Phibro
ANIMAL HEALTH CORPORATION TM

October 17, 2019

Dear Sirs/Madams:

Phibro Animal Health Corporation would like to submit for your consideration the following proposal for an addition to Annex 2 of Regulation 2019/6.

Development and protection of complex and/or novel excipients and adjuvants for vaccines

Vaccines consist of the immunologically relevant antigen plus excipients and adjuvants that improve the effectiveness and/or safety of the vaccine. Adjuvants work by attracting the right immune cells to achieve a strong and lasting immune response against the targeted pathogen. Established and proven adjuvants, as well as those in development, contain technologies that facilitate improved safety, effectiveness, and delivery. The goal is to increase the magnitude and longevity of protective immune responses whilst reducing the dose and improving vaccine safety and stability.

Development of complex and/or novel adjuvants requires a significant amount of research and investment. For proprietary adjuvants produced by specialist companies, the specific ingredients, exact content and concentrations, the sourcing of materials, blending, and all manufacture and control assays, are the result of many years of development and testing. These data and processes are highly commercially sensitive and are not revealed to the final vaccine manufacturers.

The inclusion in annex II of Regulation 2019/6 of a possibility to submit commercially sensitive data for complex or novel excipients and adjuvants via a direct route to Authorities could be made in a robust way by allowing these substances to use the provisions laid down for active substances in 4.A.1, the Vaccine Antigen Master File system.

In Title IIb, Part 2.C, last paragraph (proposed text in **bold underlined**):

"...For novel excipients, that is to say excipient(s) used for the first time in the European Union in a veterinary medicinal product or by a new route of administration, details of manufacture, characterisation, and controls, with cross references to supporting safety data, both clinical and non-clinical, shall be provided. ***For complex or novel excipients and adjuvants, data may be submitted by the excipient or adjuvant manufacturer according to the provisions laid down for active substances in 4.A.1, Vaccine Antigen Master File.*** *For colouring matters the declarations of compliance above shall be considered sufficient."*

This would provide a framework where complex or novel excipients and adjuvants could be assessed by the competent authority without having to reveal manufacturing details, including proprietary ingredients, to the vaccine producer. Moreover, it will increase the incentives for research and development of better, safer, and more robust excipients and adjuvants for the benefit of all future veterinary vaccines for animal health, welfare, and to safeguard the public from zoonosis.

Glenpointe Centre East, 3rd Floor / 300 Frank W. Burr Blvd., Ste. 21 / Teaneck, NJ 07666-6712
Direct: 1-201-329-7300 / Fax: 1-201-329-7399

In the past, the use of simple adjuvants did not necessitate specific measures, but given the innovation in modern vaccinology, the concept of an excipient or adjuvant master file system becomes important.

European authorities have so far tried to handle the delicate situation of proprietary information in the manufacture and quality control of a proprietary adjuvant by accepting the use of trade names in the dossier and the separate submission of confidential data directly to the Regulatory Authorities.

In the U.S., the adjuvant company submits a document called a "Special Outline" to the USDA Center for Veterinary Biologics (CVB) that includes the adjuvant ingredients, their concentrations, the general adjuvant manufacturing procedure, and the quality control tests conducted on the adjuvant. The Special Outline is identified with a unique number which is referenced by the customer producing a vaccine. The trade name of the adjuvant as well as the Special Outline number are included in the vaccine manufacturer's Outline of Production. Therefore, the vaccine manufacturer does not have access to the proprietary adjuvant information.

Each specific vaccine is tested for safety and efficacy according to the legal requirements in laboratory and clinical trials conducted with that vaccine and reflected in the SPC/leaflet.

There are no safety grounds to require disclosure of additional details of the proprietary adjuvant components via the dossier to MAAs or via the EPAR/SPC/product information to the public. It is fully possible for the MAA/MAH to perform all necessary in-process and final product controls, including stability testing, with general knowledge on the adjuvants provided by the adjuvant manufacturer to the MAA/MAH.

It is concerning if there will be no legal protection of proprietary information for novel or complex excipients and adjuvants in European veterinary medicines legislation because the consequence is that some new or improved vaccines may not be available to EU countries. It is also likely that proven and established adjuvants will become unavailable for use in vaccines in EU countries as adjuvant companies will be unwilling to provide this proprietary information to vaccine manufacturers.

The developers of complex or novel excipients and adjuvants are open and responsive towards the requirements from Regulatory Authorities, but they strongly need to maintain the opportunity to NOT disclose trade secrets to their customers, who purchase the proprietary adjuvants or excipients for production of the final authorised vaccines.

We therefore kindly propose to include in the legal framework an opportunity to establish a voluntary system of master files for manufacturers of excipients and adjuvants for veterinary vaccines, for example by including the above proposed sentence in Annex II to Regulation 2019/6.

Best Regards,

signature (illegible)

Greg Otto
Senior Vice President, Global Vaccines
Phibro Animal Health Corporation