WHO Technical Report Series
904

WHO EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Fiftieth Report

World Health Organization
Geneva

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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WHO Expert Committee on Biological Standardization

Geneva, 25–29 October 1999

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Introduction

The WHO Expert Committee on Biological Standardization met in Geneva from 25 to 29 October 1999. Dr M. Scholtz, Executive Director of the Health Technology and Pharmaceuticals cluster at WHO, opened the meeting on behalf of the Director-General.

Dr Scholtz explained that WHO was emerging from a period of considerable restructuring over the previous 12 months under the leadership of the new Director-General. The main goal was to foster better coordination and cooperation at all levels of the Organization. Strengthening activities in the field of biological standardization was an important objective, and additional resources were being sought to support that work. WHO was grateful to organizations that had supported biological standardization work at WHO through staff secondments to help with special projects.

The Committee would consider a large number of topics, which reflected the increasing complexity of the field of biologicals. Indeed, the number of new biological medicines was likely to outstrip the number of new chemical medicines coming to the market in the next few years. The challenge faced by manufacturers and national control authorities alike was to ensure the quality and safety of new and existing biologicals and the Committee had an important role to play in this regard.

General

Independent review of WHO's remit and activities in the field of biologicals

The 1997 World Health Assembly resolution (WHA 50.20) on the quality of biologicals moving in international commerce called for an independent review of WHO's remit and activities in this field, particularly of the Organization's Biologicals unit and the way in which it interacted with other groups within and outside WHO. The review was to recommend action to assist in the harmonization of standards and requirements, minimize duplication of activities, and enable WHO to respond to scientific developments in a timely manner.

The review team consulted widely and submitted its report to WHO in November 1998. There was a clear consensus on the continued importance of WHO's work on standardization and control of biologicals for public health programmes worldwide. Indeed, this was a constitutional obligation of WHO. The review team recommended

that the Biologicals unit should be renamed to reflect its responsibilities more accurately and that staff and resources at WHO dedicated to biological standardization should be substantially increased. The review also recommended that a clear focus should be established for policy on biological substances used in medicine, to ensure that there was "one voice for biologicals" within WHO. Finally the review also recommended that the transparency, openness, and effectiveness of the standard-setting process should be improved.

The response from WHO had taken place within the context of the wider restructuring of the Organization under the new Director-General. The former Biologicals unit, following a name change to Quality Assurance and Safety: Biologicals (QSB), had been integrated into the Vaccines and other Biologicals department in the Health Technology and Pharmaceuticals cluster. Quality and Safety of Plasma Derivatives and Related Substances (QSD) had been given greater visibility, and was located in the Blood Safety and Clinical Technology department in the same cluster. QSB and QSD would continue to work very closely together as a cross-cutting biologicals team within the cluster and would provide a clear focus for biologicals activities within WHO. The advantages of this arrangement were the necessary degree of independence for the standard-setting process, greater access to funds for priority projects, and increased potential for collaboration on quality issues that affect all types of biological medicines.

WHO also proposed that the Expert Committee on Biological Standardization should be restructured by establishing three subcommittees that covered vaccines, blood products and related substances, and biological therapeutics. The objective was to ensure greater transparency and efficiency of the standard-setting process. The WHO Informal Consultation on Cytokine Standards, already in existence, provided a successful model for the subcommittees. The possibility of a fourth subcommittee on diagnostics was under consideration, but this required wide consultation with interested parties and no decision had yet been reached.

The Committee endorsed the new management structures and the priority that WHO had placed on the importance of quality and safety in all types of medicines. The Committee encouraged WHO to ensure that responses to matters such as transmissible spongiform encephalopathies, which potentially affected all types of medicines, were appropriately coordinated. Finally the Committee strongly encouraged WHO to obtain appropriate funding and provide the resources identified by the independent review to ensure that WHO's work on

biologicals continued to respond to scientific developments in a timely and efficient manner.

Developments in biological standardization

The standardization of biologicals has an increasingly important role to play in the safety of immunizations. The Committee recalled that the safety of DNA vaccines was addressed in WHO guidelines (WHO Technical Report Series, No. 878, 1998) and that a WHO Working Group on Standardization and Control of DNA Vaccines provided scientific leadership on a number of safety questions related to these vaccines. The Committee endorsed a proposal to hold an Informal WHO Consultation to review the latest developments with respect to the safety of DNA vaccines and advise on the need to update the guidelines.

The Committee also recalled a previous decision (WHO Technical Report Series, No. 897, 2000) to establish a Task Force on cell substrates. The remit of the Task Force would be to coordinate research and quality control of the safety of all cell substrates used for production of biologicals. The Task Force would standardize methods and reagents for this purpose. The WHO-coordinated investigations into the significance of very low levels of reverse transcriptase activity in some live attenuated vaccines derived from chicken cells, which had shown that this activity was not associated with infectious particles, could serve as a model for the work of the Task Force.

The scientific assessment of alleged adverse events related to vaccines was of considerable importance. To respond to requests for advice from Member States, WHO had established a Vaccine Safety Advisory Committee. This Committee would provide independent scientific assessment and rigorous review of the latest knowledge, assess the possibility of causality, and coordinate research to obtain new data if necessary. The Expert Committee wished to work closely with the Advisory Committee to ensure that, where necessary, new standardization and control procedures would be developed. However, the Advisory Committee would need to consult closely with national vaccine safety committees to ensure that no conflicting messages on vaccine safety were issued.

In response to the recommendation of the independent review for increased transparency in the standard-setting process, QSB and QSD presented work plans to the Committee setting out their priorities for the next 2–4 years. The priorities were based on global needs, which may differ from regional or national priorities. However, it was recognized that standardized criteria for assigning

priorities would be useful. A "decision-tree" developed by the WHO Informal Consultation on Cytokine Standards had proved very useful in assigning priorities in that area and, if broadened, could also prove useful in relation to vaccines and blood production. After modification, the decision-tree was approved by the Committee. The Committee endorsed the work plans presented by QSB and QSD and all the planned activities, commending the Secretariat on the clear presentation of priorities and objectives for the near and medium terms.

The Committee suggested that, given the need to improve methods of disseminating information from the Committee, workshops in the WHO regions, involving both local manufacturers and national control authorities, should be arranged to promote and explain new guidelines and reference materials.

In the context of dissemination of information, the Committee noted with concern that the full reports of its 1997 and 1998 meetings were not yet published. Summaries of both meetings had been published in the scientific literature but proper implementation of the Committee's decisions required publication of the reports. WHO was urged to expedite publication of these reports and the report of the current meeting. However, the Secretariat had already established a WHO web page for biologicals on the Internet, under the Health Technology and Pharmaceuticals cluster (http//www.who.int/biologicals). This would be used increasingly in the future for the dissemination of information in the biologicals field.

During the meeting, the Committee considered a specific case for the replacement of a reference material that was of natural origin with a reference material of recombinant origin. The Committee concluded that, for continuation of the International Unit, a new or replacement recombinant standard should be calibrated against a natural reference material. The Committee recognized, however, that further consideration of this topic would be valuable and requested the Secretariat to develop, through a Working Group, guidelines for replacement of reference materials of natural origin by recombinant materials.

As a general consideration, the Committee also recommended that, when a recombinant material is established as a standard, the molar concentration of the substance should be given, as well as an assigned potency in International Units.

The Committee also commented on the procedure for performing collaborative studies and noted that best practice was for the WHO

Collaborating Centres on Biological Standardization and, where appropriate, other cosponsors to agree in advance the study design and methods. This had not always been the case, which could lead to difficulties in interpretation of data after completion of a study, and even to the need for further work. Study leaders were therefore encouraged by the Committee to comply with best practice in the conduct of future studies.

International Nonproprietary Names for biotechnology-derived medicinal products

The system of International Nonproprietary Names (INN) is designed to assign names to well-defined medicinal substances. Most regulatory agencies require or encourage pharmaceutical manufacturers to obtain an INN for each active substance in a preparation. The advent of medicinal products manufactured by biotechnological procedures posed important challenges for INN experts, as these products largely fell outside their areas of competence. The WHO INN Secretariat therefore proposed the nomination of experts from the Expert Panel on Biological Standardization to advise the INN programme. For this purpose, a list of experts in areas that included antibodies, blood coagulation factors and fibrinolytics, cytokines, endocrinological and related substances, enzymes, and vaccines would be established. Two specialists within the area concerned would be consulted for every individual INN request. The WHO INN Secretariat also requested assistance in identification of new groups of biotechnological entities that would need INN classification. The Committee supported these proposals and agreed to provide guidance on the specificity of definitions and principles applied to the naming of biotechnology-derived products.

International recommendations, guidelines, and other matters related to the production and quality control of biologicals

Recommendations for the production and control of oral poliomyelitis vaccine

WHO requirements for oral poliomyelitis vaccine were last revised in 1989 (WHO Technical Report Series, No. 800, 1990). Since that time, new quality control tests had been developed that introduced significant changes in control of the vaccine. The Committee was informed of these developments and considered a proposed revision of the requirements (BS/99.1895) — to be renamed "Recommenda-

tions" in line with the decision taken at its forty-ninth meeting (WHO Technical Report Series, No. 897, 2000, p. 4) — that incorporated the new procedures.

For the first time, a test for molecular consistency of production for a live virus vaccine had become available. Mutant analysis by polymerase chain reaction and restriction enzyme cleavage (MAPREC) quantifies reversion of a key base, 472C, which correlates in type 3 poliovirus vaccine with results of the WHO neurovirulence test. WHO-supported studies of the method had shown it to be a standardized, robust, and reliable procedure. Results from a WHO enquiry had shown that the MAPREC test provides a very valuable additional test for consistency of production. It was therefore desirable to introduce the method as the in vitro test of preference for control of poliovirus type 3. The Committee was informed of excellent progress with MAPREC assays for poliovirus types 1 and 2 and encouraged completion of these studies as soon as possible.

The discovery of the gene for the cellular receptor for poliovirus led to the development of transgenic mice that, unlike normal mice, were susceptible to poliovirus infection. A neurovirulence test for poliovirus vaccine had been developed in the TgPVR21 transgenic mouse line. The neurovirulence test in TgPVR21 mice was shown in WHO-supported studies to be a suitable alternative to monkeys for poliovirus type 3. The Committee was informed of excellent progress with TgPVR21 neurovirulence tests for poliovirus types 1 and 2 and encouraged completion of these studies as soon as possible.

The Committee considered that the entire cycle in the development of MAPREC and the transgenic mouse model, from basic scientific research, through method development, to standardization and application as control tests, was a paradigm for regulatory research. This work clearly illustrated the need for long-term commitment of resources in order to make significant advances in control and standardization of biologicals.

The Committee considered that the new quality control procedures had the potential to increase the stringency of control of the vaccine. This was an important consideration as the risk/benefits of using oral poliovirus vaccine were changing as a result of the marked successes of the poliomyelitis eradication initiative. Furthermore, the use of the new quality control procedures had the potential to reduce the time needed to complete testing of the vaccine and to make vaccine available for use more quickly. As the demand for oral poliovirus vaccine was higher than ever before, any procedures that shorten the supply time were to be welcomed.

The Committee was informed that the draft Recommendations (BS/99.1895) had been reviewed by an Informal WHO Consultation, which had recommended acceptance of the document. After making some additional modifications, the Committee adopted the text as Recommendations for the Production and Control of Poliomyelitis Vaccine (Oral) and agreed that it should be annexed to its report (Annex 1).

To provide for smooth and effective adoption of the new Recommendations, the Secretariat was asked to publicize the decisions of the Committee to interested parties as soon as possible. The Committee also recommended that proofs of the new Recommendations be circulated ahead of formal publication, with a caution that further editorial changes were possible, to enable laboratories to prepare for the changes in a timely manner. The editorial changes would not affect the substance of the agreed text.

Recommendations for the manufacture and control of live Japanese encephalitis vaccine

The Committee noted a draft of proposed recommendations for live Japanese encephalitis vaccine (BS/99.1907), which had been prepared at an Informal WHO Consultation in Beijing. In the view of the Committee, the document needed to provide much more guidance on the control of the vaccine. It therefore recommended that the document be reformulated as guidelines. The Committee advised on the need for further discussions on many aspects of control of this vaccine, including the validity of assays for retroviruses when applied to the primary hamster kidney-cell substrate, and the validity of the mouse assays for neurovirulence. The Committee also advised that further information be reviewed on the long-term follow-up of recipients of the vaccine. The Committee recommended that experts discuss these issues and that a revised document in the form of guidelines be resubmitted.

Mouse protection models for acellular pertussis vaccine

The Committee, at its forty-seventh meeting (WHO Technical Report Series, No. 878, 1998, p. 9), recommended that WHO should convene a Working Group to discuss topics such as collaborative studies to facilitate development, particularly in assay methods, in the field of acellular pertussis vaccines. The Working Group had been established and, at an Informal WHO Consultation in November 1998, had set up a small group to analyse a panel of coded samples of known clinical efficacy in different protection models. A total of eight laboratories would evaluate the modified Kendrick test and the

respiratory infection model (both intranasal and aerosol challenge). The Committee also considered it desirable to include the immunogenicity test. The collaborative study results would be reviewed by an Informal WHO Consultation and, if appropriate, the guidelines for acellular pertussis vaccine would be updated.

Harmonization of antigen content and potency measurement of diphtheria and tetanus vaccines

The Committee was informed of the outcome of meetings of a WHO Working Group on the harmonization of antigen content and potency measurement of diphtheria and tetanus vaccines. Diphtheria and tetanus vaccines are among the most used vaccines worldwide and are remarkably successful products. However, there are fundamental problems with the standardization and control of these vaccines, even when International Standards are used. Different potency tests are used in different regions of the world, leading to problems in the international exchange of vaccines. The Working Group had reviewed data obtained with current tests, evaluated progress with alternative methods, developed a plan of action to harmonize future approaches, and made recommendations on the antigen content for vaccines used for boosters in adults and adolescents.

The Working Group had concluded that WHO should, in consultation with other relevant bodies, continue to assess the value and limits of current potency assays and to explore alternative approaches. The Working Group had further recommended that a small group of experts be established by WHO to coordinate the development of a simple, robust, and standardized assay suitable for demonstrating consistency of immunological characteristics for batch release. Finally, the Working Group had recommended that WHO urgently develop guidelines on the antigen content and quality of diphtheria and tetanus vaccines used as boosters in adults and adolescents. The Committee endorsed these recommendations and also emphasized that, in the development of new assays, the possibilities for reducing animal usage should be taken into account.

Standardization and control of oral cholera vaccines

The Committee was informed of developments in the standardization and control of oral cholera vaccines. Two new oral vaccines had recently been developed, one a live attenuated vaccine and the other a formaldehyde-inactivated whole-cell vaccine. A WHO Working Group had met to review current production and control procedures and to assess the need for WHO recommendation. The Working Group had concluded that two new recommendations were required,

one for each type of vaccine. The killed oral preparation was a new type of vaccine and there was no precedent for its control. Work to develop appropriate quality control procedures would therefore be necessary. The Working Group had also recommended that existing WHO Requirements for parenteral inactivated cholera vaccines be discontinued to avoid the potential for confusion and any possible use of inappropriate tests to control the new oral inactivated vaccine. The Committee endorsed these conclusions.

Guidelines on preclinical and clinical evaluation of vaccines

The Committee was informed of the development of WHO guidelines on preclinical and clinical evaluation of vaccines. The guidelines, still in early draft form, were particularly aimed at developing countries, and describe the scientific principles of the development of new vaccines. The Working Group developing this document had requested advice from the Committee, particularly in the area of preclinical safety testing. Members of the Committee were invited to send their comments to WHO. The Committee recommended that WHO convene a workshop to discuss the guidelines after they have been further developed but before they are finalized.

Global project on quality assurance of plasma-derived medicinal products and plasma fractionation activities

The Committee was updated on a project concerned with quality assurance of plasma-derived medicinal products and plasma fractionation activities. The objectives were to prevent transmission of bloodborne infectious agents via plasma products, to upgrade national control authority expertise in control of plasma products, and to harmonize requirements in this field. The plan had been widely circulated to WHO Regional Advisers, major national control authorities, and relevant manufacturers' associations for comment, and a Task Force to support this activity, drawing on expertise available from different interested sectors, was proposed. The Committee supported these plans and recommended that the effectiveness of the activities covered by the project be defined in a measurable way. The Committee also requested WHO to consider including blood components in this activity, where appropriate, provided that adequate resources were available.

The Committee was also informed of an illicit trade in plasma that had been uncovered in a Member State. Plasma originally intended for diagnostic use was allegedly being used to prepare medicinal products for human use. As products manufactured in this way could

potentially be distributed worldwide, such an illicit activity could have a significant impact on public health in many countries. The Committee recognized that illegal actions of this nature were hard to detect but recommended that, when they were uncovered, WHO should help to alert the international community. The Committee considered that the development of an appropriate regulatory framework and strengthening of national control authorities would make illegal actions of this nature more difficult to perpetrate.

List of requirements for biological substances and other sets of recommendations

As recommended at the Committee's forty-ninth meeting (WHO Technical Report Series, No. 897, 2000, p. 11), the Secretariat had published for public comment the intention of the Committee to discontinue the Requirements for Parenteral Cholera Vaccine (1968) and the Requirements for Smallpox Vaccine (1966). The Committee agreed to discontinue the former Requirements for Parenteral Cholera Vaccine. However, as laboratory stocks of smallpox virus had not been destroyed as expected, the Committee recommended that the Requirements for Smallpox Vaccine should be retained.

Abnormal toxicity test

The Committee was informed of progress in evaluation of the use in WHO Recommendations/Requirements of the abnormal toxicity test to control vaccines. A survey of all WHO Recommendations/Requirements had shown considerable variations in the name and text of the test. In one case, that of the Requirements for Meningococcal Polysaccharide Vaccine (1976; addendum 1981), there was a specification for five guinea-pigs instead of the normal two. The Committee considered this to be an anomaly and therefore agreed that an addendum to the Requirements to correct this situation should be annexed to its report (Annex 2).

The Committee also noted that, in one region of the world, the abnormal toxicity test had been deleted for most products. This was linked to the implementation of, and compliance with, good manufacturing practices and, where this occurred, there was abundant evidence that the abnormal toxicity test did not provide additional assurances of the quality of the product. The Committee recommended that the Secretariat initiate an international enquiry to establish the utility of the abnormal toxicity test and play a coordination role in efforts to harmonize international approaches to abnormal toxicity testing.