17 June 2015

ITF Briefing meeting report

UNISEC, Universal Influenza Vaccines

Briefing meeting held at the European Medicines Agency (EMA) on 17 June 2015.

The objective of the ITF briefing meetings is to provide for a preparatory discussion on scientific and regulatory topics relevant to the development of new medicinal products and technologies complementing and reinforcing existing formal procedures.

Proposed product name:	**Universal Influenza Vaccines**
Applicant:	FP7 EU consortia FLUTCORE and UNISEC
Proposed active substance:	
Proposed finished product:	
Proposed indication:	

Participants

Applicant participants:

Dr. Otfried Kistner (advisory board UNISEC), Independent Consultant; Previous Senior Director Clinical Virology & Scientific Affairs, BioScience Baxter, Austria
Dr. Jim Robertson (advisory board UNISEC), Independent Consultant (NIBSC retired); WHO INN expert committee; EMA expert advisor, United Kingdom
Dr. Marcy Liu (Clinical Studies, UNISEC)
Dr. Andreas Fomsgaard (DNA vaccination / pigs, UNISEC)
Dr. Mike Whelan (IQUR FLUTCORE)
Prof. Claude Muller (FLUTCORE)
Dr. Stephen Norley (Assays, UNISEC)
Dr. Ed Schmidt (Project Manager UNISEC)

EMA participants:

Manuela Mura, Anti-infectives and Vaccines, ITF Coordinator
Falk Ehmann, ITF Secretariat (part of the meeting)
Marco Cavaleri, Head of Anti-infectives and Vaccines
Emil Cochino, Anti-infectives and Vaccines
Ragini Shivji, Quality of Medicines

VWP Experts:

Michael Pfleiderer
Marta Granstrom
Leonoor Wijnans (via AdobeConnect)
Charlotta Bergquist (via AdobeConnect)

Disclaimer presented at beginning of meeting

The views expressed in this document are the opinion of the participating members of the Innovation Task Force and the experts, and may not reflect the opinion of the EMA scientific committees. Therefore, the answers provided should not be interpreted as regulatory guidance or review recommendations for an application, but as a preliminary set of scientific considerations of the information presented.

Should aspects of the subject matter discussed herein become part of a formal data submission, application, or supplement, it is at the full discretion of the appropriate working party, evaluation team or scientific committee to completely and independently assess the product(s)/technology(ies) in question.

1. Background.

The EU is funding a number of FP7 consortia aimed at the development of universal influenza vaccine concepts. Five consortia: EDUFLUVAC, FLUNIVAC, UNIVAX, FLUTCORE and UNISEC are developing different concepts and strategies, ranging from preclinical studies to phase IIB clinical trials. World-wide a number of other companies and organizations is also developing new universal influenza vaccine concepts. The aim of this meeting is to initiate information exchange from both sites, and to obtain preliminary and informal regulatory feedback from the ITF. Since each product will have its own specific characteristics and applications, we aim to focus on the general issues these universal vaccine concepts will encounter during the registration process.

2. Topics discussed

Topic 1: Breadth of Protection for Universal Influenza Vaccines

Applicants' questions:

- Ideally, a universal IFA vaccine would protect against all major virus variants. How should "universality" be demonstrated?
- Will protection against H1, H2, H3 plus 3 pandemic strains (H5, H7 and H9) be sufficient to claim for a universal influenza vaccine?
- Will protection against most influenza A strains (including group 1 and 2) be required to claim for an universal influenza vaccine?

In the light of the information provided and the discussion held the following key points were outlined by the experts:

ITF: Key points on topic 1

- The Agency has not been exposed to universal vaccines in discussion with developers.. It is not possible from a regulatory perspective to define a priori what a 'universal' vaccine should protect against, as it is unknown and it may not be possible to fully define if a vaccine will be able to protect against all strains potentially responsible to cause disease in humans. These aspects are to be characterised based on the data obtained with a specific product, and provide

the basis for the claims that the Applicant will make in the Product Information. It is recommended to seek further regulatory guidance via scientific advice with a precise proposal.

- The pivotal question to ask at the beginning of development is whether a vaccine is protective and what are its risks. Challenge studies in ferrets can be useful as proof of concept for broadness of protection before starting human investigation and can also support the identification of immunogenicity markers that might be relevant also in humans. Animal models other than ferrets can also be used, and is important that the choice of the model is justified (in the dossier) by the Applicant. The Draft Clinical and non-clinical Guideline for influenza vaccines is published and currently undergoing finalisation following consultation, and it may provide further guidance on these aspects. It can be found on the EMA website and it is expected to enter into force by 2016.

- In a ferret model, high pathogenic strains first (lethal strains, followed by less lethal / non lethal strains followed by drift strains), may provide informative data to initially define the broadness of protection afforded by a specific vaccine, i.e. to define the potential 'universality' of a construct which could be interpreted as the possibility to induce protection against both seasonal and pandemic strains. Lethal strains have the advantage that survival as endpoint can be used together with other aspects. Indeed ferrets are of value also as disease model and secondary endpoints such as viral load or clinical symptoms are important too, e.g. in view of dose-finding.

- In general terms for a vaccine development plan, it was suggested starting small and showing that one has a vaccine that is able to show protection, and this could be easily proved against a lethal strain in an animal model, e.g. H5N1 or H7N9; then expand from there and show protection against other strains. What the vaccine will protect against will be ultimately defined by what is achieved in clinical studies and will be defined in the Summary of Product Characteristics (SmPC). "It's not what a vaccine has to achieve, it's what it does achieve…..". In principle studies in animals can help defining the potential of a vaccine, i.e. type of protection afforded by a vaccine, and this is informative for what to look for in subsequent human trials. Of course if specific products are already more advanced in development so that human data are available, then the use of animal models may be seen only as supportive, although the experts clarified that a strong rational for the definition of the breath of the protective value should be shown in a dossier for MAA, and this in principle would include animal studies.

Topic 2: Immunology / Antibody responses for Universal Influenza Vaccines

Applicants' questions:

- Will a cell immunity influenza vaccine be accepted by showing its induction capacity on influenza-specific cytokine responses?

- Is multi-parametric cytokine FACS analysis sufficient to show the effectiveness and activity of cellular immunity vaccines? If not, what additional assays are considered necessary?

- Is a staining panel containing CD4, CD8, IFN-γ, IL-2, TNF-α, and IL-4 sufficient to show the vaccine efficacy in the absence of HAI or neutralizing antibodies? If not, what additional markers are considered necessary?

- Is *ex vivo* PBMC stimulation with vaccine components and peptide pools from the vaccine constructs enough to judge the "universality" of universal influenza vaccines?
- Is *ex vivo* PBMC stimulation with live viruses required? If yes, how many strains of type A and B influenza viruses are required for inclusion to judge the "universality" of universal influenza vaccines?

- Some vaccines will not induce antibodies that cause HAI because they do not elicit antibodies to the influenza domain that cause hemagglutination. What assay can be used to prove activity?

- Can single radial hemolysis (SRH), ELISA isotyping and/or antibody dependent cell toxicity (ADCC) assays be used to judge the efficacy of non-neutralizing antibody or antibody with no hemagglutination inhibition (HI) activity?

In the light of the information provided and the discussion held the following key points were outlined by the experts:

ITF: Key points on topic 2

- ITF welcomed the efforts made or planned in measuring many CMI parameters extensively, but it was noted that it could be of value to define potential immune correlates in animal so to better focus the investigation of immunogenicity in humans. It is however acknowledged that it may be difficult to obtain good immunogenicity data in animals. Important to note: for MAA it is essential that validation or certifications of assays are produced.

- Sterilising immunity is not considered an essential claim for influenza vaccines in general and it would carry many uncertainties as to how such claim could be demonstrated. Protection against disease is required and the clinical endpoints for RCTs are essentially based on clinical endpoints such as PCR-confirmed ILI. The applicant asked if in clinical trials it would be acceptable to have less severe cases as endpoint. This proposal should be discussed further but for sure it would require a very good case definition. Endpoints such as severity of disease, death or hospitalisation are already foreseen in the guideline as secondary endpoints; in case they would need to be proposed as primary endpoints, this should be discussed upfront with regulatory authorities. It is recommended that Applicants discuss as early as possible how to design trials with alternative endpoints via Scientific Advice.

- The presence of neutralizing antibodies after vaccination is helpful, and it is expected to be addressed in the registration process but this will depend on the type of vaccine, which at the moment is not clear. Every effort should be made in animal and during clinical efficacy trials to identify potential correlates of protection, i.e. neutralising antibodies and T cell immunity, which could prevent from having to conduct large phase III efficacy trials.

Assay definitions are not specifically relevant at this stage, which does not seems very advanced, and it is difficult in this setting to answer these questions since it is not well known what the final vaccine will be and which type of immunity/protection will be able to achieve. It was highlighted to start to prove protection in the ferret model, then universality, and then assays in humans. The type of assays and endpoints to be used in clinical development should be the subject of a product-tailored Scientific Advice procedure.

Topic 3: Ongoing communication exchange between EMA and FP7 consortia

Applicants: Different concepts and strategies for the development and application of universal influenza vaccines are being developed by public-funded organizations. Each company will certainly have to initiate the individual registration process for its product. All of these products however do have common regulatory issues which would be worth to be approached in a more informal information exchange between regulators and public consortia.

In the light of the information provided and the discussion held the following key points were outlined by the experts:

EMA: Key points on topic 3

- ITF welcomes future discussions with individual applicants/consortia of universal flu vaccines at any level. ITF could continue to be a forum for discussion, however it should be noted that this advice is usually a type of high level brainstorming advice and that it is no binding for future regulatory applications since experts participate only on a voluntary basis. As such it may not be felt particularly useful to Applicants beyond a certain point. ITF recommends that scientific advice is sought from companies on individual products on quality, non-clinical and clinical aspects of development, especially for novel concepts and products such as these ones. Pre-submission meetings are organised by EMA to support applicants in preparing the dossiers for scientific advice, to ensure that these are as successful as possible and tailored to the individual product. This experience will in turn be very useful for the Agency by allowing to gather sufficient amount of information that can be reflected in appropriate guidelines.