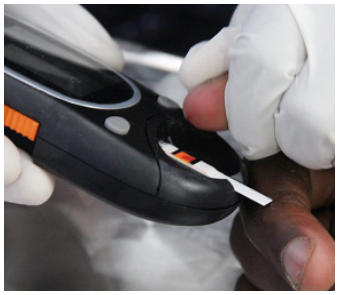
POST IMPORTATION TESTING



SAPRAA MEETING

Karen Ford

BYTES CONFERENCE CENTRE, MIDRAND
17 November 2017

Thomas Edison said :

“There is always a better way !”

POST IMPORTATION TESTING EXEMPTION

=PITE

OVERVIEW OF PRESENTATION

PART 1: INTRODUCTION and BACKGROUND

PART 2: GUIDELINES

PART 3: SUPPLY CHAIN

PART 4:PITE- RISKS

PART 5: PITE- FUTURE INITIATIVES

PART6: CLOSING

HISTORY of PIT

•1975, originated in the EU

• introduced requirement to repeat all tests, when a drug (medical) product is imported

•75/319/EEC Article 22 [3].

Scientific discussion of the importance and rationale for conducting PIT

How sure are we that the supply chain is intact during the whole transportation period ?

•The integrity of imported products could be compromised during transit

•Therefore -applicant confirms the imported product's integrity prior to release for sale in South Africa, by testing post importation

•Regulation 15 (Annexure 9A) of Act 101 of 1965, this is done by:

PIT CURRENTLY A REQUIREMENT

✓Qualitative (Identification) and quantitative (assay), and other relevant tests performed locally on the final product.

Or

✓Return of samples to overseas testing laboratories or the manufacturer that supplies the product, for identification and assay and other relevant testing.

Only if these two options are not feasible, after the company has submitted an application for PITE, including scientific based supportive evidence of the motivation,

<u>will the regulator consider exemption from the testing</u>

SA CONTEXT

Paramount Goal: Ensure the safety, efficacy and quality of medicines

- Large portion of the community consists of immune compromised individuals, vulnerable in case of substandard medicine supplied
- SA is a fare through/ gateway-supply of medicines from SA to the neighbouring countries
- Number of neighbouring countries do not have RA and depend on SA's regulatory control for safe, effective and quality medicine, as we can see from the **SADC GUIDELINE FOR IMPORT AND EXPORT (June 2006)**

STABILITY

- The results of such stability testing should be used in determining appropriate storage conditions and retest or expiry dates

- Annex 2 to WHO Technical Report Series, No. 953:

Stability testing of active pharmaceutical ingredients and finished pharmaceutical products

SA GUIDE: STABILITY

Climatic zone	Definition	*Criteria* Mean annual temperature measured in the open air/ Mean annual partial water vapour pressure	Long-term Testing Conditions
I	Temperate climate	≤ 15 °C / ≤ 11 hPa	21 °C / 45 % RH
II	Subtropical & Mediterranean climate	> 15 to 22 °C / > 11 to 18 hPa	25 °C / 60 % RH
III	Hot and dry climate	> 22 °C / ≤ 15 hPa	30 °C / 35 % RH
IVA	Hot and humid climate	> 22 °C / > 15 to 27 hPa	30 °C / 65 % RH
IVB	Hot and very humid climate	> 22 °C / > 27 hPa	30 °C / 75 % RH

South Africa is classified in CZ II. In Table 2 of the WHO guideline the long-term stability conditions for WHO Member States by Region are listed, with South Africa indicated as zone IVA. Long-term stability studies conducted at zone IVA and IVB conditions, instead of or in addition to zone II will also be acceptable

DISCUSSION IMPORTANT STORAGE CONDITION PARAMETERS

- Temperature
- Relative humidity
- Humidity and temperature control- also monitor external temp and RH

- Vibration
- Freeze

Sensitivity of vaccines to temperature fluctuations

Vaccine formulation	Heat – low sensitivity	Heat – high sensitivity	Freeze- low sensitivity	Freeze- high sensitivity
Freeze dried preparations	xxx	xxx	xxx	
Liquid, no adjuvant		xxx		xxx
Liquid, with alum adjuvant	xx	xx		xxx

Temperature Sensitivity of Vaccines, March 2014 (WHO & PATH)

Shows sensitivity of vaccines to heat and freezing

Consider exemption in the following cases:

•No approved local facility with adequate resources and equipment to perform testing

•Biological, Vaccines, Hormonal preparations, Cytotoxic products

•Orphan drugs

•Others

PART 2 :GUIDELINES

- **SA GUIDE TO GWP (v2 Nov 2015)**
- **SA GUIDE GMP (v 5 Aug 2010)**

Def:"manufacture" means all operations including purchasing of raw material, processing, production, packaging, releasing, storage, quality assurance, **importation,** exportation of medicine and scheduled substances and related control.

"Good Manufacturing Practice is concerned with both production and quality control. **The basic requirements of GMP are that all necessary facilities for GMP are provided including suitable storage and transport;"**

ADDENDUM I: RISK MANAGEMENT METHODS AND TOOLS

The purpose of this addendum is to provide a general overview of and references for some of the primary tools that might be used in quality risk management by industry and regulators. The references are included as an aid to gain more knowledge and detail about the particular tool.

20-II.5 Quality Risk Management as Part of Materials Management

Assessment and evaluation of suppliers and contract manufacturers

To provide a comprehensive evaluation of suppliers/vendors and contract manufacturers (e.g. auditing, supplier quality agreements) -

TRANSPORTATION

STORAGE, LOGISTICS AND DISTRIBUTION CONDITIONS

•To assess the **adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g. temperature, humidity, container design)**

•To determine **the effect on product quality of discrepancies in storage or transport conditions (e.g. cold chain management**) in conjunction with other ICH guidelines

•To maintain infrastructure (e.g. capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance)

➢SADC GUIDELINE FOR IMPORT AND EXPORT

•Southern African Development Community -the basic requirements for exporting and importing medicinal products in the region

•The authorized importer should alert customs officials in advance of the anticipated arrival of consignments in order that they can be transferred to the designated storage facilities without breaking the cold chain.

➢**WHO:**

•Technical supplement to WHO Technical Report Series, No. 961, 2011.Annex 9:

Model guidance for the storage and transport of time and Temperature - sensitive pharmaceutical products (August 2014) - Qualification of temperature - controlled storage areas

WHO TRS: No. 961, 2011.Annex 9: cont . . .

Def*: time- and temperature-sensitive pharmaceutical product (TTSPP)*

"***Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally***"

WHO TRS: No. 961, 2011.Annex 9: cont . . .

Importation

1.1 Port handling and customs clearance

1.1.1 Port of entry

1.1.2 Off loading

1.1.3 Temporary storage at port of entry

2.2.1 Qualification applied to temperature-controlled storage

Qualification is commonly used to validate pharmaceutical manufacturing processes but it can also be **applied to the pharmaceutical supply chain** in general, and **to temperature-controlled storage processes and equipment in particular**.

IQ OF EQUIPMENT

2.4.4 Checking environmental conditions

Check the environmental conditions in the storage area and check all installed equipment and components for cleanliness, fumes, and **vibrations**. Record the temperature and relative humidity conditions and determine whether these are within the limits designated in the IQ protocol– see Table 4.

Time and temperature sensitive pharmaceutical product (TTSPP) Any pharmaceutical good or product which, when not stored or transported within pre-defined environmental conditions and/or within pre-defined time limits, is **degraded to the extent that it no longer performs as originally intended.**

▪All temperature-controlled equipment and systems used to handle, store and distribute TTSPPs should be qualified.

•**Active temperature-controlled storage equipment, i**ncluding ultra-low freezers, freezers, freezer rooms, refrigerators, cold rooms and controlled-ambient stores.

•**Actively temperature-controlled transport equipment**. This includes refrigerated and temperature-controlled trucks and vans, refrigerated and temperature-controlled ocean containers. Refer to the companion Technical Supplement: *Qualification of temperature-controlled road vehicles*.

•**Passive temperature-controlled packaging systems (shipping containers**). This includes insulated containers used to maintain product temperature during road and air transport. Refer to the companion Technical Supplement: *Qualification of shipping containers*.

WHO TRS: No. 961, 2011.Annex 9: cont . . .

4. Temperature-controlled storage

4.1 Normative references – **USP and IATA regulations**

4.5 **Temperature and humidity control and monitoring in storage**

4.5.1 Temperature control

4.5.2 Temperature monitoring

4.5.3 Humidity control

4.5.4 Humidity monitoring

4.6 Alarm systems

4.6.1 Temperature alarms

4.6.2 Humidity alarms

WHO TRS: No. 961, 2011.Annex 9: cont . . .

4.7 Qualification of temperature-controlled stores

4.8 Cleanliness of temperature-controlled stores

4.9 Refrigeration equipment maintenance

4.10 Calibration and verification of control and monitoring devices

4.10.1 Calibration of temperature control and monitoring devices

4.10.2 Calibration of humidity control and monitoring devices

4.10.3 Alarm equipment verification

WHO TRS: No. 961, 2011.Annex 9: cont . . .

Transport and delivery

6.1 Normative references

6.2 Product stability profiles

6.3 **Transport route profiling and qualification**

6.4 Temperature-controlled transport

6.4.1 Air and sea transport

6.4.2 Temperature-controlled road vehicles operated by common carriers

6.4.3 Temperature-controlled road vehicles generally

6.4.4 **Transport of controlled TTSPPs** and TTSPPs with high illicit value

WHO TRS: No. 961, 2011.Annex 9: cont . . .

6.5 **Temperature and humidity control and monitoring during transit**

6.5.1 Temperature control in **temperature-controlled road vehicles**

6.5.2 Temperature monitoring in temperature-controlled road vehicles

6.5.3 Humidity monitoring in temperature-controlled road vehicles

6.5.4 Temperature monitoring in **passive and active shipping containers**

6.6 Qualification of temperature-controlled road vehicles

6.7 Calibration and verification of transport monitoring devices

WHO TRS: No. 961, 2011.Annex 9: cont . . .

6.8 **Shipping containers**

6.8.1 Container selection generally

6.8.2 Un-insulated containers

6.8.3 Qualification of insulated passive containers

6.8.4 Qualification of active containers

WHO TRS: No. 961, 2011.Annex 9: cont . . .

6.9 Shipping container packing

6.10 Product handling during packing and transport

6.11 Cleaning road vehicles and transport containers

9. General procedures and record-keeping

9.1 **Emergencies and contingency planning**

9.2 General record-keeping

- WHO Technical Report Series, No. 957, 2010.Annex 5

WHO good distribution practices for pharmaceutical products

WHO TRS :No. 957, 2010.Annex 5 cont . . .

Distribution is an **important activity in the integrated supply-chain management of pharmaceutical products**. **Various people and entities** are generally responsible for the handling, storage and distribution of such products.

In some cases, however, a person or entity is only involved in and responsible for certain elements of the distribution process. **The objective of these guidelines is to assist in ensuring the quality and identity of pharmaceutical products during all aspects of the distribution process.**

WHO TRS :No. 957, 2010.Annex 5 cont . .

20.5 **All reasonable steps should be taken by importers to ensure that products are not mishandled or exposed to adverse storage conditions at wharves or airports**

20.7 **The *WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce* should be used to provide data regarding quality assessment of imported pharmaceutical products.**

- **Guidelines on import procedures for pharmaceutical products**.

WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty -fourth report. Geneva, World Health Organization, 1996, Annex 12 (WHO Technical Report Series, No. 863).

SA GUIDE:POST-IMPORTATION TESTING (*Dec03 v1)*

- ***Exemptions***
- ***Guidelines for monitoring of transport***
- ***Submission to MCC for exemption based on monitoring of transport***

GUIDE:POST-IMPORTATION TESTING (Draft)

Version 2: Revised for comment March 2015
Due date for comment: 31 March 2017

- ***Exemptions***
- ***Guidelines for monitoring of transport***
- ***Submission to MCC for exemption based on monitoring of transport***
- ***Conditions of exemption***

REASON EXEMPTION/CONSIDERATIONS	PITE GUIDE v1 2003	PITE GUIDE v2,2016(draft)
Very small quantities are imported for "selected" patients, projection as to the annual usage of the relevant product.	√	√
Any other reason deemed by the applicant as being of such nature as to qualify for consideration for this exemption	√	√
Continuous monitoring of temperature and humidity, where relevant of each shipment with validated monitoring devices according to SOP as well as performing a physical identification of the product.	√	√
Evidence of compliance with the appropriate transport-storage monitoring and control of conditions.		√
If the identification and assay cannot be performed in South Africa due to complexity of testing, absence of the technology/equipment or lack of resources at local laboratories to perform such testing, proof there of should be submitted with the application		√

Transportation requirements more defined: -calibrated monitoring devices (temp and RH) -container validated - products sensitive to vibrations/agitation must be transported in vibration/agitation controlled conditions.		√
Products exempted from post-importation testing are not exempt from meeting regulatory release parameters, product release specifications and investigation of environmental condition excursions i.e. temperature and humidity.		√
Summary of the number of shipments, shipment details, including quantity of product imported during previous period of exemption.		√
Exemption, if approved, will be valid for three years	√	√
Only one renewal of post-importation testing exemptions for a further period of two years will be considered,		√

Records of quantities imported during the previous exemption period		√
Line listing of all serious adverse drug reactions reported in South Africa, in relation to the imported medicine.		√
Any changes to the transport monitoring and control equipment, methods and validations previously submitted, invalidate the post-importation testing exemption granted.		√
Copy of the accelerated stability data of the formulation being applied for, packed in the final container as specified in Module 3.2.P 7 (Container closure system) (to determine if the humidity sh	√	√
The transport monitoring method, or transport conditions should be specified in the master release document.	√	√

A tabulated summary indicating the method of transport, the conditions during transport as indicated below and the method of controlling the respective conditions should be submitted. Data from a minimum of five printouts are required, giving an account of the same product or five different products, provided that the products require the same storage conditions, and provided that the products are dispatched from the same site but by different shipments.	√	√
A copy of Module 3.2.P.5.1 and 3.2.P.5.2(Control of pharmaceutical product, Specifications and Analytical procedures) including special conditions of handling and storage e.g. "*do not freeze*", "*do not shake or agitate the contents*" and "*store at or below X°C"*.		√
A copy of the proposed master release document (MRD) in accordance with–Module 3.2.P.5.1 reflecting the specifications pertaining to the product in question: - Type of recorder - CoA - Visual identification - consignment reference - Confirmation of the integrity of the containers, seals, and labels. - Outcome of the evaluation of the transport conditions and relevant action, i.e. further testing to be performed.	√	√

-	Evidence to support that the product imported is not subject to transport delays/repackaging that may result in tampering / counterfeiting of the imported product.		√

Summary of data: transportation of product

NAME OF PRODUCT:
REGISTRATION NUMBER:
DOSAGE FORM:
APPROVED STORAGE CONDITION:
ASSURANCE: TEMPERATURE RECORDED IN EACH SHIPMENT

Name of Product	Batch Number	Maximum and minimum temperature recorded	Other transport sensitive conditions e.g. vibration measurements	Maximum humidity recorded (where relevant)	Duration of transport (Date commenced and date terminated)	Mode of Transport	Signature of responsible pharmacist who verified the printouts

Comments received on Guideline:

- Received from the whole industry, not only this group
- In the light of fairness , we want to share it with all
- Will discuss at the workshop, once arranged

SUPPLY CHAIN

MNF→DISTRIBUTOR→WS→RETAIL MARKET
↗

Import testing performed in the middle of the supply chain

- **Airfreight Shipment from India Hydarabad**

Temperature Logger shipment collected from Manufacturer:	5/11/17	18:00
Shipment received by Airline in Hydarabad:	7/11/17	15:57
Departed from Hydarabad, on Airlines via Doha:	8/11/17	14:48
Shipment arrived in Doha:	8/11/17	16:50
Shipment departed from Doha to Johannesburg:	15/11/17	02:16
Flight arrived in Johannesburg:	15/11/17	10:09
Cargo received checked into Airline Warehouse:	15/11/17	12:00
Cargo received -airside ORT:	15/11/17	12:50
Cargo released by SARS/Customs and Port of Health	16/11/17	10:00
Cargo delivered to customer	16/11/17	12:38

- **Date and Time from collection in Hydarabad to arrival in Johannesburg**
  - ✓ **5 November 2017 18:00 - 15 November 2017 10:09**
    Took 11 days for a Pharmaceutical Shipment to move from India to Johannesburg
  - ✓ Agent drew the cargo within 2 hours of flight arrival on the tarmac
  - ✓ Agent delivered in temperature controlled validated pharmaceutical truck 2 hours after SARS and Port of Health release.

Possible risks – Transportation – Supply Chain

- Delay India– trucks from manufacturer -wait up to two days to enter the airport grounds to off load cargo
- Flight to Doha relatively quick
- Delay in Doha – waiting for connecting flight (7 days) to Jhb- indicating that the cargo was not booked as special pharmaceutical cargo
- Cargo quickly picked up by agent in Jhb and placed in temperaure controlled unit (within 2 hours). Cargo can spend hours on tarmac exposure to sun - temp can rise > 50 °C
- If clearing agents do not collect cargo from tarmac, they only have access to the landside 6 hours after flight has landed

- If the flight is not booked correclty, cargo remains exposed to the sun on the tarmac until the Airline Warehouse manifests/ books it
- **High temp + high RH= moisture forming = mould forming on product / soggy**
- Monsoon season – cargo exposed to elements

- Incoterms - International Commercial TERMS
  - Costs
  - Control
  - Liability

•**Equipment:** temperature controlled unit. at airport (Igloos, cool dollies?).

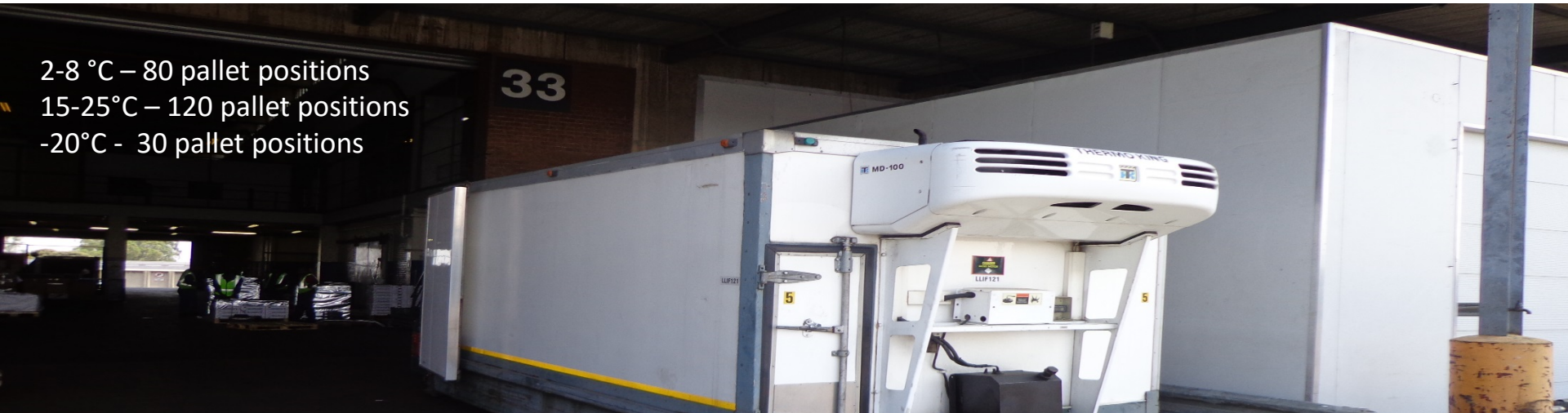
Provides access to air craft by agent

- **Vehicles**
  - Do vehicles used to move, store or handle pharmaceutical products, provide ongoing control of EC?
  - Ongoing monitoring and reporting of EC?
  - Ongoing reporting of positioning of vehicle?
  - Do vehicles transport any non-pharmaceutical products together with pharmaceuticals which could result in contamination (consolidated cargo)?

•**Processes and People**

IGLOOS


THERMO KING THERMOGUARD
18.8 C
MD-100
LLIF124
1
3


2-8 °C – 80 pallet positions
15-25°C – 120 pallet positions
-20°C - 30 pallet positions
33
MD-100
LLIF121
5
5

PITE -RISKS

POSSIBLE RISKS IF PIT IS WAIVERED

- If we do not encourage PIT, other sectors/ services can be affected and skilled people can be lost (e.g., testing labs)
- GMP-supposed to be well- established, with effective quality management systems in the manufacturing environment

Q. Then why do we still encounter non conformances, ranging from critical to major , when inspecting sites?

Q. Why do sites only become aware of non- conformances once the inspector points it out?

Q. Are GMP control systems robust enough?

Non GMP compliance can increase the risk of :

– Inadequate release testing

– Failure to detect deterioration during transportation and break in the supply chain

– Failure to detect counterfeit finished products

- Data integrity failures

-API manufacturers – recently regulated

-**Q.APR**: Batches rejected due to damage during transportation included ?

Even if rejection rate post import testing analyses is low that one batch that was rejected could cause harm or even inflict death to a patient.

PITE:POSSIBLE FUTURE INITIATIVES

❖Quality Management System (QMS), GDP and due diligence processes done for all customer supplier relationships, especially those concerned with transportation.

❖Quality be design-Quality has to be produced into the product, not tested at the end only.

❖Focus on implementing or extending wide spread Market Surveillance Studies

❖National Regulatory Authorities (NRAs), improved globally harmonized requirements and procedures following best practices

❖Continued improvements based on experience.

❖EU-GMP Guideline [1] Annex 16, provide a base for reduced specification, stating that a product batch must undergo testing in a Member State *"in accordance with the requirements of the marketing authorisation (MA)"*.If a reduced specification is approved with the MA, reduced import testing is acceptable

❖SAHPRA (SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY)

SAHPRA cont . . .

SAHPRA will address the need :

- To deal with **strategic risks and dangers** faced by state or society in terms of security, health, prosperity and wellbeing
- For **objective**, more **operational autonomy**, yet retaining **accountability** in the **delivery of service**

SAHPRA cont . .

ADVANTAGES OF SAHPRA

- Strengthen the NRA in the following ways:
  - Policies and guidelines updated and improved (expedite review of novel health technologies)
  - Improve communication - industry and public
  - Increase staff , training – more evaluators available
  - EDMS (electronic document management system)

SAHPRA cont . . .

ADVANTAGES OF SAHPRA cont . . .

- Strengthen the National Biological Control Laboratory
- Improve pharmaco vigilance
- Lead to enhanced cooperation/collaboration with other RAs

FINALE

Industry Expectations?

- Scientifically based decisions
- Solid scientific integrity
- Transparency
- Consistency
- Open channels of communication with industry

In closing

"***If your mind can conceive it, and your heart can believe it, then you can achieve it*** ."
Muhammad Ali

"***Coming together is a beginning. Keeping together is progress. Working together is success"***

Henry Ford

THANK YOU !

MCC Website: www.mccza.com

Information on:

- Registered medicines
- Licence applications
- Guidelines
- Processes
- Workshops

References:

1. Medicines and Related Act ,1965(Act 101 of 1965)
2. MCC: Guidelines on GMP
3. MCC: Guidelines on GWP
4. Dr J Gouws: Registration of Medicines. 2nd South Africa-United States Business Roundtable (27 July 2016)