EU approach to DNA and live recombinant vaccine regulation

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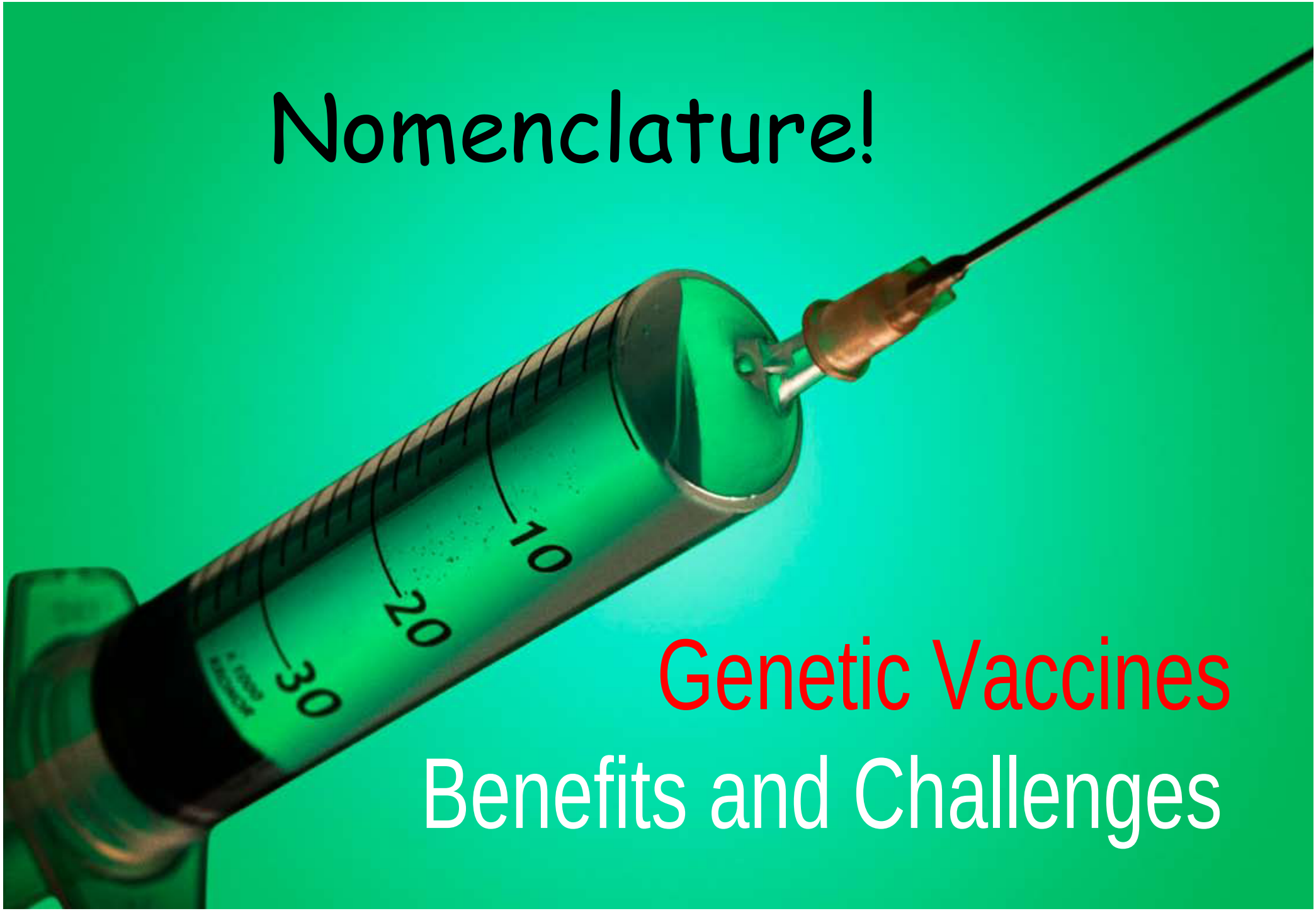
Aim of the presentation

- To consider new types of 'genetic' vaccines under development
  - DNA vaccines
  - Live recombinant vectored vaccines
- To define them, to consider their value and their impact on the environment
- To define how they will be regulated.

Nomenclature!



Genetic Vaccines

Benefits and Challenges

Genetic vaccines

- This term implies the vaccine is modifying or directly interacting with the genes of the recipient
- They do not, and there is no intention of them doing so (although there are always exceptions)
- The 'genetic' in genetic vaccines refers to the genetic engineering events that are used to create the vaccine
- This terminology is poor PR; it is misrepresentation and misinforms the public who should be the benefactors of such developments but who may be concerned about vaccines that might modify their genes

Nomenclature

- Much more appropriate and more scientific to refer to them individually as:

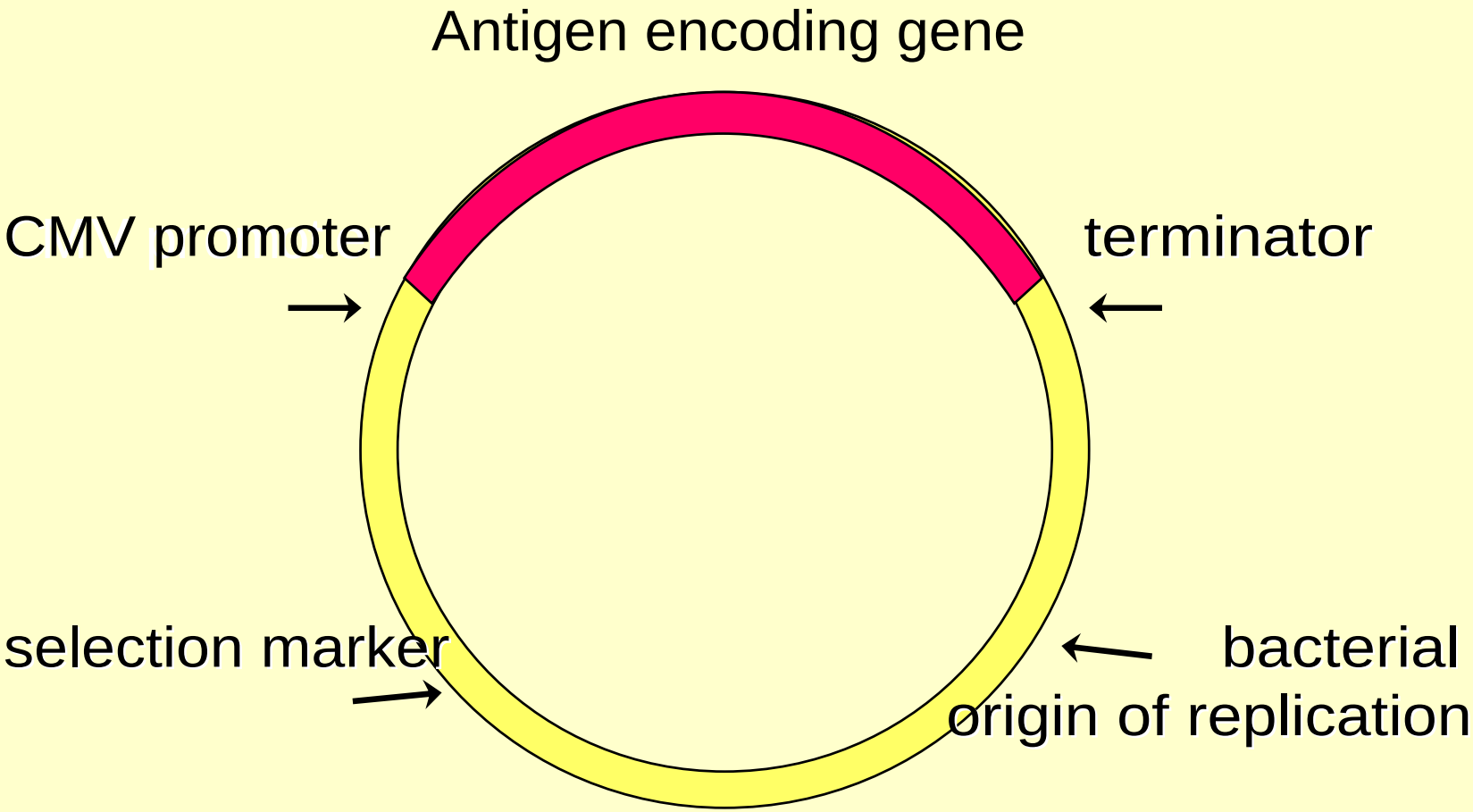
<u>DNA vaccines</u> (vaccines that are composed of DNA).

- there is nothing to be afraid of DNA – we ingest DNA constantly in foods, our cells breakdown and DNA circulates through our blood stream, and occasionally DNA/ RNA is administered parenterally via various bacterial or viral vaccines

<u>Live recombinant vector vaccines</u> (LRVV)

- similar to current highly acceptable live attenuated vaccines such as MMR, polio, etc. but where a virus/ bacterium (the vector) has been genetically engineered to express a foreign antigen (more later)

Bacterial plasmid DNA vaccine



Linear DNA vaccine

- linear expression cassettes

Promoter antigen encoding gene terminator

- DNA generated by PCR

Live recombinant vector vaccines

Vector (carrier)

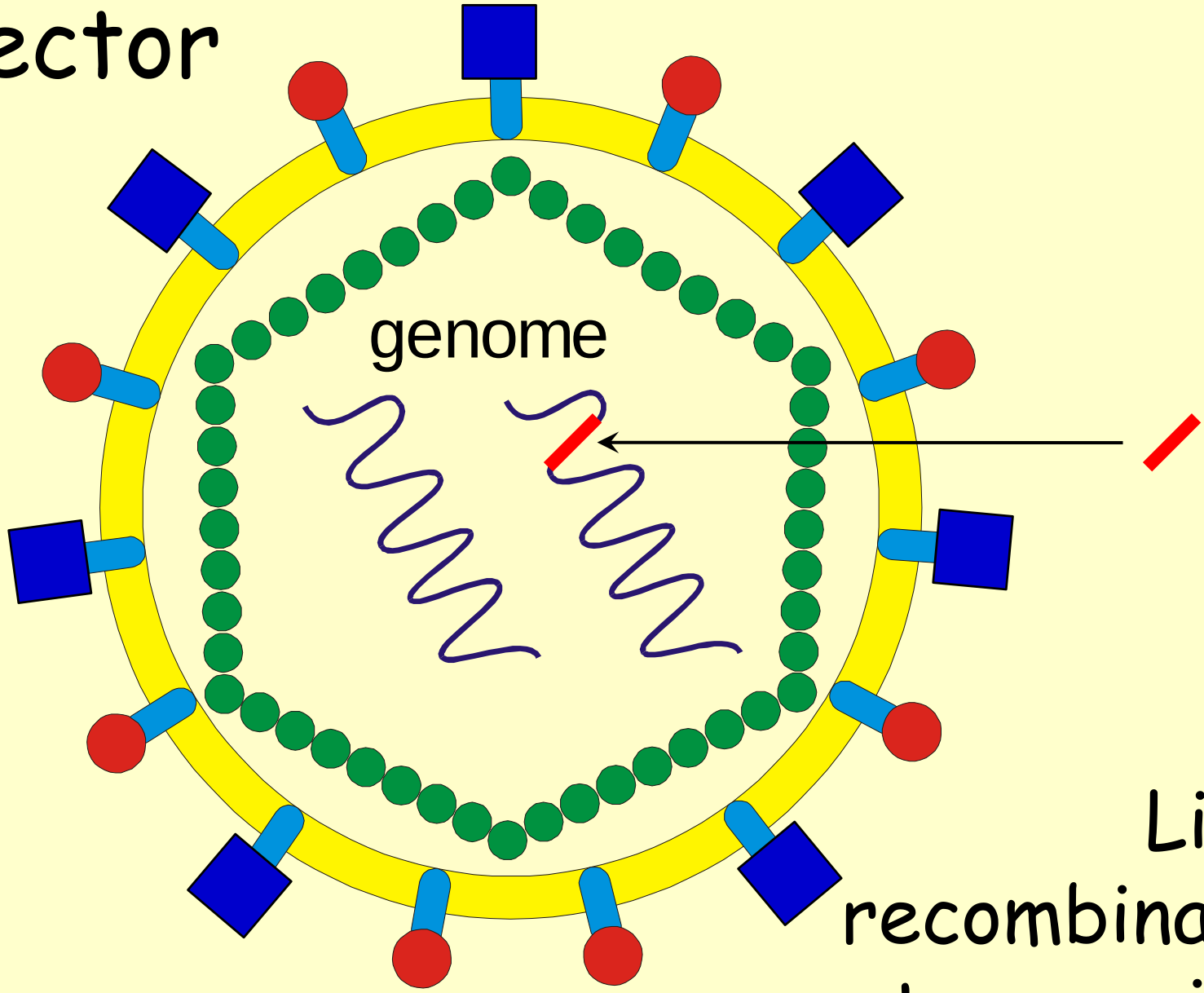
- Viral: pox viruses (MVA, avipox), adenovirus, yellow fever virus, measles virus
- Bacterial: salmonella

Heterologous (foreign) antigen

- Protein antigen from an infectious agent
- HIV, malaria, dengue, West Nile

Recombinant DNA technology is used to insert the gene encoding the foreign antigen into the vector

Vector



Live recombinant vector vaccine

Utility of these vaccines?

Potential for vaccines for diseases where vaccines don't exist, where there are difficulties in development, or where improvements are required, e.g. HIV, malaria, Dengue, West Nile virus, ebola, TB, pandemic influenza

DNA vaccines

- The potential of DNA remains to be proven in the development of human vaccines but from an immunological point of view, they have many of the positive features of a live attenuated vaccine but without any concerns of a live infectious agent

LRVV

- Current live (non-recombinant) vaccines e.g. MMR, polio, smallpox, varicella are highly efficacious
- LRVV act in the same way as live attenuated vaccines and many vectors in use are live attenuated vaccines, e.g. MVA, yellow fever vaccine

Veterinary vaccines

DNA vaccines

- West Nile virus (equine)
- Infectious haematopoietic necrosis virus (salmon)

LRVVs

- Purevax FeLV (canarypox vector)
- Vaxxitek HVT+IBD (herpes virus vector)

Environmental risks/benefits-1

Genetically Modified Organisms (GMO)

The environmental risk of a GMO is based on the likelihood of its unintended transfer or transmission to humans other than the intended person, to animals or to the environment at large, as well as the extent of its impact on the environment.

GMOs/ GMMs are regulated by two EU directives

'Contained Use' Directive 98/ 81/ EC (GMM's)

'Deliberate Release' Directive 2001/ 18 (GMO's)

Annex II - principles for the environmental risk assessment (ERA)

Environmental risks/benefits-2

DNA vaccines

- The active ingredient (DNA) is not a Genetically Modified Organism (GMO/ GMM) although the bacteria in which they are produced would qualify as a GMO/ GMM; Contained Use Dir. Applies for manufacture.

LRVV

- The active ingredient of a LRVV is a live, genetically modified infectious agent, typically a virus (most development in this area) or a bacterium
- A live recombinant vector vaccine is a GMO
- Deliberate Release Dir. applies and an ERA is required
- Shedding and the risk to non-vaccinees important

REGULATION (EC) No 726/2004
"...the authorisation and supervision of medicinal products..."

Annex

"Medicinal products to be authorised by the community

1. Medicinal products developed by means of one of the following biotechnological processes:

   - recombinant DNA technology"

   - ... ...

-> Centralised marketing authorisation by emea

European Medicines Agency

- EMEA
- Established 1995 / re-established 2004
- Regulation (EC) No 726/2004 (Title IV)
- Responsible for the protection and promotion of public and animal health through the evaluation and supervision of medicines for human and veterinary use
- Networking agency

CHMP

Committee for Human Medicinal Products

Expert advice is provided by Working Parties

- Vaccine (VWP)
- Biologics (BWP)
- Safety (SWP)
- Gene Therapy (GTWP)
- And several others

DNA Vaccine guidance

- EU – Gene transfer guideline (Q, S & E) (2001)
  - But DNA needs updating- esp. nonclincial and clinical aspects
  - New guidance being developed (Q, S & E) by VWP
  - CONCEPT PAPER on guidance for DNA vaccines CHMP/308136/07
- FDA – Considerations for Plasmid DNA Vaccines for Infectious Disease Indications 10/29/2007 (Q & S)
- WHO Guidelines for assuring the quality and nonclinical safety evaluation of DNA vaccines (2007)

DNA vaccines (WHO)

- Quality
  manufacture and control of bulk purified plasmid and final formulated vaccine
- Nonclinical
  DNA insertion
  Immunopathological reactions
  Autoimmune reactions
  Risks of genes encoding cytokines or co-stimulatory molecules
  Unwanted biological activity
  Expression of other gene sequences
- http://www.who.int/biologicals/publications/trs/areas/vaccines/dna/ Annex%201_DNA%20vaccines.pdf

Live Rec. Vector Vacc. guidance

- EU concept paper on the development of a guideline on live recombinant vector vaccines

  EMEA/CHMP/308139/2007
- Quality, nonclinical, clinical sections
- Guideline out for consultation, ~ spring 2009
- WHO informal consultation, December 2003

  "Characterisation and quality aspect of vaccines based on live viral vectors"

Clinical challenges LRVV

- pre-existing (if any) and post-vaccination immune response to the vector,
- might conceivably interfere with the ability of the construct to elicit the desired protective response against the foreign protein expressed.
- on the other hand there could conceivably be a positive benefit if there was an immune response to the vector, which would need to be considered as a secondary consideration for the overall vaccine product.

Other challenges of LRVV

- Extent and duration of vaccine shedding; potential for transmission of the live vaccine to contacts
- Potential for reversion of the viral vector to virulence
- Potential for recombination or reassortment with wild type agents that might co-incidentally occur in vaccinees around the time of dosing
- Genetic stability
- Change of tropism of vector vaccine
- Incidence of specific AEs that might reflect distribution of the vector to specific body sites
- Potential for integration of genes derived from the vector into the host genome
- Public acceptance?

Regulatory challenges

Can be and are being met:

- with a clearly defined regulatory pathway
- by careful and thorough scientific evaluation
- and by provision of guidance from those experienced in the field, including those developing such vaccines and regulators with experience in vaccine regulation