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UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org

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BIOSAFETY GUIDELINES FOR MANUFACTURE OF VACCINES AND BIOLOGICALS *

Prepared by

the World Health Organization

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INTRODUCTION

The recent advances in molecular biology have prompted the World Health Organization to assess these regarding public health application. Primary considerations have been targetted to the field of infectious diseases. As a result new or expanded initiatives have been established within WHO's Division of Communicable Diseases. These include:

1. WHO Programme for Vaccine Development;
2. New rapid diagnostic techniques;
3. Transfer of vaccine production technology to developing countries.

With these initiatives there is the commitment of the Organization to assure the safety of the product, the safety of the biotechnology industry worker, and the safety of the community from possible hazardous discharges from the industry.

WHO is called on by its constitution "to develop, establish and promote international standards with respect to ... biological ... products." Accordingly, WHO sets international biological standards and provides relevant information to national health authorities so that national standards, calibrated in international units, can be established. Through this process WHO will assure that vaccines and other biological products developed through its programmes and others offered through international trade will be safe for use by the general public.

To meet the worker and community safety requirements, WHO's Seventh General Programme of Work calls for the provision of safety guidelines for biotechnology organizations producing vaccines and biological products. Accordingly draft biosafety guidelines are being considered for laboratories and industries engaged in the manufacture or preparation of vaccines and biologicals where:

1. the process uses organisms or cells which contain foreign DNA inserted by the recombinant DNA technique;
2. the volume of culture, medium or tissue is larger than 10 litres. This definition includes the use of continuous culture where the volume of the culture vessel or of the spent culture is greater than 10 litres, and

3. the work is carried out within contained facilities.

While the proposed guidelines are primarily directed towards fermentation technology, the containment specifications and other practices may be used as a basis to derive similar containment standards for other technologies. The guidelines apply only to minimum practices and physical containment.

Existing national guidelines for large scale production of vaccines and biological products are serving as the basis of the WHO effort. However, development of the WHO guidelines is currently in abeyance to ascertain if similar guidelines being developed by the OECD or under discussion with UNIDO and UNEP would serve WHO's needs.

PROGRAMME FOR VACCINE DEVELOPMENT
RESEARCH PRIORITIES

The WHO Programme for Vaccine Development is a goal-oriented-programme which funds research only in the following priority areas:

1. Acute viral respiratory diseases of childhood

(a) Molecular cloning of individual genes of parainfluenza virus type 3 and respiratory syncytial virus.

(b) Nucleotide sequencing of the genes specifying the immunologically important polypeptides (presumed to be the two surface glycoproteins and the nucleoprotein) and subsequently the other genes and inter-cistronic regions.

(c) Expression of cloned viral genes in prokaryotic systems (to produce high yields of unprocessed polypeptides) and eukaryotic systems (for modified proteins).

(d) Production and characterization of monoclonal antibodies for definition of epitopes and for use in affinity chromatography for purification of viral polypeptides.

(e) Characterization of the function and immunogenic potential of individual virus proteins.

(f) Study of the protective immune response with emphasis on the role of cell-mediated immunity.

(g) Support of other initiatives, i.e. development of live attenuated viruses, cell receptors, etc.

2. Dengue

The main aim is to produce second generation vaccines by using the following approaches:

(a) Biochemical definition of principal neutralizing antibody-inducing epitopes on the virus glycoprotein.

(b) Definition of epitopes, which induce the formation of neutralizing versus enhancing antibodies by using monoclonal antibodies.

(c) Viral genome sequencing; cDNA cloning.

(d) Experimental studies of potential vectors, such as bacteria or viruses other than dengue.

(e) cDNA cloning of 17D yellow-fever virus to study its possible use as a vector, by substituting gene sequences coding for epitopes capable of inducing dengue neutralizing antibody.

(f) Generation of non-structural antigens as vaccines.

3. Diseases caused by encapsulated bacteria

The Programme will concentrate on developing vaccines against N. meningitides with a principal focus on oligosaccharide (LOS) antigens. The main goal is to develop an infectious replicating vector, engineered to express antigens which induce protective immunity in children. The strategy includes:

(a) Epidemiological studies of epidemic/endemic disease, with emphasis on immune responses to N. meningitides and other organisms with antigenic determinants shared with virulent Neisseria.

(b) Development of standardized isotype-specific serological tests for bactericidal (protective) antibody.

(c) Biochemical and structural analyses of relevant LOS antigens defined by monoclonal antibody and shown to be involved in protective immunity.

(d) Studies of bacterial genetics to define methods of transferring genes for oligosaccharide expression to potential vector organisms.

4. Hepatitis A and Polio

4.1 Hepatitis A

The Steering Committee recognizes that hepatitis A continues to be a problem in many parts of the world and that the development of a vaccine is highly desirable. The goal of the hepatitis A programme is to develop a cheap, safe and efficacious vaccine suitable for use in the first year of life in all countries of the world and to be included in the WHO Expanded Programme on Immunization. The strategy includes:

(a) The collection of well-characterized strains of hepatitis A viruses of diverse geographical and epidemiological origin.

(b) Studies towards an improved understanding of the pathogenesis and primary sites of replication of the virus.

(c) Establishment of a panel of monoclonal antibodies against hepatitis A virus strains for use in virus characterization and antigen analysis.

(d) Identification of critical antigenic sites of the virus relevant to protective immunity using a combination of selection and non-neutralized mutants in the presence of monoclonal antibodies and recombinant DNA technology.

(e) Molecular cloning and sequencing of the complete genomes of carefully selected hepatitis A strains in order to (i) determine the genetic basis of antigenicity and virulence of the virus and (ii) to rescue infectious virus by transfection to facilitate construction of attenuated strains by strategic modifications of the virus genome.

(f) Development of experimental vaccines using antigens prepared by controlled gene expression and synthesis of oligopeptides.

(g) Study of both humoral and cell-mediated immunity to hepatitis A infections.

4.2 Polio

(a) Determination of the molecular basis of virulence of types 1, 2 and 3 poliovirus with special reference to the Sabin strains and their reversion to virulence.

(b) Application of information from (a) for the development of safety tests of live vaccines employing molecular methods.

(c) Evaluation of prospects for the preparation of new attenuated strains of virus by precise genetic modification (e.g. of Sabin strains).

(d) Evaluation of intratypic recombinant viruses as vaccines or vectors (e.g. for hepatitis A vaccine).

(e) Collection of further data on the molecular basis of antigenicity of poliovirus and the preparation of new immunogens.

5. Tuberculosis

The strategic plan for research on the immunology of tuberculosis was prepared during an informal consultation held in Boston, USA from 7 to 9 February 1983. It was recommended that research should be conducted on the following subjects:

1. Molecular biology
2. Monoclonal antibodies
3. Immunoregulation in human tuberculosis
4. Experimental immunology of tuberculosis
5. Cloning of mycobacteria.

Research proposals, prepared on the appropriate application forms, should reach Immunology, WHO, 1211 Geneva 27, Switzerland, before the deadlines, given below:

Tuberculosis	Dengue	Hepatitis A	Encapsulated bacteria	Acute respiratory viruses
Deadlines (1986)				
2 April	26 March	18 April	9 April	25 April
Dates of Steering Committee meetings (1986)				
2-3 June	26-27 May	16-17 June	9-10 June	26-28 June