THE JENNER INSTITUTE
DEVELOPING INNOVATIVE VACCINES

UNIVERSITY OF OXFORD

PDA / IMB Conference July 2012

The Clinical BioManufacturing Facility
Our Experiences Manufacturing
Adenoviral Vectors for Human Use

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Qualified Person Clinical BioManufacturing Facility
University of Oxford

Clinical BioManufacturing Facility

- Background to the Clinical BioManufacturing Facility (formerly the Therapeutic Antibody Centre)
- Platform change from manufacturing monoclonal antibodies to manufacture of gene therapy products and the challenges we faced
- Portfolio of products manufactured to date and update of clinical use
- What have we learnt, what does the future hold

University of Oxford
Manufacturing for First in Man Clinical Trials

TAC History (Monoclonal Antibodies)

- 1995 The University of Oxford has new GMP facility for the production of Investigational Medicin Products (IMPs) to produce monoclonal antibodies and related biologics.
- 2004 First academic facility to obtain a MHRA Manufacturing Authorisation for IMPs post EUCTD
- TAC products have supported more than 5,000 patients in clinical trials worldwide.
- Star product Alemtuzumab estimated market product in peak year 2016 is $0.5 -$2 BILLION!
- 2-3 other antibodies still in phase III clinical trials -with billion dollar plus sales potential

TAC to CBF Transition (Viral vectored Vaccines and Therapies)

- Nov 2005
  Decision to move to manufacture Viral Vectors and transfer to NDM Jenner Institute
- 2006
  Update of MHRA Manufacturing Authorisation to manufacture Gene Therapy Products
- 2007
  Feb first product filled for clinical use
  Building work to allow manufacture of different viral vectors
  Oct 2007 first volunteer immunised
- Today
  10 batches vaccines in phase I/II clinical trials worldwide.
  2 manufactured and awaiting QC / QP release, others in pipeline
  vectored vaccines are where monoclonals were 15 years ago

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DEVELOPING INNOVATIVE VACCINES

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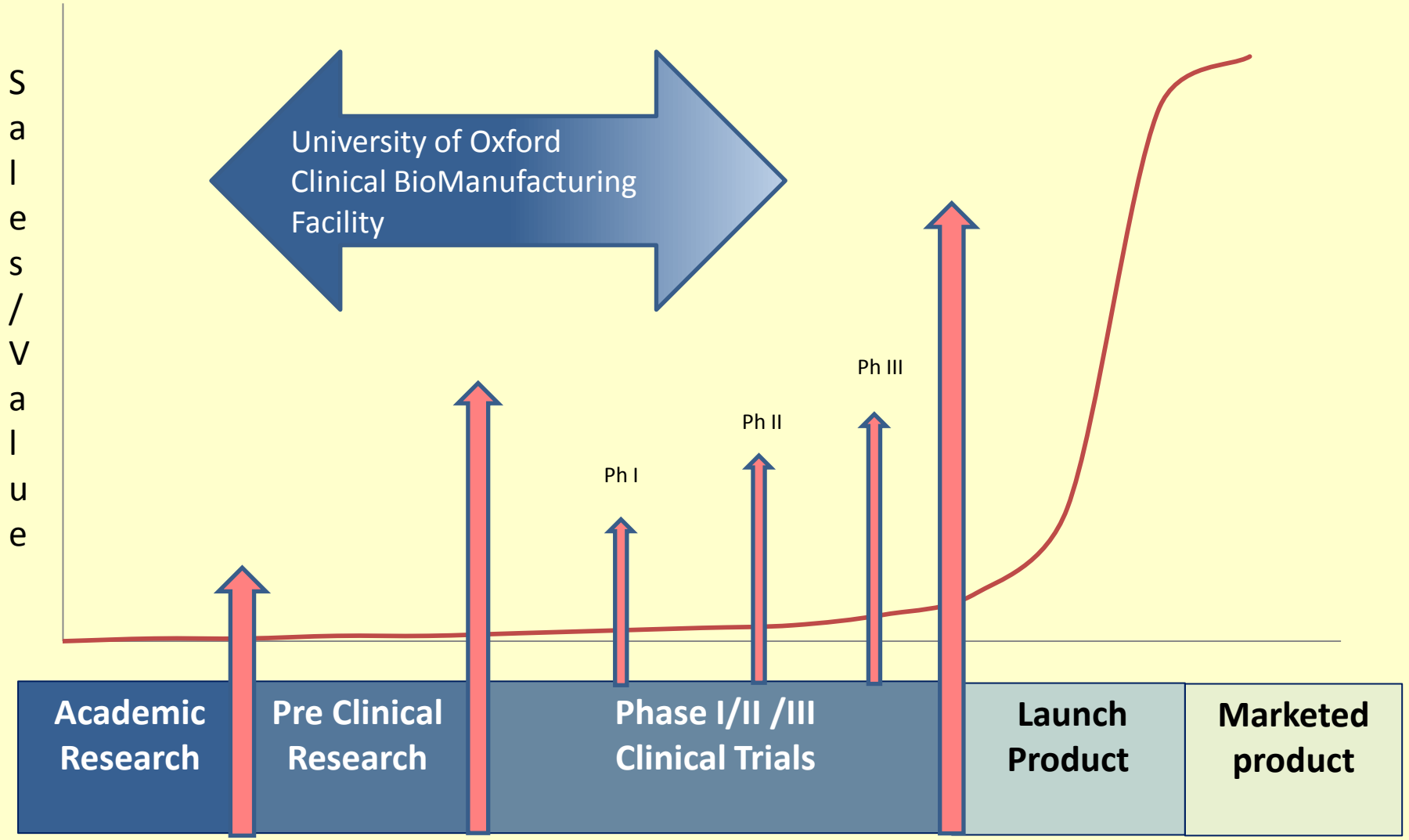
Old Rd Campus Building Research Labs (ORCB)

Clinical BioManufacturing Facility (CBF)

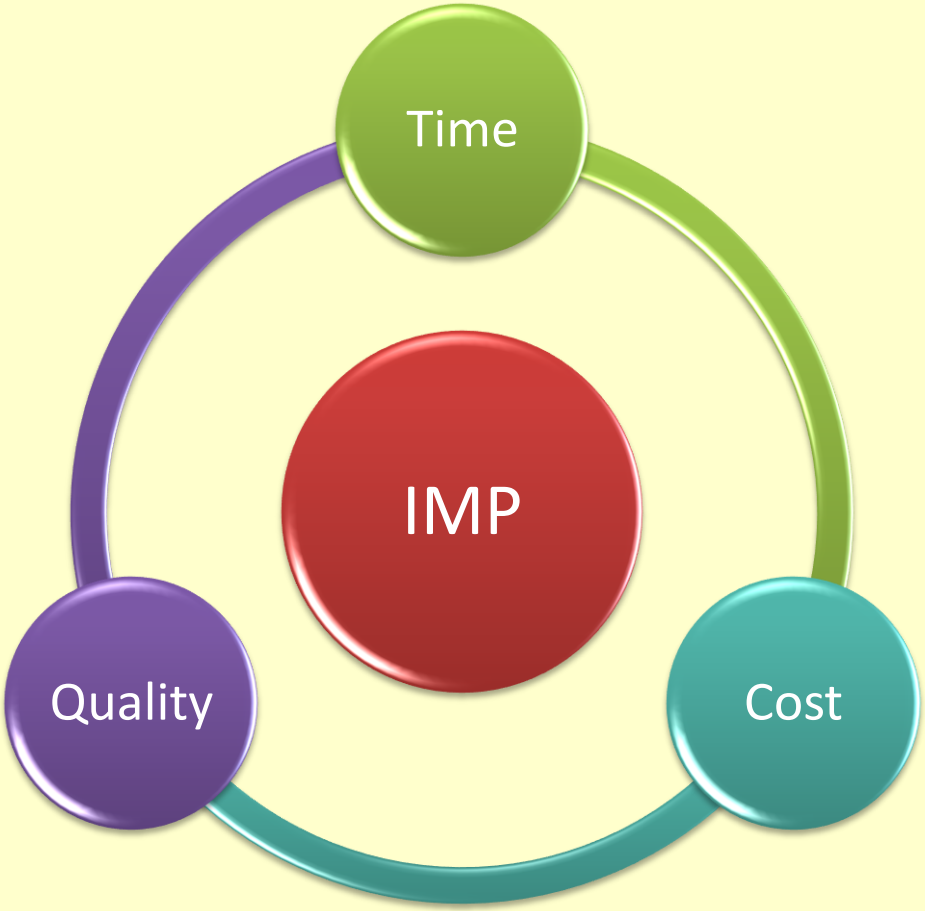
Clinical Centre for Vaccinology and Tropical Medicine (CCVTM)

Translational Research -The Valley of Death

Showing Milestones for Gene Therapy Products



Checks and Balances



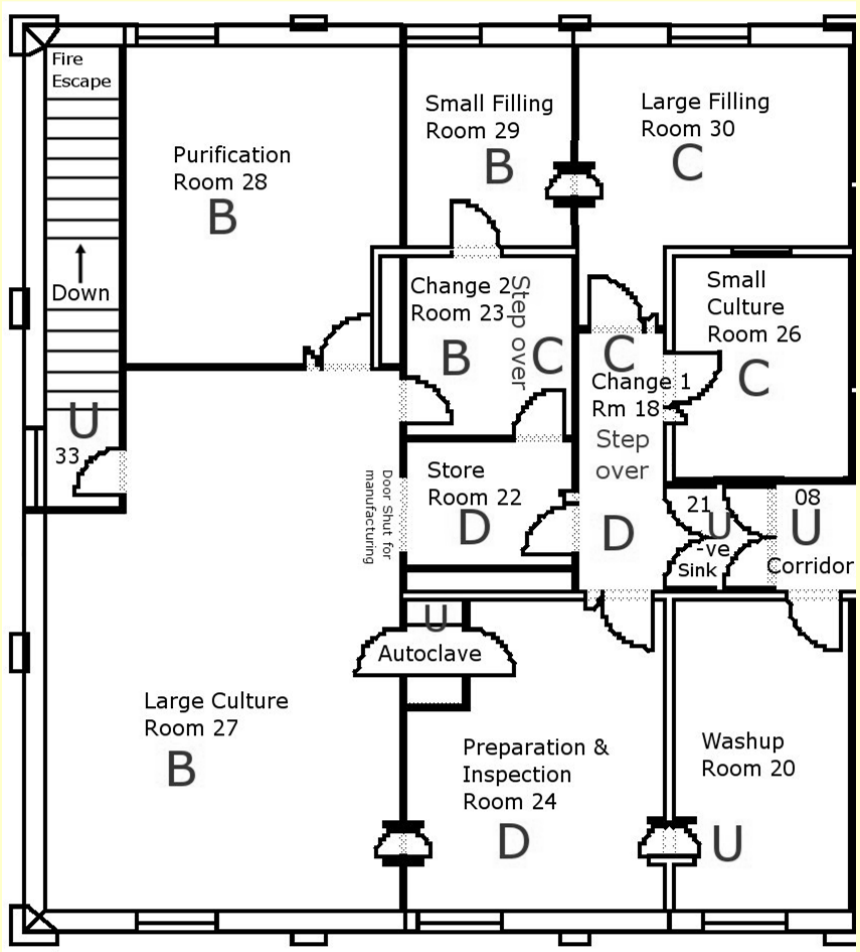
What are priorities?

- Speed to first in man?
- Smooth to manufacture?
- Short term costs?
- Long term costs?

Consider:-

- Scalability
- Bridging studies
- Multinational requirements
- Failure in manufacturing
- Failure at efficacy

Clean Room Layout



Changes to large culture – Upstream processing

- Monoclonal Antibodies

- Viral Vector Manufacture

Downstream Processing

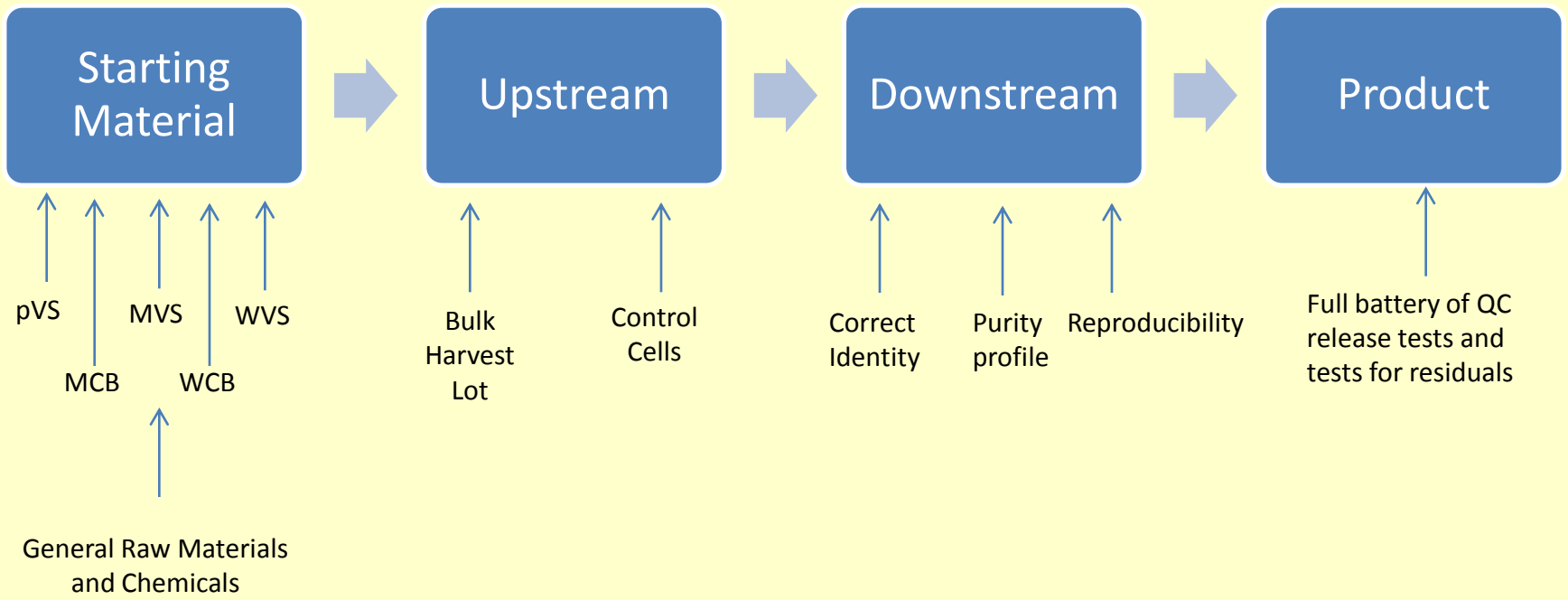
- Antibody Downstream Processing

- Viral Vector Downstream Processing

Advanced Therapy-

Viral Vectors, Cell Therapies

Differences/consistent approach required?



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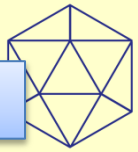
Starting Material

TRACEABLE



VIRUS			
Where was it isolated?	Primary isolate		
	Molecular clone		
	Synthetic DNA		
Where has it been grown?	Cells	Source	
		Labs	
		Tested	
		Traceable	
	Reagents	FBS	Gamma Irradiated
			Tested
		Trypsin	animal
			recombinant
		other supplements	
Other virus being grown concurrently?	Academic		
	Pharma		
	Biotech		

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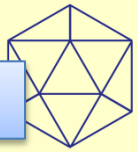
Starting Material

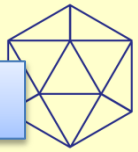
TRACEABLE



CELLS			
Source?	Primary cells	Species	
	Cell line	Human vs animal	Organ
	Previous use	Existing cell substrate	
Supplements?	Recombinant	Source	
		Labs	
		Tested	
		Traceable	
	Animal derived	FBS	Gamma Irradiated
			Tested
		Trypsin	animal
			recombinant
		other supplements	
Other factors?	Scale		
	Reliability of supply		
	Shelf life		

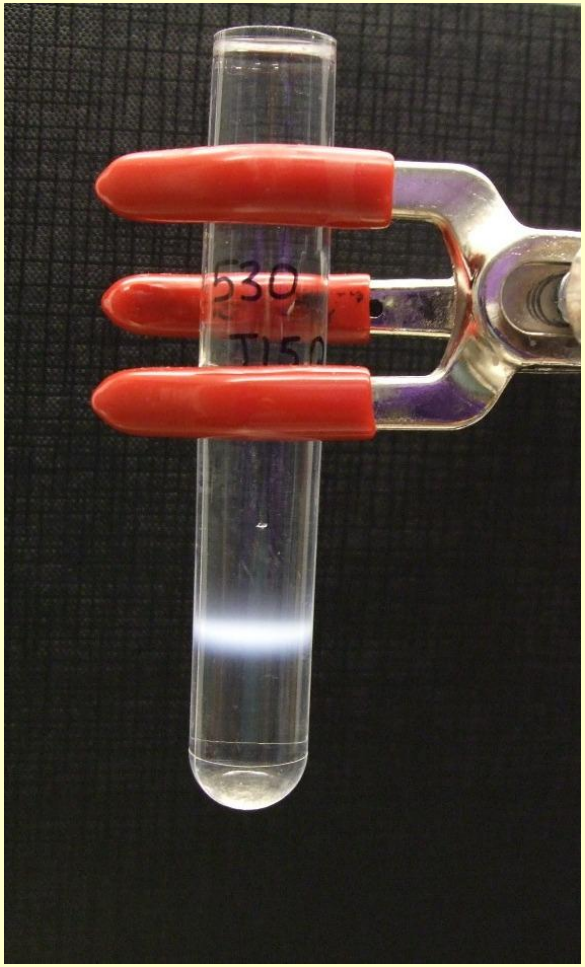
Starting Material

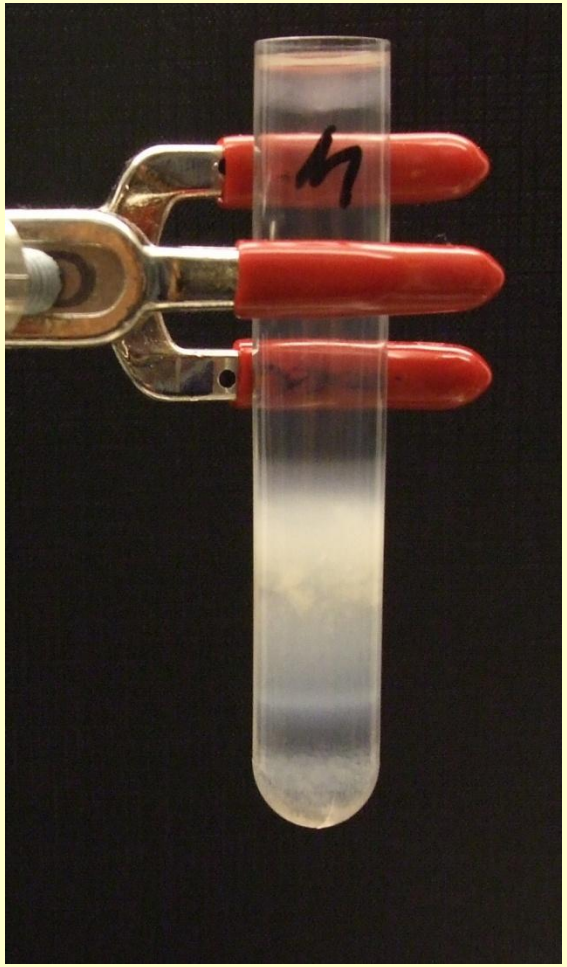
TRACEABLE

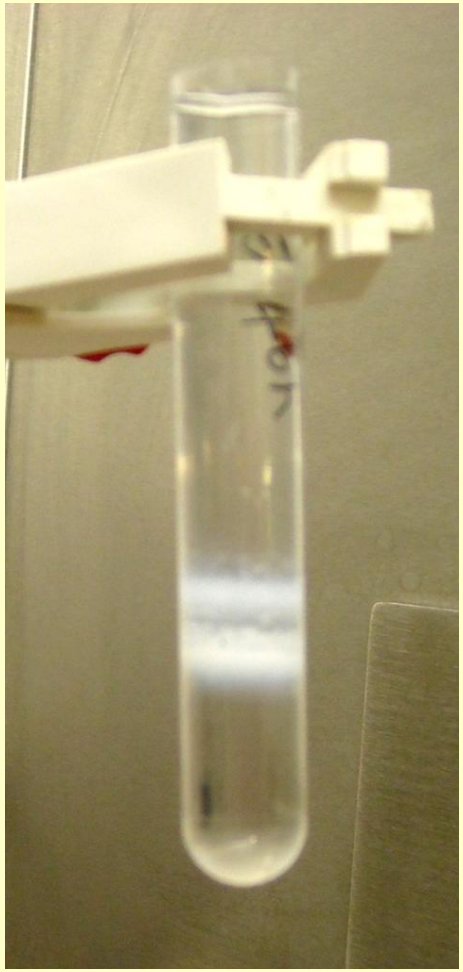


REAGENTS			
Media?	Chemically defined		
	Synthetic		
	Off the shelf		
Media?	Cells	Source	
		Labs	
		Tested	
		Traceable	
	Reagents	FBS	Gamma Irradiated
			Tested
		Trypsin	animal
			recombinant
		other supplements	
	Supply		
	Shelf life		
	Known hazards		

Purification of Adenoviral Vectors and some of problems encountered







Characterisation of GMP Adenovirus Vector Starting Material

Mycoplasma

Endotoxin by LAL assay

Sterility

Identity & Flank to Flank PCR

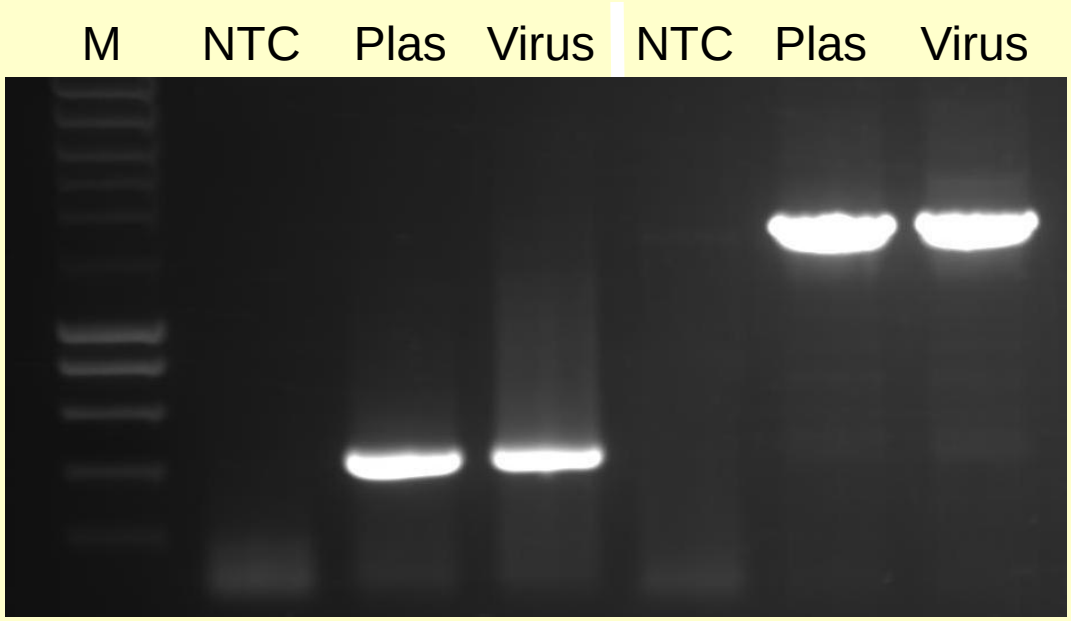
Contamination with Non-Viral Plasmid Sequence (NVPS)

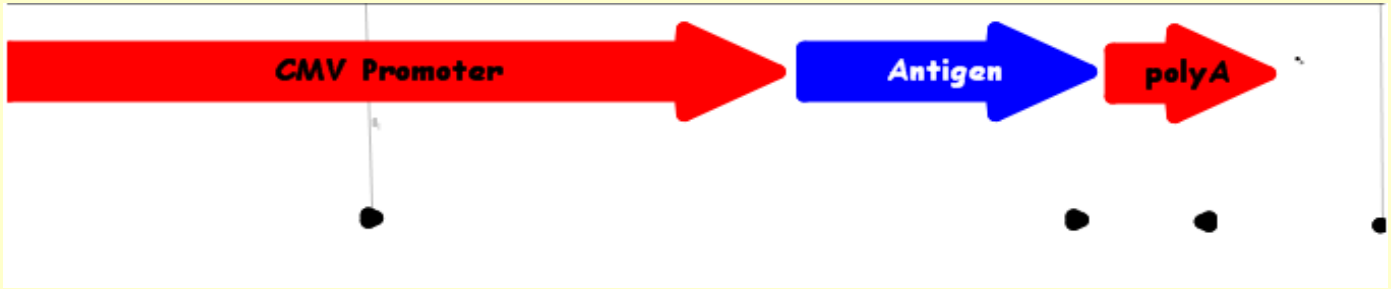
DNA sequencing of the antigen

Genetic Stability

Characterisation of GMP Adenoviral Vector Starting Material

Identity and Flank to Flank PCR





Characterisation of GMP Adenoviral Vector Starting Material

Genetic Stability –method

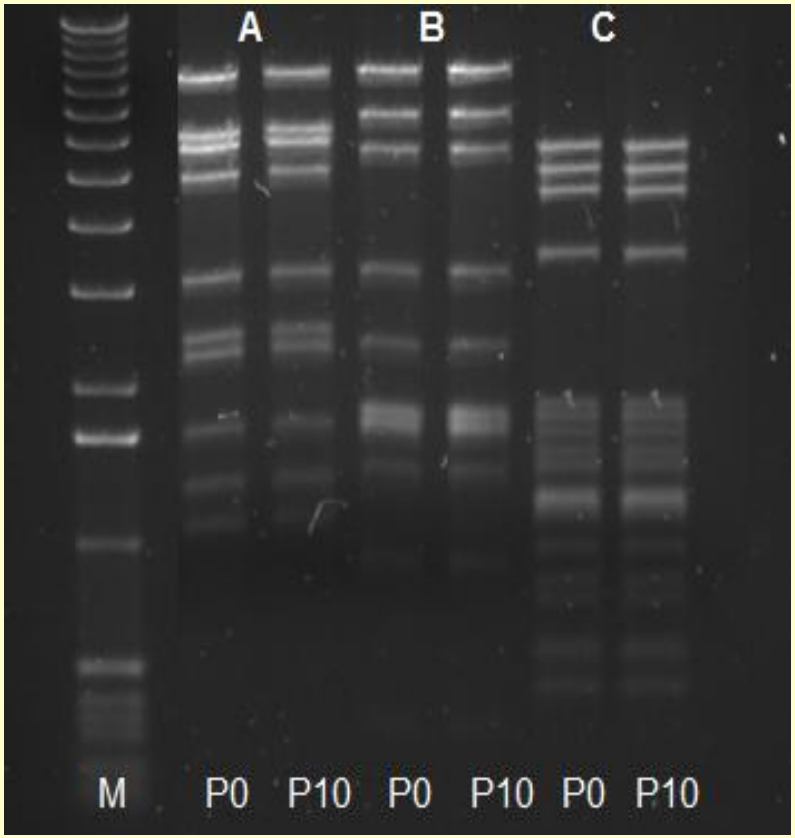
Passage virus 10 times in appropriate cell line

1. Grow up bulk prep of passage 0 and passage 10
2. Purify on Caesium Chloride gradients
3. Extract viral DNA using phenol/chloroform
4. Digest with Restriction Enzymes giving unique band patterns
5. Compare p0 and p10 virus stocks to the control plasmid

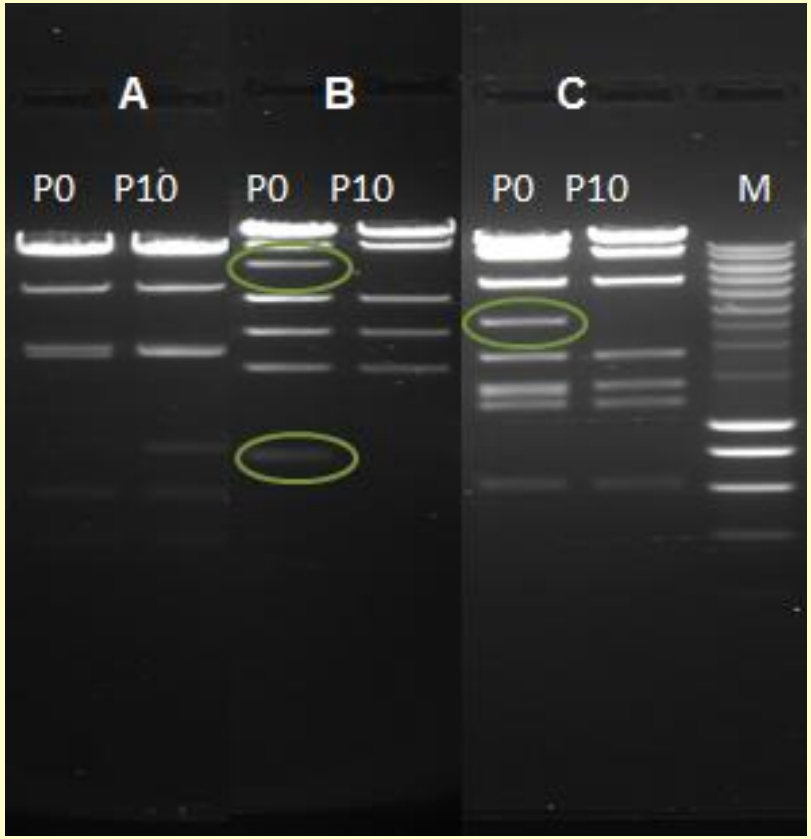
Characterisation of GMP Adenoviral Vector Starting Material

Genetic Stability

STABLE



UNSTABLE

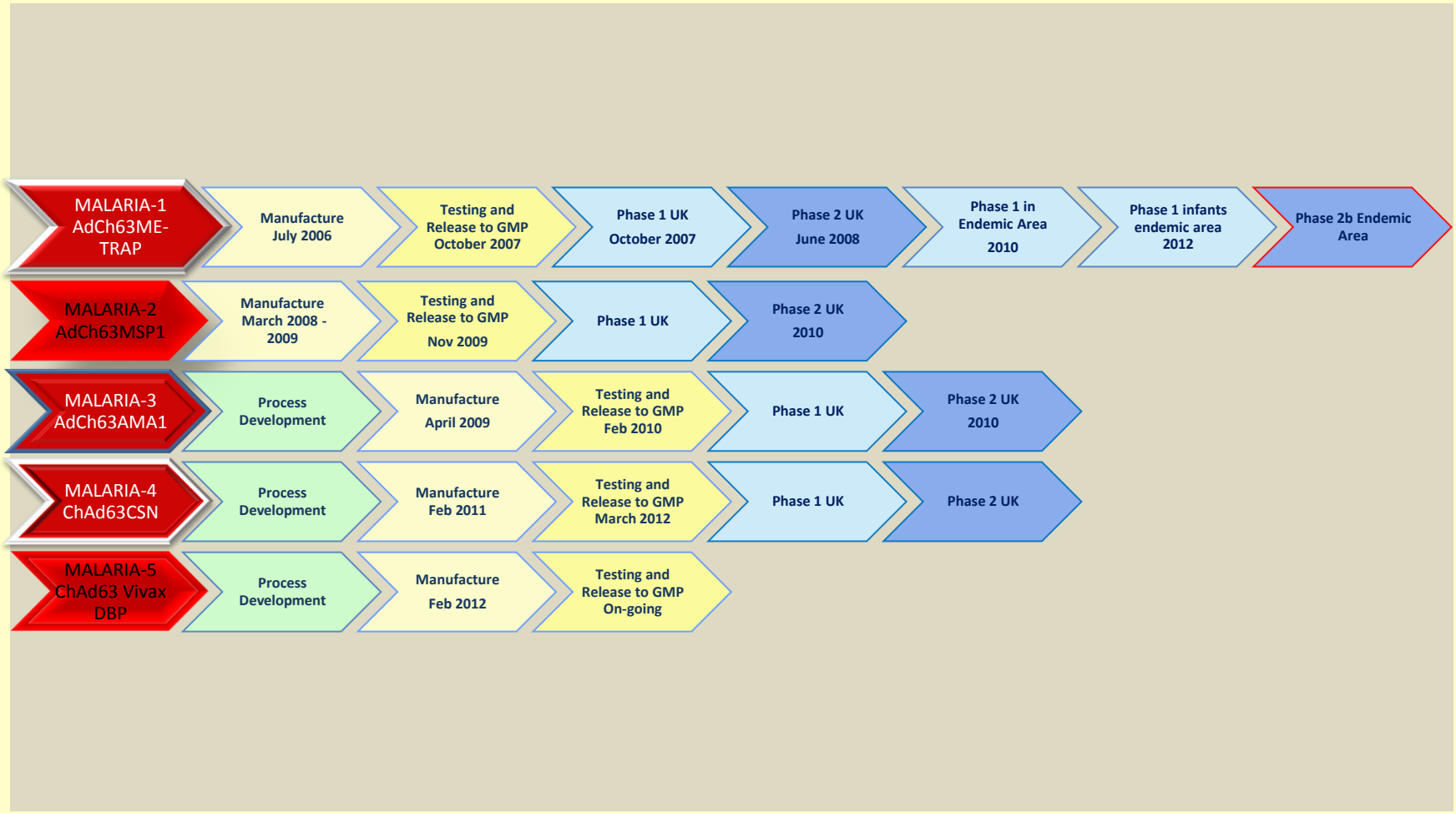


CBF Adenoviral Vector Manufacture since 2006 for First in Man Clinical Trials

6 disease areas **Malaria, Hepatitis C, Cancer, HIV , Flu** and **TB** for 2012)

Virus Backbone Human (3) chimp (3)	**Disease Areas (6)**	**Products (13)**	**Process Development**	**Manufactured (12 batches)**	**Test & Released to Clinical Trial (9 batches)**
ChAd63	Malaria Vaccine	AdCh63ME-TRAP		2007	
Ch3	Hepatitis C vaccine	AdCh3NSmut		2008	
Ad6	Hepatitis C vaccine	Ad6NSmut		2008	
ChAd63	Malaria vaccine	AdCh63MSP1		2009	
ChAd63	Malaria vaccine	AdCh63AMA1	2010		
ChAd63	Malaria Vaccine	AdCh63ME-TRAP	2010		
Ad5	WVSS of Cancer Therapy	VTP1	2010 WVSS not trial material		N/A
ChAd63	HIV vaccine	ChAdV63.HIVconsv	2010		
ChAd63	Malaria Vaccine	AdCh63ME-TRAP	2000 vials filled		2011
Ad5	Cancer Therapy	AdNRGM			on-going
ChAd63	Malaria Vaccine	ChAd63CSN	2012		
ChAdOx1	Flu Vaccine	ChAdOx1 NP + M1			on-going
Ad3/Ad11 Chimeric	PD of Cancer Therapy	ColoAd1	Completed 2011	N/A	N/A
ChAd63	Malaria Vaccine	ChAd63 Vivax DBP	on-going 2011	2012	TBD 2012
ChAdOx1	TB	ChAdOx1 85A	on-going 2011	TBD 2012	TBD 2012

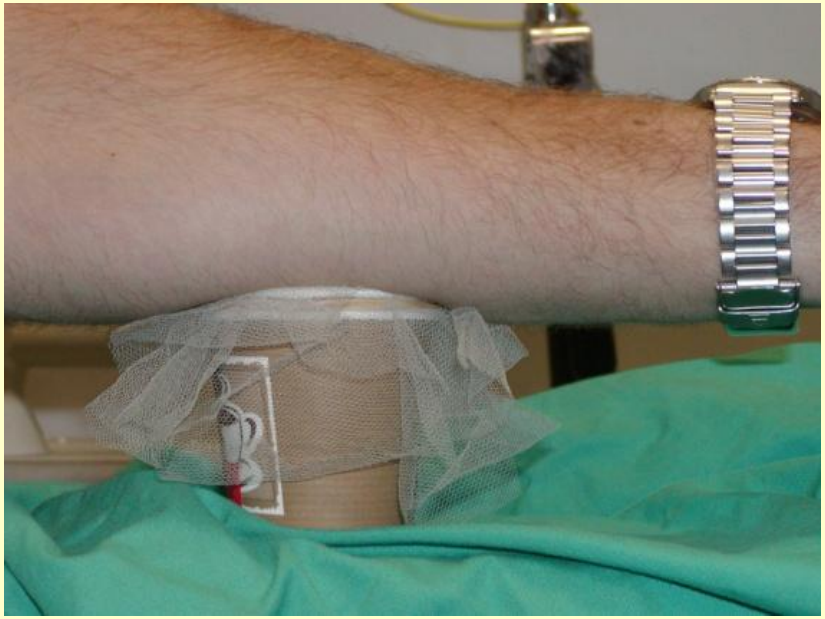
Progress and Timelines of Five new first in Man Vaccines for Malaria – July 2012



Progress of Five Malaria Vaccines Manufactured by CBF

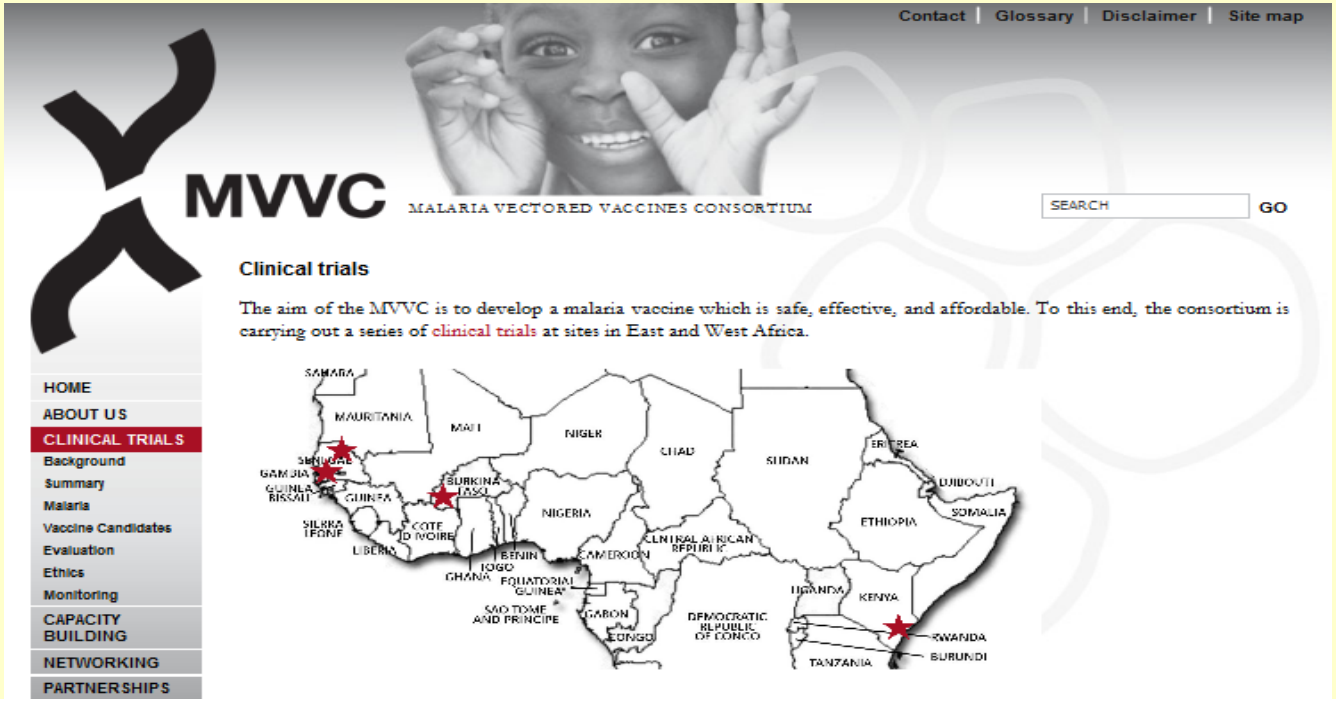
Malaria Vaccine	AdCh63 ME-TRAP	AdCh63 MSP1	AdCh63 AMA1	AdCh63 CS	AdCh63 DBP
Year manufactured	2006	2008/9	2009	2011	2012
First clinical trial	2007	2009	2010	2012	
Adults on Europe	137	45	48	12	0
Adults in Africa	106	0	0	0	0
Children in Africa	24	0	0	0	0
Infants in Africa	36	0	0	0	0
TOTAL	303	45	48	12	0

Day of Challenge…



- Five Infectious Mosquito Bites (score 2+ = >10 Pf spz)
- Monitor twice daily from day 6.5 - 14.5 and once daily from d15-21
- qPCR & thick smear microscopy for blood-stage parasitaemia at every time point

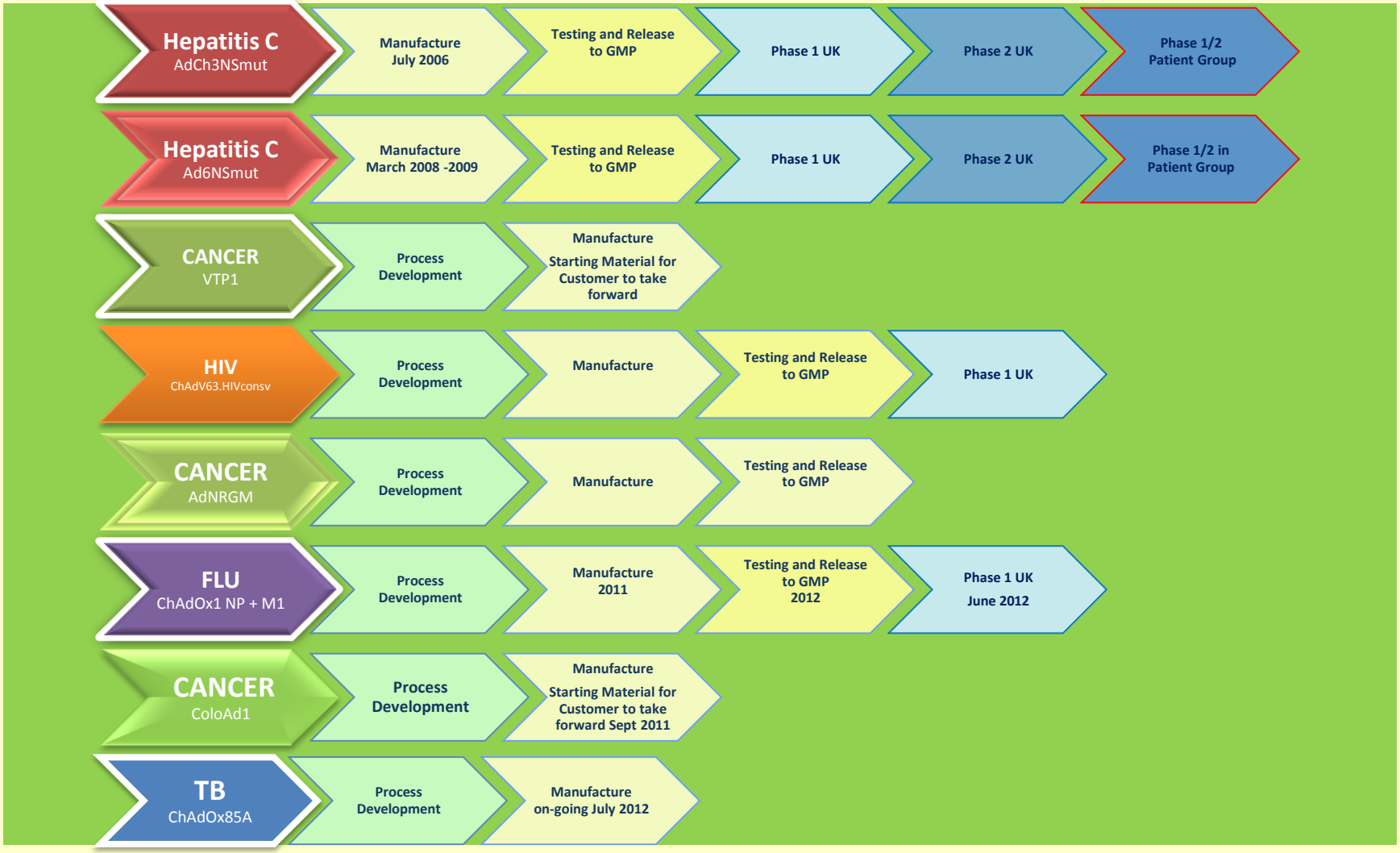
MVCC Sponsored Phase IIb Clinical Trial Sites using ChAd63 ME-TRAP in Africa



The aim of this study is to assess the safety, immunogenicity, and efficacy of the prime-boost regime against **clinical malaria in children aged 5-17 months.** To provide adequate statistical power, the study will enrol 1400 children across four sites: Basse (MRC **Gambia**), Ndoffane in **Senegal** (UCAD), Comoé in **Burkina Faso** (CNRFP), and KEMRI-Kilifi (**Kenya**).

http://www.euvaccine.eu/portfolio/project-index/mvvc

Progress and Timelines of Eight New potential First in Man Adenoviral Vectors for Other Disease Areas - July 2012



Conclusions

- Most of the translational research on ATMPs is coming from the academic community or small biotec companies and they often have no prior experience with GMP manufacturing requirements
- Process development studies are necessary to ensure successful GMP manufacture and it is never too early to consider pre-GMO requirements for ATMPs
- Essential to establish a dialogue with researchers and Regulatory Agencies early on
- Ensure researchers document research appropriately and retain all records to ensure full traceability
- CBF have successfully manufactured over 10 adenoviral vectors for first in man clinical trials
- The CBF have a model for supporting translational research where we can manufacture for proof of principal trials and remove some of the risks for future clinical development

Acknowledgements

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