GM human vaccines in South Africa

a case for the Precautionary Principle

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The African Centre for Biosafety (ACB) is a non-profit organisation, based in Johannesburg, South Africa. It provides authoritative, credible, relevant and current information, research and policy analysis on genetic engineering, biosafety, biopiracy, agrofuels and the Green Revolution push in Africa.

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Contents

1. Executive summary 5

2. Introduction 7

3. Brief history of vaccines 9

4. Types of vaccines 10

5. Legislation 11

6. Regulation 12

7. Clinical trial approval process 14

8. Clinical trials of GM vaccines in South Africa 16
- GM HIV vaccines
- GM TB vaccines
- GM measles vaccines

9. ACB biosafety submissions 23
- MRK Ad5 HIV-1 gag/pol/nef vaccine (Phambili trials)
- SAAVI MVA-C multigene HIV vaccine

10. Institutions 26

11. Multinationals 29

12. Key issues and recommendations 30
- Ethics – prior informed consent
- Which GM vaccines need to be approved by the Executive Council?
- Tracking the applications
- Access to information
- Monitoring trials
- Executive Council minutes – follow up
- Department of Health – unanswered questions
- Biosafety concerns
- Public participation

Conclusion 39

Appendix 1 40

Appendix 2 41

Appendix 3 42

Appendix 4 43

Appendix 5 44

References 46

Acronyms

ACB	African Centre for Biosafety
BCH	Biosafety Clearing House
CAPRISA	Centre for the AIDS Program of Research in South Africa
CBI	Confidential Business Information
DAIDS	Division AIDS (USA)
DHHS	Department of Health and Human Services (USA)
DoA	Department of Agriculture
DoH	Department of Health
EPI	Expanded Programme of Immunisation
GE	Genetic engineering or genetically engineered (often used interchangeably with genetic modification or genetically modified)
GM	Genetic modification or genetically modified
GMO	Genetically modified organism
HIV/ AIDS	Human Immunodeficiency virus / Auto-immune disease
ICGEB	International Centre for Genetic Engineering and Biotechnology
IIDM	Institute of Infectious Disease and Molecular Medicine (University of Cape Town)
MCC	Medicines Control Council
NIAID	National Institute of Allergy and Infectious Diseases (USA)
NIH	National Institutes of Health (USA)
PAIA	Promotion of Access to Information Act
SAAVI	South African Aids Vaccine Initiative
SAVIC	South African Vaccination & Immunisation Centre
TB	Tuberculosis
WHO	World Health Organisation

1 executive summary

Vaccines containing living genetically modified organisms (GMOs) are still at an experimental level in the world today. In South Africa, the first clinical trials for genetically modified (GM) vaccines were approved in 2003. These included several trials for HIV and TB vaccines, while several more applications for trials are pending, including those for other GM HIV vaccines and a measles vaccine. The number of applications to conduct clinical trials involving such vaccines in South Africa is steadily increasing as medical science continues to seek a cure for the HIV-AIDS and TB pandemics.

Nevertheless, one of the GM HIV vaccine clinical trials, the Phambili trials, was brought to an abrupt halt in 2007 when the vaccine appeared not to have prevented infection or reduced the levels of the virus. It also seemed that the participants may now have increased susceptibility to acquiring HIV infection.

This incident has brought into sharp focus the need for civil society to engage with the issues at play, including the biosafety discourse. Whilst there is generally, considerable oversight and regulation for human medical GMO clinical trials, a restrictive approach has been taken to biosafety issues and concerns by South African regulators and medical fraternity.

In this booklet, a brief background to vaccines is given – the history and the different types involved. This is followed by a discussion of the legislation and regulatory systems pertaining to GM vaccines. An overview is presented of the various GM vaccine clinical trials that have been approved or are still pending approval in South Africa. Two of the clinical trials in respect of which the African Centre for Biosafety (ACB) has made detailed submissions are discussed in some detail to highlight the biosafety concerns. Thereafter, a brief discussion of the South African organisations involved – public and commercial - as well as the multinationals is presented.

The final section of the booklet contains a discussion titled, “Key Issues and recommendations”. Two key recommendations stand out in respect to the use of “live” GM vaccines and the importance of public participation. First, an immediate moratorium is called for regarding the use of live GM adenoviral and MVA vectors (the ones most commonly used) in vaccines. Second, the urgency for civil society

to become engaged with the issues at play is underlined. Indeed, the vigilance of civil society is indispensable and critically important in the context of powerful interests including, the public-private partnerships between research institutions and multinational pharmaceutical companies, the huge money spinners that pharmaceutical products represent and the complete lack of understanding by the public of the biosafety discourse relating to GM human vaccines.

2 introduction

In this booklet, we draw a clear distinction between "traditional" vaccines and genetically modified vaccines. Traditional vaccines, such as polio and measles vaccines in use for decades in South Africa and which form part of the public health system are not the focus of this report. What is the focus are the "new" genetically modified vaccines, the "live" vaccines that contain living modified viruses.

At present there are no live GM vaccines commercially available in the country. These are all still at the clinical trial stage and include trials for HIV-AIDS and Tuberculosis (TB), as well as an application for clinical trials for a GM measles vaccine. These trials have proceeded with very little public awareness until the dramatic end to the Phambili Merck GM HIV vaccine trials in September 2007, when news of its abject failure elsewhere in the world, spread around the globe.

All of the vaccines currently in clinical trials are developed and produced outside the country, by companies such as Merck & Co (USA), VIRxSYS Corporation, Inc (USA) and Crucell N.V. (The Netherlands).

Globally there has been much interest in the development of these new vaccines. The World Health Organisation (WHO) note that immune responses have been obtained using genes from a variety of infectious agents, including influenza virus, hepatitis B virus, human immunodeficiency virus, rabies virus, lymphocytic chorio-meningitis virus, malarial parasites and mycoplasmas. They also note that human clinical trials for many of these have begun.[1] Most research seems to have focussed on experimental GM HIV vaccines and TB vaccines, with clinical trials occurring across the globe and in various countries in Africa, including Uganda, Kenya, Tanzania, Zambia, Rwanda, Botswana and South Africa.[2] There is increasing international debate around the many issues around these vaccines – most recently there has been The Norwegian Biotechnology Board's November 2008 vaccine workshop "Genetic vaccines – benefits and challenges".[3]

The roll out of clinical trials in South Africa is facilitated by South African research institutions, such as the South African Tuberculosis Vaccine Initiative, the Medicines Research Council and the Perinatal HIV Research Unit, Chris

Hani Baragwanath Hospital as well as by South African companies such as the Triclinium Clinical Trial Management Project.

GM vaccines present many regulatory and other challenges. As GMOs, they fall under the Genetically Modified Organisms Act, which is administered by the Department of Agriculture and used predominantly to deal with GMOs in food and farming. As medicines, they fall under the Medicines and Related Substances Control Amendment Act, which is administered by the Department of Health. This is exacerbated by the enormous difficulties faced by members of the public such as the ACB, when attempts are made to gain access to relevant non-confidential business information (non-CBI).

Nevertheless, it is our hope that this research makes a positive contribution to the discourse particularly with regard to the biosafety and ethical concerns canvassed.

3 brief history of vaccines

Vaccination has a long history which is closely intertwined with the history of smallpox. It started with the practice of variolation – the deliberate infection of a person with the smallpox virus to produce immunity. The first record of this is "of a Buddhist nun, around 1000 AD, grinding up scabs into a powder, and then blowing it into the nostrils of a non-immune person".[4] By the 1700's, this method of variolation was common practice in China, India, and Turkey. It was then introduced into England from Turkey in 1721.[5] In 1774, there was a significant development when Benjamin Jesty, an Englishman, successfully inoculated his wife and two children, not with the often deadly smallpox virus (*Variola*), but with the relatively benign cowpox (*Vaccinia*), to avoid infection with smallpox. In 1796, Edward Jenner repeated this experiment with comparable success. "In 1798, Jenner published his work *Variolae Vaccinae*, in which he emphasised the merits of inoculation with cowpox, to safeguard humankind's survival against one of the deadliest scourges faced at the time".[6] Jenner called this process "vaccination" – from the Latin *vacca* for cow and *vaccinia* for cowpox.[7] Initially "vaccination" referred to inoculation against smallpox, but is now used in a generic way.

These beginnings eventually led to a massive global vaccination campaign against smallpox in the twentieth century. As in Jesty and Jenner's work, the vaccine contained "live" *Vaccinia* – the cowpox virus as opposed to *Variola* – the highly dangerous smallpox virus. The campaign, spearheaded by the World Health Organisation (WHO), eventually led to smallpox, being officially declared as having been eradicated, in 1979.[8]

The development of vaccines in the 20th century was phenomenal and the pace is not abating in the 21st century. The different types of vaccine are covered in the following section.

4 types of vaccine

In broad terms, vaccines can be divided into:
A) Traditional vaccines – not produced through genetic engineering/modification
B) Vaccines produced through genetic engineering/modification.

A) Traditional vaccines
- i) that contain whole live organisms
  - e.g. the *Vaccinia* virus in the smallpox vaccine
- ii) that contain attenuated live organisms
  - e.g. polio and measles vaccines used in the South African Expanded Programme of Immunisation (EPI) programme.
- iii) that contain "killed" organisms or protein sub-units
  - e.g. tetanus vaccine used in the South African EPI programme.

B) Vaccines produced through genetic engineering/modification.
- i) Recombinant /genetically modified vaccines
  - (that **do not** contain a living virus)
  - e.g. the Hepatitis B vaccine used in the South African EPI programme and the new vaccines Cervarix and Gardasil that are used to fight infections of HPV (Human Papilloma Virus), a cause of cervical cancer.[9]
- ii) Recombinant / genetically modified live virus vector-based vaccines
  - (that **do** contain a living virus)
  - e.g. the HIV vaccine that uses a living adenovirus vector or the TB and proposed new measles vaccine that uses a living pox virus vector (see further details under "Clinical trials of GM vaccines in South Africa")
- iii) Edible, genetically modified plant-based oral vaccines
  - e.g. plants (maize, bananas …) that are used as a mechanism to produce vaccines

It is the secondary category of vaccines produced through genetic engineering that is the focus of this overview, that is, vaccines that contain genetically modified organisms.

5 legislation

In South Africa, there are three key pieces of legislation that govern “live” GM vaccines. These are the Genetically Modified Organisms Act, 1997 (Act No. 15 of 1997) amended in 2007, the National Health Act, 2003 (Act 61 of 2003) and the Medicines and Related Substances Amendment Control Act, 1997 (Act No. 90 of 1997).

6 regulation

6.1 The Executive Council

Under the GMO Act, the Executive Council is the regulatory body that was established as the principle decision-making body for the approval or rejection of applications to release GMOs into the environment. As such, these applications include those for importing/exporting GMOs, contained use of GMOs, clinical or field trials involving GMOs and general release of GMOs. The Council is administered by the Department of Agriculture. It consists of officials from eight national government departments: the Departments of Agriculture, Health, Environmental Affairs and Tourism, Labour, Trade and Industry, Science and Technology, Water Affairs and Forestry and Arts and Culture.

An advisory body to the Executive Council, the Advisory Committee, was also established under the Act. Members of the Advisory Committee are appointed in terms of section 10 of the Act for a period of five years. The current members are listed in Appendix 1. The Executive Council is obliged to consult with the Advisory Committee over the issuing of permits for importing GMOs or releasing GMOs into the environment (as is the case with clinical trials) or commercial release of GMOs.

Decision-making by the Council is on the basis of consensus by all the members and where no consensus is reached, the application before the EC will be considered as having been refused.[10]

6.2 The Medicines Control Council

Under the Medicines and Related Substances Amendment Control Act, 101 of 1965, the Medicines Control Council (MCC), a statutory body, was established to oversee the regulation of medicines in South Africa. It is appointed by the Minister of Health. The MCC has a statutory obligation to ensure that the drugs available in the country fulfill the necessary requirements for safety, quality and efficacy.[11]

It would therefore oversee the authorisation of clinical trials involving all vaccines whether they were GM or not.

The MCC website gives details of the 11 technical committees, with 146 members from various institutions in the country. The committees include the Clinical Committee, Pharmaceutical and Analytical Committee, Clinical Trials Committee, Scheduling Committee, Veterinary Committee, Pharmacovigilance Committee, Biological Committee, Complementary Medicines Committee, and African Traditional Medicines Committee (see Appendix 2).[12]

The national Department of Health provides administrative and technical support to the MCC and its activities. This is done through the office of the Registrar. The Registrar is also an executive secretary to the Medicines Control Council. The Registrar's office is a Chief Directorate, Medicines Regulatory Affairs, within the Department of Health. There are four Directorates, which are largely responsible for co-ordination and execution of various activities (see Appendix 3).

Research Ethics Committees

As part of MCC approval, the application also has to be approved by the relevant institutional research ethics committee/s. In correspondence from the Department of Health to the Department of Agriculture in response to questions posed by the African Centre for Biosafety, Mr D. Pretorius (Director: Food Control) details that: "These committees are regulated by the Department of Health's National Health Research Ethics Council (NHREC) provided for under sections 72 and 73 of the National Health Act, 2003 and administered by the Directorate: Health Research. All Ethics Committees must be registered with this Council and are therefore regulated by the Department of Health. Therefore the EC (Executive Council) is not entitled to oversee the activities of these committees as it would be a redundant activity."[13]

The NHREC also advises the national department and provincial departments on any ethical issue concerning research.[14] The current NHREC members and the functions of the National Health Research Ethics Council are given in Appendix 4.

7 clinical trial approval process

For a clinical trial using a live GM vaccine to proceed, approval for the trials has to be obtained from:

- The Medicines Control Council (MCC)
- The relevant local Research Ethics Committee (REC)
- The Executive Council (EC in terms of a permit issued by the Registrar)

According to the Department of Health's "Guidelines for good practice in the conduct of clinical trials with human participants in South Africa", the following steps must be taken before a clinical trial can be conducted in South Africa:

- **National Regulatory Authority Approval:** A sponsor/principal investigator (PI) must apply to the MCC for approval to conduct a trial for a non-registered drug or a registered drug for new indications;
- **Research Ethics Committee Approval:** All clinical trials to be conducted in South Africa must apply for and receive ethical approval from an accredited research ethics committee based in South Africa; and
- **Recording on South African National Clinical Trials Register (SANCTR):** Once the trial has obtained ethical approval, trial information must be forwarded to the Department of Health where the trial is allocated a unique SANCTR number – it is the responsibility of the sponsor/principal investigator to ensure that the information is sent to the Department of Health. The number will be generated within two working days of the application having been received. Only once this number is received by the sponsor/PI can begin with the trial.[15]

The MCC requires a completed application form "Application to conduct clinical trials"[16] and the Clinical Trial Protocol, Clinical Investigator Brochure and other study related documents.

These same documents are sent to the relevant institutional Research Ethics Committee. For the MCC to give approval, they must receive approval from the relevant Ethics Committee.

The Department of Health's "Guidelines for good practice in the conduct of clinical trials with human participants in South Africa" details the responsibilities of the Ethics Committee: "should safeguard the dignity, rights, safety, and well-being of all trial participants. Special attention should be paid to trials that may include vulnerable participants. The ethics committee should obtain the following documents: trial protocol(s) amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g. advertisements), written information to be provided to participants, Investigator's Brochure (IB), available safety information, information about payments and compensation available to participants, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the ethics committee may need to fulfill its responsibilities."[17]

At some institutions, e.g. the University of the Witwatersrand, besides the Ethics Committee (the longstanding University of Witwatersrand Human Research Ethics Committee),[18] there is also a Biosafety Committee,[19] that works in conjunction with the Ethics Committee and whose approval would also be required before a clinical trial could go ahead.

The Executive Council under the GMO Act requires a completed permit application form for "The intentional introduction of a GMO into the environment in South Africa"[20] to be sent to the Registrar of the GMO Act. The Registrar will check to see that the application meets the requirements of the Act (including the applicant placing a public notice in a newspaper informing the public of its application), and then will forward the application to the Advisory Committee. The Advisory Committee members review the application and a recommendation is then sent to the Executive Council (EC). The EC then takes into account the recommendation from the advisory committee and public input and if it is satisfied that a certain activity with a GMO may be conducted, the Registrar is authorised by the Council to issue the necessary permit.

8 clinical trials of gm vaccines in south africa

In 2003, the first approval for clinical trials of a vaccine containing a GMO was given for Tricilinium's GM HIV MVA vaccine. Since then there have been several approvals for clinical trials of other HIV and TB vaccines. An application for a clinical trial of a GM measles vaccine has been made, but as yet, no decision has been taken to approve the application.

A table showing all the permits approved for the import of genetically modified vaccines as well as the permits for controlled release of GMOs (the clinical trials of the vaccine) is detailed in Appendix 5.

The three tables following summarise the trials for GM HIV, TB and measles vaccines for the period 2003 to March 2008. This information was obtained from the applicants permit applications for human clinical trials involving genetically modified organisms. To obtain this information from the Department of Agriculture, ACB used PAIA, the Promotion of Access to Information Act. The application was submitted in November 2007 and the information was received in January 2008 with the "Confidential Business Information" blocked out. This process of accessing information is expensive and time-consuming, but it is the only way the public is able to obtain information on the clinical trials.

Clinical trial phases

The World Health Organisation (WHO) website on "Development of new vaccines" details the process of vaccine development and the different phases of clinical trials as follows:[21]

"Vaccine development proceeds through discovery, process engineering, toxicology and animal studies to human Phase I, II, and III trials. The process can take more than 10 years, depending on the disease.

The human trials focus initially on safety, involving small groups of people (Phase I);

then progress to moderate-sized "target" populations (persons close to the age and other characteristics for whom the vaccine is intended) to determine both safety and the stimulation of immune response (Phase II);

and finally to large target populations to establish whether a vaccine actually prevents a disease as intended (efficacy) (Phase III)."

If the clinical trials are successful, the next step for a GM vaccine would be to get the vaccine registered and licenced for sale by the MCC, and approved for commercial release of a GMO by the Executive Council.

8.1 Genetically Modified (GM) HIV vaccines

Applicant	Vaccine	Vaccine explanation	Partners	Status of clinical trials	No. of people in trial	Trial site/s
Triclinium Project Trial Management, Northlands 2016 South Africa	MVA with genes gag, pol, nef & env	Contains the GM modified vaccinia ankara virus (MVA) with four HIV genes, gag, pol, nef and env. MVA is a virus from the "pox" virus family.	**Vaccine supplier:** International AIDS Vaccine Initiative (IAVI), USA **Sponsor:** blocked out as "CBI"	Vaccine supplier: International AIDS Vaccine Initiative (IAVI), USA Sponsor: blocked out as "CBI"	111 healthy adults (90 will receive the vaccine, 21 will receive a placebo).	Specific details of trials sites blocked out as CBI, but reference to: * University of Witwatersrand, Johannesburg * Medical Research Council, Durban
MSD, Midrand 1685. South Africa	MRK Ad5 HIV-1 gag	Contains the GM adenovirus (Ad5) with the HIV gag gene inserted. HIV-1 is the most common form of HIV. Adenoviruses cause the common cold and other respiratory ailments. MRK is an abbreviation for Merck.	**Vaccine supplier:** Merck and Co., USA	Phase I trial, approved June 2004	Not detailed in GMO application	Not detailed in GMO application
Cato Research, Fourways 2055. South Africa	Autologous cells transduced with VRX496 (VRX496T)[i]	HIV infected participants' HIV-free CD4 T cells will be isolated and transduced with VRX496 and then intravenously infused back into the participant that gave them (hence the use of the term "autologous").	**Vaccine supplier** and **sponsor:** VIRxSYS Corporation, USA	Phase I / Phase II trial, approved in 2004	Approx. 30 HIV infected patients who are anti-retroviral naïve.	* Infectious Disease Unit, Wits Health Consortium, Gauteng * Perinatal HIV Research Unit, Baragwanath Hospital, Johannesburg

i * Although this application is for gene therapy, this type of gene therapy is also known as "intracellular immunisation" .

Applicant	Vaccine	Vaccine explanation	Partners	Status of clinical trials	No. of people in trial	Trial site/s
Triclinium Project Trial Management, Northlands 2016 South Africa	VRC-HIVDNA 16-00-VP and VRC-HIVADV014-00-VP	A combination vaccine - VRC-HIVDNA 16-00-VP is a DNA vaccine and VRC-HIVADV014-00-VP a recombinant adenoviral vector vaccine.	**Vaccine supplier:** Vaccine Clinical Research Branch, DAIDS, NIAID, NIH, USA ***Sponsor:*** DAIDS, NIAID, NIH and DHHS, USA	Phase II trial, approved on 5 June 2006	Healthy, HIV uninfected adults (numbers not detailed in the GMO application)	* KOSH site, Klerksdorp * Perinatal HIV Research Unit, Baragwanath Hospital, Johannesburg * Desmond Tutu HIV Research Centre, University of Cape Town
Prof. Glenda Gray, Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, 1864 South Africa	MRK Ad5 HIV-1 gag/ pol/nef vaccine	Contains the GM adenovirus (Ad5) with the HIV gag, pol and nef genes inserted. HIV-1 is the most common form of HIV. Adenoviruses cause the common cold and other respiratory ailments. MRK is an abbreviation for Merck.	**Vaccine supplier:** Merck and Co., USA	Phase II B trial, approved 21 November 2006	3000 HIV-1 sero-negative adults	* Perinatal HIV Research Unit at the Chris Hani Baragwanath Hospital, Soweto, Johannesburg * Aurum Health, Jade Square (Klerksdorp) * Desmond Tutu HIV Centre, Institute of Infectious Diseases & Molecular Medicine, University of Cape Town * Centre for the AIDS Program of Research in South Africa (CAPRISA), Durban * Medunsa HIV Research Unit, Department of Microbiological Pathology, * Medunsa, Pretoria

Applicant	Vaccine	Vaccine explanation	Partners	Status of clinical trials	No. of people in trial	Trial site/s
Triclinium Project Trial Management, Sandown 2196 South Africa	VIR201	Contains a genetically modified virus from the "fowlpox" virus family and includes the HIV genes gag and pol.	**Vaccine supplier:** Impfdstoffwek Dessau-Tornau (IDT), Germany **Sponsor:** Virax Development Pty, Ltd. Australia	Phase I/IIa trial, but decision is pending the MCC and relevant ethics committee approval of the vaccine	108 HIV infected individuals (72 will receive VIR201 and 36 the placebo)	* Desmond Tutu HIV Centre, IIDM, Cape Town * Brooklyn Medical Centre Research, Cape Town * Richards Bay Trial Centre, Richards Bay * Elandsdoorn Town, Groblersdal * Aurum HIV Vaccine Research and Treatment Centre, Klerksdorp
Prof. Glenda Gray, Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, 1864 South Africa		Contains a non-GM vaccine DNA-C2 vaccine, which is boosted by a GM vaccine, MVA-C vaccine. The MVA (modified vaccinia Ankara virus) from the "pox" virus family acts as vector or carrier for 5 HIV genes – gag, RT, tat, nef and env.	**Vaccine supplier:** NIAID, DAIDS, NIH, DHHS, USA. **Vaccine developer:** SAAVI, MRC, University of Cape Town (all SA) and Therion Biologics Corp. USA.	Phase I trial, but decision is pending.[ii]	36 HIV uninfected adults	* Desmond Tutu HIV Centre, IIDM, Cape Town * Crossroads Vaccine Centre, Nyanga, Cape Town * Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, Johannesburg

ii Stop press – report dated 29 November 2008, states that the SA Aids Vaccine Initiative (SAAVI) has announced that clinical testing of this vaccine will start in the United States next week and South Africa in January 2009 (http://www.saavi.org.za/2press2008.htm, accessed 1 December 2008).

8.2 Genetically Modified (GM) TB vaccines

Applicant	Vaccine	Vaccine explanation	Partners	Status of clinical trials	No. of people in trial	Trial site/s
Triclinium Project Trial Management, Northlands 2016 South Africa	MVA85A	Contains the GM modified vaccinia virus ankara (MVA) with the TB 85A gene. MVA is a virus from the "pox" virus family.	**Vaccine supplier:** Andrea Schaenzler, Impfstoffwerk Dessau-Tornau (IDT), Germany **Sponsor (and developer):** University of Oxford, Centre for Clinical Vaccinology and Tropical Medicine; United Kingdom	Phase 1 trial, approved 15 July 2005	12 adults with evidence of prior BCG vaccination and 12 with no evidence, followed by 12 children (aged 12-14)	* Brewelskloof Hospital, Worcester
Triclinium Project Trial Management, Sandown 2196 South Africa	AERAS-402	Contains a GM adenovirus (Ad5) with the TB genes, 85A, 85B and TB10. Intended that this vaccine would be a booster for individuals previously vaccinated with BCG.	**Vaccine developer and supplier:** Crucell Holland B.V., the Netherlands **Sponsor:** Aeras Global TB Vaccine Foundation; USA	Phase 1 trial, approved 2 March 2007	Three groups of ten healthy adult subjects, previously vaccinated with BCG	* Brewelskloof Hospital, Worcester
Triclinium Project Trial Management, Sandown 2196 South Africa	MVA85A	Contains the GM modified vaccinia ankara virus (MVA) with the TB 85A gene. MVA is a virus from the "pox" virus family.	**Vaccine supplier:** Grit Rudolph, Andreas Neubert, Andrea Schaenzler, Impfstoffwerk Dessau-Tornau (IDT) Germany **Sponsor (and developer):** University of Oxford, United Kingdom	Phase I trial, authorised on 29 October 2007	Three groups of twelve asymptomatic adults, who are infected with TB (group A), HIV (group B) ir both (Group C)	* South African Tuberculosis Vaccine Initative (SATVI), Worcester

8.3 Genetically Modified Measles vaccine

Applicant	Vaccine	Vaccine explanation	Partners	Status of clinical trials	No. of people in trial	Trial site/s
Triclinium Project Trial Management, Northlands 2016 South Africa	MVA-mBN85B	Contains the GM modified vaccinia ankara virus (MVA) which expresses the following from the wild type measles virus – the F and H glycoproteins as well as N, the nucleocapsid protein. MVA is a virus from the "pox" virus family.	**Vaccine supplier:** Bavarian Nordic Germany **Sponsor (and developer):** Bavarian Nordic A/s Denmark	Phase 1 trial, but decision is pending the MCC approval of the vaccine	30 healthy volunteers between the ages of 18 and 32 years.	* Farmovs-Parexel, Campus of the University of the Free State, Bloemfontein

9 acb biosafety submissions

The ACB has made detailed submissions to the Registrar of the GMO Act regarding two of the above GM vaccines, the MRK Ad 5 HIV-1 gag/pol/nef vaccine (Phambili trial) in 2006 and the SAAVI MVA-C multigene HIV vaccine in 2008.

9.1 MRK Ad 5 HIV-1 gag/pol/nef vaccine: Phambili trials

The ACB June 2006 submission was the first submission made by a civil society grouping regarding a GM vaccine application. The application was reviewed with the help of various independent international scientists. The numerous difficulties in accessing information were detailed in the submission (see www.biosafetyafrica.net).

The ACB submission highlighted that there were a number of unanswered questions relating to the health of the vaccinees as well as the creation of new recombinant viruses and non-target effects. There were also concerns with the use of adenoviruses, aspects of the risk assessment, the understanding of the terms "risk" and "probability" and various specific concerns and questions, e.g. the destabilisation of the adenovirus genome, testing of RCA (replication competent adenoviruses) shedding, post trial monitoring, the tumorigenicity studies carried out in new-born rats and the toxicology and safety assessments.[22]

ACB called for:

- the Precautionary Principle to be applied and a moratorium on clinical trials of AIDS vaccines based on adenoviral vectors
- for scientific concerns to be addressed
- for information on the clinical trial that will be given to participants and the Prior Informed Consent (PIC) component of the application to be released

Clinical trials for this vaccine were approved by the Medicines Control Council, the ethics committees of the University of Cape Town, University of KwaZulu-Natal and the University of Limpopo. The institutional biosafety committees and the Executive Council (under the GMO Act) also reviewed and approved the trial in South Africa.

It was this clinical trial that got the public's attention, when in September 2007, the trials came to an abrupt end. Similar trials in the US and Australia, known as the STEP study or HVTN 502 or MerckV520-023 study, were halted because the vaccine "did not prevent HIV infection nor reduce the amount of virus in those who became infected with HIV" and that "… there is the possibility that people in the vaccine arm may have increased susceptibility to acquiring HIV infection."[23]

9.2 SAAVI MVA-C multigene HIV vaccine.

In March 2008, ACB made a submission "Independent expert biosafety evaluation of the application made for trial release of genetically engineered SAAVI MVA-C multigene HIV vaccine" to the Registrar of the GMO Act (see www.biosafetyafrica.net).

Numerous biosafety concerns were raised and the recommendations were as follows:

- Clinical trials with MVA-C vaccine should not be initiated until the five risk related questions (see below) have found satisfactory scientific answers:
  1. Multiplication of transgenic and non-transgenic MVA in human and other mammalian cells
  2. Stability of transgenic MVA, loss of transgene(s), monitoring vaccine efficacy
  3. Recombination between transgenic MVA and naturally occurring orthopox-viruses
  4. Selection of participants in the SAAVI MVA-C trial "Vaccinia virus naïve persons"
  5. What kind of immune responses were anticipated?

- South African authorities are urged to make funding available for such studies, including funding for detection and mapping of orthopox viruses in domestic animals and wildlife.

- Until questions related to issues 1-5 in the biosafety evaluation have found satisfactory research-based answers, a moratorium should be put on MVA vectored vaccines in South Africa. The moratorium may be lifted when it is accepted that satisfactory answers have been delivered.

Six months later, there has been no development in the status of this application and a response from the Executive Council is still awaited.

STOP – PRESS

The South African AIDS Vaccine Initiative (SAAVI) announced on 28 November 2008 that the trials have been approved and that they will begin in early January 2009. See http://www.saavi.org.za/2press2008.htm

10 institutions involved

Although the vaccines for all of the current clinical trials are produced outside of the country, considerable resources are being ploughed into South African institutions for GM vaccine research and development. Several of these institutions have been involved in the current application for clinical trials of the SAAVI MVA-C HIV vaccine. Listed below are some of the key institutions:

i) Council for Scientific and Industrial Research (CSIR)

The CSIR, through its Biosciences Plant Biotechnology research group, is part of Pharma-Planta, a research consortium representing 39 academic and industrial institutions, 38 of them from Europe and the CSIR from South Africa. Pharma-Planta was launched in 2004 and is funded by the European Union. The mission of the Pharma-Planta consortium is "to develop efficient and safe strategies for the production of clinical-grade protein pharmaceuticals in plants, and to define procedures and methods for the production of these proteins in compliance with all appropriate regulations".[24] The pharmaceuticals planned are for vaccines and treatments against major diseases including AIDS, diabetes, rabies and TB.

The Plant Biotechnology research group also secured a multi-million rand research grant from the Department of Science and Technology (DST) to extend research into transgenic plants as a novel platform for the production of pharmaceuticals. The project leader for the research group, Dr Rachel Chikwamba, says the grant, worth R6,5 million, was announced in February (2007) and will assist the group with expanding its investigations.[25]

ii) Institute of Infectious Diseases (IIDMM) and International Centre for Genetic Engineering and Biotechnology (ICGEB)

The University of Cape Town opened the Institute of Infectious Diseases and Molecular Medicine (IIDMM) in 2005. They have links to many organisations including the South African AIDS Vaccine Initiative, the Aeras Global TB Vaccine Initiative and the MRC.[26] The institute has 6 major research areas: HIV/AIDS, Tuberculosis, Parasitic and other Infections, Molecular Medicine, Cancers and Genetic medicines.[27] In the HIV/AIDS research area it is noted that "We are in the

process of constructing locally relevant vaccines with promising candidates in the pipeline. Together with national and international partners we are testing potential vaccines, microbicides and drugs".[28] Within this research area, there is an HIV Vaccine Development Group and a Human Papillomavirus Research Group. For details on TB see v).

On 1 December 2006, it was announced that the University of Cape Town's Institute of Infectious Disease and Molecular Medicine (IIDMM) would host the third component centre of the International Centre for Genetic Engineering and Biotechnology (ICGEB). The other two centres are in Trieste, Italy and New Delhi, India.[29] The UCT centre was officially opened on 20 September 2007, by President Thabo Mbeki. The South African government, through the Department of Science and Technology, is contributing about R40 million towards the start-up costs for the UCT centre. These funds are sufficient to establish an initial three research groups, which will target infectious and non-communicable diseases, as well as drug development. The centre aims to set up a further four research groups by 2010.[30]

iii) Medical Research Council (MRC)

The MRC mission is to improve the nation's health and quality of life through promoting and conducting relevant and responsive health research.[31] It has 6 national programmes which include the MRC's 45 research units, groups, centres and Lead Programmes. The South African Aids Vaccine Initiative is included under the Programme of Infection and Immunity (see iv).[32]

iv) South African Aids Vaccine Initiative (SAAVI)

The SAAVI website details that SAAVI was established to co-ordinate the research, development and testing of AIDS vaccines in South Africa. It is based at the Medical Research Council (MRC) and "is working with key national and international partners to produce an affordable, effective and locally relevant AIDS vaccine in as short a time as possible".[33] It was formed in 1999 as a lead programme of the Medical Research Council (MRC) with primary funding received from the Department of Health (DoH), the Department of Science & Technology (DST) and Eskom.

v) South African Tuberculosis Vaccine Initiative (SATVI)

SATVI was established in 2001 and is based within UCT's IIDMM. Its mission is the development of new and effective tuberculosis vaccines and is the largest dedicated TB vaccine research group on the African continent.

v) The Biovac Institute

Biovac is a Public Private Partnership which came into effect on 1 April 2003 and was concluded between the South African Government, through the Department of Health, as a Strategic Equity Partner, The Biovac Consortium. It is now known as The Biovac Institute. "Its aim is to develop and restructure the State Vaccine Assets to ensure the country has the required domestic capacity to respond local and regional vaccination needs."[34]

At the opening of Biovac Institute's Quality Control Laboratories in Cape Town on 11 October 2007, the Minister of Health noted that "Since 2003 we have had a Public Private Partnership with the Biovac Institute to supply vaccines for the Expanded Programme on Immunisation (EPI) for a period of 5 years. This agreement recognises the need for the development of local capacity in manufacturing, research and development of new vaccines. The main aim of the agreement is to ensure an uninterrupted supply of vaccines for our immunisation programme."[35]

Besides supplying vaccines for EPI, The Biovac Institute is also pursuing the development of a broad range of polysaccharide vaccines such as *Haemophilus influenzae*, pneumococcal and meningococcal varieties and is also involved in a collaborative research project with UCT to look at the production of virus–like particles in culture (baculovirus) and tobacco plants.[36]

11 multinationals

The five biggest global vaccine providers are GlaxoSmithKline, Sanofi-Aventis, Merck, Novartis and Serum Institute of India. The first four are producing genetically modified vaccines. The fifth is planning to expand into genetically modified (recombinant) drugs.

Enormous sums of money are involved in these companies and vaccine sales play an important part, for instance Merck's worldwide sales were $6.1 billion for the third quarter of 2007 and that sales performance reflects the "strong growth of the Companies vaccines …"[37]

It is interesting to note that in 2000 the agribusiness unit of Novartis merged with that of Astra Zeneca to form the GM seed giant Syngenta, the world's second biggest player in agrochemicals and the third largest seed producer (see the Corporate Watch website http://archive.corporatewatch.org/genetics/commercialisation/syngenta.htm, accessed 1 December 2008).

12 key issues and recomendations

12.1 Ethics – prior informed consent

Much has been written about ethics around research involving human subjects - about people being properly informed and knowing their rights. Institutions such as the Steve Biko School of Ethics at the University of the Witwatersrand, SARETI (South African Research Ethics Training Initiative)[38], the HIV/AIDS Vaccines Ethics Group (HAVEG) based at the School of Psychology, University of KwaZulu-Natal, Pietermaritzburg[39] and the relevant university ethics committees are all contributing towards the development of a sound ethical approach. Documents such as "Ethical issues in HIV vaccine trials in South Africa"[40], "Ethical guidelines for Biotechnology research in South Africa"[41] and "Legal guidelines for Biotechnology research in South Africa"[42] are most useful, but they are still catering for a highly literate readership. A key ethical issue with respect to clinical trials using genetically modified human vaccines, is around Prior Informed Consent. In reading through all the applications for clinical trials, it is clear that the applicants do not perceive GM to be a contested technology. However, it is important for the participants who will be vaccinated to know this, for them to be informed that the vaccine that they will be vaccinated with contains a living GMO, that there are risks and that they with this knowledge, can decide whether to participate or not in the trial.

Recommendations:

- that participants must have an understanding of GMOs and that GM is a contested technology
- that participants understand that they will be vaccinated with a genetically modified organism
- that the information they are given on GM vaccines is adequately translated into the mother tongue of the participants
- that consideration is given to a situation where illiterate people are excluded from GM human vaccine clinical trials

12.2 Which GM vaccines need to be approved by the Executive Council?

There needs to be clarity as to exactly which genetically modified vaccines need approval from the Executive Council (under the GMO Act). Although at first, it appeared that it is all GM vaccines that contain live GMOs, there seem to be exceptions. For example, there is RotaTeq™, the anti-diarrhoea vaccine, developed by Merck which is a live oral attenuated pentavalent vaccine containing five bovine-human strains[43] and is now commercially available. There is also a potential HIV vaccine which uses the Venezuelan encephalitis virus vaccine. The specific grounds on why these are excluded need to be clarified.

Recommendation:

- that the Department of Agriculture makes available on its website the criteria that determine which GM vaccines require permits and which do not.

12.3 Tracking the applications

It is a difficult and time-consuming process tracking the different permit applications and their progress. The regulatory bodies, the Executive Council (EC) and the Medicines Control Council (MCC), have different systems and there appears to be no easy way of linking the two systems. The MCC has, for each clinical trial, a protocol number, an MCC Database Tracking number, an MCC reference number and the submission date. The Executive Council has a number for the trial, which is referred to in the Executive Council minutes and is also reflected on the Department of Agriculture (DoA) website on the "Permits approved" list. There is also a different numbering system for the actual permits for the import or use in clinical trials.

The Department of Health has a website for the South African National Clinical Trial Register (http://www.sanctr.gov.za/), but none of the GM clinical trials could be found there.

The permits for the GM clinical trials are listed on the DoA's website (www.nda.agric.za), but it is a convoluted path to get to them. One needs to go to "Regulatory and other services" and from there to "Genetic Resources" to "Plant" to "Plant Genetic Resources" to "Genetic control" (see GMO permits issued).

Recommendations:

- that the GM clinical trials are recorded on the South African National Clinical Trial Register
- that the "Biosafety Clearing House" on the DoA website becomes a functional item and that the GMO permits (including those for GM clinical trials) are listed here. This would be much simpler, than trying to find a medical trial in a section under "Plant Genetic Resources".
- that there is a link between the tracking system of the two regulatory bodies, the MCC and the EC
- that there is a link between the reference numbers used in the Executive Council minutes and the GMO permit numbers.

12.4 Access to Information

It is difficult to access information on many levels. First, it is difficult to find out what GM vaccine clinical trials are being planned. The public notification in terms of the GMO Act, 1997 (Regulation 6), states that the notification must be published as a standard notice in the print media in at least 3 newspapers circulating in each area where the proposed release will take place. However, South Africa is a large country with many languages being spoken – it is easily possible for a trial release planned in a rural part of the country not to be in a national paper, equally it is easily possible for a trial release planned in a rural part of the country not to have the public notification written in an African language.

Second, if one wants information on a clinical trial of a GM vaccine, whether proposed, current or completed, one needs to make an application using PAIA (Promotion of Access to Information Act) to the Department of Agriculture. This can be a time consuming and expensive process for a non-governmental organisation. It may also not provide all the necessary information. For instance, the information that is given to the participants who will be vaccinated, is not part of the documentation that the Registrar of the GMO Act receives. Information that is deemed "Confidential Business Information" (CBI) is also "blocked out" from the application.

For this booklet, a PAIA application was made to the Department of Agriculture for information relating to the import and clinical trials of GM human vaccines on 17 August 2007. The information was received two months later. One attempt to use PAIA to access information from the Department of Health (Registrar: Medicines)

for the Merck HIV vaccine (MRKAd5 HIV-1 gag/pol/nef) trial was unsuccessful. A PAIA application was made on 8 December 2006 for access to the information that will be given to the participants as well as the Prior Informed Consent (PIC) component of the application. Despite numerous attempts to follow this up, there was no success. Eventually, the applicant of the GMO clinical trial, Prof. Glenda Gray kindly made some of this information available, but it was not possible to get it through the formal routes.

Recommendations:

- that there is a section in the Biosafety Clearing House (on the DoA website) that lists all the applications that have appeared in public newspapers. Part of the procedure that the applicant must follow, could be to make this information available to DoA as soon as the public notice appears in the newspaper.
- that the entire application (excluding Confidential Business Information) is placed in the Biosafety Clearing House section.
- that the application fees for permits should be increased to cover the costs of placing information quickly and in an accessible manner in the public domain.
- that the regulatory authorities, not the applicant, must decide on what is Confidential Business Information (CBI) and that there is consistency in the way that CBI is applied
- that the information that will be given to the participants in the clinical trial and the Prior Informed Consent component is not regarded as CBI.

12.5 Monitoring trials

There is very little information in the public domain that details the progress and conclusion of GM vaccine clinical trials. The only trial that has received much publicity is the Merck HIV vaccine trial (MRKAd5 HIV-1 gag/pol/nef), also known as the Phambili trial, halted in August 2007.

There are also an increasing number of conditions attached to every permit given for the use of GM vaccines. It would be very helpful for applicants and civil society to see how these conditions have been met and to have easy access to this information, i.e. not to have to go through the Promotion of Access to Information Act.

There are also instances where the African Centre for Biosafety (ACB) has made a detailed submission to the Registrar of the GMO Act. The applicant was

then requested, by the Registrar, to address the issues raised and did so in a lengthy response. However, it was only as result of a personal meeting with the applicant (Prof. Glenda Gray), that one was made aware that a response existed. After several requests to the office of the Registrar of the GMO Act, the applicant's response was eventually found and sent to ACB.

Recommendations:

- that the Executive Council (EC) records the beginning and end of each clinical trial including the successes/failures at the completion of the trial. (The EC minutes are available on the DoA website.) There could also be a link to the Biosafety Clearing House.
- that if an applicant is requested to respond to a submission, that the response is then made available to the organisation making the submission.

12.6 Executive Council minutes – follow up

Working through the Executive Council minutes (available on the DoA website), there are some encouraging statements, listed below, that show the intention of placing more information in the public domain. Unfortunately it was only possible to review minutes up until January 2008, as at 22 October 2008, no other minutes for 2008 were available.

17 August 2006
Item 8.4 (i) The Council noted Mr Durham's idea that in promoting public awareness and understanding, having a document available that explains why a particular event has been approved, will add value to the SA process.

Item 8.4 (ii) The Council noted that making such a document available will have resource and capacity implications. DST will submit a document for discussion at a future Council meeting.

4 October 2006
Item 6.1 (iii) Council resolved that the Registrar must approach Prof. Ames Dhai and request that she develops guidelines on ethics for biotechnology research that could be applicable within the framework of The GMO Act, 1997.

20 November 2006
Item 6.7 (ii) The Council indicated that engagement in the future with the MCC on policies and practices, would be useful".

17 July 2007
Item 6.5 Triclinium-07/009: Trial release of GM measles vaccine, MVA-mBN85B. (i) The Council raised concerns on why SA has been chosen as the first trial site in the world as it has a rather low incidence if compared to the rest of Africa.

18 September 2007
Item 5.7 Meeting with Registrar of MCC
(i) The Council noted that a meeting took place between the act. Registrar: GMO and the Registrar: Medicines Control Council (MCC) on 26 August 2007 as an information sharing session on clinical trials.
(ii) The Council noted that the Registrars agreed that synergy between their application processes needs to be found and the Registrar: MCC assigned two officials with whom the Registrar: GMO can liaise in this regard."

23 October 2007
6.2 WITS-07/020: Extended permit for trial release of MRKAd5 HIV-1 gag/pol/nef vaccine
(ii) "The council noted that the official notification was received from the applicant confirming the suspension of further trials in SA. It was concluded that the application be withdrawn and that the Office of the Registrar should follow up on further activities by the applicant through monitoring and inspection."

Recommendations:
- that there is follow-up on these matters and where possible information is put into the public domain, so that both GMO applicants and civil society can benefit from this.
- for the Executive Council minutes to be posted timeously.

12.7 Department of Health – unanswered questions

It was difficult to get an understanding of the different roles and functions of the Department of Health (DoH) and Medicines Control Council (MCC). Contact was made with helpful staff in two of the directorates under the Medicines Regulatory Authority which comes under the DoH. These were the Directorate of Clinical Evaluations and the Directorate of Medicine Evaluation and Research. Numerous attempts to make contact with the Registrar of Medicines were without success and ended up simply being a referral back to the two previously mentioned directorates. However, it seems that the questions present at the start of this study (see below) still stand and that it is in the office of Registrar of Medicines that answers will be found. Contact was also made with the Department of Health's representative on the Executive Council, Mr Dries Pretorius (Director: Food Control).

Questions to Department of Health

1. *What is the process that the DoH follows when having to comment on a GM human vaccine application sent to the Executive Council (under the GMO Act)? I understand from Mr Pretorius, who represents the Department of Health on the Council, that a recommendation would come from the DoH. For example, in the minutes of the EC of 18 September 2007 it states that the DoH recommends approval of Triclinium-07/009: Trial release of GM measles vaccine, MVA-mBN85B. What process would DoH follow in putting forward a recommendation and what sections would be involved? Would the same process be followed for GM TB vaccines and GM HIV vaccines?*
2. *Does the DoH have any authority over research into GM human vaccines in South Africa, or is it only at the clinical trial stage that the department becomes involved?*
3. *Is there a register of organisations / individuals in South Africa who are doing research and/or clinical trials on GM human vaccines?*
4. *In the EC minutes of 19 September 2007, mention is made of a meeting between the Registrar: MCC and the Registrar: GMO Act and that the Registrar: MCC assigned two officials with whom the Registrar: GMO Act can liaise with. Is it possible to say who the two officials are and in which sections of DoH they are found?*

Recommendations:
- to find a way to get answers to these questions
- that a diagram is compiled to show the roles and responsibilities of the DoH and the MCC in terms of GM human vaccine clinical trials

12.8 Biosafety concerns

The two applications that the African Centre for Biosafety have made submissions on, have revealed major concerns with the use of "live" GM viruses in vaccines.[44] [45] (see also 9.1 and 9.2 on page 27). However, these are only two of the clinical trials – there are many others, and there is not capacity to comment on all of them. A similar situation to that described in Traavik 2002[46] was found – that the definition in vaccinology is very narrow and that the safety research focuses on unintended and unwanted side-effects with respect to the vaccinees and not the potential ecological and environmental effects of these activities.

Listed below is a summary of the recommendations from the two submissions and some general recommendations:

Recommendations from ACB submissions
- that the Precautionary Principle is applied
- for a moratorium on clinical trials of AIDS vaccines based on adenoviral vectors
- for a moratorium on clinical trials with MVA vectored vaccines until satisfactory research-based answers provided to key risk related questions for scientific concerns to be addressed
- for information on the clinical trial that will be given to participants and the Prior Informed Consent (PIC) component of the application to be public information
- South African authorities are urged to make funding available for such studies, including funding for detection and mapping of orthopox viruses in domestic animals and wildlife.

General recommendations
- that the pool of experts that the Advisory Committee to the Executive Council uses is expanded to include independent experts in GM vaccine biosafety.
- for the Medicines Control Council to add "biosafety" to its list of listed skills (the

list includes expertise in toxicology and medicine safety, clinical pharmacology, biotechnology, pharmaceutics, internal medicine, virology, pharmaceutical chemistry, neonatology, paediatrics, immunology, veterinary science, complementary medicines and law)
- for a broad based biosafety approach that looks at the broader ecological and environmental impacts as well as the vaccinnees.

12.9 Public participation

In a context of:

- HIV/AIDS and TB pandemics in the country
- powerful interests at play
- public institutions involved in the roll-out of GM vaccine clinical trials
- clinical trials and pharmaceutical products are big money
- lack of public understanding about GM and GM human vaccines
- development of increasingly dangerous technology, e.g. the production of GM vaccines in plants (that could then impact on the environment, food security…)

civil society has an important watchdog role to play

conclusion

There are many important issues around GM human vaccines – ethical, environmental, human health issues and biosafety. The challenge and the need is to address these in a holistic rigourous way.

To do this there needs to be an effective synergy between the Executive Council under the GMO Act, the Department of Health and the Medicines Control Council. There is a urgent need for independent biosafety research, to increase capacity in the country and to enable the regulatory authorities (the Executive Council and the Medicines Control Council) to draw upon such work when they take their decisions on whether to approve the clinical trials or not. We need expert, independent advice. There is an urgency for civil society to become engaged with the issues at play. This is especially considering the context of GM vaccines – the HIV/AIDS and TB pandemics in the country, the public-private partnerships between research institutions and multinational pharmaceutical companies, the huge money spinners that pharmaceutical products represent and the lack of understanding by the public of the biosafety discourse relating to GM human vaccines. But to do this, information has to be available and easily accessible. It is unacceptable that South Africa as a signatory to the UN Cartagena Protocol on Biosafety does not post information on the Biosafety Clearing House (BCH – an international website portal) and that the BCH link on the DoA website is not functional.

The situation in the country is troubling – clinical trials with vaccines using live pox viruses and adenoviruses have been approved, the Phambili trials (GM HIV vaccine) were brought to an abrupt halt when the vaccine appeared not to prevent infection or reduce the levels of the virus and that participants may have increased susceptibility to acquiring HIV infection. And now on 28 November 2008, clinical trials have been approved for the clinical trials of the SAAVI GM HIV vaccine. The ACB re-iterates its call for an immediate moratorium on all clinical trials of AIDS vaccines based on adenoviral and MVA vectored vaccines until satisfactory research-based answers are provided to key risk related questions. This is a case for the Precautionary Principle.

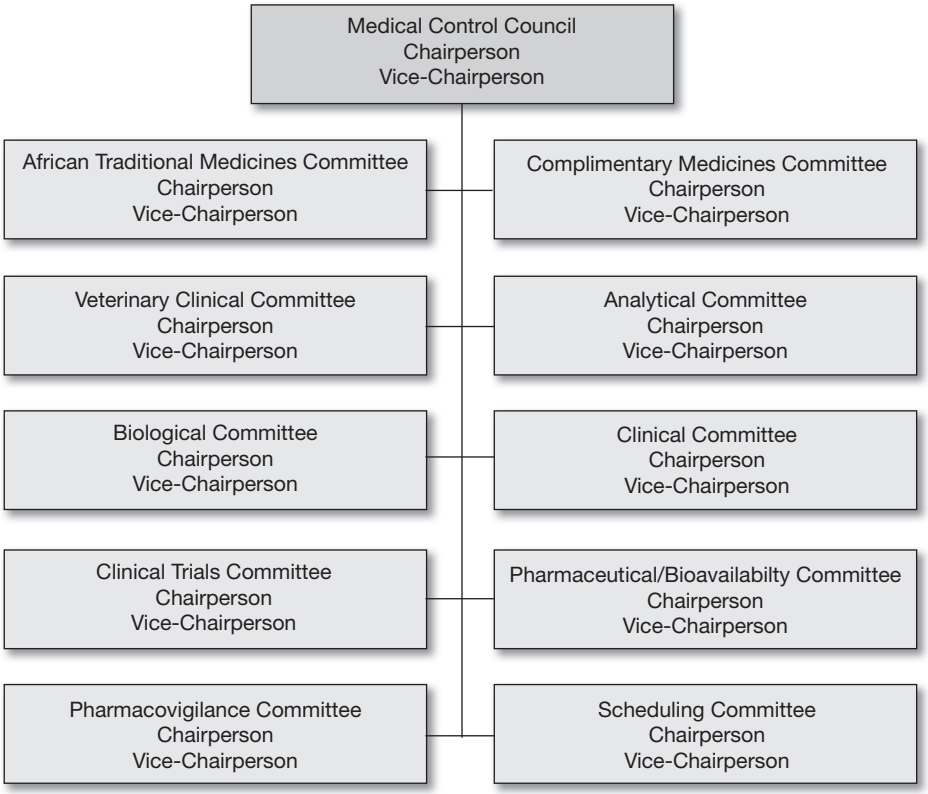
appendix 1

Members of the Advisory Committee (as of 29 January 2008)

Member	Institution
Dr G Gustav	University of the Witwatersrand
Dr HJ du Plessis	Agricultural Research Council - Infruitec
Prof. MA McGeoch	University of Stellenbosch
Ms FW Jansen van Rijssen	Groen Kloof
Mr S Cawe	Walter Sisulu University
Dr J Burger	University of Stellenbosch
Prof. A Williamson	University of Cape Town
Dr RH Westfall	Agricultural Research Council - Irene

appendix 2

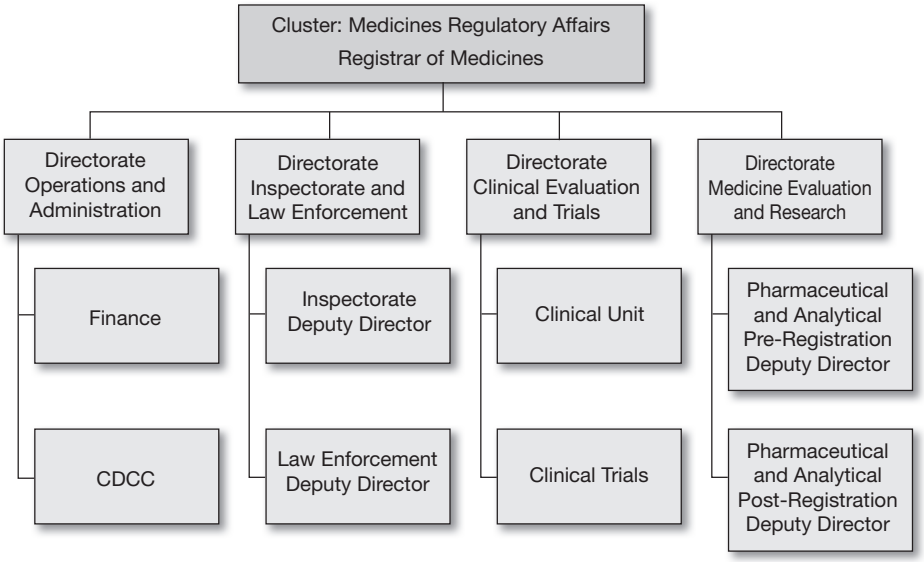
Structure of the Medicines Control Council



Source: Medicines Control Council website[47]

appendix 3

Structure of the Medicines Regulatory Authority



Source: Medicines Control Council website[48]

appendix 4

National Health Research Ethics Council

The National Health Research Ethics Council website details the current 14 NHREC members:

Prof D. du Toit (Chairperson)
Prof. A. Dhai (Deputy Chairperson)
Ms C. Slack, Mr N Ramuthaga, Dr M. Groenewald, Ms D. Biyela, Dr D. Pearmain, Dr L. Makubalo, Dr N. Khaole, Dr N. Khomo, Prof L. Mazwai, Ms M. Haskins, Prof. L. London and Ms E. Levendal.

The functions of the National Health Research Ethics Council are given as:

- Determine guidelines for the functioning of health research ethics committees;
- Register and audit health research ethics committees
- Set norms and standards for conducting research on humans and animals, including norms and standards for conducting clinical trials
- Adjudicate complaints about the functioning of health research ethics committees and hear any complaint by a researcher who believes that he or she has been discriminated against by a health research ethics committee
- Refer to the relevant statutory health professional council matters involving the violation or potential violation of an ethical or professional rule by a health care provider;
- Institute such disciplinary action as may be prescribed against any person found to be in violation of any norms and standards, or guidelines, set for the conduct of research in terms of Act no 61 of 2003; and
- Advise the national department and provincial departments on any ethical issues concerning research[49]

appendix 5

Table of permits issued by the Registrar of the GMO Act 2003 – 2007[50]

Date of approval	Company & permit no.	Vaccine	Purpose
15 August 2003	Triclinium Clinical Trial Project 17/3(2/03/090)	MVA with genes: gag, pol, nef & env (GM HIV vaccine)	Import
15 August 2003	Triclinium Clinical Trial Project 17/3(3/03/091)	MVA with genes: gag, pol, nef & env (GM HIV vaccine)	Clinical trial involving GMOs
22 April 2004	Triclinium Clinical Trial Project 17/3(2/04/058)	MVA with genes: gag, pol, nef & env (GM HIV vaccine)	Time extension of 17/3(2/03/090) for import
4 June 2004	MSD 17/3(2/04/075)	MRKAd5 HIV-1 gag (GM HIV vaccine)	Import for contained use
4 June 2004	MSD 17/3(3/04/076)	MRKAd5 HIV-1 gag (GM HIV vaccine)	Clinical trial involving GMOs
23 Sept 2004	MSD 173(2/04/130)	MRKAd5 HIV-1 vaccine (GM HIV vaccine)	Import time extension
15 December 2004	MSD 17/3(2/04/200)	MRKAd5 HIV-1 vaccine (GM HIV vaccine)	Import extension
2 February 2006	MSD 17/3(2/06/013)	MRK Ad5 HIV-1 vaccine (GM HIV vaccine)	Import extension
October 2004	Cato Research 002 17/3(2/04/159)	VRx496 (HIV)	Import
October 2004	Cato Research 002 17/3(3/04/160)	VRx496 (HIV)	Clinical trial involving GMOs

Date of approval	Company & permit no.	Vaccine	Purpose
15 July 2005	17/3(2/05/076)	MVA85A (GM TB vaccine)	Importation of GMO
15 July 2005	17/3(4/05/077)	MVA85A (GM TB vaccine)	Clinical trial involving GMOs
15 June 2006	Triclinium 004 17/3(2/06/042)	VRC-HIV DNA 16-00-VP and VRC-HIV ADV 14-00-VP (GM HIV vaccines)	Import
15 June 2006	Triclinium 004 17/3(4/06/043)	VRC-HIV DNA 16-00-VP and VRC-HIV ADV 14-00-VP (GM HIV vaccines)	Clinical trial involving GMOs
21 November 2006	Wits 017 17/3(2/06/293)	MRKad5 HIV-1 gag/pol/nef (GM HIV vaccine)	For import
21 November 2006	Wits 018 17/3(3/06/294)	MRKad5 HIV-1 gag/pol/nef (GM HIV vaccine)	Clinical trial involving GMOs
21 May 2007	Wits 019 17/3(4/07/096)	MRK HIV-1 gag/pol/nef vaccine (GM HIV vaccine)	Clinical trial involving GMOs
2 March 2007	Triclinium 17/3 (2/07/022)	AERAS-402 (GM TB vaccine)	Import
2 March 2007	Triclinium 17/3 (4/07/023)	AERAS-402 (GM TB vaccine)	Clinical trial involving GMOs
January 2007 (subject to MCC approval)	Triclinium 006	VIR20 vaccine (GM HIV vaccine)	Import and clinical trials
29 May 2007	Triclinium 17/3(2/07/106)	MVA85A (GM TB vaccine)	Import
29 October 2007	Triclinium 17/3(4/07/107)	MVA85A (GM TB vaccine)	Clinical trial involving GMOs

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