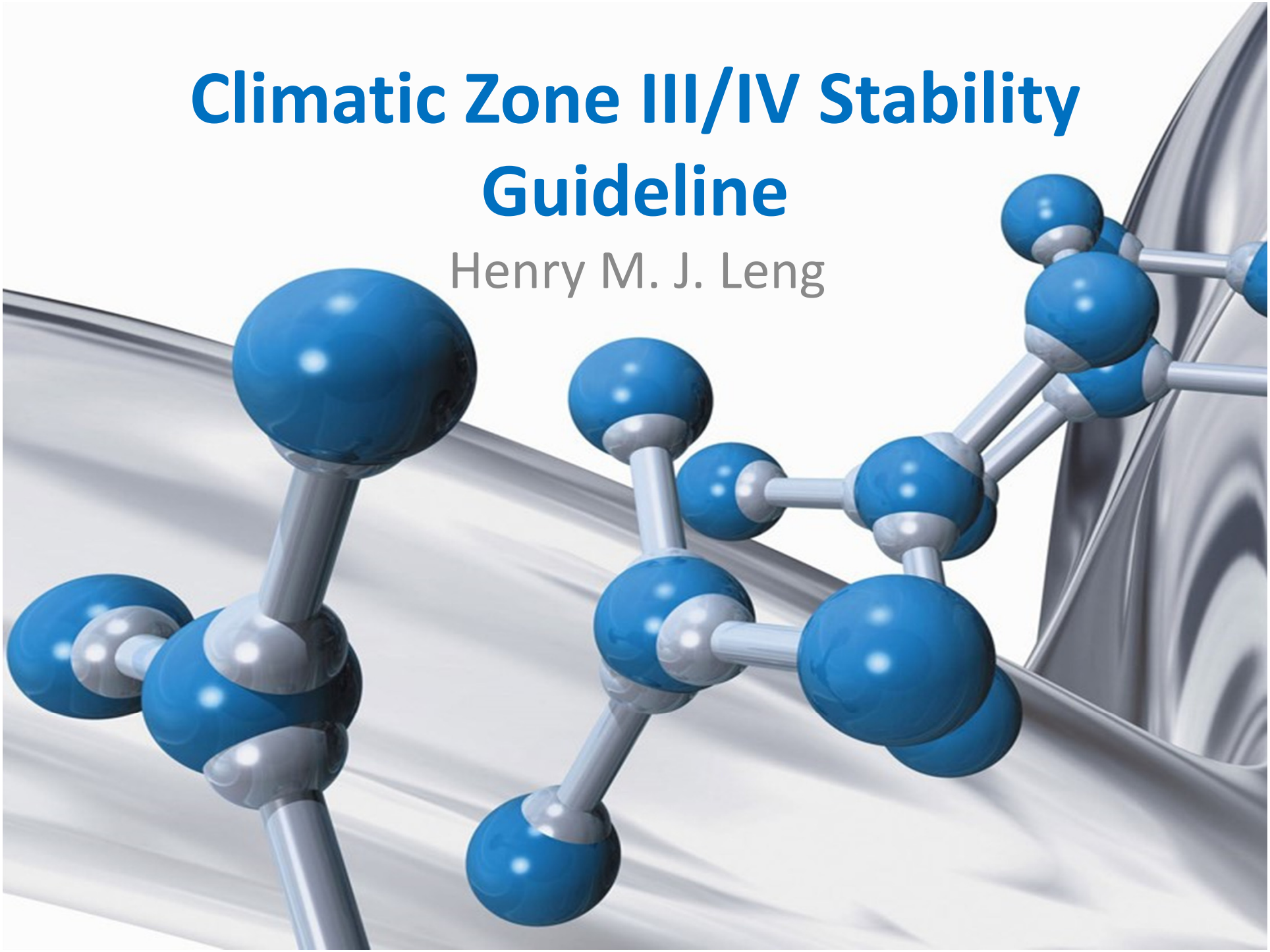
Climatic Zone III/IV Stability Guideline

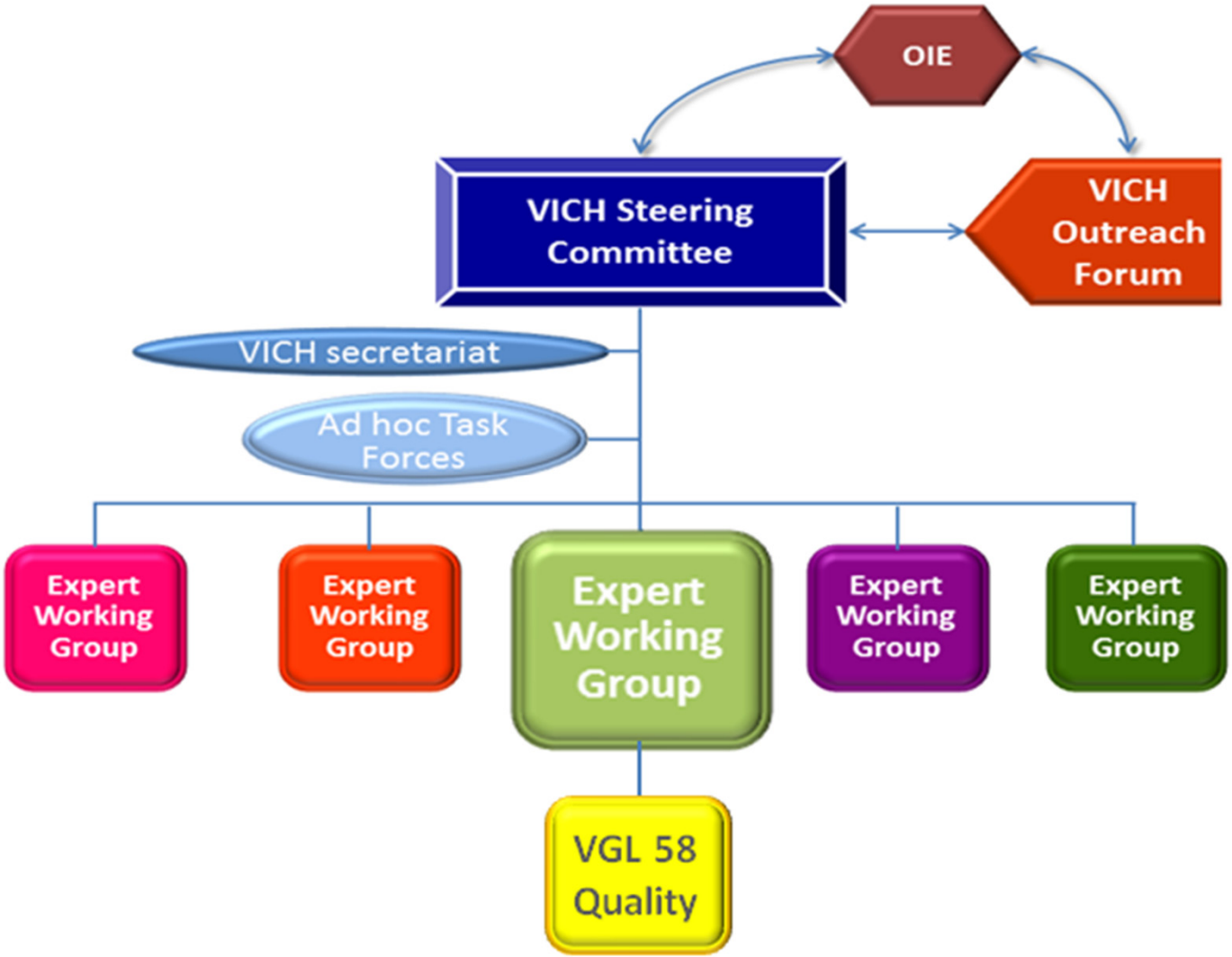
Henry M. J. Leng



Outline

1. Introduction
2. EWG Appointment
   - 2.1 Members
   - 2.2 Mandate
3. Background: VICH GL3(R)
4. VICH GL 58 (Quality)
5. Process:
   - 5.1 Communication
   - 5.2 Duration
6. Sign-off

Introduction



VICH Quality EWG Members

(As per Oct 2015)

NAME	ORGANISATION
FDA	M. HUYNH (Topic Leader)
AHI (BAYER)	R. HENRY
JMAFF	T. OGATA
CANADA VDD	J. BENOLIEL
EU (BVL)	N. MÖLLER (*expert*)
USDA	A. MORGAN (*advisor*)
JVPA (Nippon Zenyaku Kogyo Co)	A. YOSHITA (*expert*)
ANZ (MPI)-	W. HUGHES
IFAH-EU (Merial)	Th. NUGENT
IFAH-EU (Vetoquinol)	V. NERON DE SURGY (*climatic zone III and IV*)
SAHPRA	H. LENG
ANZ-	P. COGHLAN *(Advisor - climatic zone III and IV)*
CHINA (CIVDC)	X. LIANG (*climatic zone III and IV*)
CAMEVET	M. AGUIRRE (*climatic zone III and IV*)
MOROCCO (Ministry of Health)	A. ELGHAFKI (*climatic zone III and IV*)

Mandate

(26 Feb 2015)

Elaboration of a guidance document defining the stability testing requirements for a new veterinary drug substance or medicinal product for countries in climatic zones III and IV

Principles:

- **Not a revision of VICH GL3(R),** but development of a separate guidance document, while taking into account the contents of relevant existing guidelines (e.g. VICH, ICH, WHO)
- The focus of the EWG should be put on the rapid development of a **basic and simple guidance** proposing the **harmonization of storage conditions** (long-term and accelerated/intermediate testing conditions) for **climatic zones III and IV**

Background

- The parent guideline (VICH GL3(R)) describes the stability data package for the three VICH regions:
  - European Union (EU),
  - Japan and
  - the United States (US).
- These regions are all in Climatic Zones I and II and storage conditions to be used in stability trials for these regions are given below

STUDY	STORAGE CONDITION	MIN TIME COVERED BY DATA AT SUBMISSION
Long term	25 ± 2°C/60 ± 5%RH OR 30 ± 2°C/65 ± 5%RH	12 months
Intermediate*	30 ± 2°C/65 ± 5%RH	6 months
Accelerated	40 ± 2°C/75 ± 5%RH	6 months

** If an OOS result occurs under accelerated conditions, then stability should be done under intermediate conditions for 12 months*

WHO Stability Guideline

WHO Technical Report Series, No. 863, 1996

Mean climatic conditions: calculated data and derived storage conditions[1]

Climatic zone	Calculated data			Derived storage conditions (for real-time studies)	
	°C[2]	°C MKT[3]	% RH[4]	°C	% RH
I	20.0	20.0	42	21	45
II	21.6	22.0	52	25	60
III	26.4	27.9	35	30	35
IV	26.7	27.4	76	30	70

[1] Based on: Grimm W. Storage conditions for stability testing in the EC, Japan and USA; the most important market for drug products. Drug development and industrial pharmacy, 1993, 19:2795-2830.
[2] Calculated temperatures are derived from measured temperatures, but all measured temperatures of less than 19°C were set equal to 19°C.
[3] MKT = mean kinetic temperature (see p. 67)
[4] RH = relative humidity.

Southern Africa

	SOUTH AFRICA TEMPERATURE EXTREMES					
DATE	Sat 2 Feb ‘19	Sun 3 Feb ‘19	Mon 4 Feb ‘19	Tue 5 Feb ‘19	Wed 6 Feb ‘19	Thu 7 Feb ‘19
HOTTEST (max)	Phalaborwa 34.9 °C	Phalaborwa 34.8 °C	Phalaborwa 37.3 °C	Worcester 33.7 °C	Kimberley 35.5 °C	Worcester 39.7 °C
COLDEST (min)	Bethal 13.5 °C	Bethal 13.8 °C	Bethal 12.7 °C	Queenstown 9.9 °C	Bethal 12.7 °C	Queenstown 13.4 °C

VICH GL 58 (Quality)

Stability: Stability testing of New Veterinary Drug Substances and Medicinal Products in Climatic Zones III and IV

Objectives, Scope & Continuity:

- This document is an annex to the VICH parent stability guideline, *Stability Testing of New Veterinary Drug Substances and Medicinal Products (VICH GL3(R))*
- This guideline provides additional guidance on the storage conditions for stability testing in countries located in Climatic Zones III (hot and dry) and IVB (hot and very humid) which are not covered by VICH GL3(R)
- This guideline should be used in conjunction with the parent guideline (VICH GL3(R)) and subsequently published quality guidelines and/or annexes (GL4, GL5, GL8, GL17 and GL45)

Storage Conditions

General Case for Zones III & IV

STUDY	CLIMATIC ZONES	STORAGE CONDITION	MINIMUM TIME PERIOD COVERED BY DATA AT SUBMISSION
Long Term	**Zone III (Hot & Dry)**	**30° C ± 2° C/35 ± 5% RH**	**Drug substance:** 12 months **Medicinal product:** 6 months
Long Term	**Zone IVA (Hot & Humid)***	**30° C ± 2° C/65 ± 5% RH**	**Drug substance:** 12 months **Medicinal product:** 6 months
Long Term	**Zone IVB (Hot & very Humid)**	**30° C ± 2° C/75 ± 5% RH**	**Drug substance:** 12 months **Medicinal Product:** 6 months
Accelerated	**Zone III**	**40° C ± 2° C/NMT 25% RH**	6 months
Accelerated	**Zones IVA & IVB**	**40° C ± 2° C/75 ± 5% RH**	6 months

** Same conditions as for the alternative long term storage conditions for Zones I and II as described in the parent guideline.*

No intermediate storage condition for stability studies is recommended for Climatic Zones III and IV.

Storage Conditions (cont.)

Products Packed in Impermeable Containers:

Since containers provide a permanent barrier to water loss, stability studies can be conducted under normal ambient or controlled humidity conditions.

Products packaged in semi-permeable containers:

Stability studies of aqueous formulations in semi-permeable containers (LDPE & HDPE container closure systems) storage conditions are as follows:

Study	Storage condition	Minimum time period covered by data at submission
Long-term	30° C ± 2° C/35 ± 5% RH	6 months
Accelerated	40° C ± 2° C/NM) 25 ± 5% RH	6 months

Storage Conditions (cont)

Tests at elevated temperature and/or extremes of humidity:

- Permeable containers should not be used for long term storage of products for marketing in regions with extremely high humidity such as in Climatic Zone IVB, unless supported by stability data
- Stability testing at a high humidity condition, e.g., 40°C/80% RH, is recommended for solid dosage forms in water-vapour permeable packaging, e.g., tablets in PVC/Alu blisters, intended for marketing in regions with extremely high humidity conditions (Climatic Zone IVB)
- However, for solid dosage forms in primary containers designed to provide a barrier to water vapour, e.g. Alu/Alu blisters, stability testing at extremely high humidity is not considered necessary

Additional Considerations

If it cannot be demonstrated that the drug substance or product will remain within its acceptance criteria when stored at the conditions as listed as in the ***General Case for Zones III & IV*** the duration of the proposed retest period or shelf life, the following options should be considered:

1. a reduced retest period or shelf life,
2. a more protective container closure system, or
3. additional cautionary statements in the labeling.

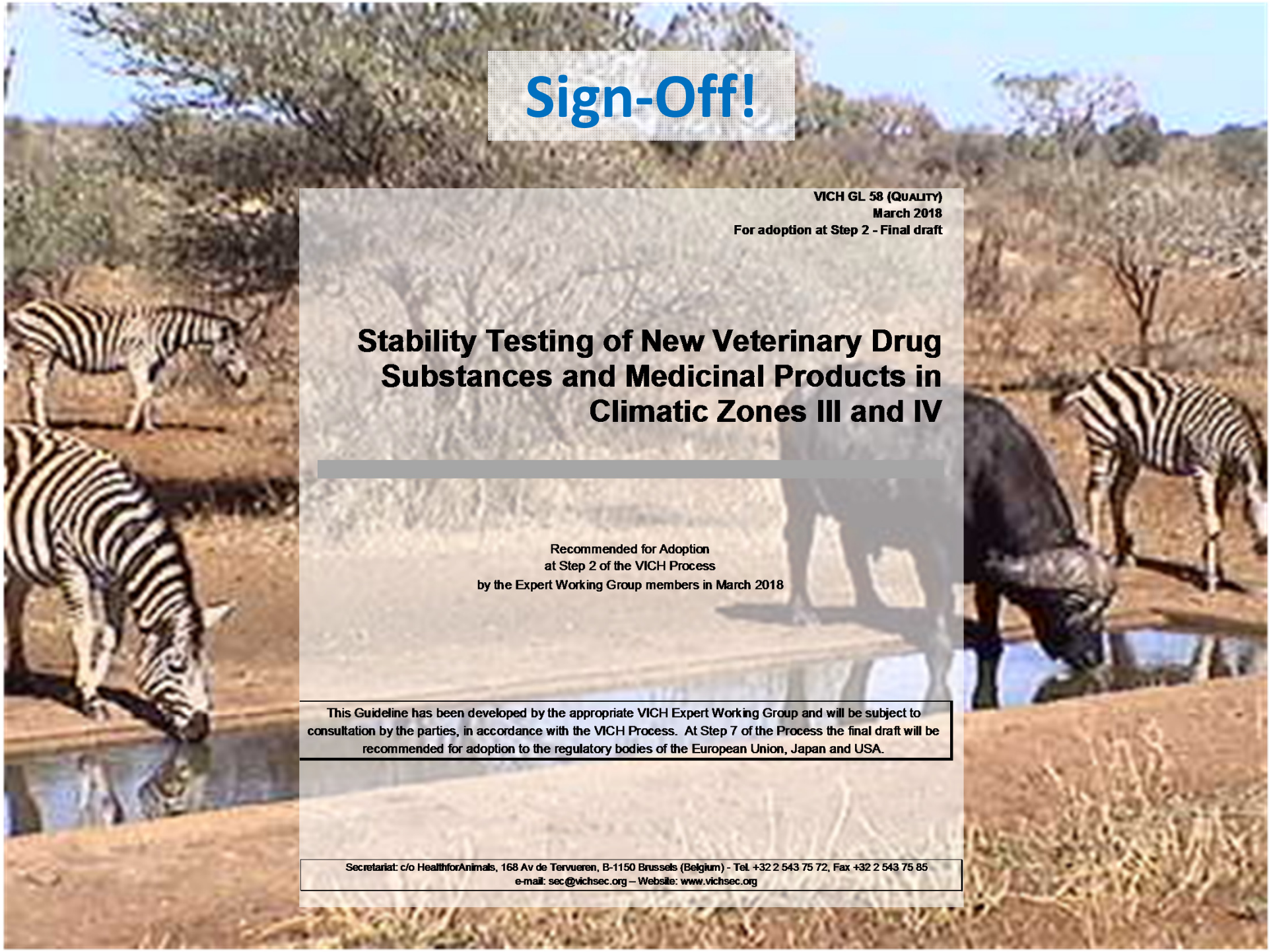
Process

Communication:

- Collaboration was primarily through email communication with one WebEx meeting on the 1st of March 2017, which resulted in a survey to quality regulators.

Duration:

- The mandate was first circulated to the QEWG (with new members from SA and Aus) on 6 Oct 2015 and the first draft of the GL was circulated on 21 April 2016.
- The GL went through 5 drafts and the final version was eventually signed off in early June 2018.
- The draft guideline was adopted by the SC members at the 36th VICH SC meeting in June 2018 and has been released for a six months public consultation period until 31st December 2018.



Sign-Off!

VICH GL 58 (QUALITY)
March 2018
For adoption at Step 2 - Final draft

Stability Testing of New Veterinary Drug Substances and Medicinal Products in Climatic Zones III and IV

Recommended for Adoption
at Step 2 of the VICH Process
by the Expert Working Group members in March 2018

This Guideline has been developed by the appropriate VICH Expert Working Group and will be subject to consultation by the parties, in accordance with the VICH Process. At Step 7 of the Process the final draft will be recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Secretariat: c/o HealthforAnimals, 168 Av de Tervueren, B-1150 Brussels (Belgium) - Tel. +32 2 543 75 72, Fax +32 2 543 75 85
e-mail: sec@vichsec.org – Website: www.vichsec.org

Special Thanks