



Manufacturers expected contribution to the progressive control of Foot-and-Mouth Disease in South Asia

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GENERAL PRINCIPLES



- FMD CONTROL PROGRAMS
- FMD VACCINE PRODUCTION

FMD Control Programs

Vaccination is recognized as an important tool in **Foot-and-Mouth Disease (FMD) control**.

The role of **Manufacturers** for a **timely** supply of **affordable** and **fit-for-purpose** vaccines in **all** regions of the world is therefore pivotal.



FMD Vaccine Production

The production of such vaccines requires a profound **scientific** and **technical** knowledge and extensive **experience** in a number of fields:

- The Manufacturers must follow internationally accepted principles of **Quality Assurance** and **Good Manufacturing Practice** as a minimum prerequisite.
- They must also know how to **select** and **adapt** new vaccine strains, how to **cost-effectively** make vaccines out of them, at the required level of **potency** and **purity**.



EPIDEMIOLOGICALLY RELEVANT STRAINS



- EPIDEMIOLOGICAL VIGILANCE
- DEVELOPMENT OF NEW VACCINE STRAINS
- r_1 VALUE AS A TOOL FOR MONITORING FIELD STRAINS

EPIDEMIOLOGICAL VIGILANCE

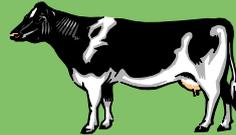
The use of the most appropriate vaccine as part of an integrated control program relies on an in-depth knowledge of the **virus strains circulating** in the **region**.

In that respect, OIE Regional Reference Laboratories play a significant role in **collecting** and **studying** field isolates, then **publishing** the epidemiological characteristics of these strains and **making them available** to manufacturers.



DEVELOPMENT OF NEW VACCINE STRAINS

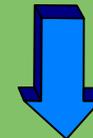
Collection of Field
Samples by Vet.
Authorities



Reference
Laboratory



Identification
& Official
Designation
of Isolate



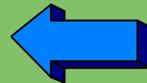
Official
Request
for Sample



TESTING & ADAPTATION

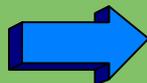
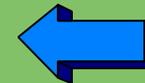
Production Unit

1. Production Yield
2. Replication Rate
3. Stability
4. Inactivation Data
5. Documentation



QC Laboratory

1. Cross Serology with Vaccine Strains by VNT
2. Replication rate in production and test cells
3. Documentation



FINAL PRODUCT CRITERIA
Antigenic Load & Potency

r1 VALUE AS A TOOL FOR MONITORING FIELD STRAINS (1/2)

Results of heterologous intra-serotypic serological tests (“r1 values”) have been extensively used for the evaluation of the **expected heterologous protection** against the current field isolates.

For that purpose, responsible manufacturers are expected to generate sets of **antisera** corresponding to their vaccine strains.

They also **monitor** these **field strains** regularly to assure that their vaccine strains (as well as the content of their antigen banks) remain up to date.

r1 VALUE AS A TOOL FOR MONITORING FIELD STRAINS (2/2)

Whenever a field strain with significantly low* r1 value against the vaccine strain **sustainably** circulates in the field, manufacturers should start the adaptation of this new strain, unless indicated otherwise by heterologous challenge studies (vaccine coverage might be **broadened** by using **high potency vaccine**, Brehm et al., 2008).

In an **endemic** situation, where large quantities of the same vaccine are routinely employed, there is clearly a significant value in matching the vaccine strain(s) to the field viruses **as exactly as possible** so that the vaccine program is optimized.

* (< 0.3 by Virus Neutralization Test according to IAH)



« IMMUNODOMINANT » STRAINS



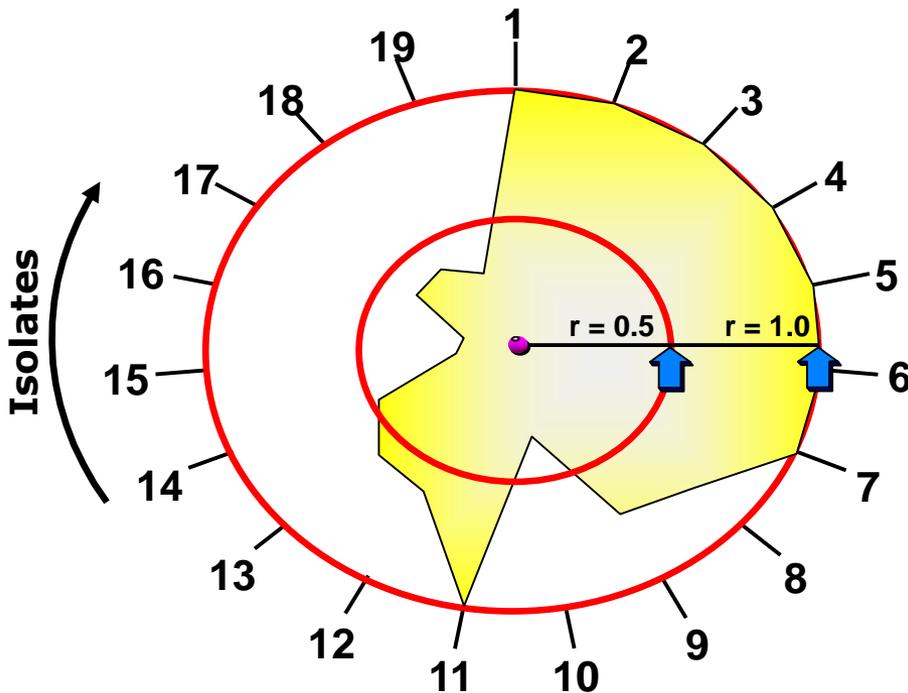
- WHAT IS AN « IMMUNODOMINANT » STRAIN?
- PRACTICAL CONSEQUENCES

WHAT IS AN "IMMUNODOMINANT" STRAIN?

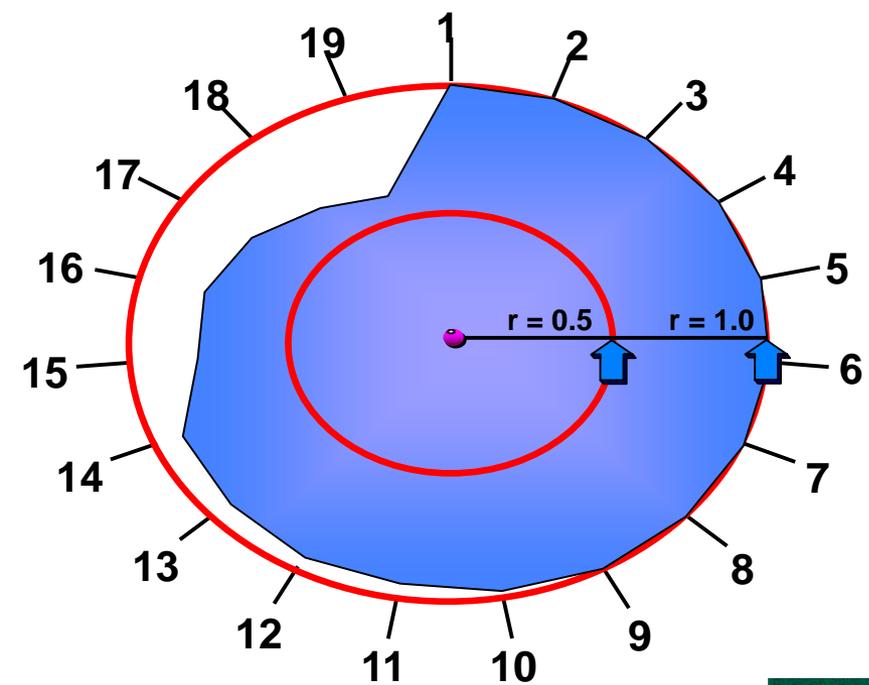
A more immunogenic strain with a broader cross-reactivity

Relative Reactivity of Vaccinated Cattle Sera with 19 Field Isolates from Saudi Arabia (Doel et al, 1995). Expressed as 'r1' Values.

O Manisa Vaccine Sera



O 3039 Vaccine Sera



If $r = 1$ then there is 100% homology between vaccine strain and field strain.
O 3039 Vaccine matches all field strains significantly better or equal to O Manisa Vaccine.

PRACTICAL CONSEQUENCES

- Beyond the need to match field and vaccine strains, the selection of “**immunodominant**” strains is of considerable importance, especially in the currently fast changing epidemiological environment of the Near and Middle-East.
- Most current vaccine strains older than 20 years have retained their value due to this characteristic.
- Clearly, the **isolate(s) chosen** by different manufacturers to adapt to tissue culture and the **methodology** used in the adaptation could result in fundamentally **different vaccine strains bearing the same generic name**.
- Of course, the probability of finding an “immunodominant” strain is directly proportional to the effort invested.



ADEQUATE POTENCY & TIMELY DELIVERY



- « HIGH » POTENCY VERSUS « REGULAR » POTENCY
- TIMELY DELIVERY

"HIGH" VERSUS "REGULAR" POTENCY

"HIGH" (>6 PD50) Potency vaccine have been proven to **protect cattle as early as four days post-vaccination** when tested by contact challenge.

They are particularly useful in **emergency situations** when vaccines are finished from antigens held in a bank and injected to naïve animals.

"REGULAR" (>3 PD50) Potency vaccine are recognized as **fit-for-purpose** when consistently used in **endemic settings** in view of controlling **clinical disease**.

TIMELY DELIVERY

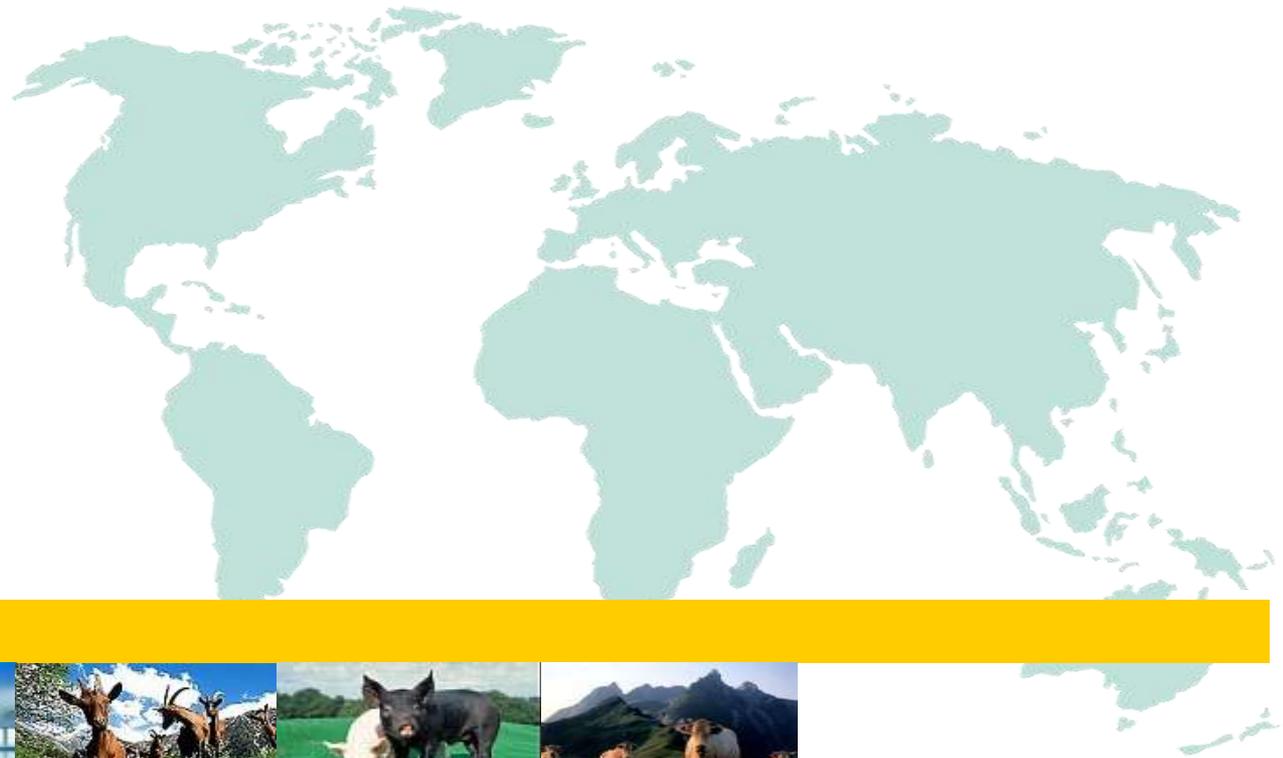


The cryostorage of concentrated, purified FMD antigens offers many advantages in relation to **emergency vaccine usage in regions free of FMDV**, but also for **endemic regions**:

- Long term **stability** of antigen
- Only used **if needed**
- Vaccine **rapidly** made

Flexibility to formulate according to the circumstances notably:

- Potency
- Dose volume
- Adjuvant
- Valency
- Packaging
- Batch size

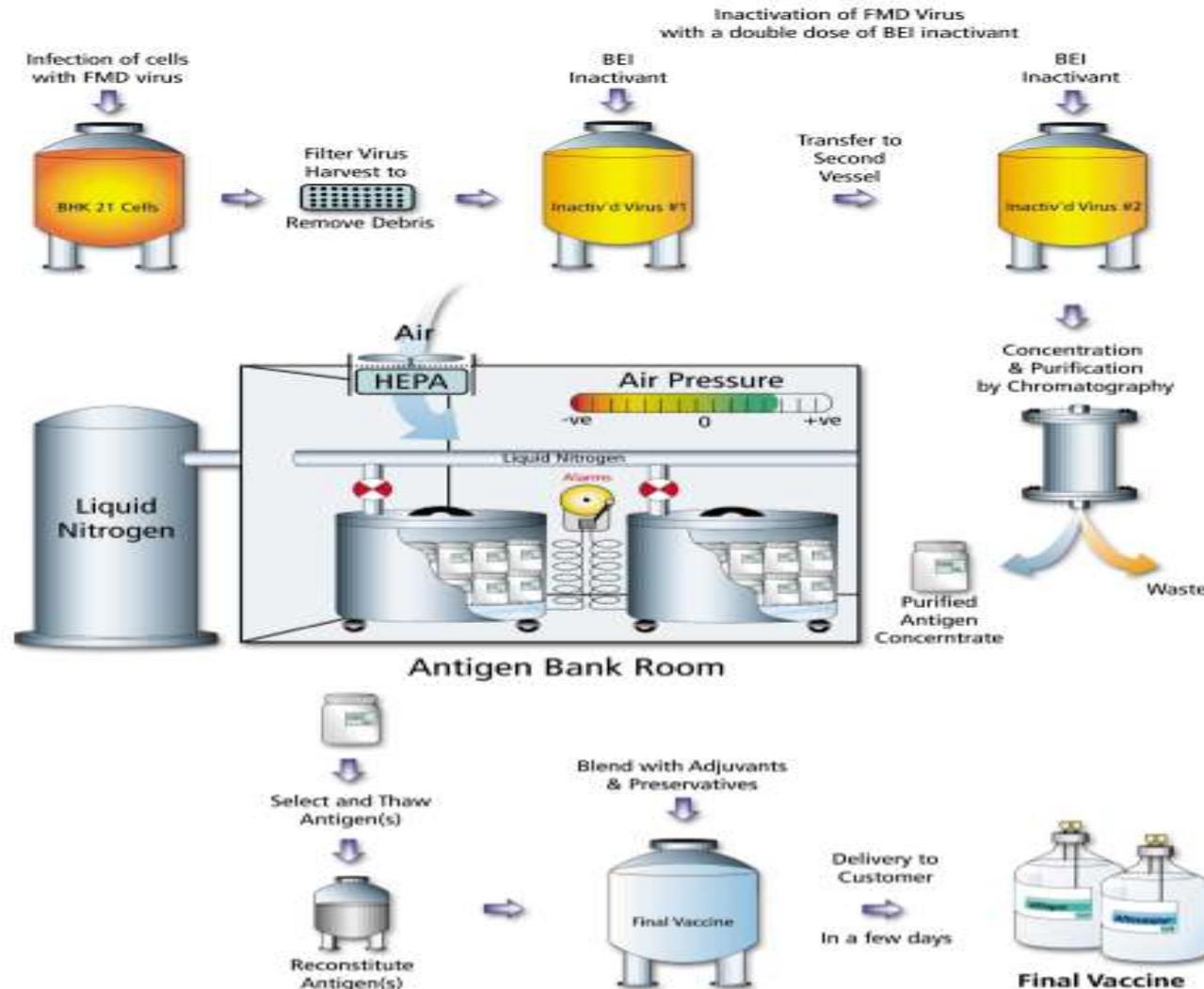


NSPs & DIVA



- PURIFICATION OF ANTIGENS AT INDUSTRIAL SCALE
- NSPs and « DIVA » VACCINES

PURIFICATION OF ANTIGENS AT INDUSTRIAL SCALE



NSPs AND “DIVA” VACCINE

Validated processes of purification of antigens remove most of FMDV Non Structural Proteins (NSPs), the marker of FMDV infection.

Consequently, vaccines produced from such purified antigens have the valuable property **not to interfere with serological surveys** carried out to identify **infected/carrier** groups of animals in the vaccinated population.



COST EFFECTIVENESS & MANUFACTURING CONSTRAINTS



- TECHNOLOGY AND CAPACITY OPTIMIZATION
- TECHNOLOGY TRANSFER
- MANUFACTURING CONSTRAINTS

TECHNOLOGY AND CAPACITY OPTIMIZATION

Cost effectiveness is achieved through **harnessing the technology** and **optimizing the capacity** of vaccine Manufacturing plants.



TRANSFER OF TECHNOLOGY

Cost effectiveness can also be achieved through transferring technology locally whenever the option is proven viable, e.g.:



The collaboration between the **Botswana Vaccine Institute** and **Meriel** started in **1978...**

... and is continuing in 2009 with the construction of a new manufacturing building.

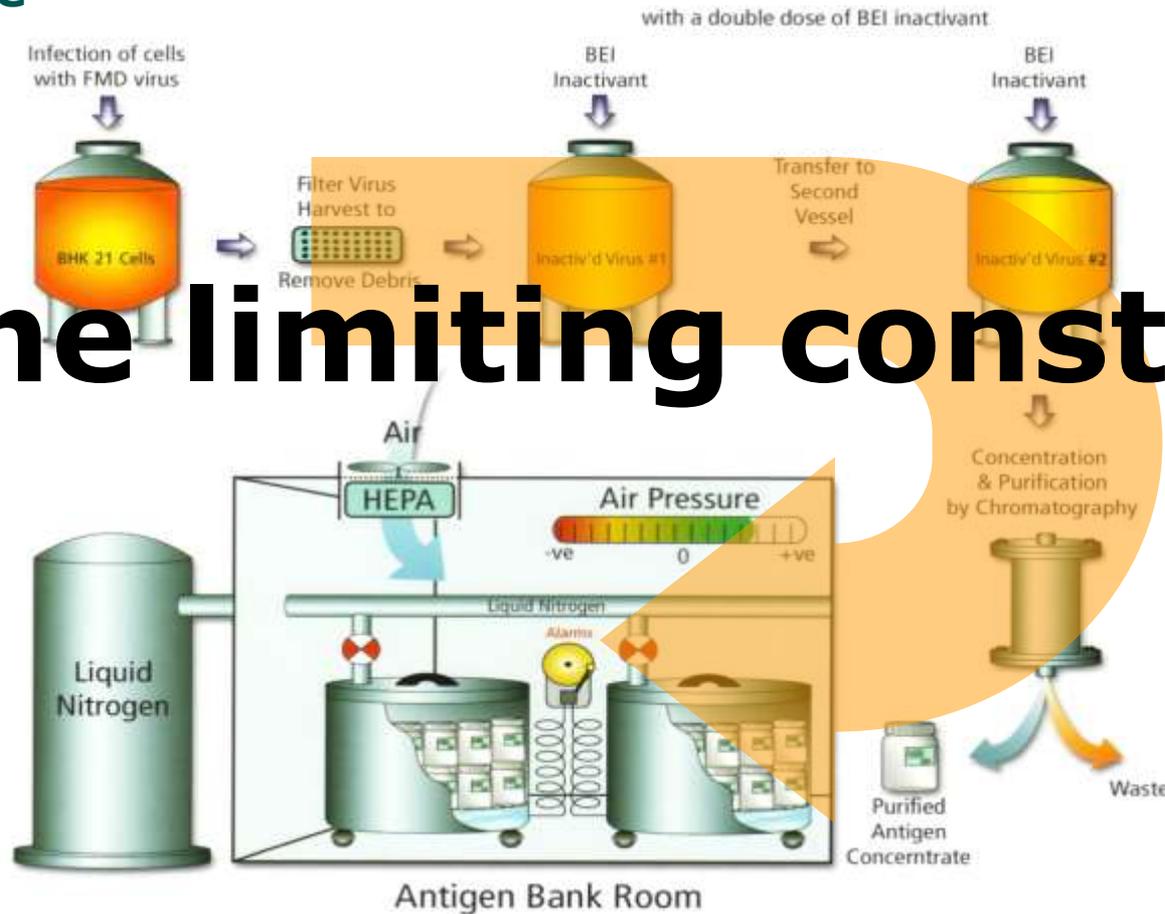


A partial technology transfer can also be considered, but it might also require significant manufacturing capacity investments and technical training that cannot be achieved in the short term

- Indeed, in order to minimize the vaccine cost component of a control program, efforts can be made to **localize** several **industrial steps** of the vaccine production process.
- For example, Vietnam has implemented an important program of FMD control, in which vaccination plays a significant role, and, for facilitating this initiative, steps of the process have been successfully extended to two Vietnamese Manufacturing partners: XNTTY and NAVETCO.
- Obviously, implementation of similar partnerships has to be considered well in advance to have the project fully operational in an optimized technical and contractual environment when required.

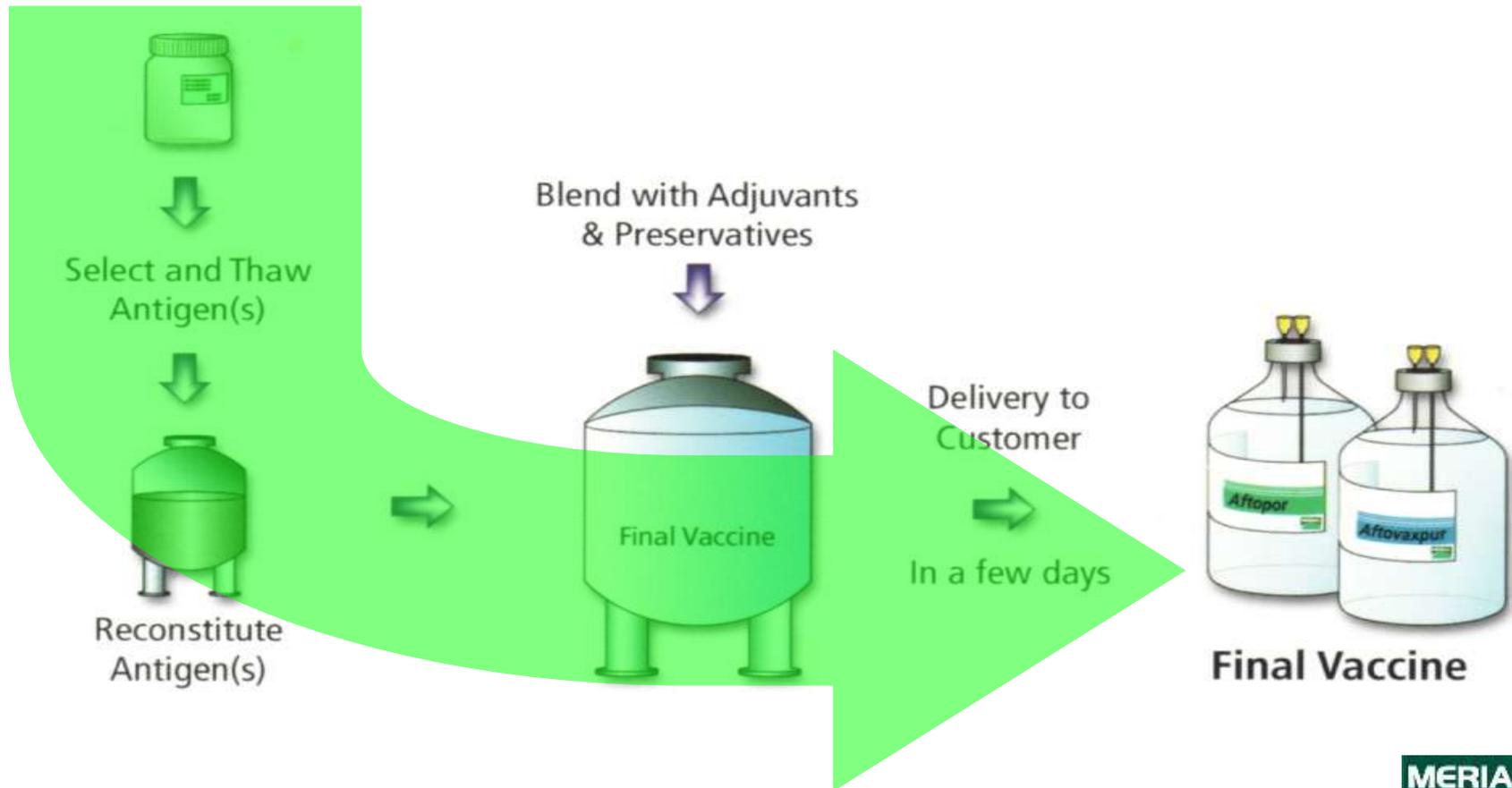
Supply of tailor made vaccines cannot be organized at short notice: the overall manufacturing and quality control takes time

time limiting constraint



3 months including tests

Final steps can be completed in a shorter period of time: 3 to 4 days to get the vaccine filled and packaged, 4-5 weeks to have it fully tested



So the antigens needed for a full vaccination campaign can be prepared and stored in anticipation, but this is subject to sufficient notice



In case of even larger demand, vaccine production might require significant capacity investments that cannot be achieved at short term



A clear visibility is therefore needed for long term preparedness of manufacturers to meet field needs

SPECIFICATIONS OF VACCINES SUPPLIED THROUGH PROGRESSIVE CONTROL PROGRAMS

In an endemic situation, where large quantities of the same vaccine are routinely employed, there is clearly a significant value in matching the vaccine strain(s) to the field viruses **as exactly as possible** so that the vaccine program is optimized.

As a consequence, tender specifications may change, requesting new strains to be included into vaccines.

To fulfill this requirement in a proper way, recommended vaccine strains should be published **well in advance** as the completion of an **adequate regulatory package** is needed before considering production and delivery.

IN CONCLUSION...

As described, manufacturers already play a significant role in a number of fields related to technical and economical improvement of FMD vaccines.

However, in order to harness novel technologies, develop more targeted products and supply cost-effective vaccines, public institutions and industry should continue to:

- direct their research efforts in vaccine development and,
- collaborate wherever possible to achieve these objectives.



IN CONCLUSION...

Manufacturers can bring a significant support in FMD progressive control programs by timely supplying adequate quantity of appropriate FMD vaccines.

Large scale highly specialized manufacturing facilities can be dedicated to large volume production, but ultimately, only **accurate previsions** provide sufficient flexibility for securing FMD vaccines in a timely and cost effective manner to meet local demands.

In this way, a **synergistic relationship** should be established between international organizations, implementing countries and manufacturers for streamlining vaccine supply for important control programs.

IN CONCLUSION...

Compulsory vaccination programs have historically been a proven strategy **as long as potency of the vaccines used has been closely and independently monitored.**



Thank you for your attention

