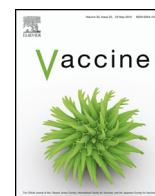




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Conference report

Better vaccines for healthier life. Part II. Conference report of the DCVMN International 14th Annual General Meeting Hanoi, Vietnam[☆]

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ABSTRACT

New vaccines are required to meet the public health challenges of the next generation and many unmet global health needs can be addressed by developing countries vaccine manufacturers such as lower-cost vaccines based on single-dose, thermostable formulations, efficacious in children with compromised gastrointestinal tracts. GMP compliance is also a challenge, as sometimes innovation and clinical development focus is not accompanied by command of scale-up and quality assurance for large volume manufacturing and supply. Identifying and addressing such challenges, beyond cost and cold-chain space, including safety considerations and health worker behavior, regulatory alliances and harmonization to foster access to vaccines, will help countries to ensure sustainable immunization. There needs to be continuous and close management of the global vaccine supply both at national and international levels, requiring careful risk management, coordination and cooperation with manufacturers. Successful partnership models based on sharing a common goal, mutual respect and good communication were discussed among stakeholders.

1. Novel Vaccine Initiatives

An update of Intravacc's Sabin IPV technology Transfer Initiative to developing countries vaccine manufacturers as a Private Public Partnership directly under the Ministry of Health in The Netherlands was provided by A. Hamidi. The Sabin-IPV project includes four main activities: (1) Seed lot production and characterization; (2) preclinical-clinical lot production, phase I/IIa; (3) technology-transfer bilateral agreements with DCVMs; and (4) process fine-tuning and dose optimization. Enough quantities of master and working seed lots are available. An optimized process has been established and a phase I/IIa, double-blind, dose-escalation trial (adults and infants) has been successfully completed, demonstrating that Sabin-IPV is safe and immunogenic. Six different adjuvant formulations with sIPV were tested to study the feasibility of increasing sIPV potency in rats and thus dose sparing effect, adjuvants used included: aluminum hydroxide, two squalene-in-water emulsions, two lipopolysaccharide (LPS) derivatives, and Venezuelan equine encephalitis (VEE) replicon particles (GVI3000). It was established that using Al(OH)₃ dose-reduction was type dependent. Six partner manufacturers from emerging countries have been selected for technology transfer. Further points to consider for product registration include: assays standardization; availability of international reference reagents and standards;

the design of clinical trials, including protection against wild and/or Sabin strains and containment strategies.

A. Nanni (AERAS) highlighted the extent of the tuberculosis (TB) epidemic in the 21st century, with US\$8 billion spent annually on TB-treatment and care in low and middle income countries (MICs). Multi-Drug Resistant (MDR) TB has been diagnosed in 77 countries. It is estimated that MDR-TB prevalence will increase by 150% by 2036, without further interventions. There are at least 13 TB vaccine candidates in the global clinical development pipeline, based on different approaches including viral vectors, protein/adjuvant, rBCG, attenuated M. Tb and mycobacterial (whole cell or extract). Clinical trials of these vaccines are also being used as opportunities to analyze correlates of risk of disease and/or protection. TB primarily strikes working-age adults and costs the global economy an estimated US\$1 billion daily, particularly in the emerging economies. For example, for China it is estimated to reach up to US\$1182 billion from 2006 to 2015, and annual cost of TB to the South African mining sector is over US\$880 million. Data generated by mathematical modeling, estimated that 30–50 million TB cases can be potentially averted by vaccines in adolescents and adults by 2050. An additional 7–10 million TB cases could be averted in infants by 2050, assuming a 2 dose routine vaccination for adolescents/adults at 10 years and mass campaigns in over 11 year olds every 10 years, and a 1 dose routine vaccination of newborns. It was estimated that a minimum of 3 suppliers would be required to meet potential demand within 10 years (Fig. 1), after vaccine introduction (about 250–300 million doses). Within the first 10 years, high income countries and China may dominate the market returns, estimated to be potentially \$13.6 billion dollars, while in the same period MICs and China may dominate the vaccine demand,

[☆] *Important note:* This report summarizes the views of an international group of experts as presented at a scientific conference in a given time point and context, and does not necessarily represent the decisions or the stated policy of any institution or corporation.

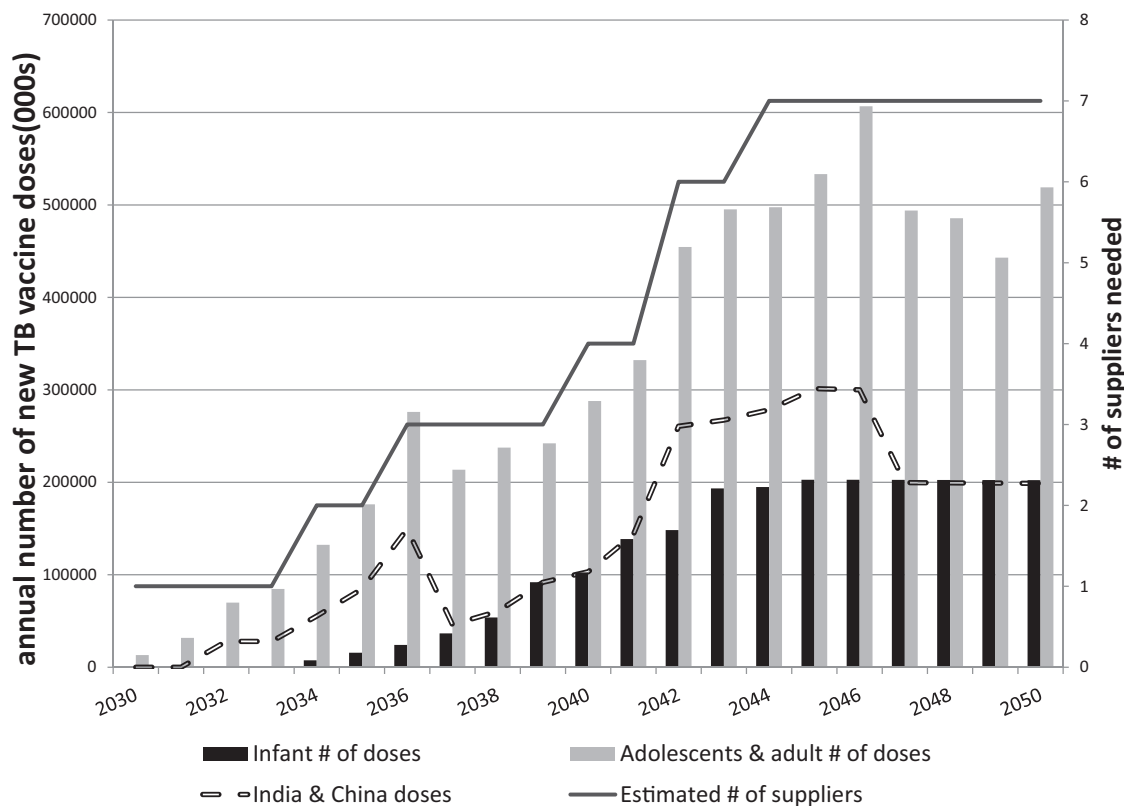


Fig. 1. Early estimates (number of doses) of potential manufacturing needs to satisfy global demand for future TB vaccines, from 2030 to 2050. Two distinct age groups have been considered: Infants (depicted by black bars) and adolescents/adults (depicted by gray bars). The dashed line represents the estimated demand of two large countries, China and India, as compared to total estimated demand (bars). Estimated number of needed vaccine manufacturers/suppliers over time is indicated at the right scale depicted by a solid line. Courtesy of A. Nanni.

estimated at about 1.6 billion doses. So far US\$600 million has been spent in efforts to develop TB vaccine candidates.

Efforts to develop a live attenuated (LA) tetravalent dengue vaccine in partnership with the National Institutes of Allergy and Infectious Diseases – NIH and the Butantan Institute were reported by A. Precioso. Dengue incidence has increased 30-fold over the last 50 years with up to 100 million infections annually in over 100 endemic countries, in tropical and sub-tropical areas. The LA vaccine approach stimulates both cellular and humoral immunity, inducing a strong memory response and durable immune response. LA vaccines for other related flaviviruses such as yellow fever and Japanese encephalitis virus have been successfully developed and LA vaccines can be very economical to produce, helping to secure vaccine access. Ideally, the vaccine must confer protective immunity against all four dengue virus serotypes. Regarding safety, the attenuated virus must not be transmissible via mosquitoes and must show genetic and potency stability. Six monovalent candidates, developed and tested in pre-clinical and initial clinical studies in the USA, demonstrated that each of monovalent vaccine candidates was attenuated and immunogenic in mice and Rhesus macaques. The monovalent candidate vaccines, evaluated in over 750 volunteers in US, were found to be safe and immunogenic when administered as a single subcutaneous dose of 103 PFU/mL. Subjects did not develop a dengue-like illness and local reactogenicity was minimal. Studies in flavivirus-naïve adults (US) demonstrated that the tetravalent mixtures are safe and viremia remained very low. Immunogenicity measured after 90 days demonstrated multivalent seroconversion rate of 74%. Phase II, stepwise, randomized, double-blind and controlled clinical trial to evaluate the safety and immunogenicity of the lyophilized

formulation of the vaccine made at Butantan started in Brazil in October 2013.

L. Yang provided an overview of a successful partnership between CNBG and PATH² for the development and global supply of a live attenuated Japanese encephalitis (JE) vaccine at the Chengdu Institute for Biological Products (CDIBP) in China. CDIBP has one of the largest development and manufacture capabilities of biological products within CNBG with an annual production capacity for more than 100 million doses and over 950 staff. The JE project's strategy at CDIBP, focused on improving the GMP level and achieving WHO prequalification. Critical success factors included the use of software tools, the organization of the project team, the teamwork spirit and defining the framework or rules for the project monitoring, measurement and improvement. Key milestones were defined in 2004 with an assessment by PATH, site inspection by WHO in May 2013 and prequalification in October 2013. CDIBP invested in 10 state-of-the-art buildings to support the project and over 200,000 person/hours have been invested in continuous personnel training. The overall documentation framework consisted of 4 levels: First: Policies and Quality Manual; Second: Guidelines and Specifications; Third: SOPs; Fourth: records and forms. A total of 12 clinical trials were performed between 1997 and 2012 in South Korea, Nepal, Philippines, Thailand, India, Sri Lanka, North Korea, Bangladesh and China, to support registration of the product and WHO prequalification. The JE vaccine has been registered in 11 countries outside of China with more than 200 million doses supplied to date. Key areas of learning include: (1) staff needed to

² China National Biotech Group-Programme for Appropriate Technology in Health.

be stimulated and inspired; (2) commitment from political leaders was very important; (3) good and clear internal and external communication was critical. Allocation of limited resources to complete the project within the planned timeframe was an ongoing challenge.

N. Imbault, from the European Vaccine Initiative, presented the African clinical trials networks, funded by different parties including European and Developing Countries Trial Partnership (EDCTP), European Commission (EC), Malaria Vaccine Initiative, PATH, and Meningitis Vaccine Project (MVP). Capacity building activities of EDCTP and upgrades of infrastructure started in 2003, by investing in long, medium and short term training activities. First round of clinical trials focused on HIV, TB and malaria. Second round will include other neglected diseases such as leishmaniasis, schistosomiasis, trachoma. The first Network of Excellence (NoE) was the Central African Network on TB HIV/AIDS and malaria (CANTAM – www.cantam.org). The second NoE, the East Africa Consortium for Clinical Research (EACCR – www.eaccr.org). The West Africa NoE for TB, AIDS and Malaria (WANETAM – www.wanetam.org). The fourth NoE, located in southern Africa, the Trials of Excellence for Southern Africa (TESA – www.tesafrica.org). Significant investment has been made by EDCTP in capacity building in ethics to enable Institutional Review Boards and Health Research Ethics Committees to be functional and independent. EDCTP has also funded the African Vaccines and Regulators' Forum (AVAREF), coordinated by WHO, as a platform for joint review and GCP inspection of Clinical Trials in Africa. EDCTP has established a site ranking process based on 10 factors ranging from laboratories to sample repository to finance and administration to ethics. To date 30 projects have been funded, for microbicides, HIV vaccine candidates, TB treatments, TB vaccine candidates, malaria treatment and malaria vaccine candidates. One example of network project is the Malaria Vectored Vaccine Consortium (MVVC), established in 2010 to develop a malaria vaccine candidate: a fully GCP compliant site with capacity in biochemistry, hematology, parasitology and immunology, management of samples and storage of investigational products such as vaccines. The MVP is another example of a project with study sites in India, Mali, The Gambia, Ghana and Senegal.

2. Partnerships for vaccines' innovation and access

C. Loucq gave an overview about the International Vaccine Institute (IVI) Technology Transfer activities in Asia. IVI is an International organization working in 35 countries with headquarters in Korea, funded by the Korean Government, Gates Foundation, Swedish government and also from Korean corporations that finance some of the projects in Ethiopia and Malawi. IVI works from "Bench to Field" on research, process development, assay development, and also on Translational research, focusing on interaction of vaccines. IVI is focused on enteric diseases, technology transfer and related training.

Notably, IVI worked in cross collaboration with VABIOTEC and Shanta Biotech for the cholera vaccine Shanchol prequalification in 2011. The vaccine was initially discovered at Vabiotech, licensed and then adjusted to WHO requirements for the prequalification. Cholera burden is likely to exceed 1 million cases annually with 120,000 deaths annually. To increase capacity and access IVI collaborates for technology transfer to Eubiotics in Korea. A clinical trial was conducted on 65,000 subjects and the vaccine provided about 65% protection for at least 3 years and shown to be safe among children aged 1–4.9 years. Larger clinical trials for licensure and WHO prequalification are planned. This vaccine is primarily aimed for a stock pile in preparing for an eventual epidemic. A second project is to make available a high quality, safe and efficacious vaccine for Typhoid fever for the population at most risk from

the infection. As Vi- polysaccharide shows low efficacy levels IVI aims to develop a conjugated vaccine for typhoid, by optimizing Vi fermentation, developing novel purification process, and improving the quality of the conjugated vaccine. The selected carrier protein was Diphtheria Toxoid. The technology is being transferred to Shanta and SK Chemicals (Korea), as well to Biofarma (Indonesia). IVI has moved from 5 to 10L fermentation batches and at the moment clinical lots are ready for Phase II and III studies in India. Conditions for technology transfer include that manufacturers operate in compliance with WHO cGMP, willing to achieve WHO-prequalification, capacity to scale up, and commitment to supply public markets. Challenges IVI faces are the changing priorities of manufacturers (due to mergers and acquisitions) delaying product development.

K. Ella reviewed challenges of adjuvanted vaccines that today include two approaches: delivery systems and immunomodulators. For instance European countries have approved innumerable adjuvanted vaccines so far, while the US FDA has approved only two. Bharat Biotech has partnerships for developing adjuvanted systems, including 23 innovative analogues so far tested in vitro for safety and toxicity. It is considering setting up a common platform to access intellectual property of adjuvants for use in products for public health benefit.

PATH's innovative approach to developing rotavirus vaccines in China and product development collaborations with developing countries manufacturers, supported by Bill & Melinda Gates Foundation (BMGF), was presented by J.-M. Préaud. Six Chinese manufacturers' facilities were voluntarily assessed for Quality Management Systems and GMP with the objective to identify gaps and develop a plan, to prepare vaccines that meet WHO prequalification. The Rotavirus vaccine development project of Wuhan Institute of Biological Products (WIBP) served as pilot to validate new GMP facilities for the manufacturing of oral rotavirus vaccine. In 2008 pilot facilities were built and validated, production processes developed, and validation of analytical methods was completed in 2012. Master and working cell banks and virus seeds banks were prepared in 2011. Mock inspection was conducted prior to manufacturing the first lots at full scale, and no critical issues were identified. Consolidation of quality systems, as recommended in the mock inspection, is being implemented and the production of clinical material of full liquid formulation based on stability data is in progress.

The Vaccine Product, Price and Procurement Data and Information Project (V3P) [1] was presented by M. Kaddar. V3P is a three year project, funded by the BMGF and led by WHO. The project aims to improve the introduction and sustainable use of priority EPI vaccines through the use of vaccine product information, price, and procurement data for evidence based decision making on policies, addressing the vaccine implementation and procurement processes. V3P's focus is on public sector procurement for national immunization programs of GAVI graduating and middle income countries.

There are multiple factors influencing vaccine prices both on the supply and demand sides. Firstly product characteristics, such as dose, presentation, formulation, and prequalification status are taken into account. Secondly, the procurement mechanism (individual country or pooled procurement), the number of supply intermediaries and mark-ups, the volumes and discounts, funding sources, taxes and payment terms are considered. Thirdly, demand and supply dynamics (R&D and production costs, production capacity, segmentation of products, trends in markets and countries, predictability of demand, vaccine pipeline, level of competition, influence of donors and partners, sources of funding, manufacturer's strategies, etc.) are of importance. The supply chain structure, from manufacturer to end user may influence costs as well.

The V3P project includes two phases: (I) collecting and analyzing information, identifying mechanisms in consultation with stakeholders and governments³ [2], and designing a tool in consultation with countries and partners; (II) testing the tool in countries, then implementing and evaluating its impact. Technical support and capacity building activities are a core component of the V3P project aimed to increase awareness of countries on the complexity of vaccine pricing and to improve the new vaccine introduction decision making process.

L. Privor-Dumm (IVAC) spoke about the additional trade-offs of primary container decisions in the context of vaccine wastage. She suggested that more than one container size may be needed within countries. Five dose vials may address issues for some products, but not all. The international community will need to provide improved container level forecasts to capture the varying needs by country to ensure production plans for smaller vial sizes match with country needs and minimize risk of missed opportunities and/or contamination of vials if not handled appropriately.

3. Regulatory science and access to vaccines

O. Mansoor summarized the activities of the Vaccine Presentation and Packaging Advisory Group (VPPAG) which is a forum for reaching consensus on vaccine product attributes established by the GAVI Alliance in 2007, in response to a query from industry on guidance about the optimal number of doses per vial for rotavirus and pneumococcal conjugate vaccines to be used in GAVI-eligible countries. The two leading child killers – pneumonia and diarrhea – can be largely prevented by new vaccines, and new technologies can help us to outreach to children in need to deliver vaccines, in the optimal presentation. Subgroups were formed in 2013: one for harmonization and the second to work on bar code, with support of GS1,⁴ a global organization that supports distribution of goods. Factors driving packaging choices include regulatory requirements, public sector preferences and guidelines, and manufacturers' choices. Over the years, an increasing number of vaccines is available to children, from 6 in the 1970s to over 15 in the year 2010 (depending on regional schedules), challenging the delivery systems, cold chain space, resources and immunization professionals. While the world is not on track to achieve its United Nations proposed Millennium Development Goal (MDG) commitment to a 67% reduction in child mortality by 2015, we believe that simple interventions like immunization can shift the balance from death to life for millions of children each year.

D. Wood discussed existing initiatives for regulatory harmonization based on use of common set of written or measurement standards, and also on bi-lateral or multilateral legal agreements, such as European Medicines Agency (EMA), Association of Southeast Asian Nations (ASEAN), Asia Pacific Economic Cooperation (APEC), East African Community, among others. On the other hand, some decisions can be reached without a legally-binding obligation to do so, which he defined as regulatory convergence. Platforms to promote regulatory convergence include leveraging decisions of others, for example through the expedited review procedure for prequalified vaccines, joint reviews such as Article 58 process of EMA, clinical trial applications for multi-country trials or the African Vaccine Regulatory Forum, AVAREF, focusing on

Malaria, TB and HIV vaccine trials that have been instrumental for consensus evaluation of trials sponsored by IFPMA members. To inform NRAs of recently developed standards and guidelines, WHO has conducted implementation workshops on stability evaluation of vaccines [3]. An additional initiative to support regulatory harmonization and convergence is the expansion of the WHO collaborating centers for standardization and regulatory evaluation of vaccines, to include 10 centers from 10 different countries, to support a global regulatory science agenda [4] and develop new regulatory tools to improve access to vaccines of assured quality.

T. Kohei, WHO adviser to Vietnam office, reported on the Regional Alliance for Vaccine National Regulatory Authorities in Western Pacific. The objective of this regional alliance is to support and strengthen regulatory systems and required functions through effective and efficient coordinated mechanisms. A task-force committee then met in Canberra, 31 May–1 June 2012, developed a concept paper, workplan, governance and road map, and the alliance was officially launched on 14 March 2013. Eleven countries in the region conducted self-assessment and developed indicators of performance in eight areas of regulation (while WHO has defined 6 areas of expertise). It was agreed that countries with functional NRA will provide support to other countries.

J. Petricciani presented an overview of the International Alliance for Biological Standardization (IABS) and proposed opportunities for collaborations with DCVMN. IABS is a scientific society established in 1965, in Switzerland, to promote consensus building on contemporary and emerging issues related to medical, scientific, and technological developments in human and veterinary biologicals, through interdisciplinary discussions, conferences, publications and partnerships. Today it counts over 300 individual members and 12 institutional members. It has four committees working on Human Vaccines, Veterinary Vaccines, Biotherapeutics, Cell & Gene therapy. Dr. Petricciani invited DCVMN to participate in the Human Vaccines Committee and provide perspectives on issues/topics to be considered at future conferences.

Global activities of the UK National Institute for Biological Standards and Control to improving vaccine quality assurance were outlined by I. Feavers. The global vaccines landscape shows an expanding manufacturing base that has resulted in increased access to existing vaccines, as well as new vaccines for regionally important diseases, with tailored formulations (different serotypes) and new targets (e.g. Hep E, EV71, Vi-conjugates, etc.) contributing to health as well as economic development for producer countries. Diseases prevented by vaccines disappear, resulting in complacency, altered apparent risk/benefit ratio, and a fragile public confidence. Ensuring continued supply of safe and effective vaccines requires accurate and consistent dosing (potency), consistency of manufacturing quality, and assuring safety.

For example, *Streptococcus pneumoniae* is a leading cause of bacterial pneumonia, meningitis, and sepsis in children, and responsible for 0.7–1.0 million child deaths every year worldwide. Over 90 serotypes of pneumococcus exist, and most disease caused by a limited number of serotypes show regional differences in serotype distribution. Ten- and 13-valent polysaccharide conjugate vaccines are widely used in Europe, the US and Australia, and protection is related to IgG, assessed by ELISA. Two vaccine manufacturers are unlikely to meet global demand. Thus serological criteria are essential for the evaluation of new formulations and new serotypes, and head-to-head comparison with licensed product is the preferred method of efficacy evaluation. Recommendations for pneumococcal conjugated vaccines were revised in 2009 [5] and the 1st. International Standard for Human

³ Algeria, Angola, Armenia, Azerbaijan, Bhutan, Cape Verde, Congo, Egypt, EMRO MIC (10 countries), Indonesia, Latvia, Moldova, Mongolia, Morocco, Nepal, PAHO countries (Ecuador, Paraguay, Bolivia, El Salvador), Pacific Islands VII (13 countries), Philippines, Sri Lanka, South Africa, Swaziland, Thailand.

⁴ <http://www.gs1.org/>.

Pneumococcal Serum was established [6] and is available [7] for strengthening the capability and the breadth of expertise in vaccines and to facilitate development of new vaccines and diagnostics.

V. Halkjaer-Knudsen, from Sandia National Laboratories for biorisk management, provided an overview of vaccine GMP production and containment programs for eradicating, emerging, carcinogenic, genetically modified organisms and other risks related to the biotechnology and vaccine industry. While GMP aims to protect end-users from an unsafe agent, biosafety aims to protect the environment from harmful agents, and biosecurity, to protect bio agents from harmful uses. Vaccine production facilities should thus identify the chain of potential infectivity, from storage of pathogens, buildings and equipment procedures, to administrative controls and decontamination, ensuring that risks are controlled through surveillance and quarantine, as needed. Regulatory best practices, codes and standards, such as ISO guidance are widely available to manage risk related processes [8–15]. An international biorisk management document (CWA 15793:2011) [16], used by the WHO Smallpox Lab inspection program, and the WHO GAP III draft [17] lay out a risk based strategic approach for mitigation measures and controls for emerging and re-emerging infectious diseases. New tailored facilities evolved to single-use bioreactors widely implemented, that matured to a range of single use products for cell cultivation, upstream and downstream processes, resulting in cost-effective flexible and scalable production suites, requiring almost no-cleaning validation, for easy switch of products, projects, and low cost start up process, increasing the complexity of regulatory oversight on equipment, disposable, and leachables. She recommended that manufacturers study the guidelines, reflect on risk analysis, and decide on solutions to be discussed with health authorities.

A satellite symposium on new technologies for vaccine development and supply was hosted by Merck Millipore. M. Payne and S.Y. Lau provided an overview on cleaning and process validation with special emphasis on filter validation and integrity testing and considered validation master plan. Implementation of single use technology including risk assessment approach to design and validation of single use components in vaccine manufacturing were discussed.

4. Conclusion and outlook

G. Harshavardhan, Vice-President of DCVMN, concluded the meeting acknowledging all speakers and participants for their invaluable contributions and sharing knowledge on global health needs, procurement and supply of vaccines, product developments, regulatory science, manufacturing technologies and tools. Remarkably, in recent years innovative vaccines such as EV71, HepE, typhoid conjugate, cell based influenza vaccines, and other vaccines are coming out of research by manufacturers from developing countries. While affordability is demanded from manufacturers at the same time innovation and R&D is expected based on return on investments, which is challenging. Further regulatory harmonization and regulatory convergence in developing countries should be fostered. Dr. Harshavardhan emphasized that DCVMN is fostering a culture of professional partnerships and continuous improvement among members, to supply better vaccines for healthier lives and thus achieve our common global health goals.

Conflict of interest

The authors are employees of the respective indicated organizations, and have no conflict of interest to declare. DCVMN International did not provide any financial support to speakers or moderators to participate at this meeting.

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Sonia Pagliusi^{a,*}

Patrick Tippoo^b

Venkatraman Sivaramkrishnan^c

Thuvan Nguyen^d, DCVMN Executive Committee¹

^a DCVMN International, Chemin du Canal 5, 1260 Nyon, Switzerland

^b *Biovac Institute, 15 Alexandra Road, Pinelands Cape
Town 7430 WP, South Africa*
^c *Genome Valley, Shameerpet Mandal, Hyderabad
500078, Andhra Pradesh, India*
^d *Vabiotech, Yersin Street, Hanoi, Viet Nam*

Corresponding author. Tel.: +41 791245544;
fax: +41 22 3628211.

E-mail addresses: s.pagliusi@dcmn.org
(S. Pagliusi), patrick@biovacinstitute.co.za
(P. Tippoo), venkatraman2065@bharatbiotech.com

(V. Sivaramakrishnan), thuvan@vabiotech.com.vn
(T. Nguyen).

¹ Mahendra Suhardono (Biofarma, Indonesia),
Akira Homma (Biomanguinhos, Brazil), Gutla V.J.A.
Harshavardhan (Bharat, India), Morena Makhoana,
Biovac, S.Africa), Mahima Datla (Biological E, India),
Luciana Leite (Butantan, Brazil), Suresh Jadhav
(Serum Institute of India), Yonglin Wu (CNBG,
China), Yongzhong Gao (Innovax, China).

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