Stability testing conditions of pharmaceuticals

Department:
Water and Environmental Affairs
REPUBLIC OF SOUTH AFRICA

SAPRAA

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Overview

- Factors that influence medicine stability
- Climatic Zones (CZ)
- Storage conditions
- Climatic Classification of South Africa
- RSA worst case scenario
- Aspects to consider
- Conclusion
- References

Factors that influence stability of medicines

- **Product related factors, i.e.**
  - **API physical and chemical stability,**
  - **dosage formulation,**
  - **manufacturing process,**
  - **container closure system,**
  - **packaging material properties**
- **Environment, i.e.**
    - **ambient temperature,**
    - **humidity and light –**
  - **storage conditions and the climate**

Medicines must maintain quality and efficacy for the whole of their shelf-life

- **An appropriate shelf-life – balance between**
  - **Ensuring the quality (safety and efficacy) of the medicine for the full shelf-life and**
  - **Not being wasteful by**
    - **assigning an unnecessarily short shelf-life, or**
    - **requiring excessively protective packaging**
- **for the given climatic condition for the country or region**
    - **Too strict – reformulation, unnecessary cost, price to patient**
    - **Too lenient - increased risk of marketed product failure**

Climatic Zones

To avoid having to carry out special storage tests for each country, four climatic zones

CZ	Definition	Criteria Mean annual temperature measure in the open air/Mean annual water vapour pressure	Long term testing conditions
I	Temperate climate	≤ 15 °C / ≤11 hPa	21 °C / 45 % RH
II	Mediterranean and subtropical climate	>15 to 22 °C/ >11 to 18 hPa	25 °C / 60 % RH
III	Hot and dry climate, arid zones	>22 °C / ≤15 hPa	30 °C / 35 % RH
IVA	Hot and humid climate	>22 °C / >15 hPa	30 °C / 65 % RH
IVB	Hot and very humid climate	>22 °C / >15 hPa	30 °C / 75 % RH

Criteria and storage conditions for Climatic Zones

[derived values]	I UK, USA, N Eu, Cda, Japan	II USA, S Eu, Japan	III Iran, Iraq, Sudan	IV Brazil, Ghana, Philippines, Singapore
Definition	Temperate	Subtropical & Mediterranean	Hot, dry	Hot, humid
Mean annual temp open air °C	≤ 15	> 15 ≤ 22	> 22	> 22
Calculated mean annual temp (< 19 °C as 19 °C)	≤ 20,5	> 20,5 ≤ 24	> 24	> 24
MKT °C (RT)	<21	21 to 25	>25	>25
[Derived °C]	[21]	[25]	[30]	[30]
% RH [derived % RH]	42 [45]	52 [60]	35 [35]	70 [70]
Mean annual water vapour partial pressure hPa	< 11 [11,2]	11 to 18 [19,0]	< 15 [15,0]	> 15 [30]
Storage conditions °C / % RH	21 / 45	25 / 60	30 / 35	30 / 65 or 75

Mean Kinetic Temperature

- **The single calculated temperature at which the total amount of degradation equals the sum of individual degradation that would occur at the individual temperatures**

  Differs to some degree from the annual temperature and usually would equal none of the monthly temperatures.

  The virtual temperature may be said to exist in effect, not in fact

- **USP Controlled Room temperature:**
  - **Working environment usually 20 to 25 °C**
  - **Excursions 15 to 30 °C**
  - **MKT ≤ 25 °C**

Effect of various storage regimens on MKT					
(Months) (°C)	1	2	3	4	5
1 to 9	25	25	25	25	22,5
10	25	25	25	30	30
11	25	30	30	30	30
12	30	20	30	30	30
Arithmetic mean	25,42	25,00	25,83	26,25	24,38
Mean Kinetic mean	25,53	25,33	26,04	26,51	24,99

Storage conditions

General	**CZ II Long-term**	**----**	**25 ± 2 °C / 60 ± 5 % RH**
	CZ II Intermediate 12 months ≥ 8 090 h	**CZ IVA Long-term**	**30 ± 2 °C / 65 ± 5 % RH**
	Accelerated ≥ 3 months = ≥ 2 016 h		**40 ± 2 °C / 75 ± 5 % RH**
Semi-permeable containers	**CZ II Long-term**	**----**	**25 ± 2 °C / 40 ± 5 % RH**
	CZ II Intermediate 12 months ≥ 8 090 h	**CZ IVA Long term**	**30 ± 2 °C / 65 ± 5 % RH**
	Accelerated ≥ 3 months = ≥ 2 016 h		**40 ± 2 °C / 25 ± 5 % RH**
Refrigerator	**Long-term testing**		**5 ± 3 °C**
	Accelerated ≥		**25 ± 2 °C / 60 ± 5 % RH**
Freezer	**Long-term testing**		**-20 ± 5 °C**
	Accelerated ≥ 3 months = ≥ 2 016 h		**5 ± 3 °C**
	or		**25 ± 2 °C**

Climatic classification of RSA

- Köppen-Geiger Climate Classification
- Fauna and flora
- South African Weather Service (SAWS)
- Zahn et al
- Stability guideline

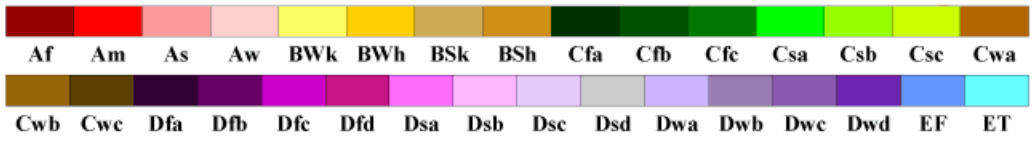
Köppen-Geiger Climate Classification

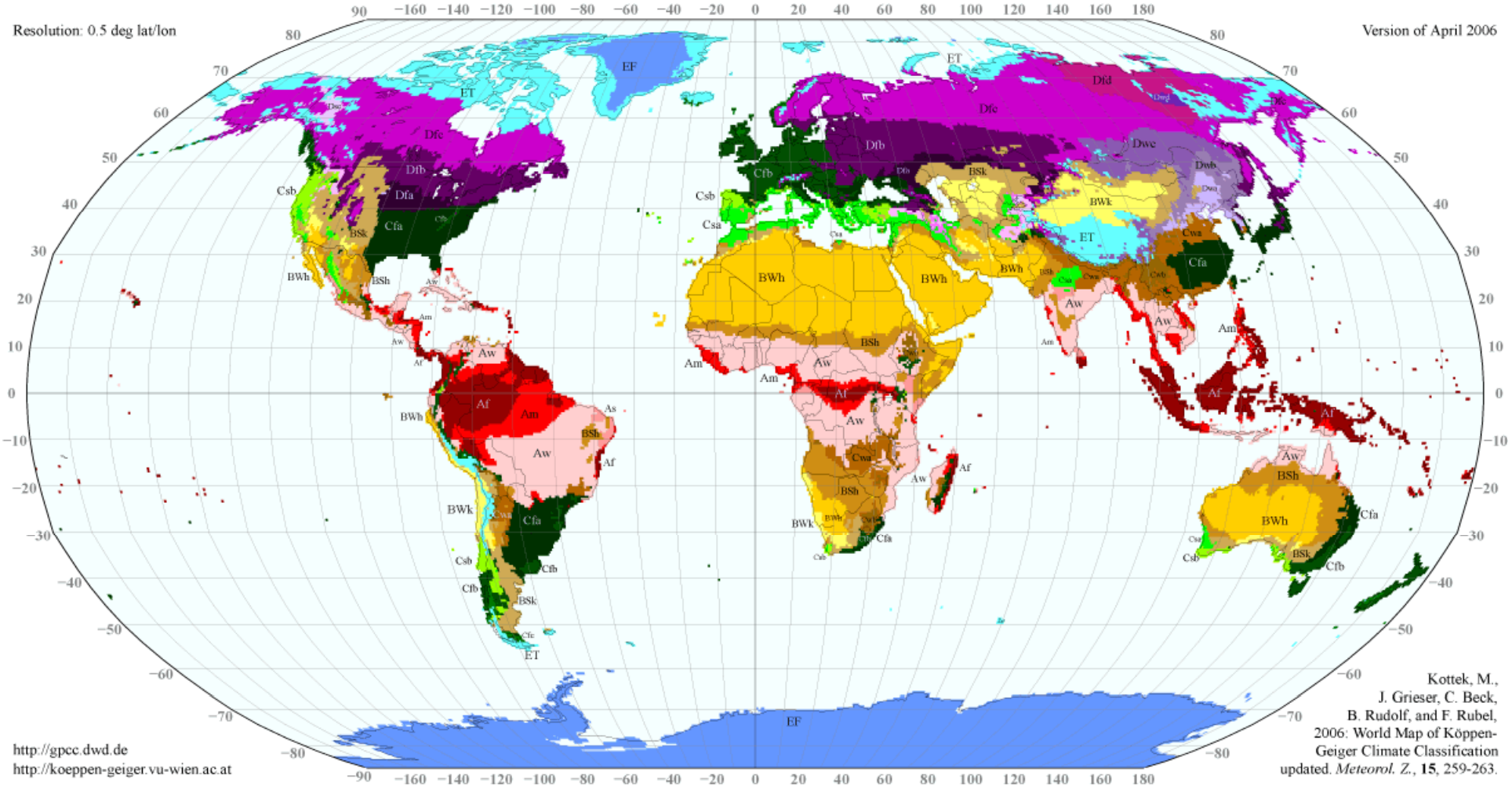
?

World Map of Köppen−Geiger Climate Classification

updated with CRU TS 2.1 temperature and VASClimO v1.1 precipitation data 1951 to 2000

Main climates	Precipitation	Temperature	
A: equatorial	W: desert	h: hot arid	F: polar frost
B: arid	S: steppe	k: cold arid	T: polar tundra
C: warm temperate	f: fully humid	a: hot summer	
D: snow	s: summer dry	b: warm summer	
E: polar	w: winter dry	c: cool summer	
	m: monsoonal	d: extremely continental	





Fauna and flora

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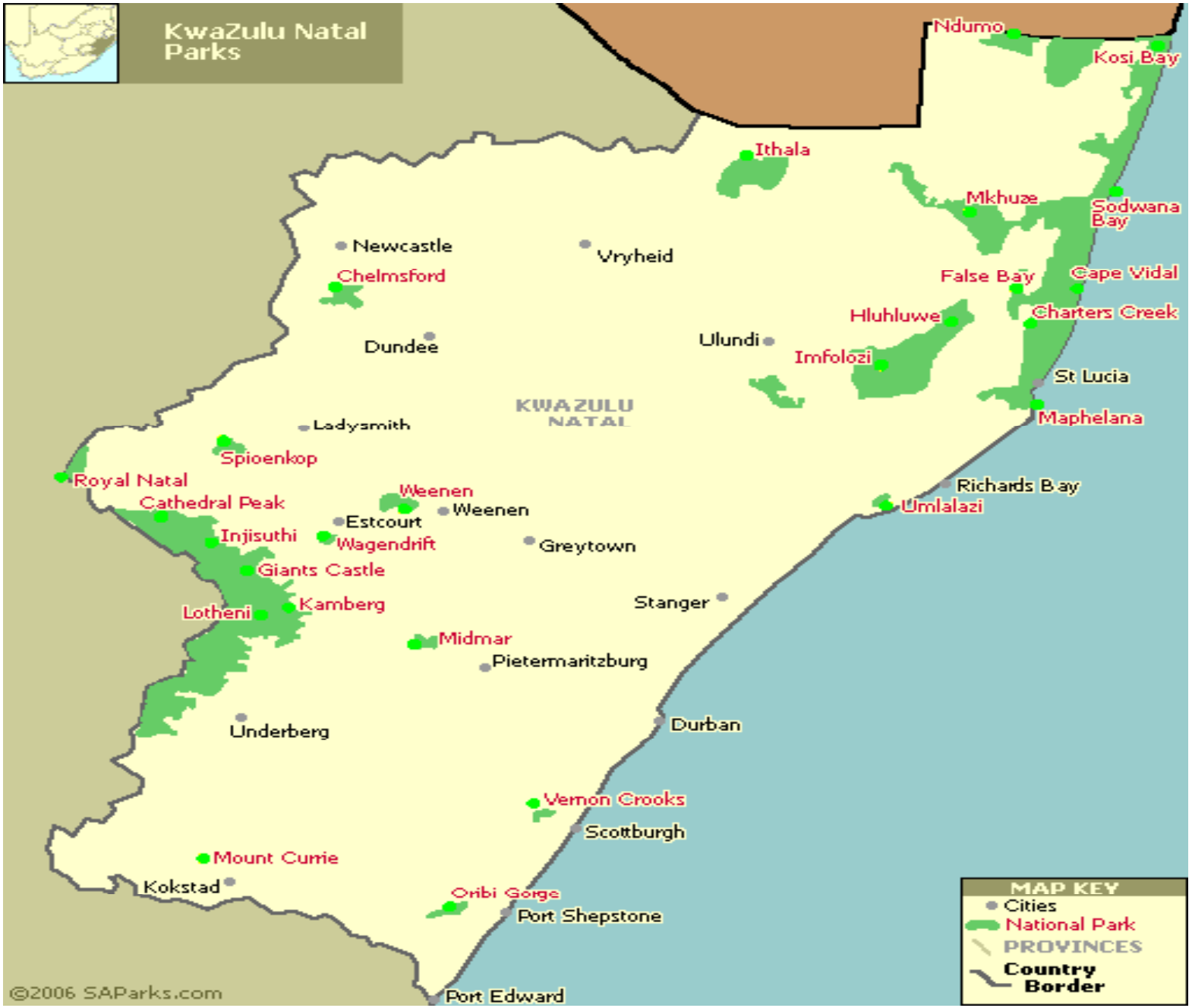
Google Map of South Africa

Fauna and flora



Fauna and flora

Fauna and flora

South African Weather Service (SAWS)

1961 to 1990

?

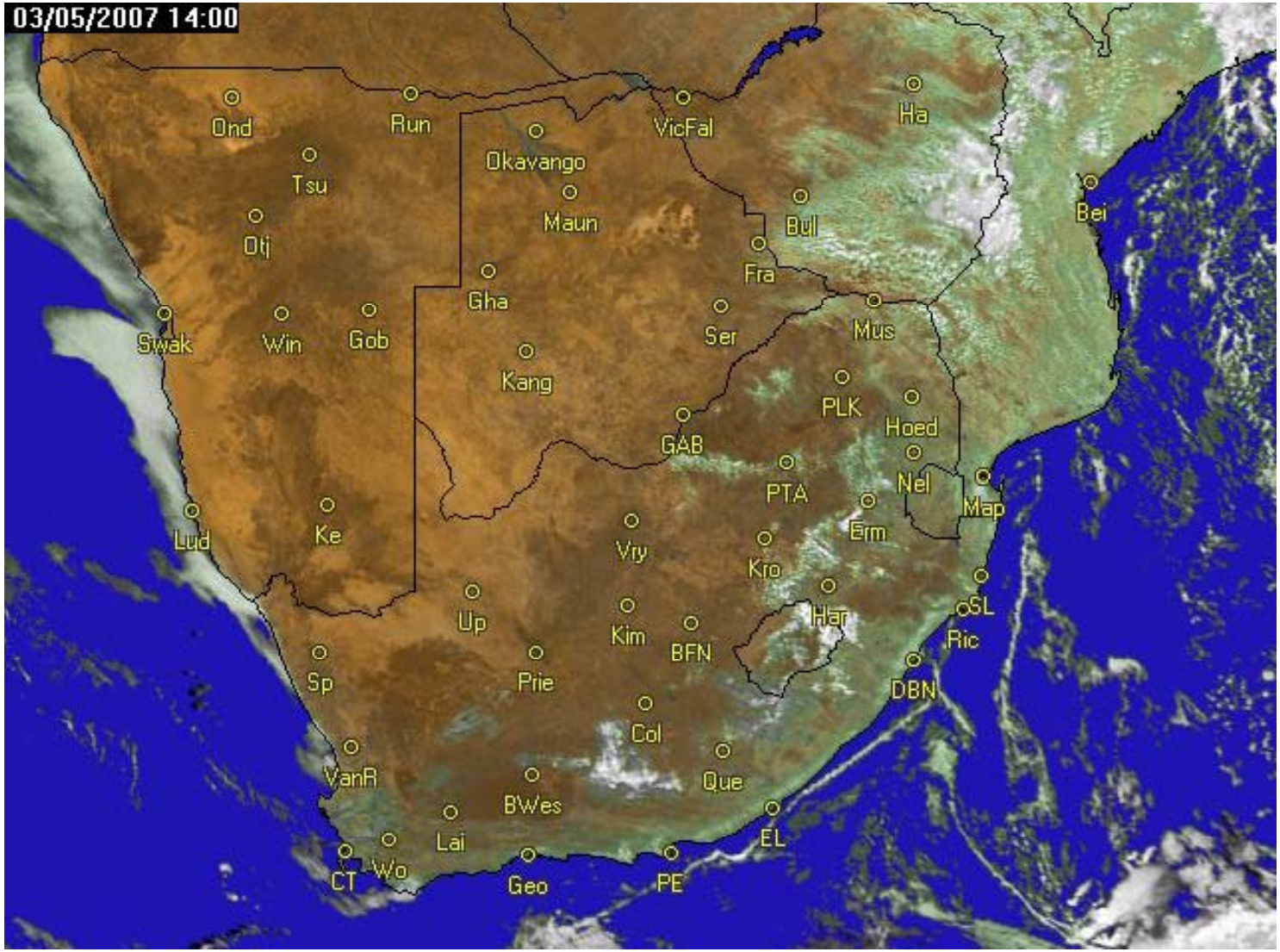
Köppen Climatic classification of RSA 1961 – 1990 by SAWS

- ***BW***: Desert (arid)
- ***BS***: Steppe (semi-arid)
- ***Csa***: Winter rain with hot summers
- ***Csb***: Winter rain with cool summers
- ***Cwa***: Summer rain with hot summers
- ***Cwb***: Summer rain with cool summers
- ***Cfa***: All-year rain with hot summers
- ***Cfb***: All-year rain with cool summers
- Global warming predicted 2 °C next century (2003)

South African Weather Service (SAWS)

1990 to 2009

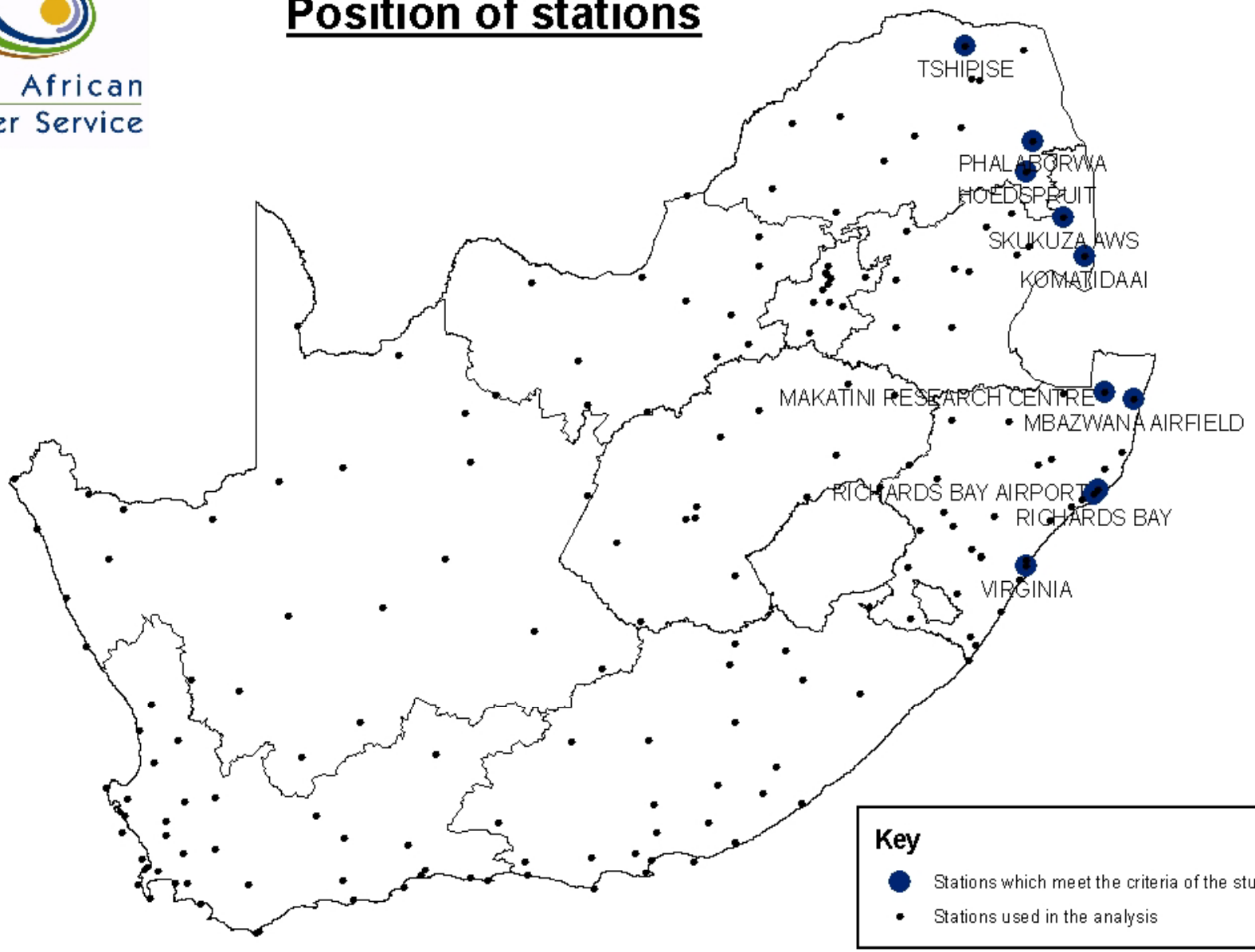
?



Of the two *Cfa* areas identified for South Africa, the northern part of the Eastern Coastal Bushveld area along the eastern coastline of KwaZulu Natal (KZN), is the hottest and most moist area and will therefore have the most affect on the stability of pharmaceuticals in South Africa . This area is approximately 0,64 % of the total surface area (approximately 15 600 km^2 of 1 219 090 km^2) of South Africa.

South African Weather Service

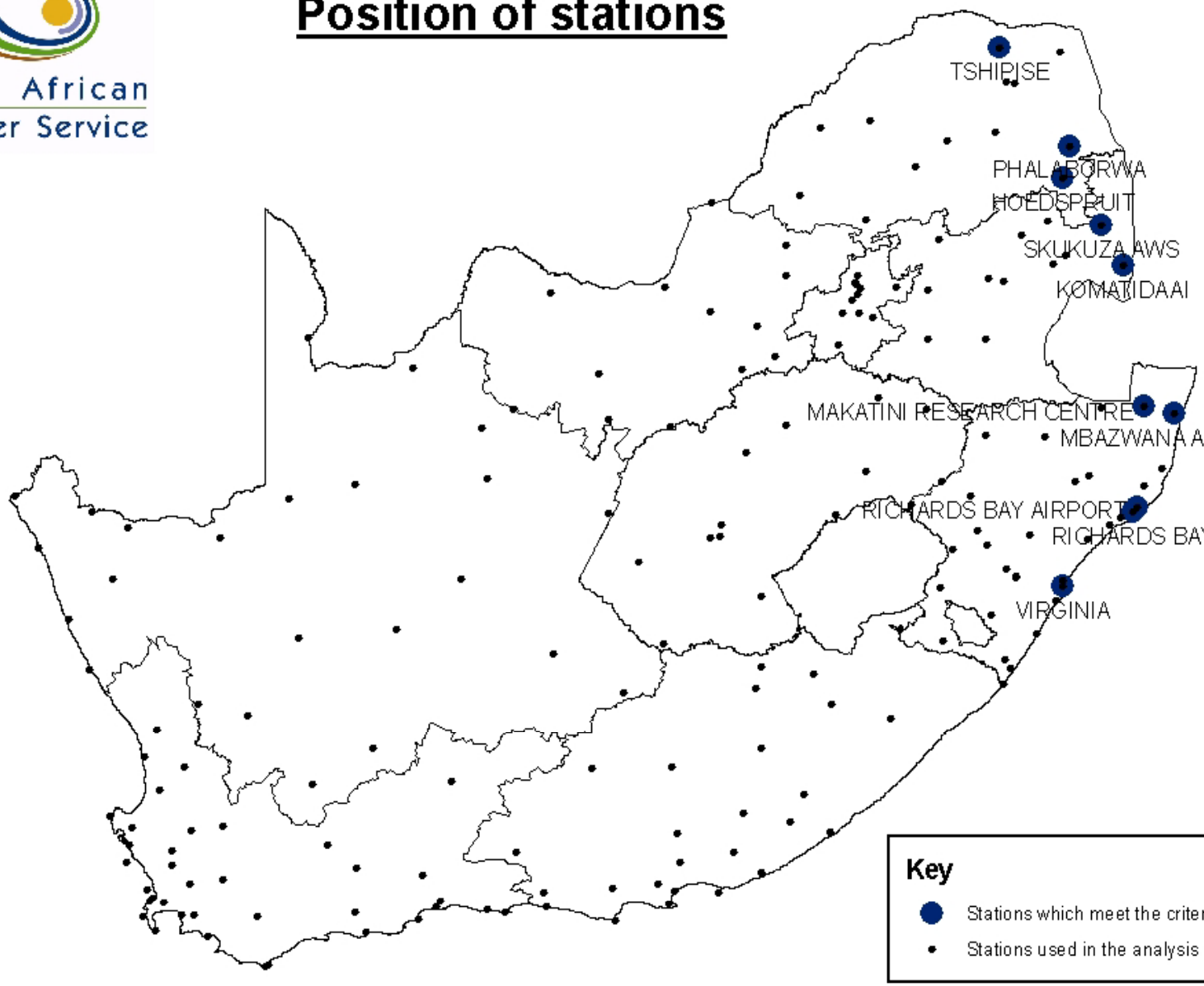
Position of stations



SAWS

South African Weather Service

Position of stations



5/13

1/17

4 +1/12

2/6

1/18

1/2

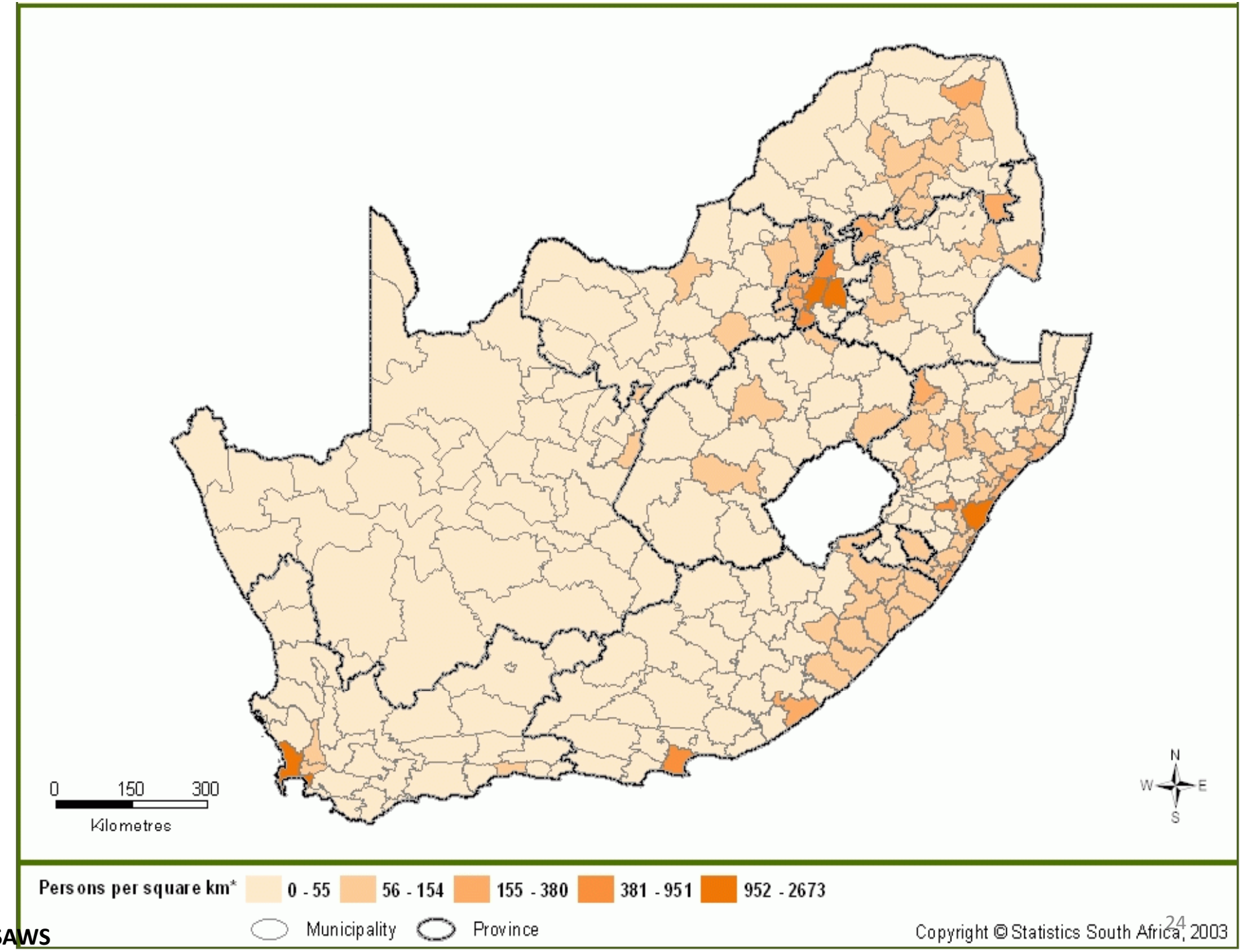
6/10

1/9 - 1/6

1/15

1/14 > 18 hPa 1/18 >15 hPa

SAWS


0 150 300
Kilometres
N
W
E
S
Persons per square km*
0 - 55
56 - 154
155 - 380
381 - 951
952 - 2673
Municipality
Province
Copyright © Statistics South Africa, 2003

Umkhanyakude District Municipality

Jozini Local Municipality	uMhlabuyalingana Local Municipality
Hlabisa Local Municipality	Big 5 False Bay Local Municipality
Mtubatuba Local Municipality	

Stations recording mean annual temp > 22 °C and mean annual vapour pressure ≥ 18 hPa

Times met /number years Station name	Latitude	Longitude	Year criteria met	Temp °C	Humidity %	Vapour Pressure hPa	Station opening date	Station closed
5/13 TSHIPISE	-22,62	30,17	1997	22	62,9	16,3	1993	2006
TSHIPISE	-22,62	30,17	1998	23,5	61,8	17,7	1993	2006
1/17 PHALABORWA	-23,93	31,15	1998	22,2	75,6	20,2	1992	open
1/12 HOEDSPRUIT	-24,35	31,05	1998	22,2	70,6	18,2	1996	open
2/6 SKUKUZA AWS	-24,98	31,58	2002	22,2	60,1	15,4	2001	2007
1/18 KOMATIDRAAI	-25,52	31,9	1995	23,5	49,7	15,1	1990	open
6/10 MBAZWANA AIRFIELD	-27,48	32,6	1998	22,5	83,3	22,8	1997	open
1/ 2 MAKATINI RESEARCH CENTRE	-27,39	32,18	2008	22,1	69,6	18,1	2006	open
1/6 RICHARDS BAY AIRPORT	-28,73	32,08	2008	22,9	80,7	22,5	2002	open
1/ 15 VIRGINIA	-29,77	31,05	1999	22,9	84,9	24,1	1994	open

South African Worst Case Scenario

CZ II
or
CZ IVA ?

Stability

Zahn et al 2006

A Risk-Based Approach to Establish Stability Testing Conditions for Tropical Countries

- **Risk based approach – hottest and most humid place – worst case in each country**
- **Global climatic data from the ERA-40 analysis of ECMWF**
- **Safety margin formula - Δ actual and test temperature & vapour pressure**

- **Temperature and safety margins (°C / %)**

Cape St Lucia	(22,3 / 11)	Cape Town	(16,7 / 47)
De Aar	(16,7 / 30)	Durban	(20,6 / 19)
Kimberly	(17,6 / 23)	Little Namaland	(21,4 / 6)
Musina	(21,5 / 10)	Port Elizabeth	(18,8 / 31)
Pretoria	(17,5 / 30)		

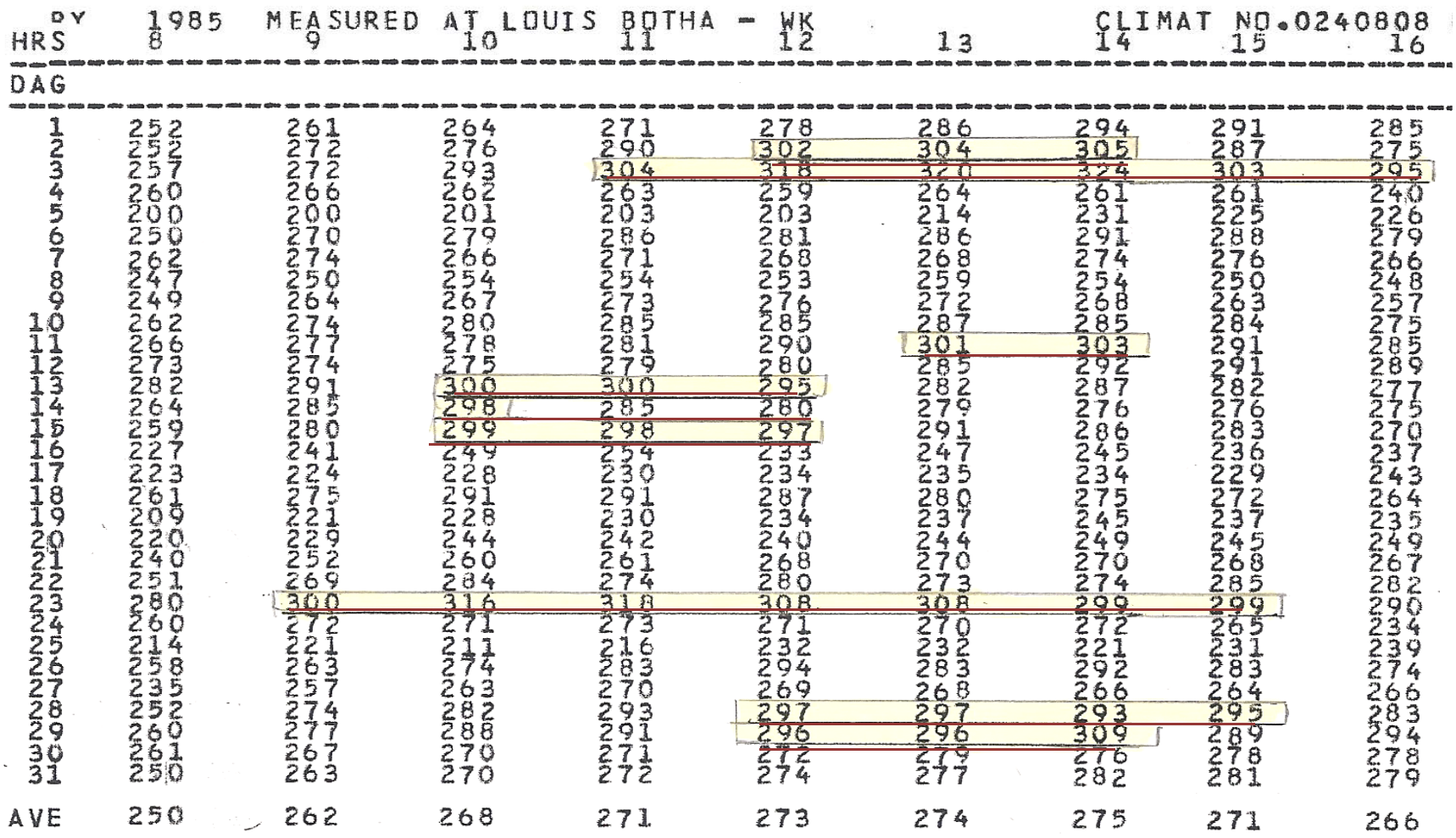
Zahn et al 2006 *contd*

- At 25 °C and at 60 % RH
  - Positive safety margin for temperature
  - Negative safety margin vapour pressure
    St Lucia -8 and Durban -1

	Mean partial water vapour pressure	RH [%]	RH at 25 °C [%]	Vapour pressure Safety margin at 25 °C/60 RH [%]	RH at 30 °C [%]	Vapour pressure Safety margin at 30 °C /65 RH [%]
Saint Lucia	20,66	76,9	65,2	- 8	48,6	34
Durban	19,28	79,4	60,8	- 1	45,4	43

Hourly temperatures

Durban January 1985



DY	1985	MEASURED AT LOUIS BOTHA - WK					CLIMAT NO.0240808		
HRS	8	9	10	11	12	13	14	15	16
DAG									
1	252	261	264	271	278	286	294	291	285
2	252	272	276	290	302	304	305	287	275
3	257	272	293	304	318	320	324	303	295
4	260	266	262	263	259	264	261	261	240
5	200	200	201	203	203	214	231	225	226
6	250	270	279	286	281	286	291	288	279
7	262	274	266	271	268	268	274	276	266
8	247	250	254	254	253	259	254	250	248
9	249	264	267	273	276	272	268	263	257
10	262	274	280	285	285	287	285	284	275
11	266	277	278	281	290	301	303	291	285
12	273	274	275	279	280	285	292	291	289
13	282	291	300	300	295	282	287	282	277
14	264	285	298	285	280	279	276	276	275
15	259	280	299	298	297	291	286	283	270
16	227	241	249	254	233	247	245	236	237
17	223	224	228	230	234	235	234	229	243
18	261	275	291	291	287	280	275	272	264
19	209	221	228	230	234	237	245	237	235
20	220	229	244	242	240	244	249	245	249
21	240	252	260	261	268	270	270	268	267
22	251	269	284	274	280	273	274	285	282
23	280	300	316	318	308	308	299	299	290
24	260	272	271	273	271	270	272	265	234
25	214	221	211	216	232	232	221	231	239
26	258	263	274	283	294	283	292	283	274
27	235	257	263	270	269	268	266	264	266
28	252	274	282	293	297	297	293	295	283
29	260	277	288	291	296	296	309	289	294
30	261	267	270	271	272	279	276	278	278
31	250	263	270	272	274	277	282	281	279
AVE	250	262	268	271	273	274	275	271	266

Hourly humidity

Durban January 1985

HOURLY VALUES OF HUMIDITY DATA JANUARY 1985 MEASURED AT LOUIS BOTHA - WK

HRS / DAG	8	9	10	11	12	13	14	15	16
1	87	79	77	71	68	65	63	65	69
2	79	75	70	66	62	62	61	68	76
3	82	75	62	58	53	51	52	61	66
4	60	67	77	77	83	78	77	76	92
5	98	98	98	98	98	93	82	91	87
6	77	76	73	70	72	72	74	74	81
7	68	55	68	66	68	70	67	62	64
8	61	65	63	64	66	65	69	69	74
9	75	71	72	68	72	75	79	83	88
10	83	74	79	75	77	75	77	81	87
11	73	78	77	71	70	65	67	70	79
12	84	85	83	81	81	79	76	77	80
13	73	71	57	64	72	85	83	83	82
14	76	53	42	55	72	74	80	80	80
15	94	79	58	59	58	66	74	79	82
16	95	81	73	69	89	73	72	83	82
17	97	97	93	97	97	97	97	97	97
18	55	76	71	67	67	71	75	75	76
19	62	62	61	60	59	57	57	62	67
20	81	88	63	63	66	67	67	68	67
21	71	62	56	52	51	54	56	64	63
22	78	77	68	70	73	76	76	67	75
23	70	60	54	54	63	65	68	67	76
24	74	67	67	64	66	72	71	73	97
25	91	86	91	91	79	80	89	88	87
26	75	72	71	64	60	61	64	68	76
27	96	80	76	71	70	74	80	80	76
28	82	72	65	59	61	64	68	65	66
29	84	79	73	68	64	64	61	72	72
30	79	73	76	71	69	66	73	73	71
31	75	76	64	67	70	68	65	67	71
AVE	79	74	71	69	70	70	72	74	76

Appropriateness of CZ II : Durban

- **Temperature**
  - **January 1985 24 hours > 30 °C**
  - **Average over 29 years : 23 days per annum**
  - **Equivalent approx 100 hours per annum**

- **Relative humidity**
  - **12 months in 15 years > 65 %; (>75 % RH @ < 25 °C)**

- **Stability testing accelerated conditions**
  - **3 months = > 2 000 hours @ 40 °C / 75 % RH**
  - **12 months = > 8 000 hours @ 30 °C / 65 % RH**
  - **Vit A : 5 weeks @ 42 °C ≡ 2 years @ RT**
  - **Developmental data: e.g. 1 month at 50 °C, literature**

Assigning stability testing conditions
Other considerations

- **Air-conditioning a dispensing licence requirement**

  Adequate dispensary facilities, at or below 25 °C with air-conditioning in good working order, are required for Wholesale pharmacies, Community pharmacies, Institutional (hospital) pharmacies, Primary Health Care Facilities and Persons licensed to dispense medicine in terms of the Pharmacy Act, Act ..of 19.., as amended.[12] [13]

- **Excursion period(s)**

  The period that a medicine is not stored under controlled conditions and exposed to excursions outside the long term testing conditions is therefore relatively limited to the time of physical distribution and also storage conditions provided by the patient.

- **Recent NAPM survey re product failure complaints from KZN rare**

Summary

- North Eastern coastline area, small, sparsely populated area, (includes a national park - wetland) met CZ IVA criteria 6 of 10 years
- Eastern coastal Durban area,
  - met CZ IVA once in 15 years (<10 %)
  - has a positive temperature safety margin
  - can be more humid than CZ II criteria – negative vapour pressure safety margin
- Eastern coastal area with higher humidity is at lower temperature than true CZ IVA, the higher moisture level would therefore have less kinetic impact on product stability than that of a true CZ IVA area
- Air-conditioning, storage at or below 25 °C is a requirement for a dispensing licence
- Excursions outside storage temperature limited to distribution and post dispensing and addressed by accelerated stability testing
- Pharmaceuticals to be stored at room temperature (at or below 25 °C) demonstrate adequate stability at

  40 °C/75 % RH for 3 months (> 2 000 hours), alternatively at
  30 °C/65 % for 12 months
- Product complaints from KZN rare according to the recent NAPM survey

Conclusion

- **The assignment of CZ II, instead of CZ IVA, stability testing conditions for pharmaceuticals to be stored at or below 25 °C in South Africa appears to be justified – supported by**
  - **Köppen-Geiger Climate Classification,**
  - **Fauna and flora,**
  - **SAWS reports**
  - **Safety margin formula – Zahn et al**
  - **Other considerations.**

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The ERA-40 Reanalysis conducted by the European Centre for Medium-Range Weather Forecasts (ECMWF) is a process in which global weather observations are assembled to form a regular mesh covering the earth with a resolution of about 125 km. Measurements take place every 6th hour. Reanalysed temperatures and dew points from 1979 to 2002 were averaged into monthly means at 00:00 UTC, 06:00 UTC, 12:00 UTC and 18:00 UTC (Coordinated Universal Time). Vapour pressures – applying an updated version of Wexler's equation – and relative humidities were then determined using basic thermodynamic relationships. For further details see Uppala S. M., et al. 2005. The ERA-40 Reanalysis. Quarterly Journal of the Royal Meteorological Society 131:2961-3012.

Sodwana Bay National Park, South Africa.
(Photograph by John Morrison)

Kosi-Bay

Thank you

Acknowledge : NAPM, J&B Pharm Cons