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# A decade of adaptation: Regulatory contributions of the World Health Organization to the Global Action Plan for Influenza Vaccines (2006–2016)

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ABSTRACT

The Global Action Plan (GAP) for Influenza Vaccines is a decade-long initiative that brings together a diverse range of stakeholders to work towards reducing anticipated global shortage of influenza vaccines and ensuring more equitable access to vaccines during the next influenza pandemic. Since its inception in 2006, significant progress has been made towards all the main objectives of GAP, namely: (1) an increase in seasonal vaccine use, (2) an increase in vaccine production, and (3) progress in research and development of more effective vaccines. The Technology Transfer Initiative (TTI), conceived and managed by WHO under the GAP, contributed to increasing regional influenza vaccine production capacity. This was achieved by facilitating technology transfer in 14 low- and middle-income countries, through grants to manufacturers to establish or strengthen influenza vaccine production capacity and support to their national regulatory authorities. Five of the countries subsequently licensed locally produced influenza vaccines; two pandemic and three seasonal vaccines received WHO prequalification. The success of GAP can be largely attributed to the regulatory support provided by WHO to both manufacturers and regulators. This support had two components: (1) direct regulatory support to GAP/TTI, and (2) support to GAP-related WHO programmes, such as the Pandemic Influenza Vaccine Deployment Initiative in 2010 and the Pandemic Influenza Preparedness Framework since 2013, especially in non-vaccine-producing countries. Temporary adaptation of the assessment process for influenza vaccines in the WHO Vaccine Prequalification Programme to the A(H1N1) pandemic situation in 2009 was instrumental to the success of the WHO Pandemic Influenza Vaccine Deployment Initiative in its attempt to meet the demand for pandemic vaccines in countries that received donated vaccines.



## 1. Introduction

Vaccine regulation, as an integral part of regulation of medicines in general, aims to ensure that vaccines offered to the public to prevent disease are safe and effective. Activities cover all stages of vaccine development and marketing, from early development, through marketing and post-marketing authorization, to the permanent removal of the product from the market. Regulatory support has been essential to the success of the Global Action Plan (GAP) for Influenza Vaccines, the subject of this special issue of *Vaccine*. The GAP is a multi-stakeholder, multi-partner initiative aimed at ensuring that populations throughout the world can be protected through vaccination in the event of an influenza pandemic. This paper provides an overview of the regulatory contributions of the World Health Organization (WHO) to GAP since the Plan's inception in 2006.

Vaccines are generally regulated by national jurisdictions, although in some areas supranational regulatory oversight has recently emerged, e.g. in the European Union. National regulatory authorities (NRAs) are the principal executors of vaccine regulation.

WHO is not itself a regulatory agency for vaccines or any other medicines. However, by bringing together strategic stakeholders from around the world, the Organization plays an important catalytic role in promoting convergence in the field of vaccine regulation. The GAP is a good example of how the continuous adaptation of the global regulatory milieu to sudden challenges, such as the emerging avian influenza threats, is instrumental in controlling disease outbreaks. It is widely accepted that regulators with multiple regulatory pathways in place now are better prepared to face

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the challenges of a future influenza pandemic. Through relevant initiatives, such as the GAP, WHO has played an important role in promoting this positive development.

## 2. WHO and the biannual production of seasonal influenza vaccines

The causative virus of human influenza disease was discovered in the early 1930s by Smith et al. [1]. Soon after the discovery, attempts were made to develop influenza vaccines and over the next three decades both inactivated and live attenuated vaccines were marketed and used in annual vaccination campaigns in many regions of the world. Active immunization is the main public health weapon in reducing morbidity and mortality due to influenza. Because of the ever-evolving nature of the influenza virus, immunization needs to be carried out every year in seasonal campaigns.

A periodic relicensing process has been established by regulators to meet this yearly challenge. The manufacturing logistics of influenza vaccines are complex. The rapid spread of drifting influenza viruses during and between epidemics represents a continuous challenge for timely production of a vaccine that antigenically matches the circulating virus. Two sets of influenza vaccine are manufactured in each 12-month period, distinguished as northern and southern hemisphere vaccines. Following a highly complex, time-sensitive preparatory process, which involves a wide range of technical contribution from five continents in a WHO-coordinated effort, the vaccines are produced in a race against time [2,3].

The preparatory process consists of three steps:

(1) selection of vaccine virus strains;
(2) development of high-yield candidate vaccine viruses, through either classical reassortment methods or reverse genetics technology;
(3) preparation of vaccine potency reagents.

Since 1973, WHO has made formal recommendations for the composition of influenza vaccines, based on the information provided by the WHO Global Influenza Surveillance and Response System. High-yield candidate vaccine viruses are then developed in WHO collaborating centres and selected independent laboratories, and distributed to manufacturers. For final formulation and lot release of the vaccine, the necessary reference reagents are developed by WHO essential regulatory laboratories, with active contributions from the vaccine industry as the antigen source [4]. This well established framework has ensured a steady, well balanced regulatory environment for influenza vaccines over many years. Apart from a relatively minor revision in 1990, the WHO regulatory guidance documents for inactivated and live attenuated influenza vaccine remained unchanged from the late 1970s until the mid-2000s [5–7].

## 3. Regulatory challenges and the inception of the GAP

Around the turn of the century, a public health emergency arose that threatened both human and veterinary health. The apparent threat of an imminent influenza pandemic of devastating proportions and an anticipated case-fatality rate potentially over 50% dramatically changed public perceptions. The effects inevitably spilled over into the regulatory arena.

It started in 1997, with the first-ever reported outbreak of A (H5N1) avian influenza in humans in Hong Kong [8,9]. The outbreak was halted through the territory-wide slaughter of millions of chickens and additional control measures [10,11]. However, the global public health alert level remained high, mainly because of three factors: the extremely high case-fatality rate observed during the outbreak; the anticipated shortfall of billions of doses of vaccine in the event of a pandemic; and the lower than expected immunogenicity observed in candidate pre-pandemic A(H5N1) vaccines [12,13].

Following six years of silence, human infections due to A(H5N1) were again seen in 2003. Since then, a total of 850 laboratory-confirmed human cases, causing 449 deaths, have been reported from 16 countries in Asia, Africa and Europe [14].

In view of the threat of an influenza pandemic, and in response to two World Health Assembly (WHA) resolutions, the GAP was initiated in late 2006 [15]. Resolution WHA56.19 in 2003 requested that seasonal influenza vaccine coverage should be increased. Resolution WHA58.5 (2005) requested the WHO Secretariat to seek ways to reduce the global shortage of influenza vaccines for both epidemics and pandemics, including vaccination strategies that economize on the use of antigens.

This comprehensive multi-stakeholder initiative, originally known as Global pandemic influenza action plan to increase vaccine supply, aims to reduce the global shortage of influenza vaccines and the inequitable access to them. It has three main objectives:

1. an evidence-based increase in use of seasonal vaccine;
2. an increase in vaccine production capacity and strengthened national regulatory competencies;
3. research and development of more effective vaccines.

WHO's regulatory contribution to GAP has two components:

- regulatory activities in support of TTI, a specific WHO initiative under GAP which, through technology transfer, aimed at establishing influenza manufacturing capacities in low- and middle-income countries;
- other indirect regulatory support activities linked to the overall objectives of the GAP.

## 4. The A(H1N1) influenza pandemic in 2009–10 and its effect on the GAP

June 2009 saw the first influenza pandemic of the twenty-first century, following inter-related outbreaks due to a previously undetected A(H1N1) virus in North America. The TTI, even in its early developmental stage, was able to contribute to global immunization efforts, with pandemic vaccines being developed, produced, and licensed within the framework of the GAP. At the same time, the pandemic provided an opportunity to review activities and adjust them to take account of lessons learnt.

In mid-2011, WHO and its partners from national governments, United Nations agencies, funders, regulatory authorities, non-governmental organizations, vaccine manufacturers and academic research held a meeting to review the progress made and lessons learnt. This meeting aimed to refine the objectives of the GAP and to provide a roadmap for technical implementation and a sustainable approach to pandemic preparedness. While the primary objectives of the GAP remained the same, consideration was given to expanding the Action Plan and incorporating new activities.

In the regulatory area, emphasis was given to improving national and regional regulatory processes, improving vaccine deployment capabilities, and creating more responsive post-marketing monitoring of vaccine effectiveness and safety in order to allow public concerns to be addressed promptly [16].

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