

Expert Committee on Biological standards 2009 outcomes - similar biological products; live attenuated influenza vaccine; pneumococcal conjugate vaccine; a hepatitis B genotype panel; and many other reference preparations established.

Developing standards for quality, safety and quality assurance of biological products and associated reference materials through WHO's Expert Committees and Expert Panels is a key priority for the Organization. The Expert Committee on Biological Standardization met in Geneva from 19-23 October 2009 to enable the Organization fulfill one of its constitutional responsibilities to "...develop, establish and promote international standards for biological products". The Committee advises the Organization on international biological standardization and key developments affecting the quality, safety and efficacy of vaccines, biological therapeutics, blood products and biological diagnostics.

More innovation in biological medicines is occurring in more countries than ever before. Furthermore, the supply chain for biological medicines is increasingly complex and international in nature. Despite technological advances, controlling the quality, safety and efficacy of biologicals remains difficult and highly specialized. Therefore, strengthening biological standardization and its implementation, in particular in emerging economies, remains a fundamental function for WHO. The aim is to provide tools that will translate into appropriate regulation of new biologicals of potential public health benefit; or quality assurance of biological components in the supply chain.

The Committee established at its meeting in 2009 the following guidelines:

- (a) Guidelines on evaluation of similar biotherapeutic products
- (b) Revision of current WHO Recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines
- (c) Revision of current WHO Recommendations to assure the quality, safety and efficacy of live attenuated influenza vaccines

New WHO guidelines on the regulatory evaluation of "similar biotherapeutic medicines".

These products have a successful record in treating many life-threatening and chronic diseases. However patients particularly in developing countries have limited access to such medicines. The expiration of patents and/or data protection for the first major group of innovative biotherapeutics is ushering in an era of products "similar" to the originals, with the potential to significantly enhance accessibility. The guidance developed by WHO on appropriate regulation of this new class of products is in response to requests by many developing countries.

Revised WHO recommendations to assure the quality, safety and efficacy of influenza vaccine

The purpose of these recommendations is to provide vaccine manufacturers and national regulatory authorities with guidance that can be applied in developing specific processes for the production and control of influenza vaccines (human, live attenuated). These recommendations are also intended to provide guidance on the non-clinical and clinical evaluation of influenza

vaccines (human, live attenuated). These recommendations apply to the production and control of influenza vaccines (human, live attenuated) using embryonated hen's eggs as substrates. The future possibility to produce influenza vaccines (human, live attenuated) using cell cultures as substrates is anticipated, and therefore, guidance is also provided for this eventuality. The recommendations with possible modifications apply to influenza vaccines (human, live attenuated) produced with seasonal vaccine strains for use during the interpandemic period as well as vaccines produced with strains for use during pandemics.

Revised WHO recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines

Infections caused by *Streptococcus pneumoniae* are responsible for substantial morbidity and mortality, particularly in the very young and in the elderly. Pneumococci are grouped into many serotypes (~ 91) on the basis of their chemically and serologically distinct capsular polysaccharides. Certain serotypes are much more likely than others to be associated with clinically apparent infections, to cause severe invasive infections and to acquire resistance to one or more classes of antibacterial agents. The development of pneumococcal conjugate vaccines, in which each of the selected bacterial capsular polysaccharides is coupled with a protein carrier molecule, has been a major advance in the prevention of invasive pneumococcal disease (IPD). Since 2006, WHO has recommended that all countries should incorporate pneumococcal conjugate vaccines in routine immunization schedules for children aged less than 2 years with prioritization of their introduction in countries with high child mortality rates and/or high rates of HIV infection. A 7-valent pneumococcal conjugate vaccine (7vPnC) that employs CRM197 as the carrier protein for all seven serotypes was the first to be developed. This vaccine was first licensed in the USA in 2000 and subsequently has become available in approximately 90 countries worldwide. Pneumococcal conjugate vaccines that contain three or six serotypes in addition to those in the 7vPnC vaccine have recently become available in some countries. The 10-valent vaccine includes tetanus toxoid, diphtheria toxoid or a novel protein derived from non-typable *Haemophilus influenzae* (protein D) as the carrier proteins while the 13-valent vaccine uses only CRM197 as the carrier protein. WHO recommendations for pneumococcal conjugate vaccine production and control were first established in 2003 and were published in the WHO Technical Report Series (TRS) 927, annex 2. Since the 7vPnC vaccine was already approved in many countries it was considered unethical to assess the protective efficacy of future pneumococcal conjugate vaccines in infants and toddlers in comparison to an unvaccinated control group. Therefore, the recommendations discussed the design of immunogenicity studies that should be performed to support the licensure of new pneumococcal conjugate vaccines (including those containing conjugated capsular polysaccharides of serotypes additional to those in the 7vPnC vaccine) intended to prevent IPD and for administration to children aged less than 2 years. It was considered essential that the immunogenicity studies with a new pneumococcal conjugate vaccine should provide a link back to the vaccine efficacy against IPD that was

demonstrated for the 7vPnC vaccine. Therefore, it was recommended that immune responses to each serotype in the 7vPnC vaccine that is also included in a new pneumococcal conjugate vaccine should be directly compared in randomized clinical studies and that the primary comparison of immune responses should be based on serotype-specific IgG antibody concentrations measured by enzyme-linked immunosorbant assay (ELISA). In order to facilitate these comparisons a WHO reference ELISA assay was established that includes pre-adsorption of sera with pneumococcal C polysaccharide (C-PS) and serotype 22F polysaccharide. Prompted by issues raised during the development of newer pneumococcal conjugate vaccines since the publication of TRS 927 annex 2 in 2003, the WHO held a consultation in 2008 to consider new scientific evidence and to discuss the need to provide revised guidance for manufacturers and licensing authorities. The Expert Committee on Biological Standardization established a revised document that had been developed to take into account the most recent developments in the field.

New reference preparations

The WHO International Biological Reference preparations serve as reference sources of defined biological activity. These preparations help to ensure consistency and reproducibility in manufacturing processes and batch production, saving repeating determinations in laboratories and reducing human resources and financial costs. They are used by regulatory authorities, blood transfusion services, medical laboratories and manufacturing settings as well as physicians and scientists involved in patient care, to communicate results in a common language worldwide and the traceability of test results between countries.

The Committee established this year new international standards and reference panels aiming to improve detection of blood-borne infectious agents and other infectious diseases. It is meaningful to highlight the 1st Reference panel for Hepatitis B, covering the most prevalent Hepatitis B genotypes (A-G) worldwide, which will facilitate the detection of relevant genotypes by all countries as well as improvement of the quality of Hepatitis B diagnostic devices. With similar importance, the 1st International Standard for detection of HIV-2 in nucleic acid amplification technologies constitutes a major step to help detection of the HIV-2 group of viruses as well as to improve the quality of diagnostic tests. Furthermore, the International Standards for the control of essential medicines such as Heparin and Blood Coagulation Factor VIII (WHO Essential Medicines List) or reagents such as Thromboplastin for the control of anticoagulant therapy underpin the medical activities and the regulation of blood products and *in vitro* diagnostic devices at global level. In the vaccines area, International Standards to control the production or oral poliovirus vaccine, pertussis vaccine, BCG vaccine, diphtheria vaccine and human papillomavirus vaccine.

The above mentioned preparations are submitted annually to the ECBS following extensive validation of candidate materials with the collaboration of wide scientific and regulatory networks and the support of relevant WHO Collaborating Centres.

Further details of the written standards and reference preparations established by the Committee can be found through the following websites:

www.who.int/biologicals and www.who.int/bloodproducts