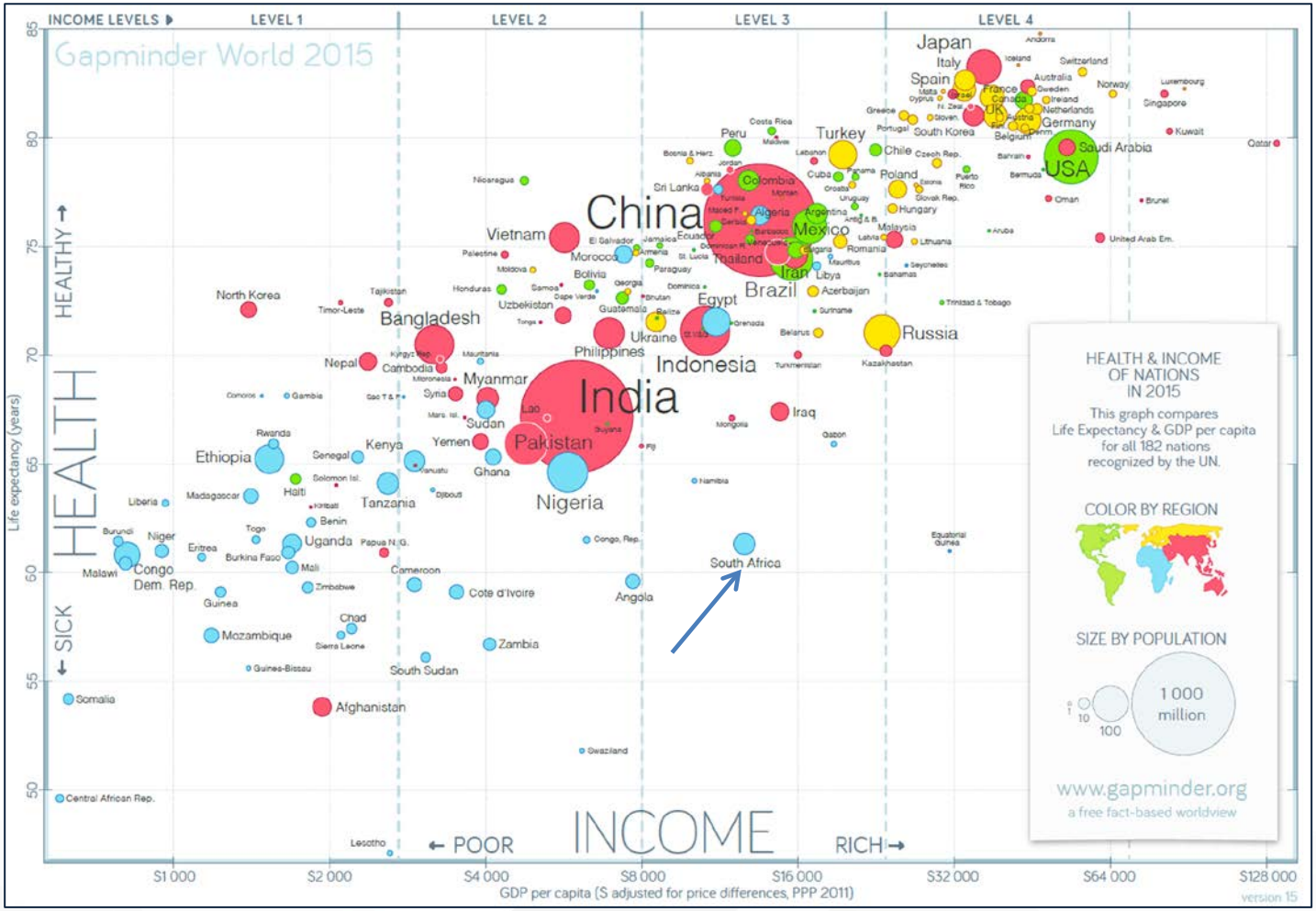
IDEAS THAT WORK FOR INDUSTRIAL DEVELOPMENT

Enabling local production of biopharmaceuticals in South Africa

Dr Tsepo Tsekoa, PhD

CSIR
our future through science

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	Public Sector
About **16% of the population** (7 million people) can afford high quality private healthcare	The over-stretched public healthcare institutions cover the majority of the South African population, around **84% of the population** (42 million people)
7 million people	42 million people
84% of the total pharma expenditure	**16%** of the total pharma expenditure
29,926 million ZAR	5,622 million ZAR

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

Provision: Public healthcare provision is primarily based on tertiary hospital facilities

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

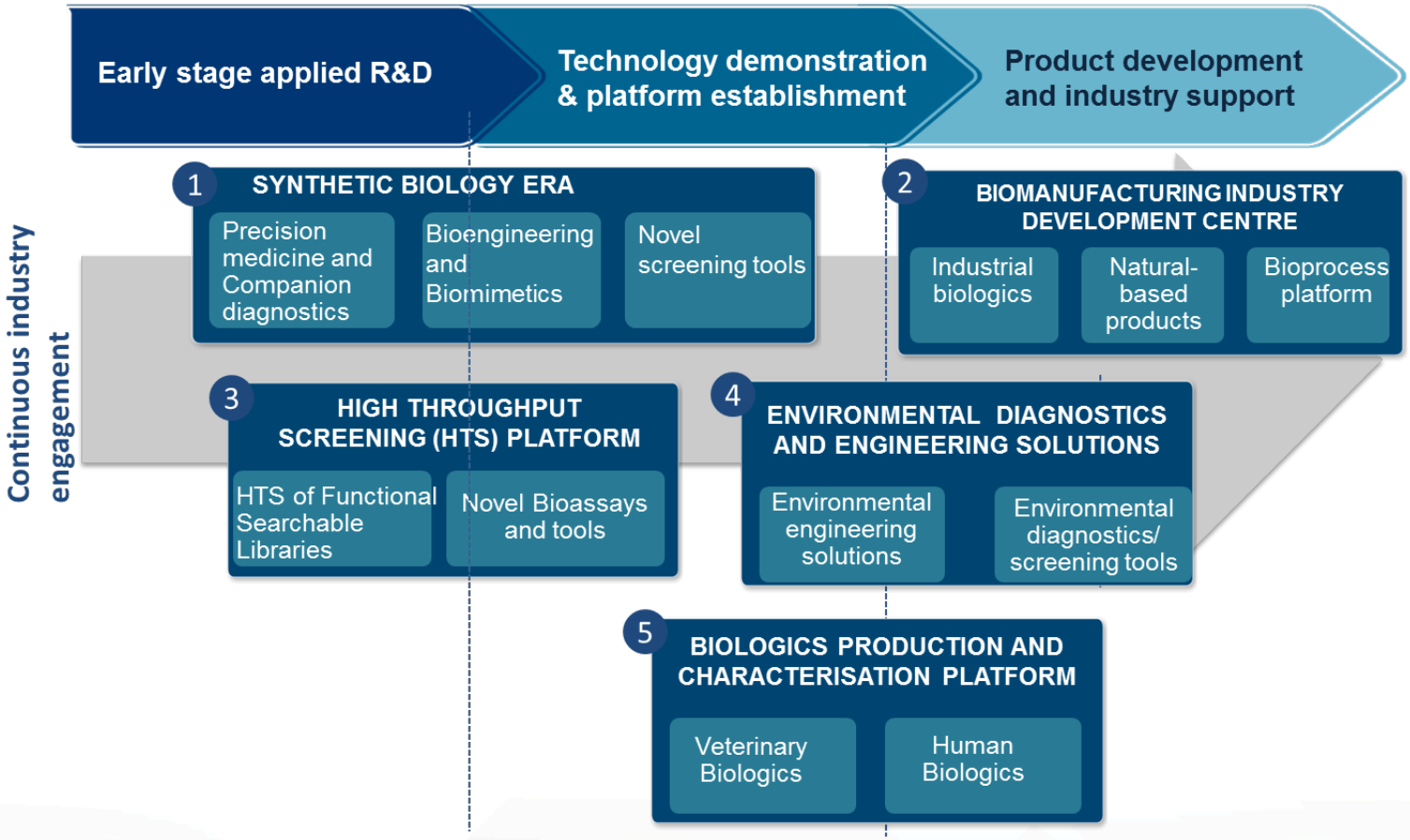
Relevant national priorities and strategic context

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."

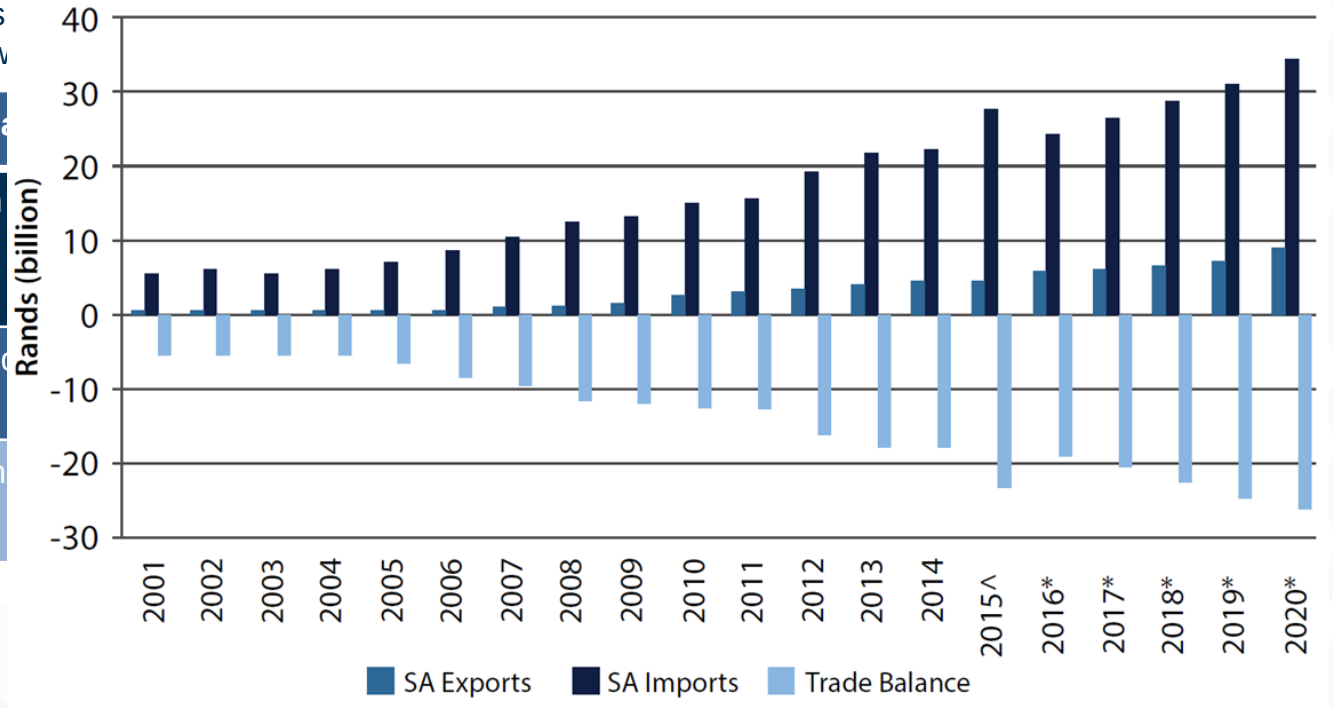
The Bio-economy Strategy
"By drawing on these capabilities, South Africa will be able to manufacture active pharmaceutical ingredients, vaccines, biopharmaceuticals, diagnostics and medical devices to address the disease burden, while ensuring a secure supply of essential therapeutics and prophylactics."

CSIR platforms in response



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
- Dis ctors persists (Tw



Biopha

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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

World Health Organization

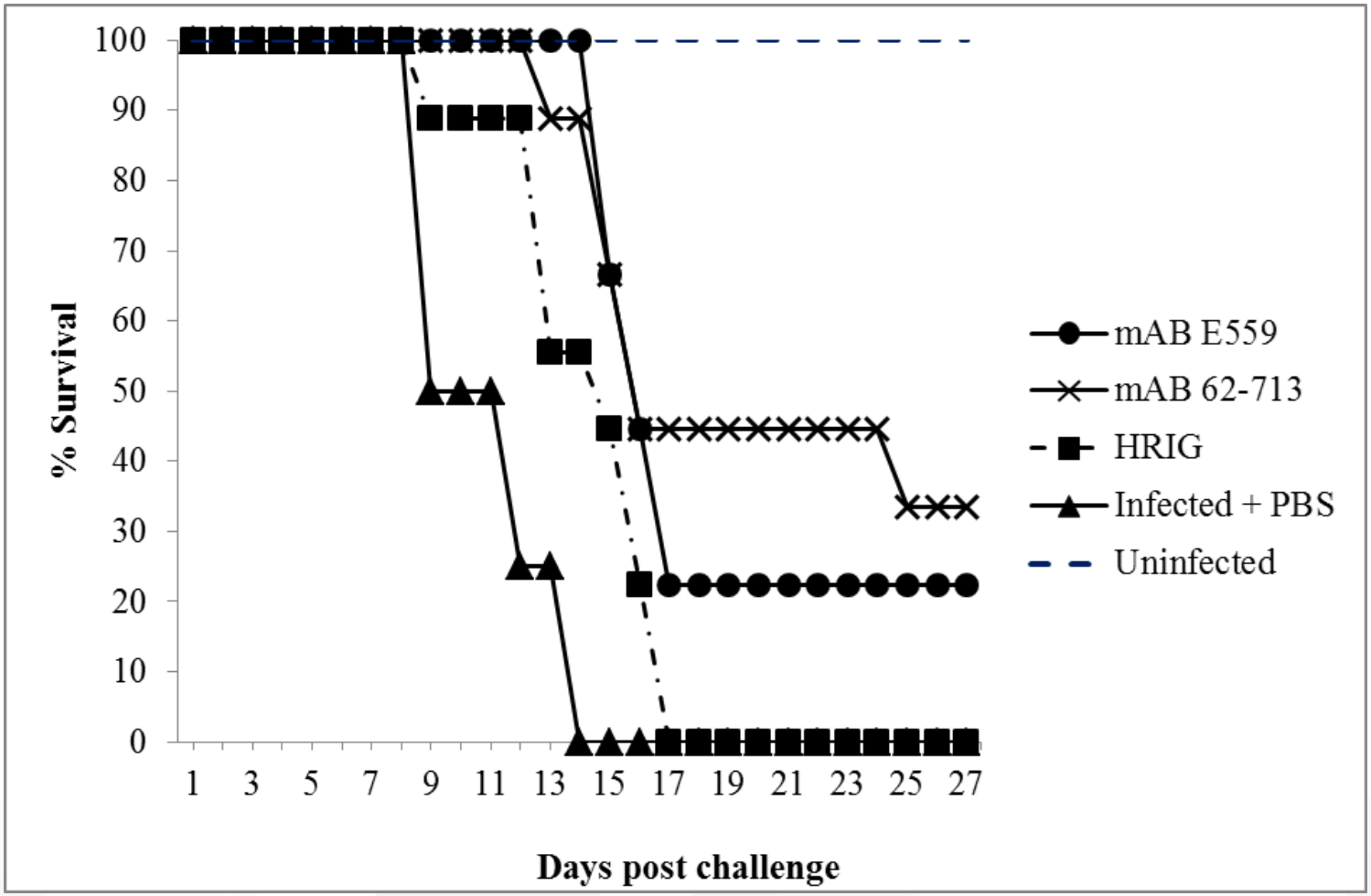
Mapp Biopharmaceutical

KBP KENTUCKY BIOPROCESSING

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

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


Journal of Applied Microbiology

ORIGINAL ARTICLE

Co-expression of sulphydryl oxidase and protein disulphide isomerase in *Escherichia coli* allows for production of soluble CRM_{197}

R. Roth, P. van Zyl, T. Tsekoa, S. Stoychev, S. Mampotha, S. Buthelezi and M. Crampton

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

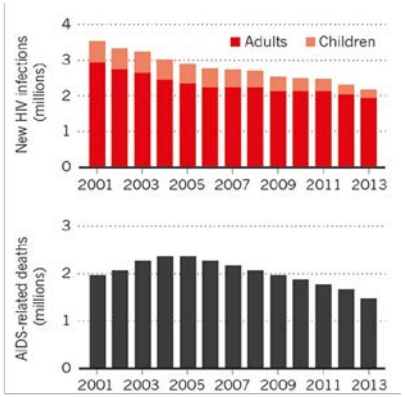
HIV prevalence in young pregnant women in rural Vulindlela, South Africa
(2009-2012)

Age Group (Years)	HIV Prevalence (N=1029)
≤16	8.4
17-18	18.6
19-20	25.4
21-22	32.8
23-24	44.8

Quarraisha and Salim Abdool Karim

~5,500 new HIV infections every day

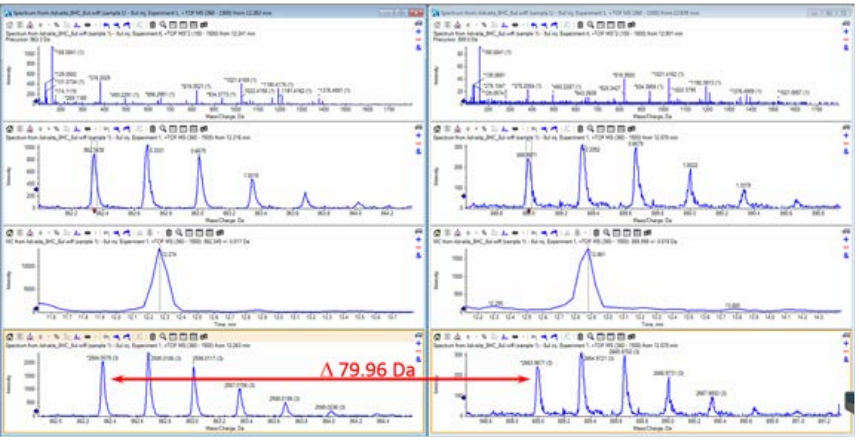
~4,000 AIDS deaths every day

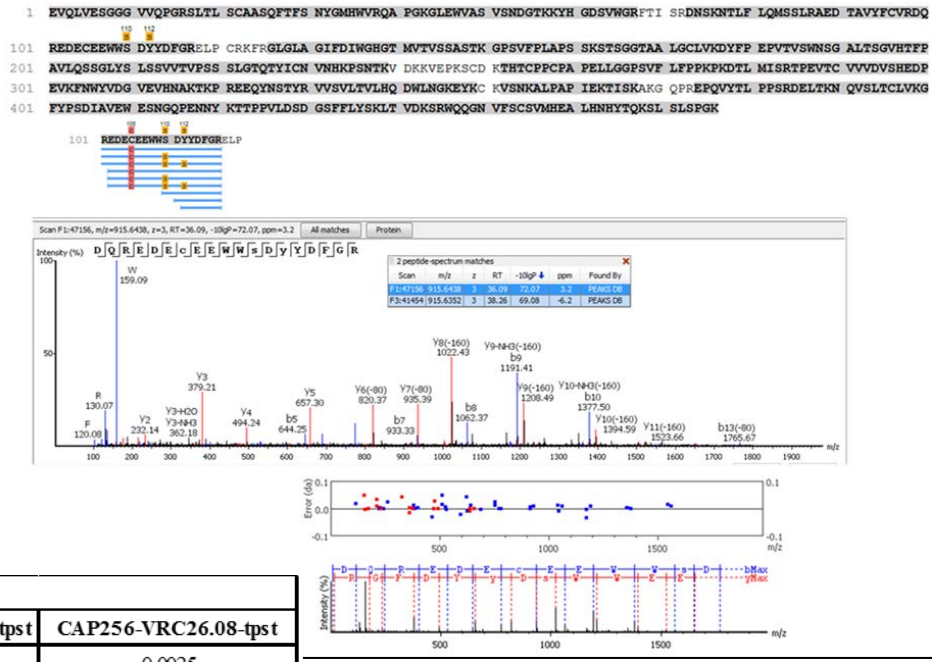


UNAIDS

World Health Organization

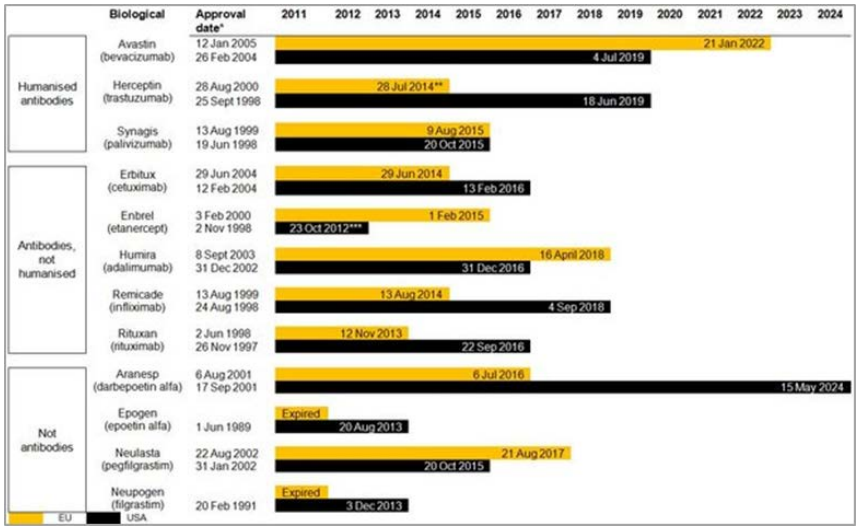
Case study 3: Plant-based production of CAP256-VRC26 HIV antibodies

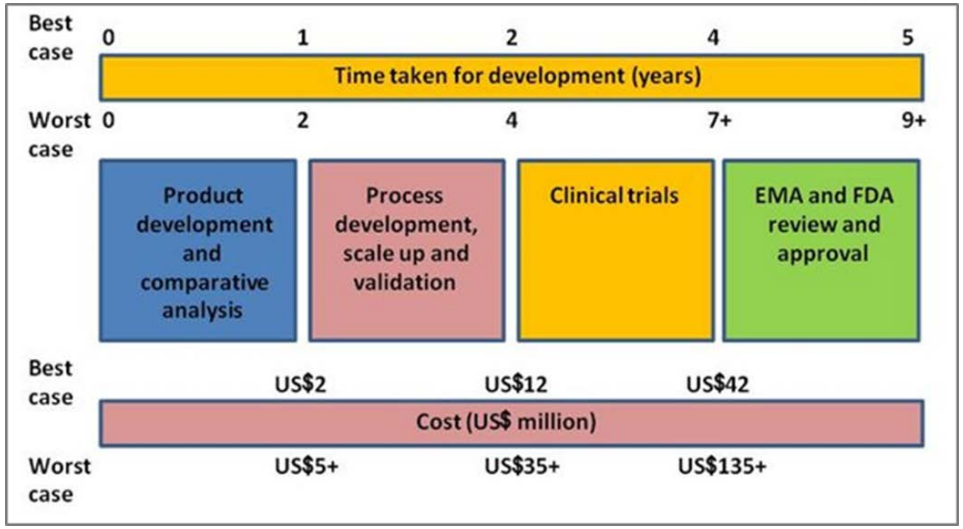




Envelope	Subtype	IC50 (μg/mL)			
		CAP256-VRC26.09	CAP256-VRC26.08	CAP256-VRC26.09-tpst	CAP256-VRC26.08-tpst
ZM53M.PB12	C	0.0028	0.0031	0.0025	0.0025
ZM233.6		0.028	0.0050	0.0050	0.0085
CAP239.G3		0.0047	0.0048	0.018	0.008
Du156.12		0.025	0.02	0.08	0.06
Du151.2		0.018	0.013	0.069	0.037
Du172.17		>50	>50	>50	>50
6535	B	>50	>50	>50	>50
TRO.11		>50	>50	>50	>50
Q23.17	A	11.1	1.1	5.5	1.6
Q461		0.37	0.50	0.47	0.613
Q168.a2		0.088	0.18	0.11	0.11

The biosimilars opportunity?





	Generics	Biosimilars	Originators
No. of patients in various phases of development	20–50 patients	~ 500 patients	~ 1000–2000 patients
Time to market	2–3 years	7–8 years	8–12 years
Development costs	USD 2 million – 3 million	USD 100 million – 150 million	USD 500 million – 1 billion
Success probability	90–99%	50%	5%

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

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- **CDC Atlanta:** Prof Charles Rupprecht
- **WHO Collaborating Centres for Rabies Surveillance and Research:** Dr Thomas Muller

IDEAS THAT WORK FOR INDUSTRIAL DEVELOPMENT

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)

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