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Short communication

A Veterinary Vaccine Development Process Map to assist in the development of new vaccines

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ABSTRACT

The UK Government recognised the importance of vaccines in the control of new emerging disease threats and in 2015 established the UK Vaccine Network to focus on specific areas of need. One of these was the understanding of what is involved in the development of a new vaccine and what are the potential bottlenecks to a rapid response in the face of an epidemic such as Ebola, MERS and more recently COVID-19. A Working Group was established to initially produce a Vaccine Development Process Map for a Human Vaccine. However, in view of the importance of animal wellbeing and the significant impact of diseases with Zoonotic potential, a similar Map has been created outlining the Veterinary Vaccine Development Process. This paper describes the production of that Map and covers the process from the generation of a Target Product Profile (TPP) through Discovery and Feasibility, and on to Product Development and Registration.

1. Introduction

The UK Government established a Vaccine Network in 2015 with a view to bringing together industry, academia and relevant funding bodies in order support the understanding and investment in vaccines for infectious diseases with epidemic potential [1] such as Ebola, MERS and more recently COVID-19 (https://www.gov.uk/government/groups/uk-vaccines-network). A Working Group was established to document the vaccine development process and identify key rate limiting steps (Bottlenecks). Outputs from this group included both Human [2] and Veterinary Vaccine Process Maps for vaccine development. This paper describes the Veterinary Vaccine Development Process Map and highlights the key differences between the human and veterinary vaccine development processes. It can be used as a guide and point of reference in order to facilitate the development of new veterinary vaccines. It will be of particular interest to those within academia who are less familiar with the details of a commercial vaccine development process and the complexity of the associated regulatory requirements.

2. Methods

Three flowcharts or Maps were created covering veterinary vaccine Discovery/Feasibility, Early-Phase Development, and Late-Phase Development and Registration. The graphic templates for the Maps were designed by the MRC Regulatory Support Centre using Adobe Illustrator and placed on a dedicated website created with Dreamweaver using HTML5 coding (http://vaccinedevelopment.org.uk). Within the website they appear as colour coded flowcharts with annotated nodes, which enable the user to navigate the flow. They distinguish between the standard process, ethical/regulatory approvals and target product profile review steps. Potential Bottlenecks within the process can be highlighted by the user. These detailed Maps have been simplified and converted to black and white for the figures within this paper. The website also includes descriptions of the TPP, Regulatory Affairs and Ethical Approvals.

3. Results

The veterinary vaccine product development process can be divided into stages such as Discovery, Feasibility, Development and Registration. Discovery often occurs within an academic environment but, as a project moves into feasibility and on into full development, a commercial organisation will be required to take on a leading role in order to successfully develop and register a

Abbreviations: MRC, UK Medical Research Council; TPP, Target Product Profile; GMP, Good Manufacturing Practice; TSEs, Transmissible Spongiform Encephalopathies; R&D, Research and Development; ATC, Animal Test Certificate.

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new vaccine. It is important to involve experts with a knowledge of commercial regulatory requirements very early in a vaccine's development, since this will avoid the possibility of erroneous actions which can render the vaccine unfit for registration.

3.1. Target product Profile (TPP)

The first step in any vaccine development project with a commercial target in mind should be the creation of a TPP. This sets out clear parameters for the characteristics of the desired end product, and ensures that various disciplines are aligned on required outcomes, product characteristics and measures of success. The TPP also guides the design, conduct and analysis of safety and efficacy trials. Thus, it allows the development team to focus on the characteristics of the vaccine and to ensure that the proposed regulatory trials generate the required data. A good TTP should identify the "optimal target" and a "minimal target." For example, an optimal target for dosage schedule may be one vaccination that lasts a lifetime and a minimally acceptable target may be a series of vaccinations over a certain time period with a more limited duration of immunity. The online Map identifies a number of critical points throughout the process at which the TPP should either be reassessed or revised.

3.2. Discovery/Feasibility Phase

For veterinary vaccines a Discovery/Feasibility Phase (Fig. 1) replaces the human Pre-Clinical Discovery Phase. Early Discovery work may be carried out in laboratory animals in order to screen a number of potential vaccine candidates and select promising formulations. However, such laboratory animal models are often poor indicators of a vaccine's safety and protective efficacy within the target species. Therefore, studies within the host animals are generally used in veterinary vaccine research to identify promising vaccine candidates and reach an early demonstration of efficacy for the intended product. This early testing involving the host is a key difference between veterinary and human vaccine discovery. Another important component of the Discovery Process is the understanding of the pathogen and the immune response within the intended target species. This in turn will facilitate the development of a suitable challenge model designed to mimic natural infection that can be used to assess the protective efficacy of experimental vaccines.

Once an appropriate immunogenic formulation has been identified then a project can move into the Feasibility Phase. Many of the steps are essentially the same for human and veterinary vaccines and are targeted at identifying a lead candidate for development. However, the veterinary Feasibility Process will include proof-of-concept safety and efficacy studies within the target species for the vaccine. It is important to ensure that the immune response elicited by the vaccine correlates with protection within the host and thus the optimum immunisation strategy can be developed. This will result in the identification of a lead vaccine formulation(s) to proceed into full development. At this stage it is wise to ensure that that you have freedom to operate with regards to any pre-existing intellectual property and to file for patent protection of your vaccine, if it is sufficiently novel. With a veterinary vaccine there is generally a greater degree of confidence for successful licensure at the end of the Feasibility process based on clinical trial results within the relevant host before the vaccine enters the more costly Development Phase.

3.3. Early-Phase development

Once there is confidence that the experimental veterinary vaccine candidate elicits an immune response that provides suitable protection then this lead vaccine can be moved into Early-Phase Development (Fig. 2). It is necessary at this stage to prepare and safely store a pre-Master Seed and subsequently a GMP Master Seed of the chosen production antigen. In doing so it is important to have clear traceability on the source material, knowledge of all materials used in the handling of the antigen, and documentation to confirm the quality. The Veterinary Early-Phase Development replaces the human Pre-Development Phase and it is focussed on addressing the three key elements of a Regulatory Dossier, which within the United Kingdom (UK) and European Union (EU) are broadly defined as Quality (Manufacture), Safety and Efficacy.

The Quality data package should address the purity and consistency of the final manufactured product and ensure that each batch of vaccine is fit for purpose. Particular requirements at this phase include the qualitative and quantitative details of the vaccine's constituents (seeds, adjuvants, preservatives, stabilisers, etc), an outline description of the manufacturing process, details of the starting materials, certification on the freedom from TSEs, details of quality control tests, a description of batch safety testing, batch to batch consistency data, stability testing data and a product release potency test. The potency test confirms the suitability of each vaccine batch and it can be either an *in vitro* or *in vivo* assay [3]. A good test will guarantee the efficacy of the finished vaccine

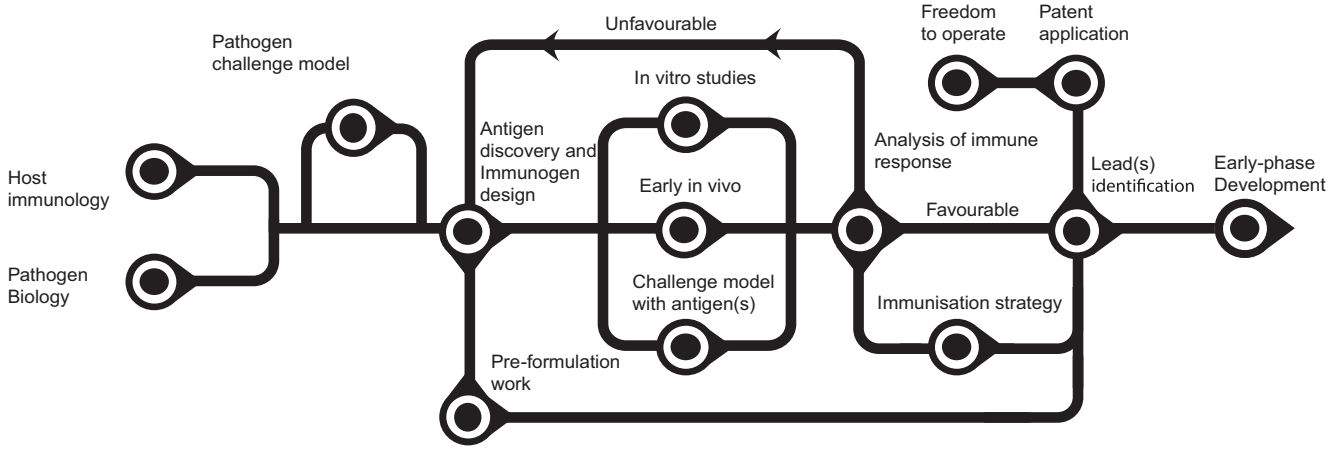

Fig. 1. Discovery/Feasibility Phase of a Veterinary Vaccine. Map showing the process flow from early Host Immunology and Pathogen Biology through to the identification of a Lead Vaccine Candidate.

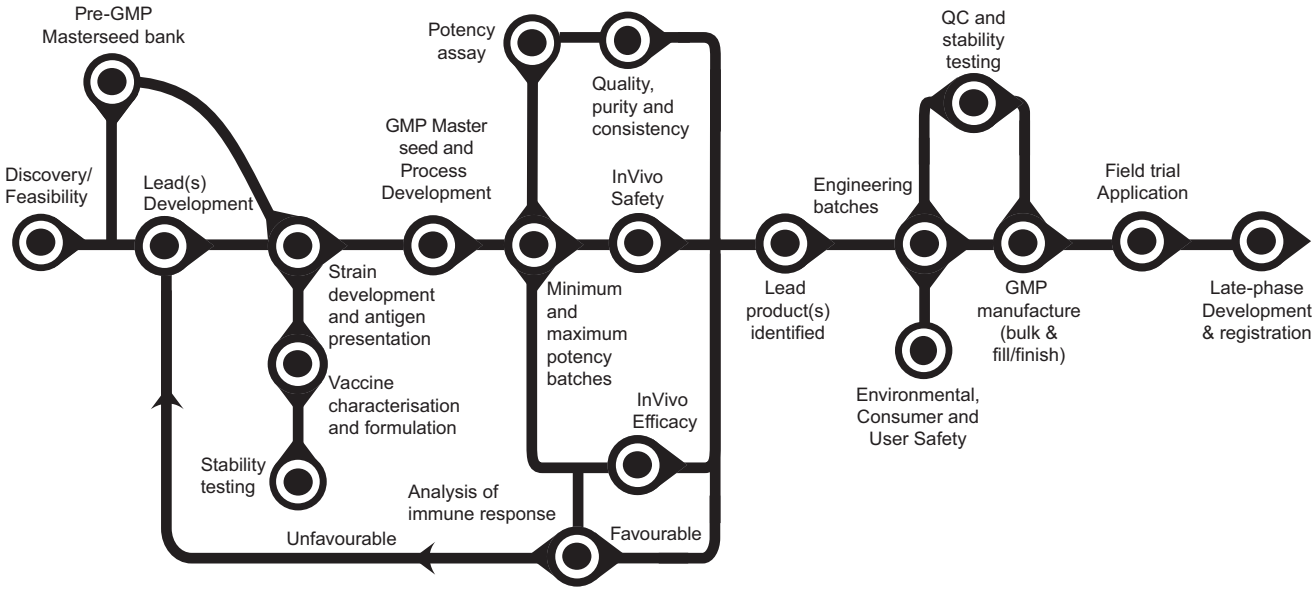

Fig. 2. Early-Phase Development of a Veterinary Vaccine. Map showing the process flow from a generation of a Pre-GMP Master Seed for the Lead Vaccine Candidate through to GMP Manufacture and a Field Trial Application.

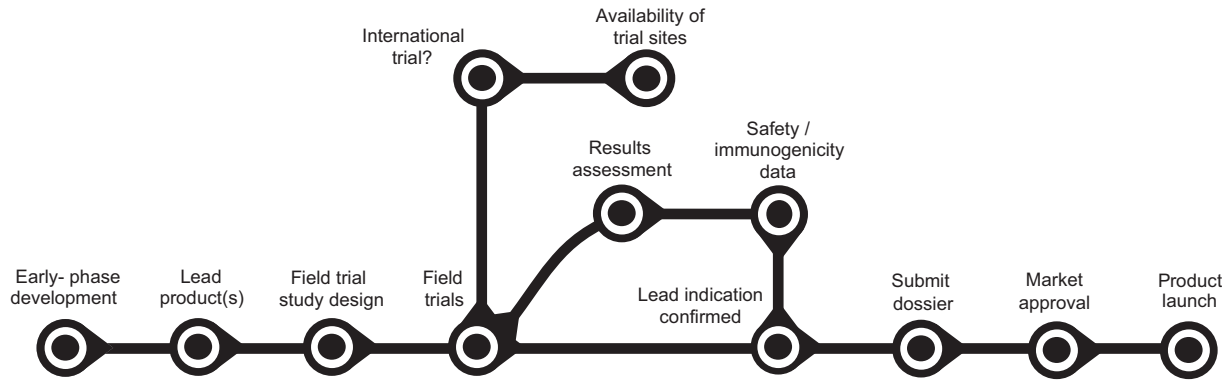

Fig. 3. Late-Phase Development and Registration of a Veterinary Vaccine. Map showing the process flow from a Field Trail Design for the Lead Vaccine Product through to Product Launch.

over its product shelf-life and it will generally be used to generate real time stability data on the vaccine.

The Early-Phase Development Safety Testing should be carried out according to the principals of Good Laboratory Practice (GLP) and will be dependent on the nature of the vaccine (live attenuated, inactivated, sub-unit, recombinant, etc) [4]. This will generally include single, repeat and possibly overdose studies carried out with maximum titre/potency product in minimum age animals. Further studies will also be required for animals in pregnancy or birds in lay. Additional live vaccine studies should include a study of the vaccine's shed and spread, its potential for reversion to virulence, the biological properties and a review of any potential for recombination. Safety studies must also cover any effects of the vaccine on normal immunological functions, environmental safety and end user safety.

Finally, the Efficacy data should include onset and duration of immunity studies conducted with minimum titre/potency product in each category of animal for which the vaccine is intended. It may also involve efficacy in the face of maternally derived antibodies, a study of the requirement for booster doses and an investigation into the immune mechanisms involved in the hosts response to the vaccine (humoral antibody, secretory antibody, cell mediated immunity, etc). These studies, which will generally include virulent challenge protection data, must cover each route of immunization and each component within a multivalent vaccine.

During Early-Phase Development the pilot scale manufacturing process should be validated and scaled-up to levels more reflective of the final manufacturing scale. This should eventually result in three GMP manufactured consistency batches and finished filled product that can be used in stability tests and field trials.

3.4. Late-Phase development

Data from Early-Phase Development is used to apply for an ATC to conduct field trials as part of Late-Phase Development (Fig. 3) to ensure that the vaccine is both safe and efficacious under field conditions, designed to mimic its "everyday" use [5]. The ATC application should include analytical information such as qualitative and quantitative particulars relating to the product and details of any data relevant to the safety of the product. It may also include preliminary laboratory efficacy data from Early-Phase Development or justification as to why such data cannot be generated within a laboratory environment and thus field efficacy testing is required. Field Trials should be conducted according to the VICH Guideline

(GL9) on Good Clinical Practice (GCP). This will provide a unified standard for the UK, EU, Japan, Australia, New Zealand and the USA to facilitate the mutual acceptance of clinical data by the relevant regulatory authorities. The details of the trials will depend on the species for which the vaccine is being developed. At this stage the veterinary vaccine development process is different to the human vaccine process since there is no requirement for Clinical Phase I, Phase II and Phase III trials.

The Registration Phase (Fig. 3) will be dependent on the regulatory strategy and intended markets for the product [6]. It is important to consider the recommended dose and route of administration for each species and category of animal in which the vaccine is intended for use. This Map has principally focused on the development of a vaccine for the UK and EU and leads to the generation of a product data package that would be used to compile a regulatory dossier for marketing approval. Other global markets will have their own regulatory agencies and specific regulatory requirements.

3.5. Potential Bottlenecks

As part of mapping the development process careful consideration has also been given to the definition of Bottlenecks generally encountered with vaccine R&D. Within veterinary vaccine development these Bottlenecks tend to be associated with the availability of appropriate test facilities, legal permissions, master seed production, vaccine manufacture and regulatory requirements. They are also dependent on the availability of appropriate regulatory, legal and manufacturing expertise. The potential Bottlenecks can all be individually identified and highlighted on the online process map.

4. Conclusion

In conclusion, the Process Map described within this paper can be used to recognise some of the critical steps, identify potential bottlenecks and illustrate the complexity of the vaccine development process. The development process for a veterinary vaccine typically takes between 3 and 6 years in total, depending on the country in which the product is being registered, the technology being used and the target species. By contrast the Human Vaccine Development Process can take between 10 and 20 years. The details of the process will de dependant on the nature of the vaccine that is being developed. For more traditional vaccine approaches it will depend on whether they are live (attenuated) or killed (inactivated) products [7]. The development process will also need to be modified to take account of vaccines that are based on novel recombinant technology [8]. The online veterinary process Map was launched in September 2019 and can now be found on the MRC Vaccine Development website (http://vaccinedevelopment.org.uk). This Process Map is intended to be a general guide to help those working on new vaccines and facilitate the vaccine R&D process. It should only be used in consultation with the relevant experts and it is important to recognise that every vaccine development project will have its own unique requirements.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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