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Meeting report

WHO Working Group meeting on standardization of acellular pertussis vaccines: Potency assay Beijing, China, 7–9 November 2007☆

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ABSTRACT

New acellular pertussis vaccines have recently been developed in China and India. In this context, potency testing and potential improvements of the protective animal models with inclusion of a reference material were recognized as critical issues in the quality assessment of acellular pertussis vaccines. One of these models, namely Modified Intracerebral Challenge Assay (MICA), is currently used as a potency assay in Japan, China and Korea. A collaborative study comparing whole cell references, a candidate acellular pertussis vaccine reference (JNIH-3) and various acellular pertussis products was undertaken in 2006. The results of the collaborative study showed that MICA worked reliably and gave consistent results between laboratories. JNIH-3 was found to give similar dose–response lines to a variety of acellular pertussis vaccines and DTaP formulations, irrespective of the differences in acellular pertussis components. The WHO Working Group agreed that proposal for establishing JNIH-3 as the First International Standard for acellular pertussis vaccine in MICA should be submitted to the Expert Committee on Biological Standardization at its meeting in October 2008.

1. Background information

At the meeting of the WHO Working Group on acellular pertussis vaccines held in March 2006, St. Albans, United Kingdom [1], it was noted that there are no globally agreed methods for evaluation and licensing of new acellular pertussis vaccines. New vaccines have recently been developed in China and India, as reported to the Working Group. In this context, potency testing and potential improvements of the protective animal models with inclusion of a reference material were recognized as critical issues in the quality assessment of acellular pertussis vaccines. One of these models, namely Modified Intracerebral Challenge Assay (MICA), is currently used as a potency assay in Japan, China and Korea. At present, different whole cell pertussis vaccines are used as reference standards in these assays. However, the suitability of whole cell pertussis vaccines as reference preparations for acellular pertussis vaccines in the MICA had not been studied. Therefore, consideration of the establishment of an acellular pertussis vaccine derived International Standard and subsequent switch to secondary standards based on acellular pertussis vaccines was identified as an important step towards standardization of these vaccines as determined by MICA. To take this issue forward, a collaborative study was undertaken in 2006 with the following objectives:

(1) to evaluate the dose–response relationships of the 3rd International Standard for whole cell pertussis vaccines (3rd IS wP) as well as those for various in-house wP references currently used for control of acellular pertussis vaccines;
(2) to compare JNIH-3 and various in-house wP references;
(3) to review the consistency of potency estimates for acellular pertussis vaccines using 3rd IS for whole cell pertussis vaccine, in-house whole cell pertussis vaccine reference preparations and JNIH-3 as reference standards.

Fourteen laboratories including NCLs and manufacturers from China, Japan and Korea were involved in the study, which was coordinated by NIBSC, NICPBP (China), NIID (Japan), KFDA (Korea). Vaccine samples used in the study included DTaP vaccines with various pertussis formulations including 2 component (purified); 2 component (co-purified); 3 components (purified) and 5 components (purified) DTaP.

This meeting was co-organized by the National Institute for Control of Pharmaceutical and Biological Products in Beijing and the Quality, Safety and Standards Team of the Immunization, Vaccines and Biologicals Department of the World Health Organization in Geneva. The aim of the meeting was to review the outcomes of the collaborative study with the study participants and coordinators and to develop a plan of action towards improved standardization in this area. Moreover, the meeting served as an opportunity to consider the use of protective assays in the future and to develop a plan for the revision of WHO guidelines for acellular pertussis vaccines [2].

☆ *Disclaimer*: This report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization.

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2. Introduction and objectives of the meeting

On behalf of WHO, Dr. Knezevic welcomed all participants and thanked them for their willingness to assist WHO in its effort towards standardization of acellular pertussis vaccines. She emphasized the role of the National Control Laboratories (NCLs) in setting up lot release systems at the national level and establishing appropriate testing for new vaccines. Dr. Knezevic pointed out the importance of conducting regulatory research, highlighting the example of NIID, NICPBP and KFDA in the area of acellular pertussis vaccines and encouraged other NCLs to take a lead in the areas of their interest. Substantial progress in the development and approval of new acellular pertussis vaccines made in China was a reason for organizing this discussion in Beijing. All participants greatly appreciated the kind hospitality of NICPBP staff in Beijing who hosted this meeting.

Dr. Knezevic reminded participants that the WHO guidelines for acellular pertussis vaccines were adopted in 1996 [2] with a number of unresolved issues in terms of quality control, due to the lack of knowledge at that time. To improve the situation, WHO set up a Working Group on pertussis vaccines in 1998 and since then discussions on quality, safety and efficacy of these vaccines were held as follows: Washington DC in 2000; Ferney-Voltaire 2003, Geneva 2005 and St. Albans 2006. In addition, several collaborative studies were conducted to resolve issues for which there was no data or no consensus. One of these issues is potency testing which is the focus of this meeting.

Dr. Hadler from the WHO Office in China highlighted that China has achieved excellent success in its immunization program, vaccinating about 90% of its newborn children, eradicating polio, and ensuring effective control of other vaccine preventable diseases, notably diphtheria and pertussis. After many years with a relatively simple national immunization schedule, which included 5 vaccines—DTP, BCG, OPV, measles, and hepatitis B. The Chinese government made a momentous decision in February 2007 to greatly expand national support for childhood immunization. Beginning in January 2008, the Chinese government will invest 2.5 billion RMB annually to purchase 12 vaccines, and autodisposable syringes, for all children in China. In addition to the 5 vaccines currently used, the program will now also include MMR, Japanese encephalitis, meningococcal polysaccharides A + C, and hepatitis A. Currently only Beijing utilizes DTaP for infant vaccination. With the introduction of the new program, the DTwP vaccine currently used in almost all provinces will be replaced by DTaP. This will be a big change affecting a large population and WHO involvement would be important.

On behalf of State Food and Drug Administration (SFDA), the National Regulatory Authority (NRA) in China, Professor Yin indicated that there is rapid social and economic progress in China, with 34 vaccine manufacturers producing 47 different vaccines against 26 diseases. SFDA faces a great challenge in the regulation of both domestically produced and imported products. Chinese Authorities appreciate the role that WHO plays in setting standards for biological products and facilitating communication among relevant experts at the global, regional and national level. Professor Yin expressed willingness to host future WHO activities in China in the area of biologicals, and in particular of vaccine products.

Dr. Jin briefly introduced the duties of the National Institute for the Control of Pharmaceutical and Biological Products (NICPBP). The Institute is the National Control Laboratory in charge of lot release of all vaccines and other biological products used in China, with the essential role of monitoring the quality, safety and efficacy of vaccines. The Institute is responsible for the establishment of national reference standards used for quality control of vaccines and is the key player in ensuring the quality of vaccines used for the national immunization programme. Dr. Jin mentioned the importance of WHO activities in improving the health of Chinese people and highlighted that China welcomes the opportunity to collaborate with WHO and other organizations in regulatory and laboratory testing activities. One example is the recent establishment of a Memorandum of Understanding with the National Institute for Biological Standards and Control (NIBSC) in the UK with the objective to exchange information and expertise in the area of vaccine quality control.

The Consultation appointed Dr. Michael Corbel as Chairman and both Dr. Maria Baca Estrada and Dr. Dorothy Xing as Rapporteurs.

Dr. Corbel (NIBSC) reminded the participants that WHO has been involved in developing guidance for the assessment of acellular pertussis vaccines for 20 years. The first acellular pertussis vaccines were developed in Japan and subsequently different formulations have been developed by many manufacturers. There is no “generic” approach to the production process and many different formulations have been developed and used successfully. The establishment and standardization of a potency test for acellular pertussis vaccines has been a priority for the WHO for a number of years. The Japanese approach of using the MICA to assess the potency of acellular pertussis vaccines has been adopted by other countries including Korea and China. It appears that the MICA is a suitable model to assess the potency of acellular pertussis vaccines of different pertussis antigen compositions. The immunogenicity assay is used to assess the consistency of production of vaccines licensed in Europe and North America. It is important to note that these products have undergone clinical efficacy trials and consistency criteria were established using the data generated for the clinical trial batches. However, as effective vaccines are currently available, limiting the prevalence of the disease, there is great practical and ethical difficulty in carrying out clinical trials for licensing of new vaccines. Thus, there is a great need to standardize relevant animal protection models and to establish reference standards for the assessment of potency that will permit comparison between new and existing products.

The JNIH-3 reference standard is the only acellular pertussis preparation which has continuity with vaccine efficacy clinical studies, since a preparation from the same bulk (JNIH-6) was tested in Sweden in an efficacy trial and demonstrated 69% protection. The current collaborative study assessed whether the JNIH-3 preparation could be used as a reference standard in the MICA potency assay. The use of JNIH-3 may provide a means of bridging new acellular pertussis vaccines to material tested in clinical trials and thereby facilitate characterization of these new formulations for licensing.

3. Revision of WHO guidelines for acellular pertussis vaccines in the context of the developments in the WHO biological standardization

Dr. Knezevic gave an overview of the WHO Biological Standardization Program, emphasizing the issues related to the standards currently under development or revision. WHO provides both written standards (guidelines and recommendations for production, quality control and evaluation of vaccines and other biologicals) and measurement standards (International Standards and International Reference Preparations).

Written standards are based on the translation of scientific developments into recommendations for issues that are relevant to global public health. One aim of this WHO program is to generate, analyze and disseminate timely and reliable evidence based standards, particularly for risk management purposes. It was recognized that the standardization of biological products in some