Enabling local production of biopharmaceuticals in South Africa

Dr Tsepo Tsekoa, PhD
SA has high disease burden despite relatively strong GDP per capita

SA spends > R135 billion annually; about 11% of total budget and close to the Abuja Declaration recommendations, yet poor life expectancy persists.
## South Africa has a two-tier health system

### Private Sector

- **Provision:** Healthcare is delivered by private general practitioners and specialists, and 211 private hospitals. The sector is increasingly dominated by corporate for profit groups.

- **Financing:**
  - Private healthcare is available through Medical Aid Schemes.
  - Schemes are financed by contributions from employees and sometimes employers (who usually pay 50% each).
  - Various plans with varying contributions and consequent levels of coverage.

### Public Sector

- **Provision:** The over-stretched public healthcare institutions cover the majority of the South African population, around **84% of the population** (42 million people).

- **Financing:**
  - Public health is financed through the government, primarily through taxes.
  - Healthcare expenditure at the local level is subsidised by central government, which refunds anything from 33% to 100% of the costs to the local authorities.
  - Subsidies depend on the type of service provided and whether or not the drugs provided are on the Essential Drugs Lists.

---

**Source:** IMS South Africa Market Prognosis Report, 2014
Relevant national priorities and strategic context

**National Development plan**

Recommends “the development of a diversified, dynamic economy at the core of creating a more inclusive society and providing economic opportunity for all people in the country.” “burden of disease”

**Industrial Policy Action Plan**

“A broadened manufacturing base in SA; import substitution; technology and skills upgrading; value-added exports; employment creation; reduction of the negative trade deficit – all in support of the increased long term competitiveness of the pharma industry.”

**The Bio-economy Strategy**

“By drawing on these capabilities, South Africa will be able to manufacture active pharmaceutical ingredients, vaccines, biopharmaceuticals, diagnostics and medical devices to address the disease burden, while ensuring a secure supply of essential therapeutics and prophylactics.”
CSIR platforms in response

Early stage applied R&D

1. SYNTHETIC BIOLOGY ERA
   - Precision medicine and Companion diagnostics
   - Bioengineering and Biomimetics
   - Novel screening tools

2. BIOMANUFACTURING INDUSTRY DEVELOPMENT CENTRE
   - Industrial biologics
   - Natural-based products
   - Bioprocess platform

3. HIGH THROUGHPUT SCREENING (HTS) PLATFORM
   - HTS of Functional Searchable Libraries
   - Novel Bioassays and tools

4. ENVIRONMENTAL DIAGNOSTICS AND ENGINEERING SOLUTIONS
   - Environmental engineering solutions
   - Environmental diagnostics/screening tools

5. BIOLOGICS PRODUCTION AND CHARACTERISATION PLATFORM
   - Veterinary Biologics
   - Human Biologics

Continuous industry engagement
Biopharmaceuticals opportunity and local needs

- Biopharmaceuticals are highly effective large macromolecular-based drugs.
- Include antibodies, hormones, replacement enzymes, nucleic acids.
- R2 billion spent on importing vaccines and biologics (2010), with growing local and global market (~USD240 billion with 9.9% CAGR).
- Huge dependence on imports, major contributor to trade deficit

Disparities persist (Two-tier system)

<table>
<thead>
<tr>
<th>Biopharmaceutical</th>
<th>Public health sector</th>
<th>Private health sector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>75% use of recombinant insulin analogs</td>
<td>33% of biologicals spend</td>
</tr>
<tr>
<td>Antibodies</td>
<td>Practically no use</td>
<td>3% by volume, 33% by value</td>
</tr>
<tr>
<td>Influenza Vaccine</td>
<td>14% immunization rate</td>
<td>1% immunization rate, yet 30% of nation at risk of severe influenza outcomes</td>
</tr>
</tbody>
</table>

Disparity in procurement and use of biopharmaceuticals between public and private healthcare sectors persists (Two-tier system).
Case study 1: Rabivir: new-generation rabies post-exposure prophylaxis

- **Problem:** Rabies is a widespread and fatal zoonotic disease that disproportionately affects poor children
- **Need for safer alternative treatment to plasma-derived HRIG and ERIG for rabies prophylaxis**
- **Solution:** A new-generation affordable plant-produced mAb cocktail to address the limitations of current rabies prophylaxis
- **Stage:** Ready-to-enter IND-enabling pre-clinical studies
- **Collaborators:** KBP, ARC-OVI, WHO, BOKU Vienna, MAPP, CDC

**OUTCOMES:**
- State-of-the-art technology ready for pre-clinical trials
- Outstanding model for international collaboration
- Networks with global leaders in the field
- HCD in cGMP and scale-up of plant-based pharmaceuticals.
Case study 1: Rabivir, new-generation rabies post-exposure prophylaxis
Case study 2: Microbial production of biosimilar CRM197 carrier protein

- **Problem/Need:** Accessible and cost-competitive paediatric vaccines
- Prohibitively expensive pricing of protein reagent (CRM197) used in manufacture of conjugate vaccines for children (e.g. multivalent pneumococcal vaccine)
- **Solution:** Fermentation-based production in recombinant *E. coli*
- **Stage:** Proof of concept complete
- **Collaborators:** The Biovac Institute

**OUTCOMES:**

- Clone development and process development yielded scalable and techno-economically viable production
- Co-expression option for high level production of structurally sound CRM197
- Huge leap in CSIR capacity for implementation of cGMP-like principles in ferm-based bioprocess development for biologics
Case study 3: Plant-based production of CAP256-VRC26 HIV antibodies

- **Need/Problem:** HIV remains prevalent in Sub-Saharan Africa and SA in particular. Need for cost-effective biomanufacturing alternative option to mammalian culture to facilitate further development for broadened access of HIV Abs for passive vaccination or prophylaxis against the virus.

- **Solution:** Transient expression of CAP256 bnAbs in tobacco

- **Stage:** Proof of concept complete, potent HIV neutralisation efficacy against a panel of isolates demonstrated, ready to enter *in vivo* study.

- **Collaborators:** NICD, MAPP, BOKU Vienna, MRC SHIP

### HIV prevalence in young pregnant women in rural Vulindlela, South Africa (2009-2012)

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>HIV Prevalence (N=1029)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤16</td>
<td>8.4</td>
</tr>
<tr>
<td>17-18</td>
<td>18.6</td>
</tr>
<tr>
<td>19-20</td>
<td>25.4</td>
</tr>
<tr>
<td>21-22</td>
<td>32.8</td>
</tr>
<tr>
<td>23-24</td>
<td>44.8</td>
</tr>
</tbody>
</table>

~5,500 new HIV infections every day

~4,000 AIDS deaths every day
Case study 3: Plant-based production of CAP256-VRC26 HIV antibodies

<table>
<thead>
<tr>
<th>Envelope</th>
<th>Subtype</th>
<th>IC50 (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZM33M.PB12</td>
<td>C</td>
<td>0.0028</td>
</tr>
<tr>
<td>ZM233.6</td>
<td>C</td>
<td>0.038</td>
</tr>
<tr>
<td>CAP239.G3</td>
<td>C</td>
<td>0.0047</td>
</tr>
<tr>
<td>Du156.12</td>
<td>C</td>
<td>0.025</td>
</tr>
<tr>
<td>Du151.2</td>
<td>C</td>
<td>0.018</td>
</tr>
<tr>
<td>Du172.17</td>
<td>C</td>
<td>&gt;50</td>
</tr>
<tr>
<td>6535</td>
<td>B</td>
<td>&gt;50</td>
</tr>
<tr>
<td>TRO.11</td>
<td>B</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Q23.17</td>
<td>A</td>
<td>11.1</td>
</tr>
<tr>
<td>Q461</td>
<td>A</td>
<td>0.37</td>
</tr>
<tr>
<td>Q168.a2</td>
<td>A</td>
<td>0.088</td>
</tr>
</tbody>
</table>
The biosimilars opportunity?

### Biologicals Approval Dates

|------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|

### Time Taken for Development (years)

- Best case: 0-1 years
- Worst case: 2-5 years

### Product Development and Comparative Analysis

- Best case: US$2 million
- Worst case: US$5 million

### Process Development, Scale-Up and Validation

- Best case: US$12 million
- Worst case: US$35 million

### Clinical Trials

- Best case: US$42 million
- Worst case: US$135 million

### EMA and FDA Review and Approval

- Best case: 0-1 years
- Worst case: 2-5 years

### Comparison Table

<table>
<thead>
<tr>
<th>Generics</th>
<th>Biosimilars</th>
<th>Originators</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients in various phases of development</td>
<td>20–50 patients</td>
<td>- 500 patients</td>
</tr>
<tr>
<td>Time to market</td>
<td>2–3 years</td>
<td>7–8 years</td>
</tr>
<tr>
<td>Development costs</td>
<td>USD 2 million – 3 million</td>
<td>USD 100 million – 150 million</td>
</tr>
<tr>
<td>Success probability</td>
<td>90–99%</td>
<td>50%</td>
</tr>
</tbody>
</table>
Focus for the future

- **Emphasis on industrial partnership**
  - Biopharmaceutical (and broader pharmaceuticals) technology evaluation, licensing and localisation support
  - Scale-up and process development
  - Comprehensive suite of solutions including mammalian production capacity

- **Goal of broadened access to effective medicines for the poor in SA and the continent**
  - Biosimilars opportunity
  - Alternative cost-competitive production platforms (Plant biopharming)

- **National capacity cGMP process development and piloting?**
  - Major gap in vaccine and biopharmaceutical national value chain
  - Large investment and commitment from national system necessary
  - What is the most suitable model for hosting this?

- **What about small molecule APIs?**
  - Strong chemistry capacity at the CSIR
  - A focus on scale-up of novel, cutting-edge production technologies
    - Flow chemistry
    - Green approaches (biocatalysis)
  - Drug repurposing, reformulation
  - Technology partner for localisation
Acknowledgements

- **CSIR:** Dr Rachel Chikwamba, Advaita Singh, Sindisiwe Buthelezi, Dr Ereck Chakauya, Dr Ofentse Pooe, Dr Alex Alexandre, Dr Stoyan Stoychev, Dr Therese Stark, Dr Lusisizwe Kwezi, Dr Robyn Roth, Dr Michael Crampton, Dr Petrus van Zyl, Taola Shai, Sipho Mamphutha, Gugu Ngwenya, Albert Mabetha, Stella Manganye
- **ARC/OVI:** Dr Claude Sabeta, Wonderful Shumba, Baby Phahladira
- **NICD/CAPRISA:** Prof Lynn Morris, Dr Jinal Bhiman
- **Biovac:** Dr Ike James, Dr Ebrahim Muhamed, Dr Seanette Wilson
- **MAPP:** Dr Michael Pauly, Dr Kevin Whaley, Dr Larry Zeitlin
- **KBP:** Josh Morton, Steve Hume
- **BOKU:** Prof Herta Steinkellner
- **CDC Atlanta:** Prof Charles Rupprecht
- **WHO Collaborating Centres for Rabies Surveillance and Research:** Dr Thomas Muller
Science will only fulfil its promises when the benefits are equally shared by the really poor of the world

― César Milstein, Un Fueguito

(Nobel prize 1984 for discovery of the principle of production of monoclonal antibodies)