THE UNIVERSITY of EDINBURGH

Regulatory aspects of veterinary vaccine development

A. R. Peters

University of Edinburgh

And

Arpexas (Scotland) Ltd.

A bit about me:

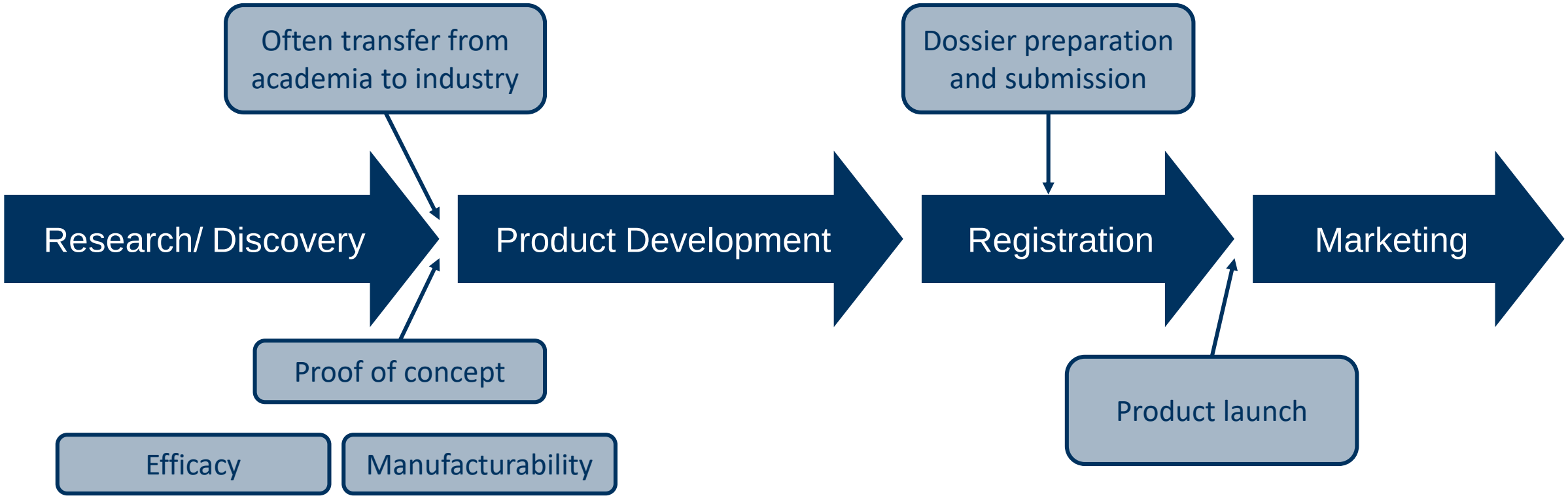
1970s	Veterinarian, PhD	
1980s	Reproductive endocrinology, beef cattle	
1990s	Industry, regulation and QA	Professor Animal Health, RVC
1998-2005	Vaccine development Pfizer AH	
2005-	Consultant vaccines *Arpexas Ltd.*	GALVmed
2013-2016	Asst. Principal International, SRUC	
2016-	Supporting Evidence Based Interventions (SEBI), University of Edinburgh	

20+ years as member of UK Veterinary Products Committee (VPC)
8 years as member of Advisory Committee on releases to the Environment (ACRE)

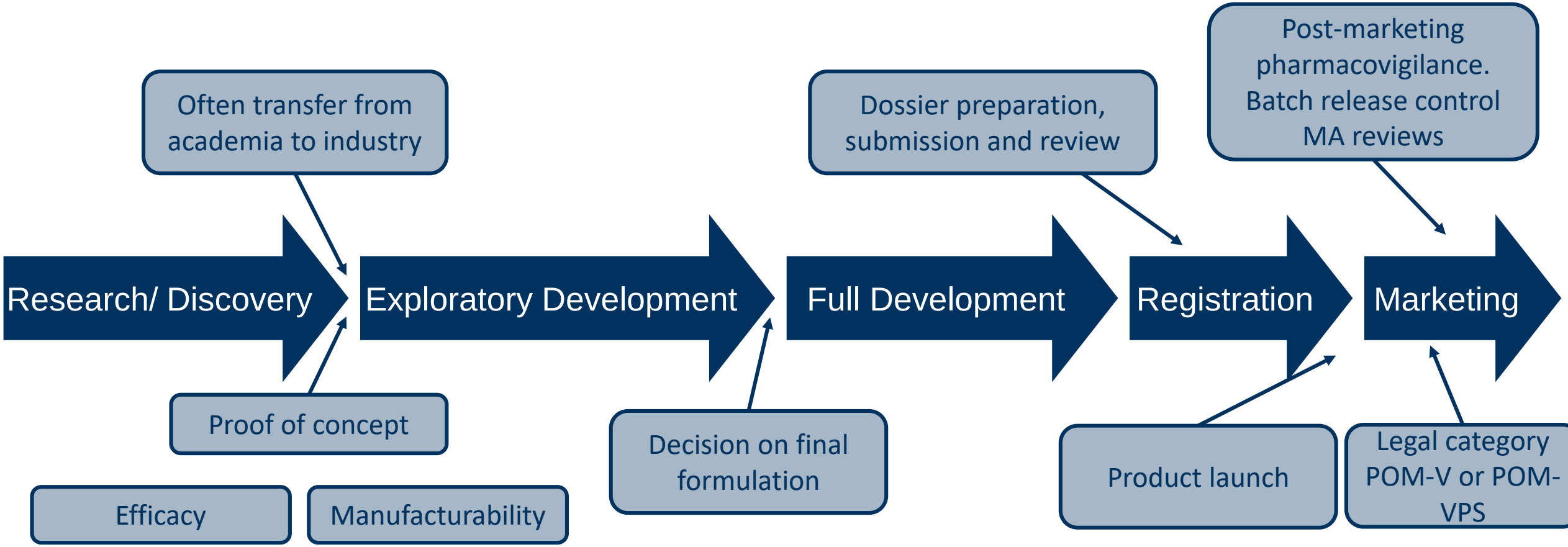
Regulation of veterinary vaccines

- Immunological veterinary medicinal product (IVMP)
- Data requirements for registration:
  - Quality
  - Safety
  - Efficacy

Simplistic representation of the new product development process



Simplistic representation of the new product development process



Quality, Safety and Efficacy

Criterion	Description
Quality	• Pharmaceutical: chemistry and pharmaceutical aspects of the active ingredient and product • Vaccine (biological) this is about identity and characterization of the antigen. • In both, the other quality aspects concern manufacture, purity, stability, batch reproducibility, quality control etc., with emphasis on validation.

Safety	• For a food animal product this concerns safety for:
	  • the target animal,
	  • the human consumer of animal products,
	  • any operator handling or administering the product,
	  • the environment.

Efficacy	Ability to produce the desired result. Does it do what is claimed? Does it work?

EUROPEAN MEDICINES AGENCY

Data requirements 1994 to 2004:

- Increase in quality, safety and efficacy requirements to ensure that products on the market are safe for animals, the public and environment.
- Products are manufactured to a consistent quality and provide the level of protection expected from the product literature.

3

EUROPEAN MEDICINES AGENCY

Data requirements 1994 to 2004:

- Increase in quality, safety and efficacy requirements to ensure that products on the market are safe for animals, the public and environment.
- Products are manufactured to a consistent quality and provide the level of protection expected from the product literature.

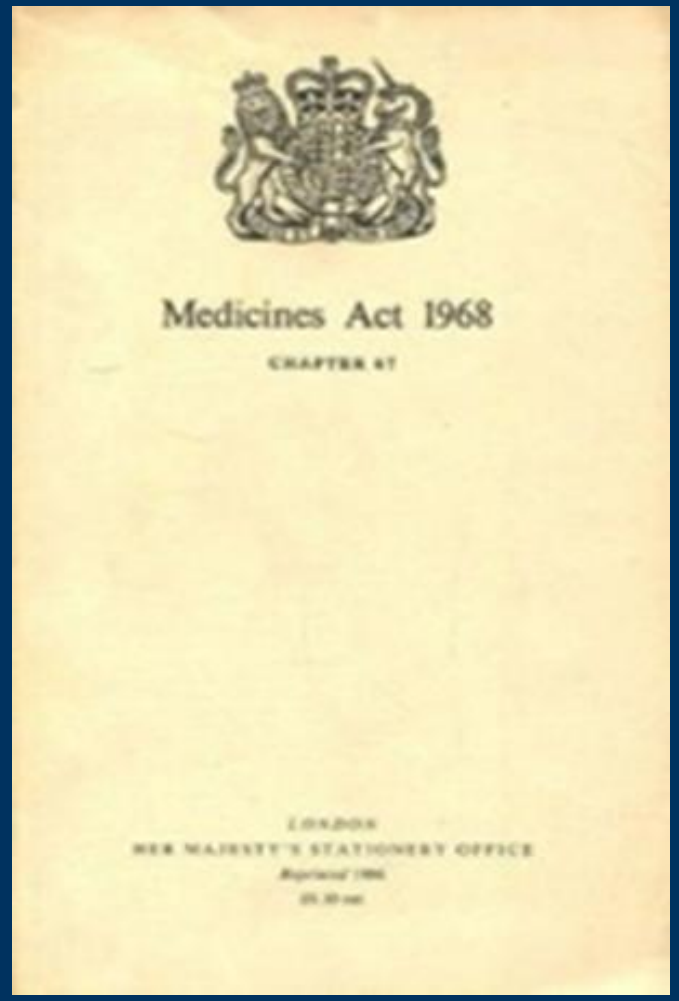
2018

3

Major EC directives and regulations controlling the licensing of veterinary medicines

Directive 81/851EC	Approximation of the laws of the Member States relating to veterinary medicinal products
Directive 81/852/EC	Approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products
Directive 90/677/EEC	Extended scope of vet med directives to immunologicals
Directive 2001/82/EC	On the Community code relating to veterinary medicinal products
Regulation EC 726/2004	Laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
Directive 2004/28/EC	Amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products

UK legislation



Medicines Act 1968

CHAPTER 67

LONDON
HER MAJESTY'S STATIONERY OFFICE

2013 No. 2033

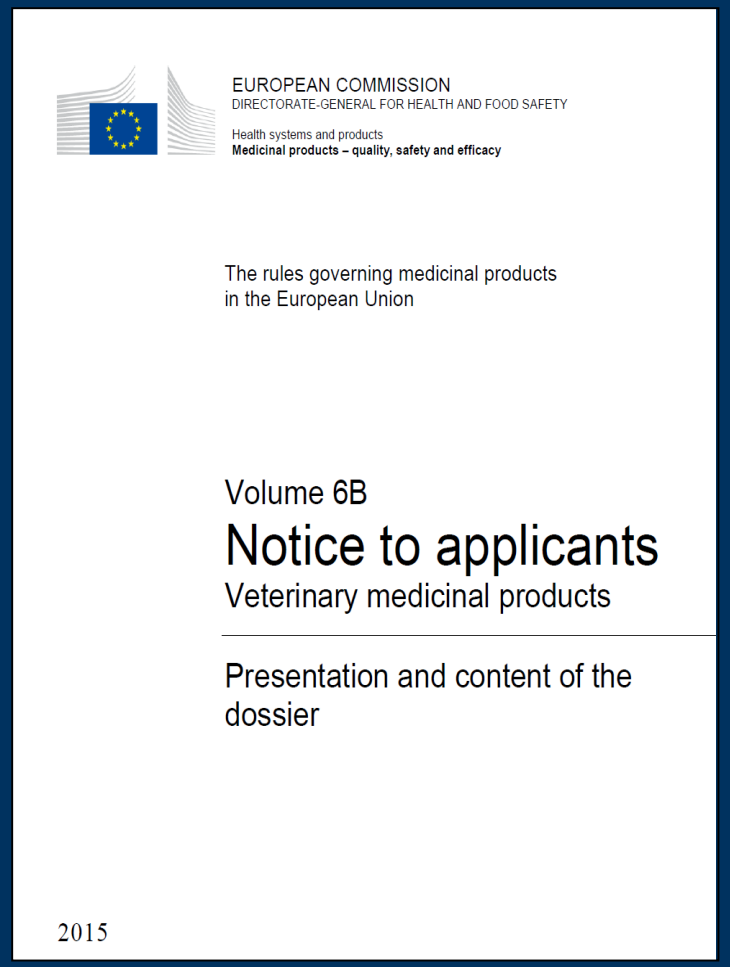
MEDICINES

The Veterinary Medicines Regulations 2013

Made - - - -	*6th August 2013*
Laid before Parliament	*20th August 2013*
Coming into force - -	*1st October 2013*

CONTENTS

Dossier content



EU routes to registration

1. The Centralised Procedure allows a marketing authorisation (MA) to be obtained and made available in all the Member States. This applies to high technology products defined in the Annex to Regulation 726/2004.

2. The National Procedure allows an MA to be obtained in a single country or in a country that will be the origin of a mutual recognition procedure.

3. The Decentralized Procedure: applications for authorisation of a product are obtained in a single Member State (the 'Reference Member State') by means of a national procedure. Following approval in the Reference Member State, applications are made, to other 'Concerned' Member States for identical authorisations to be granted on the basis of 'mutual recognition'.

The **centralised** procedure and the EMA

- ONE Marketing authorisation application
- ONE Scientific Evaluation by the Committee for Veterinary Medicinal Products (CVMP)
- ONE Authorisation in all EU MS (28) + EEA (3)
- ONE Invented name
- ONE Product information
  - Summary of product characteristics (SPC)
  - Labelling
  - Package leaflet (PL)

ALL EU languages

Summary of veterinary vaccine dossier contents for EU registration

Part	Title	Contents
1	Summary of the dossier	• Administrative information (Company details, site of manufacture etc.) • Summary of Product Characteristics, labelling and package leaflet • Detailed and Critical Summaries (Expert reports)
2	Quality	Details of identity and characterization of the antigen and product. Manufacture, quality control, reproducibility, stability, etc.
3	Safety	• Safety to the target animal • Safety to the consumer • Safety to the environment • Safety to operators / user
4	Efficacy	Ensures that the product meets its claims on the SPC and other labelling
5	Particulars and summaries	• Introduction • Outline requirements for laboratory studies • Outline requirements for field studies • General conclusion on the benefit : risk assessment of use of the product
6	Bibliographical references	List of references used in the dossier

Part 2 of the dossier. Chemical, pharmaceutical and biological / microbiological information

A	Qualitative and quantitative particulars of the constituents	Active ingredient details, excipients, usual terminology (PhEur etc.), quantitative amounts of all actives and excipients
B	Description of the manufacturing method	Premises, methodology, validation
C	Control of starting materials	Provenance and QC tests on starting materials Packaging and closures TSE compliance
D	Control tests at intermediate stages	QC tests
E	Control tests on finished product	Specifications, compliance with specification. Safety tests e.g. contaminants endotoxins etc.
F	Stability	Shelf life of active, product both in storage and in-use
G	Further information	Batch to batch consistency

GMP and the Orange guide

Part 3: Safety 1

A	Introduction and general requirements	**Comments**
B	Laboratory tests 1. Safety of administration of one dose 2. Safety of one administration of an overdose 3. Safety of the repeated administration of one dose 4. Examination of reproductive functions 5. Examination of immunological performance	**All to GLP standard.** Usually small numbers of animals (n≤10) vaccinates plus controls, monitored clinically for 14 days after vaccination. Only necessary where there is a suggestion that starting materials or product could be a risk factor.

Part 3: Safety 2

B	6. Special requirements for live vaccines	**All to GLP standard**
	6.1 Spread of vaccine strain	e.g. from vaccinates to non-vaccinates.
	6.2 Dissemination in the vaccinated animal	Faeces, urine, milk, eggs, oral and nasal secretions.
	6.3 Reversion to virulence of attenuated vaccines	Using Master seed. Specifically designed study to assess likelihood of reversion.
	6.4 Biological properties of the vaccine strain	Study of intrinsic biological properties e.g.neurotropism.
	6.5 Recombination or genomic re-assortment of the vaccine strain	Probability of these events must be discussed.

Part 3: Safety 3

B		**All to GLP standard**
	7. User safety	Discussion of possible effects in humans with a view to warning statements etc
	8. Study of residues	Not normally necessary for vaccines unless excipients e.g. adjuvants suggest the possibility of residues in foodstuffs.
	9. Interactions	Any interactions with other veterinary products shall be described.

Part 3: Safety 4

C	Field studies	Results from lab studies usually supplemented with data from field studies. Normally done in combination with field efficacy study. GCP standard.
D	Environmental risk assessment	Assess possible risk to environment and to identify any precautionary measures.
E	Assessment required for veterinary medicinal products containing or consisting of genetically modified organisms.	In the case of veterinary medicinal products containing or consisting of genetically modified organisms the application shall also be accompanied by the documents required under Article 2 and Part C of Directive 2001/18/EC.

Efficacy Studies

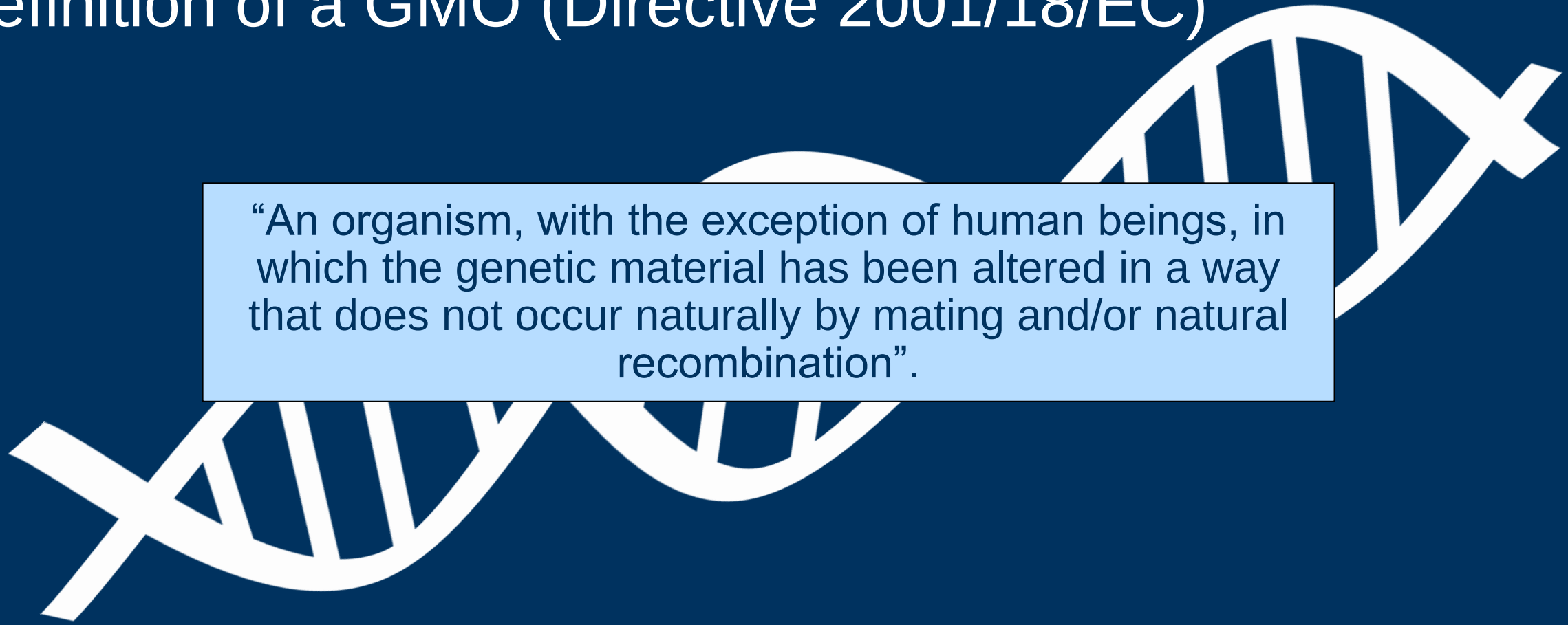
Chapter 1	General principles Performance of trials	The need to support any claims by data for specific trials. Need for formal, protocols, design, GCP etc.
Chapter 2		
A	General requirements	Justification of antigen choice. Need for controlled trials etc. Need for assessment of companion diagnostic test if DIVA claim made.
B	Laboratory trials	Need for well-controlled lab challenge trials, minimum titre/ potency. If possible immune mechanism demonstrated. Onset of immunity. Duration of immunity
C	Field trials	Results from lab studies usually supplemented with data from field studies. Normally done in combination with field safety study. GCP standard.

Genetically modified organisms

EU legislation relevant to the use of GMOs in veterinary medicinal products	
Directive 90/219	On the contained use of genetically modified micro-organisms
Directive 2001/18	On the deliberate release into the environment of genetically modified organisms

Directive 2001/18/EC requires the submission of a dossier containing an "Environmental risk assessment" (ERA) known as a "Part B" when applying for permission to release for the purposes of a field trial in an unlicensed product and known as a "Part C" when applying for a full MA.

Definition of a GMO (Directive 2001/18/EC)



"An organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination".

Abstract from Directive 2001/18 Annex 1A.

Techniques of genetic modification referred to in Article 2(2) (a) are inter alia:

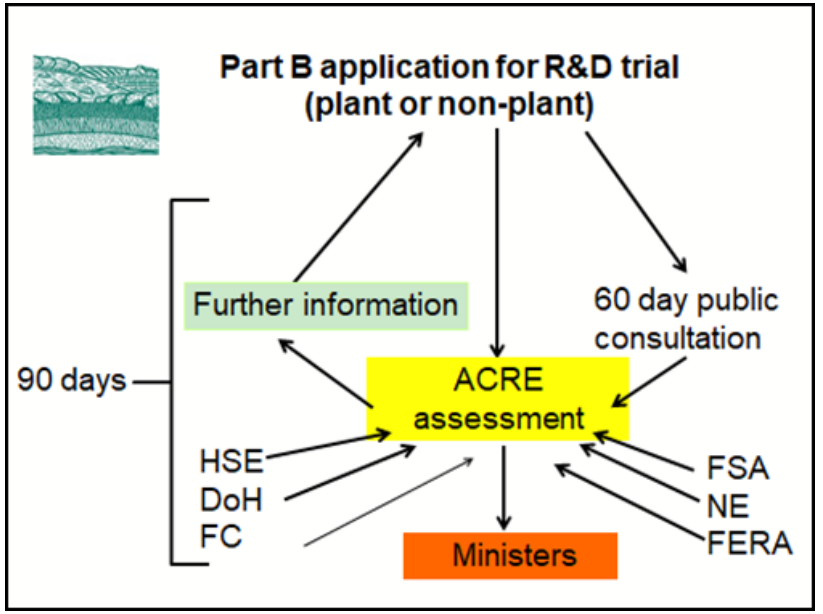
(1) recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation;

(2) techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-injection, macro-injection and micro-encapsulation;

(3) cell fusion (including protoplast fusion) or hybridisation techniques where live cells with new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally.

Definition of a GMO (EU)

- Definitions were drawn up in the 1990s
- The science has moved on considerably since then
- These definitions have become quite contentious,
- However they currently remain as the basis of the legal framework.
- Some have since argued that the definition should be based on the phenotype of the product (as in the US) and not the means by which it is produced e.g. Pollock and Hails (2014).



Principles of the environmental risk assessment (ERA) for GMO releases (per Directive 2001/18/EC)

A	Objective	To identify and evaluate potential adverse effects, **on human health and the environment** which deliberate release or the placing on the market of GMOs may have. The ERA should be conducted with a view to identifying if there is a need for risk management and if so, the most appropriate methods to be used.
B	General principles	To apply the precautionary principle in a scientifically sound manner to identify any current or potential risks to the environment
C	Methodology C1. Characteristics of the GMO and its release C2. Steps in the ERA	 Technical details regarding the construct and how it will potentially interact with the environment Identification and evaluation of potential risks to the environment
D	Conclusions on the potential environmental impact from the release or the placing on the market of GMOs	Likely fate in the environment and the potential risk of direct or indirect adverse effects on the environment

Information required in the notification of release of GMOs (other than higher plants; per Directive 2001/18/EC).

I.		**General information about the applicant and nature of application**
II.		Information relating to the GMO
	A	Characteristics of the donor and recipient
	B	Characteristics of the vector
	C	Characteristics of the modified organism
		1. Information relating to the genetic modification
		2. Information on the final GMO
III		Information relating to the conditions of release and the receiving environment
	A	The release
	B	The environment
IV		Information relating to the interaction between the GMO and the environment
	A	Characteristics affecting survival, multiplication and dissemination
	B	Interactions with the environment
V		Information on monitoring, control, waste treatment and emergency response plans
	A	Monitoring techniques
	B	Control of the release
	C	Waste treatment
	D	Emergency response plans

Matrix used to assess the environmental risk of a GMO

Estimation of risk posed by each identified characteristic of the GMO (taken from 2002/623/EC):

Consequence of hazard	Likelihood of hazard			
	High	Moderate	Low	Negligible
Severe	High	High	Moderate	Negligible
Moderate	High	High	Moderate/Low	Negligible
Low	Moderate/Low	Low	Low	Negligible
Negligible	Negligible	Negligible	Negligible	Negligible

Actions: Negligible / low: Allowable
Moderate: Allowable with mitigation?
High: Probably not allowable

Advice on regulatory strategy and dossier preparation

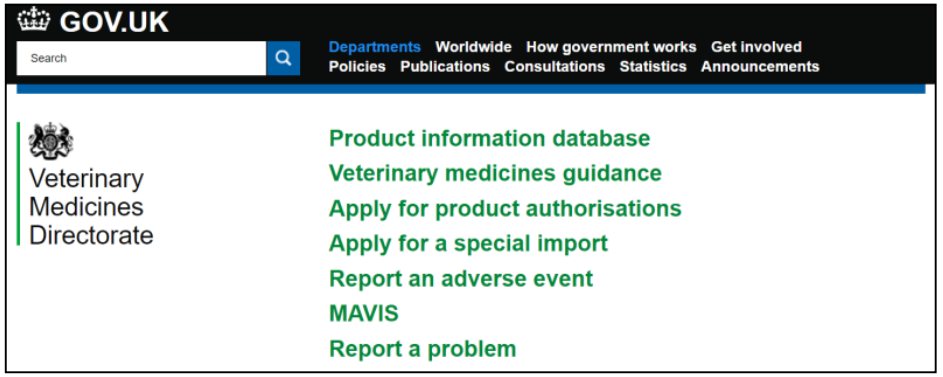
The European Medicines Agency (EMA) is based in Canary Wharf, London.

In addition to being the EU regulatory body it can also offer formal Scientific Advice as follows:

"on the appropriate tests and studies in the development of a veterinary medicine. This is designed to facilitate the development and availability of high-quality, effective and acceptably safe medicines".

How would this work when we are outside the EU?

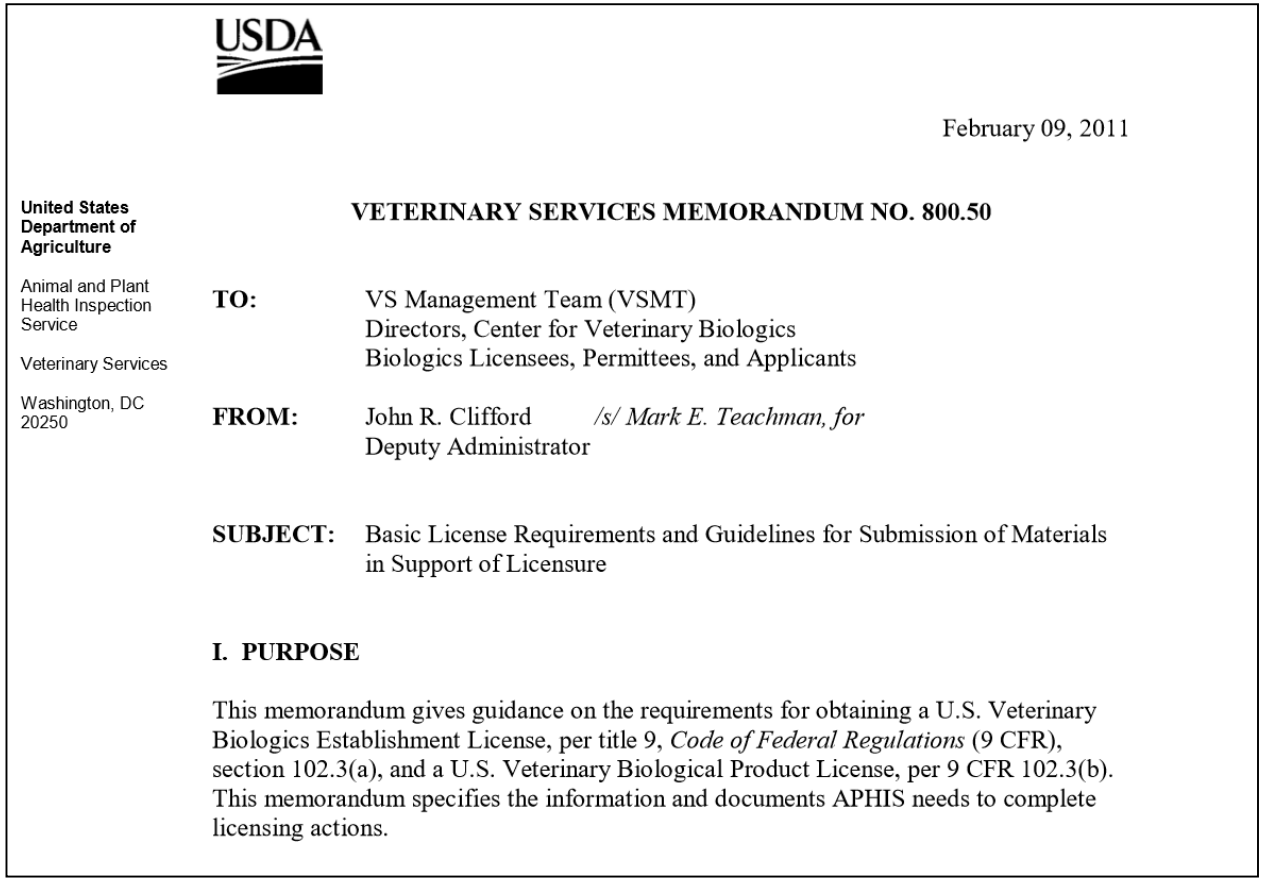
- EMA moving to Amsterdam
- Likely that we would be member of the European Economic Area / EFTA e.g. Norway
- Therefore we would comply with EU requirements for veterinary medicine regulation and adopt the same Regulations.
- Would probably need an EU base from which to apply.
- Still work in progress and VMD not saying much



Regulation of veterinary vaccines in the US

- All pharmaceuticals and human vaccines regulated by FDA
- Veterinary vaccines (biologics) regulated by USDA
  - Virus-Serum-Toxin Act of 1913 as amended by the Food Security Act of 1985.
- Animal and Plant Health Inspection Service (APHIS)
- Center for Veterinary Biologics (CVB) Ames, Iowa
- Requirements in Veterinary Services Memorandum No. 800.50.
- New applicants encouraged to contact informally first.

USDA Veterinary Services Memorandum No. 800.50



USDA

February 09, 2011

United States Department of Agriculture

Animal and Plant Health Inspection Service

Veterinary Services

Washington, DC 20250

VETERINARY SERVICES MEMORANDUM NO. 800.50

TO: VS Management Team (VSMT)
Directors, Center for Veterinary Biologics
Biologics Licensees, Permittees, and Applicants

FROM: John R. Clifford */s/ Mark E. Teachman, for*
Deputy Administrator

SUBJECT: Basic License Requirements and Guidelines for Submission of Materials in Support of Licensure

I. PURPOSE

This memorandum gives guidance on the requirements for obtaining a U.S. Veterinary Biologics Establishment License, per title 9, *Code of Federal Regulations* (9 CFR), section 102.3(a), and a U.S. Veterinary Biological Product License, per 9 CFR 102.3(b). This memorandum specifies the information and documents APHIS needs to complete licensing actions.

The USA. GMOs. Differences in approach between markets

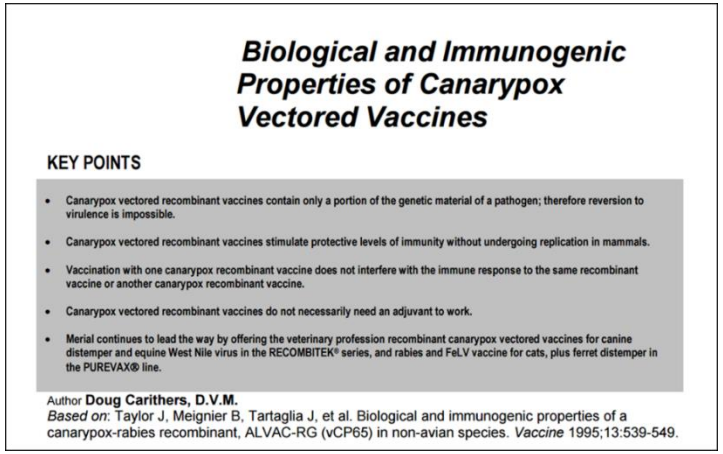
- No federal US legislation specific to GMOs *per se.*
- Regulation through health, safety and environmental legislation governing conventional products.
- Focused on the nature of the products, rather than the process in which they were produced.
- Compared to other countries, regulation of GMOs in the US is relatively favourable to their development.
- GMOs are an economically important component of the biotechnology industry, which now plays a significant role in the US economy. For example, the US is the world's leading producer of genetically modified (GM) crops.

Key differences between the EU and US systems of veterinary vaccine regulation and manufacture

	EU	US
1	GMP required	GMP not required but quality ensured through Outline of Production document
2	Dossier divided in to several distinct parts, in particular Safety, Quality and Efficacy	Quality, Safety and Efficacy sections not used
3	Separate legislation and process for GMOs	No separate legislation or process for GMOs but still have an ERA which takes account of the same issues
4	Dossier submitted as a completed document (separate submission for permission for field trials)	Dossier submitted in phases
5	Fixed times between submission by applicant and response	No fixed time between submission and response
6	No requirement to submit protocols to EMA before trial conducted	Protocols have to be approved by CVB before field trials conducted
7	No routine requirement to submit samples or pre-licensing serials to EMA.	Requirement to submit some samples and pre-licensing serials to CVB for confirmatory testing

Examples of GMO vaccine platforms registered in at least one region

Vaccine range	Vector	Company
Vectormune / Vaxxitek	Turkey herpes virus	Ceva
Alvac / Purevax / Recombitek	Canary pox virus	BI Merial
Trovac	Fowlpox virus	BI Merial
Nobivac Myxo-RHD	Myxovirus	MSD



"Mutual recognition" between regions

1. Free sales certificates and certificates of licensing and inspection
    I. E.g. USDA and Latin American countries
    II. Possibly for Africa
2. VICH: Veterinary International Cooperation on Harmonisation
    I. US, EU and Japan with other observers
    II. Harmonised tests for quality and safety
3. New EU Regulation (2020)
    I. Contains specific provision under Article 138 (1) for the CVMP (or other) to give a "Scientific opinion for international organisations for animal health" which would in effect allow assessment of products on behalf of 3rd countries.
4. Regional groups in Africa e.g. UEMOA, possibility of using S. Africa free sales certificate system

Council of the European Union

Brussels, 21 December 2017
(OR. en)

Interinstitutional File:
2014/0257 (COD)

15296/17
ADD 1 REV 1

LIMITE

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PHARM 60
MI 911
IA 206
CODEC 1985

NOTE

From:	General Secretariat of the Council
To:	Delegations
No. Cion doc.:	13289/14 COM(2014) 558 final
Subject:	Proposal for a Regulation of the European Parliament and of the Council on veterinary medicinal products

Africa

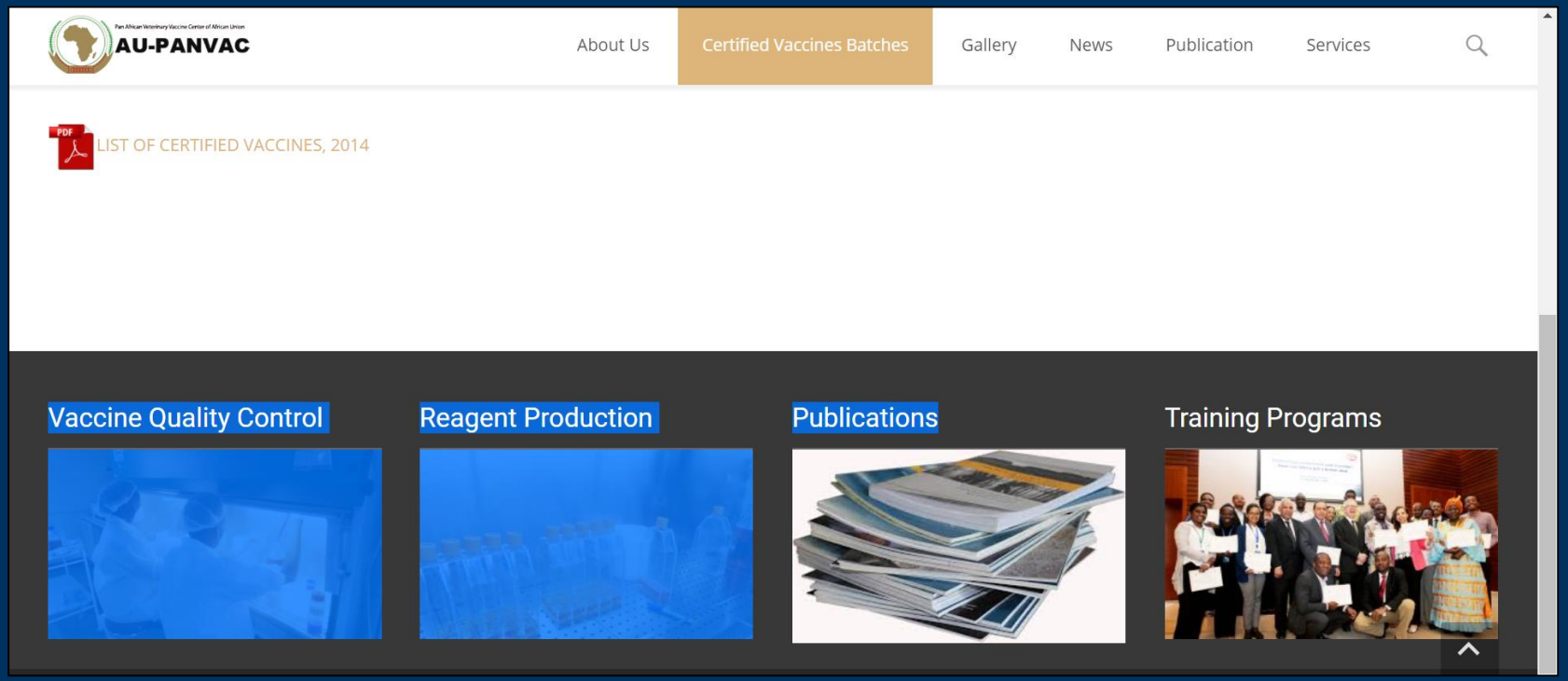
Individual national regulatory agencies.
Mostly linked to human regulatory agencies.
Standards vary.

Mutual recognition in West Africa

Recent development of MR in East Africa

South Africa most advanced

AU - PANVAC


AU-PANVAC
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LIST OF CERTIFIED VACCINES, 2014
Vaccine Quality Control
Reagent Production
Publications
Training Programs

The Masaka Vet Pharmacy Uganda

East Coast Fever (*T. parva*) ITM – registration

EAST COAST FEVER
(*Theileria parva*)
Muguga Cocktail

Registration dossier and Technology transfer document

Volume 2
Parts 3 and 4
Safety and Efficacy

Prepared by
The Global Alliance for Veterinary Medicines (GALVmed)

and

The International Livestock Research Institute (ILRI)

January 2008

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(r 6)

THE PHARMACY AND POISONS ACT
(*Cap.* 244)

THE PHARMACY AND POISONS (REGISTRATION OF DRUGS) RULES

REGISTRATION OF DRUGS CERTIFICATE

Number V2009/20456/028

It is hereby certified that the drug as described hereunder, has been registered subject to the conditions indicated hereunder:

1. Trade name under which marketed: MUGUGA COCKTAIL
2. Approved name: MUGUGA COCKTAIL
3. Form of preparation: VACCINE
4. Active ingredients and quantities per unit: KIAMBU 10^4–10^5; MUGUGA 10^4–10^5; SERENGETI TRANSFORMED 10^4–10^5 PER ML
5. Condition(s) under which medicine is registered: UNCONDITIONAL
6. Name and business address of manufacturer: INTERNATIONAL LIVESTOCK RESEARCH INSTITUTE (ILRI) P.O BOX 30786 00100 NAIROBI
7. Registered in the name of: INTERNATIONAL LIVESTOCK RESEARCH INSTITUTE
   Business address: P.O BOX 30786 00100 NAIROBI
8. Date of Registration: 22ND OCTOBER 2009
9. Expiry date of Registration: 22ND OCTOBER 2014

Date 23RD OCTOBER 2009

Registrar,
Pharmacy and Poisons Board

TANZANIA FOOD AND DRUGS AUTHORITY

TFDA

REF. NO:-CB.84/101/01/18 Tuesday, 29 December 2009

RECEIVED 25 JAN 2010 OPEN REGISTRY

Department of Livestock Development
Ministry of Water and Livestock
Development, Livestock Department, Kilimo 2,
P.O.Box 9152
Dar-es-salaam,
TANZANIA.

RE: NOTICE OF DRUG APPROVED FOR REGISTRATION

Reference is made to the application for registration of your product in Tanzania.

We are pleased to inform you that the Tanzania Food and Drugs Authority has considered and granted registration of your medicinal product listed hereunder.

The respective registration certificate is being prepared and when it is ready it will be issued to you. In the meantime you can use this letter as a proof of registration of the product. The certificate will, unless earlier revoked or suspended be valid for five years from the date of issue provided that:

(a) Annual retention fees of US$ 100.00 per product are timely paid before the end of January of each calendar year.
(b) The product continues to comply with the requirements as prescribed in Tanzania Food, Drugs and Cosmetics Act 2003.
(c) All changes regarding the product are notified to and approved by the Authority.

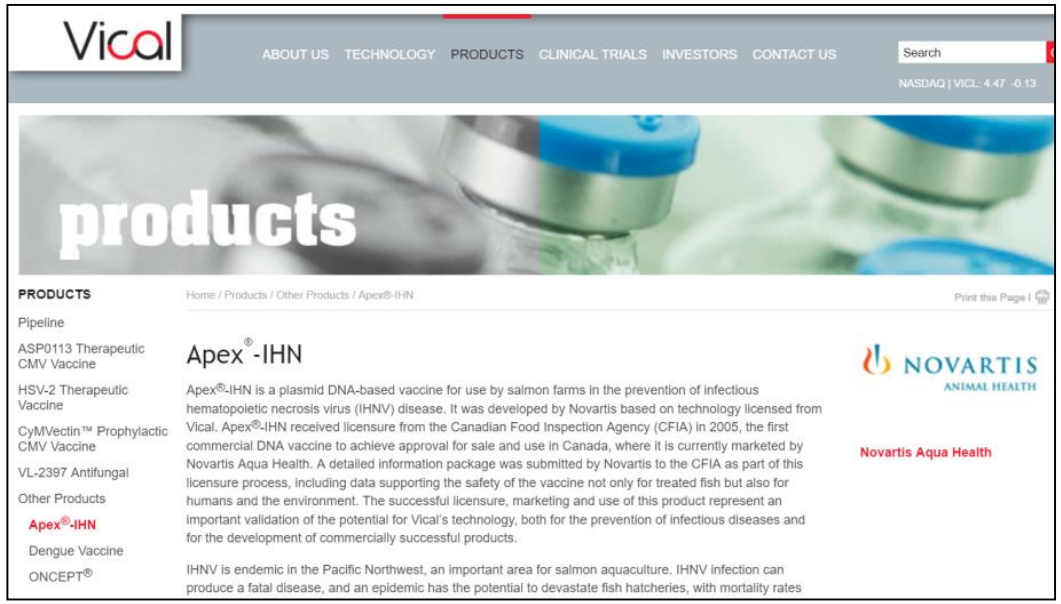
With effect from the date of this letter till the certificate expires and upon compliance to the relevant provisions of the Tanzania Food, Drugs and Cosmetics Act, 2003 and any other written law the product may be imported or manufactured for sale in Tanzania

The product is as follows:

1. NDIGAVAC SUSPENSION

M. Ndomondo-Sigonda
DIRECTOR GENERAL

DNA vaccines in fish
(first in Canada now in EU)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 April 2016
EMA/CVMP/281226/2016
Press office

Press release

First DNA vaccine in the EU recommended for use in salmon

Clynav to protect Atlantic salmon from serious infectious disease

The European Medicines Agency (EMA) has recommended granting a marketing authorisation in the European Union (EU) for Clynav, a DNA vaccine to protect Atlantic salmon against Salmon Pancreas Disease (SPD) caused by salmon alphavirus subtype 3.

EUROPEAN MEDICINES AGENCY

Key messages

- DNA vaccines are new innovative veterinary products for regulators
- DNA vaccines are not classified as GMOs
- Safety studies should be undertaken as if the plasmid was a live vaccines:
  - Dissemination studies in the target animal and spread to the environment
  - Overdose conducted at 10X maximum DNA plasmid content
- Potential integration into the genome of the vaccinated animal is a critical safety issue
- An ERA should be conducted as far as possible, in line with 2001/18/EC
- The ERA should be a quantitative risk assessment with consequence analysis

How to engage with regulators

A number of reasons to contact regulators:

- Informal advice during product development
- Formal scientific advice during product development
  The more data that the company has, the more value to these meetings
- To apply for field trial permits / deliberate release
- To apply for a marketing authorisation

Routes to market

Product Development
Spin out companies
License or sell technology

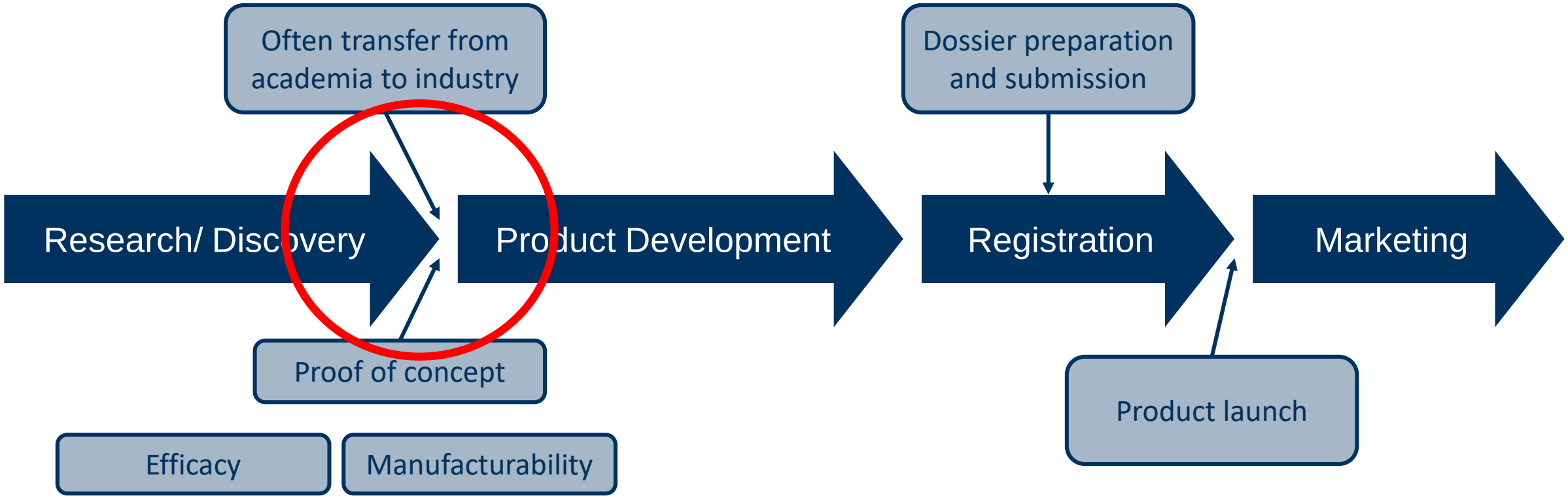
Attention to target markets
Antigen content
(registration is product specific, not by 'platform')
Developed and developing countries

Likely partners
Global AH company
Regional company
Start-up company

Some decisions for product development

- Which product / which antigen?
- Which market?
- Public or private good?
- Likely return on investment
- Route to market / commercial partner etc.
- Exploratory studies to optimise formulation
- Cost of goods
- Decide on final formulation and focus on development
- Define “Product profile” (SPC)
- Draw up product development plan
  - Necessary activities, timelines, roles and responsibilities

Simplistic representation of the new product development process



Working with industry

First meeting between a company R&D director and an academic researcher

‘I ve developed a new vaccine for lumpy cow disease’

‘How big is the market?’

‘Well er- quite a few farms around here are affected’

‘How effective is it, have you patented it and how much does it cost to make?’

‘Well when I say a vaccine I mean I think we might have identified some candidate protective antigens’

‘You mean they protect cattle against challenge?

‘Err no, but they seem quite effective in mice. We did an experiment in 2 calves but the results were a bit equivocal, although one did seroconvert.’

Companies are risk averse
What do they want?

- Proof of concept
  - An IPR position i.e. some property that they can own / license
  - Convincing and reproducible evidence that the antigen(s) is likely to be protective in the target species using an appropriate challenge model
  - A degree of confidence that a registerable product can be manufactured at a profit
- The ‘gap’ often comprises
  - one or more critical experiments of adequate power to demonstrate the second point above.
  - Period of 1-2 years
  - Translational funding
  - Mutual understanding!

Thank you