0	
6	0	59	0	
12	0	29	0	

months

Mean		
Time	Dark	Light
0	98	98
0.5	103	79
1	102	52
2	97	34
3	97	21
6	95	20
12	92	10

months



## Comparison ergometrine vs. methylergometrine injection (2 brands each)

Remarks: Comparison made both for dark storage at 30C and room temperature in light  
Values represent mean level of active ingredient of two batch values  
Batch value represents mean of two separate ampoule values .

Special production (E3 and M4)\*

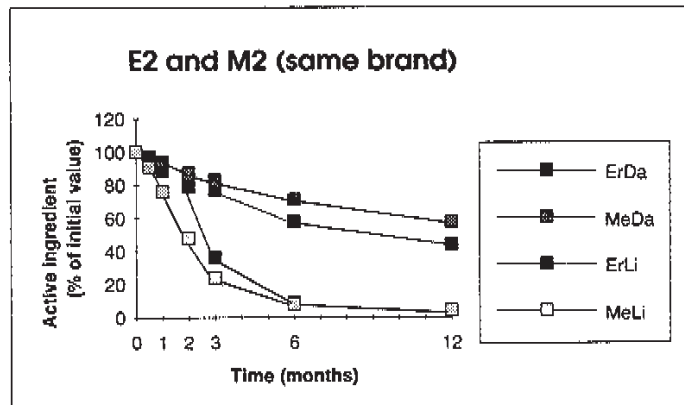
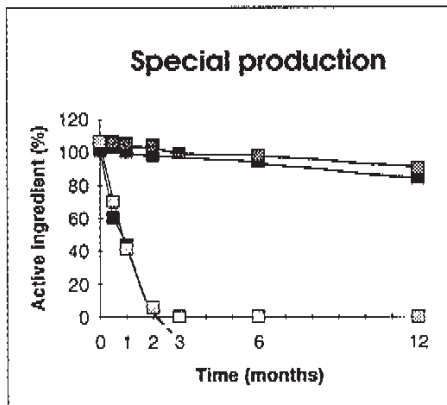
Time	Dark, 30C		Light, 21-25C	
	ErDa	MeDa	ErLi	MeLi
0	101	106	101	106
0.5	103	106	60	70
1	100	105	44	41
2	98	104	6	6
3	99	99	0	0
6	94	98	0	0
12	84	90	0	0

\* Active ingredient, as % of stated amount

E2 and M2 (same brand)\*\*

Time	Dark, 30C		Light, 21-25C	
	ErDa	MeDa	ErLi	MeLi
0	100	100	100	100
0.5	97	94	96	91
1	94	90	88	76
2	84	87	79	48
3	77	83	36	24
6	58	71	9	8
12	44	58	4	4

\*\* As percentage of initial amount of active ingredient



### LEGEND

Er = ergometrine; Me = methylergometrine; Da = dark, 30C; Li = light, 21-25C