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Journey of the Dengue Vaccine

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Singapore: Dengue, also known as break bone fever, is currently the most common vector-borne disease. The World Health Organization (WHO) estimates that dengue affects nearly 50 million people across geographies, causing serious morbidity and mortality. The disease is now endemic in over 128 countries across the globe and in 2013 and the WHO ranked dengue as the fastest spreading vector-borne disease with an epidemic potential.

Dengue poses substantial economic and disease burden in Southeast Asia and health officials estimate that direct cost incurred due to the sporadic epidemics occurring in the region sums up close to $1 billion per year. Today, more than 3.9 billion people are directly threatened on a daily basis, 390 million per year are infected and 500,000, develop the severe form of the disease, requiring hospitalization. Since the first sporadic outbreaks recorded in the late 18th century in Jakarta, Cairo and Philadelphia, the number of dengue cases has grown, multiplying more than 30-fold over the last 50 years.

With no cure or vaccine available, affected nations scramble as the dengue outbreak sweeps through the Asian continent almost every monsoon. The growing threat of dengue coupled with its huge financial burden made it imperative to develop a vaccine that can curb the disease. Though lot of researchers across the globe were brainstorming on newer molecules for a vaccine or a drug since 1940, it was Sanofi Pastuer, a France-based drugmaker that tasted success. Sanofi is now close to launching a vaccine that can combat all four serotypes of dengue virus. However, this was not easy. It is a story of 20 years of research, repeated clinical studies, management shuffles, funding challenges and recurring failures.

"The battle against dengue started almost 70 years ago," recalled Dr Anh Wartel, senior director, clinical development, R&D, Sanofi Pasteur, "During World War II, science started to address dengue in a systematic way. This lead to virus isolation and

identification. Renowned virologists, Dr Albert Sabin and Dr Walter Schlesinger together discovered serotype 1 and 2 in in 1944 and Dr Bill Hammond discovered serotype 3 and 4 in 1956. In parallel, scientists were striving to develop a vaccine. In 1944-45, Mr Sabin and Mr Schelsinger developed the first monovalent dengue vaccine, a live attenuated vaccine against serotype 1. More than 20 years later, during 1970-80s, Dr Natth Bhamarapravati at the Mahidol University in Thailand developed a tetravalent classical live attenuated vaccine against all four serotypes. In 1994, Sanofi Pasteur signed a partnership with the University of Mahidol leading to proof of concept of a tetravalent live attenuated dengue vaccine in 2001."

"Sanofi Pasteur was the first vaccine company to invest in the research and development of a dengue vaccine," claimed Dr Wartel. "The decision to commit to this project was challenged internally, as it was one of the toughest project with little hopes of success. Moreover the new vaccine had to be effective against all serotypes of the virus. Eventually, the strongest supporter of the decision was then CEO of Sanofi Pasteur. He had caught dengue while he was travelling to Cambodia, he had lived with it, and understood it to be a terrible disease."

Clinical investigation conducted in Thailand on this first generation live attenuated tetravalent vaccine showed promise in early trials. However, the study was soon stopped due to reactogenicity and under attenuation of serotype 3. Sanofi soon decided to adopt a new approach and developed the second generation live attenuated vaccine using recombinant vaccine technology.

"This initial failure shattered our hopes. We were dejected, however, our commitment to research encouraged us to look for a solution. We experimented different methods of vaccine formulation and found recombinant technology to be the most effective. Initially, Sanofi took license from a vaccine company called Acambis, to access its recombinant vaccine technology. After years of efforts that involved multiple failures and experiments, the team finally reached a proof of concept for the second generation vaccine in 2007," said Dr Wartel.

The Making of Dengue Vaccine

Sanofi Pasteur's current dengue vaccine is a live attenuated vaccine. The attenuation is achieved using recombinant DNA technology. The immunogenic properties of each of the four dengue serotypes are combined with the well characterized attenuated profile of the YF-17D vaccine strain (used for the yellow fever vaccine). The structural YF-17D genes have been deleted and replaced by the corresponding genes of each dengue serotype. Thus, the vaccine expresses envelope proteins of the four dengue serotypes responsible for inducing the neutralizing immune response, while the YF-17D structural genes are no longer present.

"This is an innovative, first-of-a-kind vaccine," explained Dr Wartel, "The vaccines for all the four serotypes is produced separately in a stainless steel equipment and then combined into a single vaccine. The product is filled in vials and then lyophilized. Most of the industrial cycle time is dedicated to testing. The overall industrial cycle time end to end from the drug substance up to the drug product of this dengue vaccine is between 18 and 24 months. The vaccine should be stored at +2 to +8°C."

Clinical studies

After formulation, the next challenge was to test whether the vaccine was safe and immunogenic against different dengue virus serotypes. The clinical trials for the dengue vaccine was conducted in many countries involving nearly 40,000 participants. The studies showed the vaccine to be genetically, phenotypically stable and non-hepatotropic. In vitro and in vivo preclinical studies showed that the vaccine induced controlled stimulation of human dendritic cells, and significant immune responses in monkeys. Preclinical studies also helped Sanofi to conclude that immunization should be spaced several months apart to prevent interference between serotypes, and the importance of a 3-dose regimen in 1 year.

"Conducting clinical trials was the biggest hurdle," mentioned Dr Wartel, "There is no immunocompetent animal model available for dengue and hence we could not test for efficacy in animals. Also clinical trials in emerging markets needed special approvals. It was also important to ensure that the study sites had good basis of dengue epidemiological data to determine the statistical power of the study design. Despite the risks and unknowns of clinical development, Sanofi's leadership strengthened its commitment to the dengue vaccine."

In 5 phase I studies conducted in the United States, Mexico, and the Philippines, 400 participants between 2 - 45 years old received the candidate dengue vaccine. In 12 phase II studies conducted in the Philippines, Australia, Mexico, the United States, Colombia, Honduras, Puerto Rico, Vietnam, Thailand, Peru, Singapore, Brazil, and India, 5400 participants between 12 months to 45 years old received the candidate dengue vaccine.

In 8 phase III studies conducted in Australia, Philippines, Thailand, Vietnam, Malaysia, Indonesia, Brazil, Colombia, Honduras, Mexico, Puerto Rico, and Peru, >23,000 participants between 9 months to 60 years old received the candidate

dengue vaccine. Results of the last stage of the clinical study showed that the vaccine offered 95.5 per cent protection against severe dengue and an 80.3 per cent reduction in the risk of hospitalization. The vaccine also showed protection against dengue hemorrhagic fever, the most severe form of the disease.

Findings of these two pivotal phase III efficacy studies were published in two of the world's top peer-reviewed medical journals, The Lancet (CYD14, the Asian study) and the New England Journal of Medicine (CYD15, the Latin American Study). Safety data and dengue cases occurring during the phase III efficacy studies were reviewed by both Sanofi Pasteur and an Independent Data Management Committee (IDMC).
Marketing and regulatory approvals.

"We will file for registration of our dengue vaccine in endemic countries in the first half of 2015. Subject to regulatory approval, the world's first dengue vaccine could be available in the second half of 2015. We are committed to making the vaccine available first in areas where dengue is a public health emergency," noted Dr Wartel.

Post approval there is always a question on whether the company will be able to provide enough dosses in a short period of time. Sanofi leadership team made the early decision to fund a manufacturing facility near Lyon to produce the vaccine before even knowing the clinical trial results. Dr Wartel added, "The facility is ready to produce 1 billion doses of the vaccine over the next 10 years. The decision to build the manufacturing facility was risky since the results of the clinical program were not known yet however it was a risk worth taking."

In June 2010, due to increased disease burden and many outbreaks, the USFDA granted fast track designation to Sanofi's investigational vaccine candidate. "This was an early success for us," exclaimed Dr Wartel. "This meant that the FDA may accept completed portions of a license application for review prior to receipt of the entire application."

Sanofi Pasteur's dengue vaccine was developed without subsidies. It was a complex vaccine to develop and manufacture, requiring 20 years of research and large investments to build sufficient capacities to respond to a world demand.

"Dengue vaccine development represents one of the largest financial commitments made by Sanofi in the past decade," said Dr Wartel. "Investment in production infrastructure (upstream production steps: bulk + formulation) dedicated to the dengue vaccine is around 350 million Euros. Of this amount, approximately 300 million Euros are dedicated to the new vaccine production site near Lyon. Other investments are made on existing industrial sites."

The WHO has set the target to reduce dengue mortality by 50 percent and reduce morbidity by 25 percent by 2020 and Sanofi's vaccine will be an important tool in achieving this target. Sanofi aims to establish collaboration with individual countries to maximize the impact of this vaccine and make dengue a vaccine preventable disease.

"We believe that it is important to develop partnerships to accelerate the introduction of the vaccine to areas where it is needed most," concluded Dr Wartel, "We have already collaborated with the World Health Organization, Dengue Vaccine Initiative, Bill and Melinda Gates Foundation, and health authorities in dengue endemic countries to ensure that the vaccine reaches the maximum number of people."