



The Vaccine Formulation Laboratory: A platform for access to adjuvants

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ABSTRACT

Adjuvants are increasingly used by the vaccine research and development community, particularly for their ability to enhance immune responses and for their dose-sparing properties. However, they are not readily available to the majority of public sector vaccine research groups, and even those with access to suitable adjuvants may still fail in the development of their vaccines because of lack of knowledge on how to correctly formulate the adjuvants. This shortcoming led the World Health Organization to advocate for the establishment of the Vaccine Formulation Laboratory at the University of Lausanne, Switzerland. The primary mission of the laboratory is to transfer adjuvants and formulation technology free of intellectual property rights to academic institutions, small biotechnology companies and developing countries vaccine manufacturers. In this context, the transfer of an oil-in-water emulsion to Bio Farma, an Indonesian vaccine manufacturer, was initiated to increase domestic pandemic influenza vaccine production capacity as part of the national pandemic influenza preparedness plan.

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1. Introduction

With the exception of aluminium salts, adjuvants that can be used in prophylactic vaccination have mostly been developed by a few large vaccine manufacturers. Gaining access to these adjuvant systems has been challenging for academic researchers, small biotechnology companies and developing countries vaccine manufacturers (DCVMs). Even for adjuvants free of intellectual property barriers, expertise on how to select, use and characterize appropriate adjuvant systems remains scarce and is in the hands of a small number of industry experts. To facilitate access to adjuvants, the Vaccine Formulation Laboratory was established in January 2010 at the University of Lausanne (UNIL), Switzerland, under the auspices of the World Health Organization (WHO). This initiative complements the creation in 2007 of a centre dedicated to the research and development of adjuvants at the Infectious Disease Research Institute in Seattle, United States of America. The Vaccine Formulation Laboratory is hosted by the UNIL Department of Biochemistry, a WHO collaborating centre on immunology, and brings together adjuvant and formulation experts. The Vaccine Formulation Laboratory's mandate is to act as a platform for the transfer of adjuvant technology (with a focus on mature technologies such as aluminium salts and oil-in-water emulsions), to provide access to adjuvant systems including generic formulations, commercially available adjuvants and proprietary adjuvants provided under material transfer agreements, and to support adjuvant

users through training and custom vaccine formulation services. In addition, the laboratory is involved in the harmonization of methods to evaluate adjuvants. The primary recipients of these services are public sector institutions, small biotechnology companies and DCVMs.

2. Application of the adjuvant technology transfer platform to the formulation of pandemic influenza vaccines

In June 2010, the United States Department of Health and Human Services' Biomedical Advanced Research and Development Authority (US HHS BARDA) announced a funding opportunity entitled "Development and Sustainable Manufacturing of Adjuvanted Pandemic Influenza Vaccines in Developing Countries". This was part of a set of grants aimed at increasing access to effective vaccines in developing countries at the onset of a potential pandemic. Recent forecasts, as well as experience from the 2009 (H1N1) pandemic, indicate that current influenza vaccine production capacity remains insufficient to allow the global surge capacity needed within the timeframe of an emergency response [1,2]. In October 2010, US HHS BARDA selected the Vaccine Formulation Laboratory to transfer technology for the production and characterization of an oil-in-water emulsion for adjuvantation of pandemic influenza vaccines in Indonesia [3].

2.1. Selection of adjuvant technology

The choice of oil-in-water emulsions for pandemic influenza vaccine adjuvantation was based on several factors.

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Firstly, the licensed oil-in-water adjuvants AS03 (GlaxoSmithKline (GSK)) and MF59 (Novartis), as well as AF03 (Sanofi Pasteur) have demonstrated remarkable antigen-sparing capacity (i.e. a reduction in the amount of antigen required per vaccine dose) for pandemic influenza vaccines. For H5N1 influenza vaccines based on split or subunit antigens, two doses of 90 µg (haemagglutinin (HA) content) are normally required to induce an immune response that meets registration criteria. Although adjuvantation with aluminium salts allows moderate antigen-sparing, the formulation of pandemic influenza vaccines with oil-in-water emulsions can achieve immunity with as low as 3.5–7.5 µg per vaccine dose [4,5]. Therefore, the antigen-sparing properties of oil-in-water adjuvants permit significant enhancement of existing production capacity in the event of a pandemic. Manufacturing facilities producing seasonal vaccine for a small domestic market could rapidly scale up production capacity by formulating reduced amounts of vaccine antigen with an oil-in-water adjuvant.

Secondly, oil-in-water emulsions improve vaccine responses against seasonal influenza in elderly populations, immunocompromised patients and children [6]. They can also broaden the immunogenicity of pandemic vaccines as shown by the MF59-induced epitope spreading from HA2 to neuraminidase and HA1, thus providing cross-clade neutralization and potentially improving *in vivo* protection [7].

Thirdly, the safety profile of oil-in-water emulsions is well documented: MF59 and AS03 have been used successfully in over 100 million people including children. Novartis' seasonal influenza vaccine containing MF59 is routinely and extensively used in the elderly [8], and both GSK's AS03-adjuvanted pandemic (H1N1) 2009 influenza vaccine and Novartis' MF59-adjuvanted pandemic (H1N1) 2009 influenza vaccine were used worldwide in 2009 and 2010.

It is worth noting that the technology transfer of an emulsion containing metabolizable oil and surfactant in the absence of block-copolymer from a European centre to DCVMs does not infringe any intellectual property. Access by DCVMs to this adjuvant technology would therefore be highly advantageous not only for pandemic influenza vaccines, but could trigger benefits for further applications since oil-in-water emulsions have been widely investigated in numerous clinical trials with several subunit antigens, such as HIV, hepatitis B virus and hepatitis C virus antigens [9]. In addition, the capital investment needed to produce oil-in-water adjuvants is relatively modest and the cost of materials adds only marginally to the cost of antigen production.

2.2. Development of processes

The manufacturing process for oil-in-water emulsions has been described in detail [10]. The Vaccine Formulation Laboratory has established the production processes and prepared oil-in-water emulsions that meet all expected physical, chemical and biological (adjuvant activity) parameters. We are currently screening a range of raw material sources and evaluating the acceptability of the products for use in clinical-grade emulsions. This is particularly important for materials of biological origin such as squalene (prepared from shark liver) and heterogeneous surfactants such as Tween80 and Span85. In order to develop all standard operating procedures and relevant documentation for Good Manufacturing Practice (GMP) production, a collaboration has been developed with The Netherlands Vaccine Institute (NVI) in Bilthoven, The Netherlands.

3. Operationalization of the adjuvant hub

Bio Farma, Indonesia, a grantee of the WHO initiative to transfer the capacity to produce influenza vaccines to DCVMs, is the first technology transfer partner of the Vaccine Formulation Lab-

oratory. The first phase of the project comprises the installation of equipment required for production and characterization of oil-in-water emulsions, the establishment of relevant standard operating procedures, training of laboratory staff, and on-site validation of the transferred processes. Once production of the oil-in-water emulsion is established locally, preclinical studies compliant with national regulatory requirements will be conducted prior to human clinical testing of oil-in-water adjuvanted pandemic influenza vaccines.

4. Provision of adjuvants, support for vaccine formulation and training

The Vaccine Formulation Laboratory is facilitating access to adjuvants that are either not covered by intellectual property rights or can be made readily available under licence agreements, and is providing support for vaccine formulation. This activity was initiated as a part of TRANSVAC, a collaborative infrastructure project funded under the European Commission's Seventh Framework Programme. The laboratory will also provide practical training courses on vaccine formulation, the first of which is scheduled for 2012.

5. Harmonization platform for adjuvant comparison

One challenge in the field of vaccine adjuvants is the lack of comparative data that would facilitate their preclinical selection. The Vaccine Formulation Laboratory is engaged in the development of an immunological read-out methodology for harmonized adjuvant evaluation and down-selection by collaborating in the PHARVAT project with the Biomedical Primate Research Center (Rijswijk, The Netherlands), the European Vaccine Initiative (Heidelberg, Germany) and WHO. The results from this project will be published and adjuvants, antigens, reference sera and the immunization protocol will be made available to allow adjuvant and vaccine developers to test their products in direct comparison with PHARVAT's reference materials.

6. Concluding remarks and prospects

Adjuvants are increasingly being used in modern vaccinology. However, aside from aluminium salts, which have been in use since the 1920s, very few adjuvant technologies are readily accessible to the public sector, small biotechnology companies or DCVMs. Although this situation is evolving, as several vaccine adjuvant systems are now (or soon will be) in the public domain, access to adjuvants is only of value if accompanied by access to vaccine formulation know-how. The establishment of a platform to transfer adjuvant technology and formulation expertise to public sector vaccine developers and DCVMs addresses these needs. As demonstrated by the success of the International Technology Platform for Influenza Vaccines at NVI, a centralized hub with specific pilot-plant material and hands-on training courses is sustainable when there is demand for the technology. Several DCVMs have already indicated interest in acquiring the adjuvant technology developed at the Vaccine Formulation Laboratory for their pandemic influenza preparedness plans. The oil-in-water technology will be transferred to new beneficiaries and programmes targeting other diseases are also being considered.

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