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Geneva, 22–29 October 1991

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Introduction

The WHO Expert Committee on Biological Standardization met in Geneva from 22 to 29 October 1991. The meeting was opened on behalf of the Director-General by Dr Hu Ching-Li, Assistant Director-General.

Dr Hu emphasized the importance of the biological standardization programme for countries with developing health programmes and stressed the need for the Committee, in making recommendations, to take account of the procedures essential for assuring the safety and efficacy of biological products, but to avoid specifying unnecessarily stringent or restrictive conditions.

General

Good manufacturing practices for biological products

The Committee noted that the WHO Secretariat had prepared a document entitled "Good manufacturing practice for biological products" (BS/91.1656),[1] intended to provide guidance for biological products supplementary to that given in the more general "Good manufacturing practices for pharmaceutical products" (WHO Technical Report Series, No. 823, 1992, Annex 1). After making some modifications to the draft text, the Committee agreed that the document should be annexed to its report (Annex 1).

Distribution of International Biological Standards and Reference Reagents

The Committee noted the distribution of international reference materials by the four main International Laboratories for Biological Standards during 1990 (Table 1) (BS/91.1677). It noted a slight decline in the number of standards distributed by comparison with 1989 (WHO Technical Report Series, No. 814, 1991, p. 3) and requested that for distributions made during 1991 a more detailed analysis by product category be provided. The Committee also requested the WHO Secretariat to obtain similar information on the distribution of international reference materials held and distributed on behalf of WHO by other cooperating laboratories.

The Committee was informed that, in accordance with the request made in

[1] References prefixed "BS/..." are to unpublished working documents of the World Health Organization. They are not issued to the general public, but a limited number of copies may be available to professionally interested persons on application to Biologicals, World Health Organization, 1211 Geneva 27, Switzerland.

Table 1
International Biological Standards and Reference Reagents distributed in 1990 by the International Laboratories for Biological Standards[a]

WHO region	Number of items distributed by International Laboratories for Biological Standards					
	Amsterdam	Copenhagen	Potters Bar	Weybridge	Total	% of total for all regions
Africa	31	12	68	6	117	0.9
Americas	134	354	979	12	1 479	11.0
Eastern Mediterranean	0	126	14	5	145	1.1
Europe	2 612	1 545	6 171	131	10 459	77.9
South-East Asia	7	132	599	9	747	5.6
Western Pacific	84	123	258	13	478	3.6
Total	2 868	2 292	8 089	176	13425	

[a] Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, Netherlands: items distributed during the calendar year 1990. State Serum Institute, Copenhagen, Denmark: items distributed during the calendar year 1990. National Institute for Biological Standards and Control, Potters Bar, Herts., England: items distributed between 1 March 1990 and 30 April 1991. Central Veterinary Laboratory, Weybridge, Surrey, England: items distributed during the calendar year 1990.

its forty-first report (WHO Technical Report Series, No. 814, 1991, p. 2), the WHO Secretariat had obtained some information on the ways in which international reference materials were used. Many users had stressed the key role played by international reference materials in harmonizing the quality of biologicals at both national and international levels. The Committee emphasized that standardization and control of biologicals could not be fully achieved without the provision of internationally accepted reference materials, and that in the present era of vanishing borders and increased demands for international harmonization, the role of international biological reference materials was even more important than in the past. In view of these factors, the Committee urged national health administrations to continue to support the biological standardization programme at the highest level possible.

Revision of the publication *Biological substances: International Standards and Reference Reagents*

The Committee was informed that the revision of the WHO publication on international reference materials referred to in its forty-first report (WHO Technical Report Series, No. 814, 1991, p. 4) had been published as *Biological substances: International Standards and Reference Reagents, 1990.* The Committee noted some improvements in format and acknowledged the contribution of the Secretariat in compiling this publication.

International reference materials: procedure for disposal of discontinued materials

The Committee noted some factors to be considered in disposing of stocks of discontinued international reference materials (BS/91.1662), and discussed the difficulties that might arise from uncontrolled distribution of such preparations. The Committee therefore agreed that, in most cases, a certain quantity of the discontinued preparation should be kept for reference and historical purposes, and that the rest, depending on the circumstances, should either be offered to any national control authority retaining an interest in it, to the WHO Collaborating Centre for Chemical Reference Substances, or to the original supplier, or be destroyed. The Committee requested that any proposed action concerning stocks of individual discontinued preparations be brought to its attention.

Vitamin D

The Committee noted that during the previous three years no requests had been received for the second International Standard for Vitamin D, established in 1949 (WHO Technical Report Series, No. 2, 1950, p. 10) (BS/91.1666). The Committee was informed that preparations of vitamin D can be fully characterized by chemical and physical means. The lack of demand for the International Standard also reflected the replacement of bioassays for measuring vitamin D in fish oils by physicochemical methods. The Committee therefore decided to discontinue the International Standard for Vitamin D. Because International Units of Vitamin D might continue to be used for some time in the labelling of certain preparations, the Committee requested the WHO Secretariat to include, in the list of discontinued international biological reference materials (see Annex 6), a note on equivalence, an International Unit of Vitamin D being widely taken to be equivalent to the activity in 25ng of pure colecalciferol.

Guidelines and requirements[1]

The Committee emphasized that its objective in adopting guidelines and requirements for biological products was to draw attention to the factors considered essential for assuring the availability of safe and efficacious products. The Committee recognized that national circumstances might demand additional or alternative procedures.

Guidelines on quality assurance for biologicals

The Committee noted that, in accordance with the undertaking given in its forty-first report (WHO Technical Report Series, No. 814, 1991, p. 14), the WHO Secretariat had prepared a revised draft of the guidelines for national authorities and manufacturers on quality assurance for biological products and had circulated the draft for comment (BS/91.1655). The Committee reviewed the draft and the comments received on it. Most of the information directed to manufacturers had now been included in the documents "Good manufacturing practices for pharmaceutical products" (WHO Technical Report Series, No. 823, 1992, Annex 1) and "Good manufacturing practices for biological products" (Annex 1). The Committee therefore modified the draft text so that it was directed only to national authorities and, after making further changes to it, agreed that it should be annexed to its report under the title "Guidelines for national authorities on quality assurance for biological products" (Annex 2).

The Committee was informed that consideration was being given to publishing the requirements and guidelines relating to biological products as a cumulative compendium separate from the Committee's reports. The Committee recommended that the Secretariat prepare an additional document addressing post-manufacturing and post-marketing issues, for inclusion in such a compendium.

Monoclonal antibodies for use in humans

The Committee noted that the WHO Secretariat had prepared requirements for monoclonal antibodies for clinical use in humans (BS/91.1657) following an informal consultation in February 1991 and subsequent receipt of additional comments. After making some modifications, the Committee adopted the document as "Guidelines for assuring the quality of monoclonal antibodies for use in humans", and agreed that it should be annexed to its report (Annex 3).

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[1] For a summary list of all the requirements for biological substances and other sets of recommendations, see Annex 7.

Requirements for influenza vaccine (inactivated): endotoxin content

The Committee noted that, since the revision in 1990 of the Requirements for Influenza Vaccine (Inactivated) (WHO Technical Report Series, No. 814, 1991, p. 38), evidence had been received that some commercially available inactivated influenza vaccines contained variable amounts of endotoxin, which might be expected to induce fever in some recipients (BS/91.1658). However, the clinical implication of this evidence was unclear. It was recognized that the variable levels of endotoxin might reflect differences in manufacturing practice. The Committee was informed that the European Pharmacopoeia was considering the inclusion of an upper endotoxin limit of 100 International Units per human dose in its monograph on influenza vaccine (inactivated) and that some national control authorities had imposed, or were considering imposing, other limits. The Committee deferred a decision on inclusion of a recommended upper limit for endotoxin in section A.5.5 of the Requirements for Influenza Vaccine (Inactivated) until more information was available.

Requirements for measles, mumps and rubella combined vaccines (live)

The Committee noted that the WHO Secretariat had prepared draft Requirements for Measles, Mumps and Rubella Combined Vaccines (Live) (BS/91.1653 Rev.l) that combined the existing Requirements for Measles Vaccine (Live) (WHO Technical Report Series, No. 771, 1988, Annex 5), Requirements for Mumps Vaccine (Live) (WHO Technical Report Series, No. 760, 1987, Annex 7), and Requirements for Rubella Vaccine (Live) (WHO Technical Report Series, No. 610, 1977, Annex 3, and No. 658, 1981, Annex 12). The Committee was informed that, following circulation of the draft to members of the Expert Advisory Panel on Biological Standardization, a number of comments had been received and that further modifications would be made to the text. The Committee agreed that, in view of the conflicting comments received, the neurovirulence tests for virus master seed lots should be retained in the Requirements, and that the revised draft should be submitted to it at a future meeting for possible adoption.

Antibiotics

Gramicidin

The Committee was informed that stocks of the International Reference Preparation of Gramicidin were depleted (BS/91.1663). Gramicidin is a mixture of linear peptides, and despite the availability of chromatographic methods for examining its composition, the need for a microbiological assay is expected to continue.

The Committee therefore agreed that a replacement preparation was needed and requested the National Institute for Biological Standards and Control, Potters Bar, to obtain suitable material and to organize a collaborative study.

Gentamicin

The Committee noted that stocks of the International Reference Preparation of Gentamycin (International Nonproprietary Name: gentamicin) were depleted (BS/91.1664). Gentamicin is widely used and, because it consists of a mixture of structurally related components, the need to assay it microbiologically is expected to continue. The Committee was informed that the composition of gentamicin from different sources may vary and that differences in composition between a reference preparation and a test sample may give rise to problems in the assay.

The Committee therefore requested the National Institute for Biological Standards and Control, Potters Bar, to carry out a survey through national control laboratories in order to identify sources of gentamicin, and to establish whether the composition of gentamicin is specified and whether difficulties have been observed with assays.

The Committee further requested the National Institute for Biological Standards and Control, Potters Bar, to review the information received and, if appropriate, to obtain suitable material to replace the International Reference Preparation and organize a collaborative study.

Requirements for antimicrobic susceptibility tests
I. Agar diffusion tests using antimicrobic susceptibility discs

At its forty-first meeting, the Committee had requested the WHO Secretariat to investigate other mechanisms, not involving the Committee, by which the disc code list in the Requirements for Antimicrobic Susceptibility Tests could be updated and published, and by which the Requirements could be revised (WHO Technical Report Series, No. 814, 1991, p.13). At its present meeting, the Committee again reviewed the need for international recommendations for the identification of antimicrobial agents and for the Requirements themselves. In view of the fact that the Requirements, apart from the code list, had not been revised from some years, that there was now no intention by the Committee to draft further parts of the Requirements, and that other publications covering the same subject had appeared more recently, the Committee agreed that the Requirements for Antimicrobic Susceptibility Tests: I. Agar Diffusion Tests Using Antimicrobic Susceptibility Discs (Requirements for Biological Substances No. 26) should be discontinued. The Committee nevertheless recommended that the list of disc codes should be maintained, but decided that in the future it would not annex lists of codes to its own report.

The Committee agreed that the centralized international assignment of codes, publication of the code list, and its regular updating were essential to avoid the likelihood of allocation of codes by individual manufacturers, or at national or regional level, which would probably result in different codes being adopted for a single substance. The Committee recommended that WHO should continue to maintain, revise and publish the code list, and that an appropriate mechanism should be found to do so; this might usefully be associated with the nomenclature programme for new drug substances. The Committee noted that since the publication of the 1990 addendum to the Requirements for Antimicrobic Susceptibility Tests (WHO Technical Report Series, No. 814, 1991, p. 71), the WHO Secretariat had received further requests for the allocation of codes for new antimicrobial substances, and that a draft addendum had been prepared (BS/91.1665). The Committee adopted this further addendum with minor modifications, and agreed that it should be annexed to its report (Annex 4).

Antibodies

Anti-toxoplasma serum, human

The Committee was informed that stocks of the second International Standard for Anti-Toxoplasma Serum, Human, established in 1980 (WHO Technical Report Series, No. 658, 1981, p. 14), were nearly exhausted and that a replacement was needed. The Committee therefore requested the State Serum Institute, Copenhagen, to obtain suitable replacement material and to organize a collaborative study.

Rabies immunoglobulin

The Committee was informed that the individual blood samples used to produce the only candidate replacement material for the current International Standard for Rabies Immunoglobulin, referred to in its forty-first report (WHO Technical Report Series, No. 814, 1991, p. 7), had been pooled before a test for antibody to hepatitis C virus was available and had not been tested. Taking into account the urgent need for a replacement standard, the amount of immunoglobulin per ampoule, and the fact that safety warnings would be provided with samples of the replacement standard, the Committee requested the State Serum Institute, Copenhagen, to continue with the organization of a collaborative study.

Anti-poliovirus serum

The Committee noted that nine laboratories in eight countries had participated in the collaborative study referred to in its forty-first report (WHO Technical Report Series, No. 814, 1991, p. 7), organized by the National Institute for Biological Standards and Control, Potters Bar, and that the results had been analysed (BS/91.1660). The Committee noted

that the candidate reference material was a human serum containing antibodies to all three poliovirus types and had been found to be negative in tests for hepatitis B surface antigen (HBsAg) and for antibodies to human immunodeficiency virus, but had not been tested for antibody to hepatitis C virus. The Committee further noted that the study had revealed significant interlaboratory differences in the relative potencies observed when human sera were compared with hyperimmune monkey sera.

The Committee decided that, to avoid confusion, the material should be established as the second International Standard, although it was a trivalent preparation and replaced the three previously established monovalent standards, and that it should be issued with a safety warning that it had not been tested for antibody to hepatitis C virus.

The Committee therefore established the material studied, in ampoules coded 66/202, as the second International Standard for Anti-Poliovirus Serum Types 1, 2 and 3 and, on the basis of the results of the collaborative study, assigned an activity of

25 International Units of Anti-Poliovirus Serum (Type 1), Human,
50 International Units of Anti-Poliovirus Serum (Type 2), Human, and
5 International Units of Anti-Poliovirus Serum (Type 3), Human

to the contents of each ampoule.

The Committee recommended that, to avoid the difficulty experienced in estimating the neutralizing activity of human sera relative to a hyperimmune monkey serum, national standards of anti-poliovirus serum should be prepared using human sera.

Antigens

Rabies vaccine

The Committee noted the results of the collaborative study in 14 laboratories in eight countries referred to in its thirty-ninth report (WHO Technical Report Series, No. 786, 1989, p. 18), which compared three different rabies vaccines (including the proposed replacement reference material) with the International Standard for Rabies Vaccine in immunogenicity assays in mice (NIH test) and in different antigenicity tests measuring envelope glycoprotein, a major antigen in rabies vaccine (BS/91.1654). The Committee also noted the results of a collaborative study in which 49 lots of rabies vaccines produced by four different producers and representing six different combinations of rabies virus strains and cell substrates were compared using the NIH test as well as *in vitro* antigenicity tests for glycoprotein, primarily the single radial immunodiffusion test (BS/91.1661). Both studies confirmed that glycoproteins from different viruses are immunologically distinct. The relative glycoprotein estimates, although very reproducible, did not reflect

the relative potencies obtained in the NIH test when the vaccines compared differed in regard to virus strain or cell substrate. The Committee therefore concluded that the N M test should not be replaced by tests for estimating glycoprotein content.

The Committee established the proposed replacement vaccine, in ampoules coded PISRAV, as the fifth International Standard for Rabies Vaccine[1] on the basis of the results obtained in the collaborative study using the NIH test and, in accordance with the proposal contained in the report of the study and agreed to by the participants, assigned a potency of 16 International Units of Rabies Vaccine to the contents of each ampoule.

The Committee noted the need to standardize tests for rabies virus glycoprotein and ribonucleoprotein, which appear to be important for the protective activity of rabies vaccine (BS/91.1659). In view of this, and since glycoproteins and perhaps also ribonucleoproteins are to some degree strain-specific and the replacement reference material was derived from the Pitman-Moore (PM) strain of virus, the Committee also established the material in ampoules coded PISRAV as the first International Standard for Rabies Virus PM-Glycoprotein and the first International Standard for Rabies Virus PM-Ribonucleoprotein, and assigned 10 International Units of Rabies Virus PM-Glycoprotein and 135 International Units of Rabies Virus PM-kbonucleoprotein to the contents of each ampoule.

Acellular pertussis vaccines

The Committee was informed that acellular pertussis vaccines containing several different antigens were undergoing clinical trial and that there might be a need for reference preparations to enable these vaccines to be uniformly controlled. The Committee concluded, however, that further data would be required before a decision to prepare international reference materials could be made and requested the WHO Secretariat to monitor developments.

Vi typhoid vaccines

The Committee was informed that an informal WHO consultation had been held on requirements for Vi typhoid vaccines and that proposed requirements would be circulated later.

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[1] Strictly speaking, the proposed replacement reference material should have been established as the "second" International Standard since it replaces a material established in 1983 (WHO Technical Report Series, No. 700, 1984) as the first International Standard. However, the first International Standard replaced the third International Reference Preparation, and had it been possible in 1983 to anticipate the Committee's decision in 1986 that "when an international reference preparation is replaced by a new preparation designated as an international standard, then the international standard should be numbered as the next in sequence after the preceding international reference preparation" (WHO Technical Report Series, No. 760, 1987), the material would have been established as the fourth rather than the first International Standard.

Yellow fever vaccine

The Committee noted that further changes had been made to the list of laboratories approved by WHO for the production of yellow fever vaccine and agreed that the revised list should be annexed to its report (Annex 5).

Blood products

Alpha-thrombin, human

The Committee noted that the National Institute for Biological Standards and Control, Potters Bar, had completed the analysis of the results of the collaborative study referred to in its forty-first report (WHO Technical Report Series, No. 814, 1991, p. 9). This study, of a preparation of purified human alpha-thrombin, had involved eight laboratories in five countries (BS/91.1669).

The Committee established the material studied, in ampoules coded 89/588, as the International Standard for Alpha-Thrombin, Human and, on the basis of the results of the collaborative study and the agreement of the participants, assigned an activity of 100 International Units of Alpha-Thrombin, Human to the contents of each ampoule. This Standard, which is of prime use for accurate calibration and precise measurement of thrombin inhibitors, notably hirudin (p. 11), exists in addition to the International Standard for Human Thrombin, established in 1975, which continues to be of value for calibrating thrombins of unknown potency.

Plasma fibrinogen, human

The Committee noted that the results of the collaborative study of a preparation of plasma fibrinogen, referred to in its forty-first report (WHO Technical Report Series, No. 814, 1991, p. 10), had been analysed (BS/91.1670). The results of the collaborative study, in which 22 laboratories in nine countries had participated, indicated a mean content of 2.4 mg of plasma fibrinogen in each ampoule of the material studied, in ampoules coded 89/644. The Committee noted also that the stability of the preparation 'was being investigated in four laboratories. The Committee deferred a decision on the establishment of the preparation as the International Reference Reagent for Plasma Fibrinogen until satisfactory stability data were available.

Plasminogen-activator inhibitor-I (PAI-1)

The Committee was informed that the measurement of plasrninogen-activator inhibitor-1 (PAT-1) concentrations in plasma is important in assessing the tendency to develop thrombotic disease and that availability of a reference material would facilitate such measurements, which are difficult because PAI-1 is present in plasma as a functional latent form, as an active form and as complexes. The Committee was further informed

that the National Institute for Biological Standards and Control, Potters Bar, was organizing a study of a candidate preparation, in ampoules coded 87/512.

Single-chain urinary-type plasminogen activator

The Committee was informed that single-chain urinary-type plasminogen activator was secreted by certain cell cultures and was under investigation for the treatment of myocardial infarction; this form of urolunase required activation to the two-chain form before it could be assayed. A limited study using the International Standard for High Molecular Weight Urokinase had indicated that it might be a suitable immunological assay standard. A larger study was planned by the National Institute for Biological Standards and Control, Potters Bar, under the auspices of the International Society on Thrombosis and Hemostasis, to investigate whether this International Standard was suitable for use in both functional and antigen assays.

Recombinant hirudins

The Committee noted that recombinant hirudin was available from several manufacturers and was under investigation for therapeutic use as an anticoagulant (BS/91.1667). The Committee also noted that a collaborative study had shown that the activity of natural and recombinant hirudins could be assayed using the material established as the International Standard for Alpha-Thrombin, Human (p.10), but that the interlaboratory reproducibility would be improved if a reference material for hirudin were available. The Committee requested the National Institute for Biological Standards and Control, Potters Bar, to investigate the possibility of establishing such a preparation.

Blood coagulation factor VIII and von Willebrand factor

The Committee was informed that, because of heavy demand, stocks of the second International Standard for Factor VIII and von Willebrand Factor in Plasma were being depleted and would require replacement. The Committee therefore requested the National Institute for Biological Standards and Control, Potters Bar, to obtain suitable material and organize a collaborative study.

Protein S

The Committee noted that measurement of protein S concentrations in plasma, in which it is present both free and bound to C4b-binding protein, is useful in the clinical diagnosis of thrombotic disorders and that such assays are frequently performed (BS/91.1668). In the absence of an International Standard, assays are calibrated with plasma pools or commercial standards. The Committee agreed that a need existed for an

international reference material. However, a collaborative study of a lyophilized plasma in 11 laboratories organized by the National Institute for Biological Standards and Control, Potters Bar, had revealed that current assay methods for protein S would require further evaluation before a formal collaborative study could be organized.

Liver ferritin, human

The Committee noted that stocks of the International Standard for Human Liver Ferritin Protein were depleted (BS/91.1678). It was informed that a preparation in ampoules coded 80/578, included in the collaborative study that formed the basis for establishing the current International Standard, was available as a replacement. The Committee requested the National Institute for Biological Standards and Control, Potters Bar, to carry out a limited study on the preparation to confirm that the results of the previous collaborative study were still valid.

The Committee noted that, in the collaborative study leading to the establishment of the first International Standard for Human Liver Ferritin Protein, preparations 80/602 (which became the International Standard) and 80/578 contained ferritin from liver and spleen, respectively (BS/84.1457). The Committee further noted that in the majority of assays for ferritin in the serum these two preparations were not immunologically distinguishable.The Committee agreed that, if the preparation 80/578 was found to be suitable as a replacement material for the current International Standard for Human Liver Ferritin Protein, it would be appropriate to establish it as the second International Standard for Ferritin.

The Committee stressed that, on any similar occasion in future (i.e. if a preparation included in the original collaborative study was under consideration as a replacement international reference material), it would be important that limited comparative studies of the proposed replacement material were performed against the existing International Standard.

Apolipoprotein A-I

The Committee was informed that a report had been received by the WHO Secretariat of a study, performed by the International Federation of Clinical Chemistry (IFCC), proposing the establishment of a preparation of apolipoprotein A-l in a serum matrix as an International Standard. The Committee agreed that there were deficiencies in the report and deferred a decision pending clarification.

The Committee was informed that there was an urgent need to harmonize measurements of apolipoprotein A-l, which were increasingly used in screening for cardiovascular disease. As an interim measure, the WHO Secretariat would arrange for the proposed reference material to be made available on request. The Committee noted that the IFCC report stated

that, when the contents of one vial of the proposed standard were reconstituted with 1 ml of distilled water, the resulting fluid contained the equivalent of 1.5 g/litre of apolipoprotein A-1.

Haemoglobin F and haemoglobin A_2

At its thirty-eighth meeting (WHO Technical Report Series, No. 771, 1988, pp. 24 & 25), the Committee recognized the need for international reference materials for haemoglobin F and haemoglobin A_2. At its present meeting, the Committee was informed that the International Council for Standardization in Haematology had obtained materials to serve as candidate reference preparations for these haemoglobins, and had confirmed their stability and organized collaborative studies. The Committee was further informed that, when the analyses of the studies were complete, portions of each batch would be offered to WHO for possible adoption as International Standards.

Endocrinological and related substances

Human calcitonin

The Committee noted that, in accordance with the request made in its forty-first report (WHO Technical Report Series, No. 814, 1991, p. 11), the National Institute for Biological Standards and Control, Potters Bar, had obtained a preparation of human calcitonin suitable to serve as a replacement for the International Reference Preparation of Human Calcitonin for Bioassay and had arranged a collaborative study (BS/91.1675). The Committee noted that the material studied, in ampoules coded 89/620, was of adequate stability, and established it as the second International Standard for Human Calcitonin. On the basis of the results of the collaborative study, involving 16 laboratories in 12 countries, and the agreement of the participants, the Committee assigned an activity of 17.5 International Units of Human Calcitonin to the contents of each ampoule, based on estimates made by the rat hypocalcaemia bioassay.

Porcine calcitonin

The Committee noted that, in accordance with the request made in its forty-first report (WHO Technical Report Series, No. 814, 1991, p. 11), the National Institute for Biological Standards and Control, Potters Bar, had obtained a preparation of porcine calcitonin suitable to serve as a replacement for the International Reference Preparation of Porcine Calcitonin for Bioassay and had arranged a collaborative study (BS/91.1674). The Committee noted that the material studied, in ampoules coded 89/540, was of adequate stability as determined by bioassay and established it as the second International Standard for

Porcine Calcitonin. On the basis of the results of the collaborative study, involving 16 laboratories in 12 countries, and the agreement of the participants, the Committee assigned an activity of 0.8 International Unit of Porcine Calcitonin to the contents of each ampoule, based on estimates made by the rat hypocalcaemia bioassay.

Thyroxine-binding globulin

The Committee noted that, in accordance with the request made in its thirty-ninth report (WHO Technical Report Series, No. 786, 1989, p. 25), the National Institute for Biological Standards and Control, Potters Bar, had obtained a preparation of thyroxine-binding globulin suitable to serve as an International Standard and had arranged a collaborative study in six laboratories in four countries (BS/91.1671). The material studied, in ampoules coded 88/638, had been assessed by immunological methods and was of adequate stability. The Committee therefore established it as the International Standard for Thyroxine-binding Globulin and, on the basis of the results of the collaborative study and the agreement of the participants, defined the activity of the contents of each ampoule as 30 International Units of Thyroxine-binding Globulin. The Committee noted that the content of 30 International Units per ampoule was equivalent to the nominal ampoule content of 30 µg of thyroxine-binding globulin as estimated by ultraviolet spectrophotometry. However, the Committee cautioned that such an equivalence might not apply to other preparations of thyroxine-binding globulin.

Anti-thyroid microsome serum

The Committee noted that, in accordance with the request made in its forty-first report (WHO Technical Report Series, No. 814, 1991, p. 11), the National Institute for Biological Standards and Control, Potters Bar, had provided information on the present demand for the preparation of anti-thyroid microsome serum coded 66/387 and on its stability (BS/91.1672). However, the Committee concluded that the data available were insufficient to justify adoption of the preparation of anti-thyroid microsome serum as an international reference material and requested the National Institute for Biological Standards and Control, Potters Bar, to consider whether further experimental studies were necessary.

Somatropin

The Committee noted that the collaborative study of a candidate preparation of recombinant growth hormone (somatropin), referred to in its thirty-ninth report (WHO Technical Report Series, No. 786, 1989, p. 22), was in progress (BS/91.1673).

Nerve growth factor

The Committee was informed of the need for a reference material for nerve growth factor and requested the National Institute for Biological Standards and Control, Potters Bar, to obtain a suitable preparation and organize a collaborative study.

Epidermal growth factor

The Committee noted that, in view of the discussion in its forty-first report (WHO Technical Report Series, No. 814, 1991, p. 1), the National Institute for Biological Standards and Control, Potters Bar, had obtained four candidate reference preparations of epidermal growth factor (BS/91.1676). The Committee also noted that three of the preparations had been ampouled and that stability studies were in progress.

Basic fibroblast growth factor

The Committee noted that, following the discussion at its forty-first meeting (WHO Technical Report Series, No. 814, 1991, p. 1), the National Institute for Biological Standards and Control, Potters Bar, had obtained and ampouled three candidate reference preparations of basic fibroblast growth factor (BS/91.1676). The Committee also noted that preliminary stability studies were complete and that a collaborative study had commenced.

Acidic fibroblast growth factor

The Committee noted that, in view of the discussion in its forty-first report (WHO Technical Report Series, No. 814, 1991, p. 1), the National Institute for Biological Standards and Control, Potters Bar, had obtained two candidate reference preparations of acidic fibroblast growth factor, but that further preparations were being sought before a collaborative study would commence (BS/91.1676).

Platelet-derived growth factor

The Committee noted that, following the discussion at its forty-first meeting (WHO Technical Report Series, No. 814, 1991, p. 1), the National Institute for Biological Standards and Control, Potters Bar, had obtained a candidate reference preparation of platelet-derived growth factor, but that further preparations were being sought before a collaborative study would commence (BS/91.1676).

Recombinant thyroid-stimulatinghormone

The Committee was informed that, because of the difficulty of obtaining thyroid-stimulating hormone of pituitary origin, manufacturers would make increasing use of preparations of recombinant thyroid-stimulating hormone as standards in immunoassay kits. The Committee requested the

National Institute for Biological Standards and Control, Potters Bar, to obtain suitable material and to organize a collaborative study to establish whether preparations of recombinant hormone could be calibrated adequately by immunoassay in terms of the existing International Reference Preparation of pituitary TSH.

Recombinant follicle-stimulating hormone

The Committee was informed that recombinant follicle-stimulating hormone intended for therapeutic use was available from several sources, and that calibration of these products against existing international reference materials containing follicle-stimulating hormone of pituitary or urinary origin might be inappropriate. The Committee therefore requested the National Institute for Biological Standards and Control, Potters Bar, to organize a study to establish whether a new international reference material was required for the recombinant hormone.

Insulin-like growth factor-binding protein

The Committee was informed that there was a rapidly growing interest in insulin-like growth factor-binding protein, which was available as a product of recombinant-DNA technology, and in its potential applications for diagnosis and therapy. The Committee recognized the need for an international reference material and requested the National Institute for Biological Standards and Control, Potters Bar, to obtain suitable materials and to organize a collaborative study.

Tumour necrosis factor

The Committee noted that the results of the collaborative study of a preparation of recombinant human tumour necrosis factor alpha (rhTNF-α), referred to in its forty-first report (WHO Technical Report Series, No. 814, 1991, p. 12), had been analysed (BS/91.1681). The results of the study, performed in 20 laboratories in eight countries, had shown that a preparation with the full molecular structure of rhTNF-α was the most suitable for biological assays of TNF. The Committee therefore established the material, in ampoules coded 87/650, as the International Standard for Human Tumour Necrosis Factor Alpha, and defined its potency as 40 000 International Units of Human Tumour Necrosis Factor Alpha per ampoule.

The collaborative study had revealed that the International Standard might be inappropriate for the assay of preparations of TNF-a of modified structure, and that it was unsuitable for use as a reference material for assays of human tumour necrosis factor beta (hTNF-β) and of recombinant mouse tumour necrosis factor alpha (rmTNF-α). Because of the pressing need for reference materials for these last two substances, the two preparations that were included in the collaborative study will be available from the National Institute for Biological Standards and Control,

Potters Bar, with arbitrary unitages assigned to them, until International Standards are established. The Committee emphasized that the units for rhTNF-α, hTNF-β and rmTNF-α do not correlate with one another.

The Committee was informed of a collaborative study being organized by WHO of the assay of TNF in sera from patients with various diseases, including malaria and meningitis, in order to assess the prognostic values of such assays. The Committee would be advised in due course of the results of the study.

Cytokines

Progress report

In view of the rapid developments in this field, steps had been taken to obtain a number of candidate materials and assess their suitability to serve as International Standards. The Committee noted that ampouled preparations of cytokines for which collaborative studies had been completed could be obtained from the National Institute for Biological Standards and Control, Potters Bar, and the National Institutes of Health, Bethesda, before formal establishment as international reference materials.

Interleukin-I receptor antagonist

The Committee was informed of the need for a reference material for interleukin-1 receptor antagonist and requested the National Institute for Biological Standards and Control, Potters Bar, to obtain a suitable preparation and organize a collaborative study.

Granulocyte/macrophage colony-stimulating factor

The Committee noted that the collaborative study on the proposed international reference material for granulocyte/macrophage colony-stimulating factor, referred to in its forty-first report (WHO Technical Report Series, No. 814, 1991, p.12), was complete and that the results were being analysed (BS/91.1679 & 80).

Granulocyte colony-stimulating factor

The Committee noted that the collaborative study on the proposed international reference material for granulocyte colony-stimulating factor, referred to in its forty-first report (WHO Technical Report Series, No. 814, 1991, p.12), was complete and that the results were being analysed (BS/91.1679 & 80).

Macrophage colony-stimulating factor

The Committee was informed that, in accordance with the request made in its thirty-ninth report (WHO Technical Report Series, No. 786, 1989,

p.26), the National Institute for Biological Standards and Control, Potters Bar, had obtained three candidate reference preparations of macrophage colony-stimulating factor, and a collaborative study was in progress involving a wide variety of assay systems.

Interleukin-3

The Committee was informed that, in accordance with the request made in its thirty-ninth report (WHO Technical Report Series, No.786, 1989, p.26), the National Institute for Biological Standards and Control, Potters Bar, had obtained and ampouled three candidate reference preparations of interleulun-3. The Committee was also informed that stability studies were complete and that a collaborative study had been organized.

Interleukin-4

The Committee was informed that, in accordance with the request made in its thirty-ninth report (WHO Technical Report Series, No.786, 1989, p.26), the National Institute for Biological Standards and Control, Potters Bar, had obtained and ampouled three candidate reference preparations of interleukin-4. The Committee was also informed that stability studies were complete and that a collaborative study had been organized.

Interleukin-5

The Committee was informed that, in view of the need for a reference preparation of interleukin-5, the National Institute for Biological Standards and Control, Potters Bar, had obtained and ampouled a candidate preparation and a stability study was in progress.

Interleukin-7

The Committee was informed that, in view of the need for a reference preparation of interleulun-7, the National Institute for Biological Standards and Control, Potters Bar, had obtained and ampouled two candidate preparations and stability studies were in progress.

Interleukin-8

The Committee was informed that, in accordance with the request made in its thirty-ninth report (WHO Technical Report Series, No.786, 1989, p.26), the National Institute for Biological Standards and Control, Potters Bar, had obtained and ampouled two candidate reference preparations of interleukin-8. The Committee was also informed that stability studies were complete and that a collaborative study would be organized.

Leukaemia inhibitory factor

The Committee was informed that, in view of the need for a reference

preparation of leukaemia inhibitory factor, the National Institute for Biological Standards and Control, Potters Bar, had obtained and ampouled a candidate preparation and stability studies were in progress.

Transforming growth factor beta

The Committee was informed that, in view of the need for a reference preparation of transforming growth factor beta, the National Institute for Biological Standards and Control, Potters Bar, had obtained and ampouled a candidate preparation and a stability study was in progress.

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Annex 1
Good manufacturing practices for biological products

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1. Scope of these guidelines

These guidelines are intended to complement those provided in "Good manufacturing practices for pharmaceutical products" **(1).**

The regulatory procedures necessary to control biological products are in large part determined by the sources of products and methods of manufacture. Manufacturing procedures within the scope of these guidelines include:

- growth of strains of microorganisms and eukaryotic cells,
- extraction of substances from biological tissues, including human, animal and plant tissues (allergens),
- recombinant DNA (rDNA) techniques,
- hybridoma techniques,
- propagation of microorganisms in embryos or animals.

Biological products manufactured by these methods include allergens, antigens, vaccines, hormones, cytokines, enzymes, human whole blood and plasma derivatives, immune sera, immunoglobulins (including monoclonal antibodies), products of fermentation (including products derived from rDNA) and diagnostic agents for in *vitro* use.

2. Principles

The manufacture of biological products shall be undertaken in accordance with the basic principles of good manufacturing practices (GMP). The points covered by these guidelines should therefore be considered supplementary to the general requirements set out in "Good manufacturing practices for pharmaceutical products" **(1),** and relate specifically to the production and control of biological products. In drawing up these guidelines, due consideration was given to the draft "Guidelines for national authorities on quality assurance for biological products", the final version of which appears as Annex 2 to the forty-second report of the WHO Expert Committee on Biological Standardization (2).

The way in which biological products are produced, controlled and administered makes some particular precautions necessary. Unlike conventional pharmaceutical products, which are normally produced and controlled using reproducible chemical and physical techniques, biological products are manufactured by methods involving biological processes and materials, such as cultivation of cells or extraction of material from living organisms. These processes display inherent variability, so that the range and nature of by-products are variable. For this reason, in the manufacture of biological products full adherence to GMP is necessary for all production steps, beginning with those from which the active ingredients are produced.

Control of biological products nearly always involves biological techniques that have a greater variability than physicochemical determinations. In-process controls take on a great importance in the manufacture of biological products because certain deficiencies may not be revealed by testing the finished product.

The present guidelines do not lay down detailed requirements for specific classes of biological products, and attention is therefore directed to other guidance issued by WHO, and in particular to the Requirements for Biological Substances, which include requirements for vaccines (2, Annex 7).

3. Personnel

3.1 The manufacturing establishment and its personnel shall be under the authority of a person who has been trained in the techniques used in manufacturing biological substances and who possesses the scientific knowledge upon which the manufacture of these products is based. The personnel shall include specialists with training appropriate to the products made in the establishment.

3.2 Personnel required to work in clean and aseptic areas should be selected with care, to ensure that they may be relied upon to observe the appropriate codes of practice and are not subject to any disease or condition that could compromise the integrity of the product

microbiologically or otherwise. High standards of personal hygiene and cleanliness are essential. Staff should be instructed to report any conditions (e.g. diarrhoea, coughs, colds, infected skin or hair, wounds, fever of unknown origin) that may cause the shedding of abnormal numbers or types of organisms into the working environment. Health checks on personnel for such conditions should be required before employment and periodically thereafter. Any changes in health status that could adversely affect the quality of the product shall preclude the person concerned from working in the production area.

3.3 Only the minimum number of personnel required should be present in clean and aseptic areas when work is in progress. Inspection and control procedures should be conducted from outside these areas as far as possible.

3.4 During the worlung day, personnel shall not pass from areas where live microorganisms or animals are handled to premises where other products or organisms are handled unless clearly defined decontamination measures, including a change of clothing and shoes, are followed. Persons not concerned with the production process should not enter the production area except for essential purposes, and in that case they shall be supplied with sterile protective clothing.

3.5 The staff engaged in the manufacturing process should be separate from the staff responsible for animal care.

3.6 The names and qualifications of those responsible for approving lot processing records (protocols) should be registered with the national control authority.

3.7 To ensure the manufacture of high-quality products, personnel should be trained in good manufacturing and laboratory practices in appropriate fields such as bacteriology, virology, biometry, chemistry, medicine, immunology and veterinary medicine.

3.8 Training records should be maintained and periodic assessments of the effectiveness of training programmes should be made.

3.9 All personnel engaged in production, maintenance, testing and animal care (and inspectors) should be vaccinated with appropriate vaccines and, where appropriate, be submitted to regular testing for evidence of active tuberculosis. Apart from the obvious problem of exposure of staff to infectious agents, potent toxins or allergens, it is necessary to avoid the risk of contamination of a production batch with these agents.

3.10 Where BCG vaccines are being manufactured, access to production areas shall be restricted to staff who are carefully monitored by regular health checks. In the case of manufacture of products derived from human blood or plasma, vaccination of workers against hepatitis B is recommended.

4. Premises and equipment

4.1 As a general principle, buildings must be located, designed, constructed, adapted and maintained to suit the operations to be carried out within them. Laboratories, operating rooms and all other rooms and buildings (including those for animals) that are used for the manufacture of biological products shall be designed and constructed of materials of the highest standard so that cleanliness, especially freedom from dust, insects and vermin, can be maintained.

4.2 Interior surfaces (walls, floors and ceilings) shall be smooth and free from cracks; they shall not shed matter and shall permit easy cleaning and disinfection. Drains should be avoided wherever possible and, unless essential, should be excluded from aseptic areas. Where installed they should be fitted with effective, easily cleanable traps and with breaks to prevent back-flow. The traps may contain electrically operated heating devices or other means for disinfection. Any floor channels should be open, shallow and easily cleanable and be connected to drains outside the area in a manner that prevents ingress of microbial contaminants.

4.3 Sinks shall be excluded from aseptic areas. Any sink installed in other clean areas shall be of suitable material such as stainless steel, without an overflow, and be supplied with water of potable quality. Adequate precautions shall be taken to avoid contamination of the drainage system with dangerous effluents. Airborne dissemination of pathogenic microorganisms and viruses used for production and the possibility of contamination by other types of viruses or substances during the production process, including those from personnel, shall be avoided.

4.4 Lighting, heating, ventilation and, if necessary, air-conditioning should be designed to maintain a satisfactory temperature and relative humidity, to minimize contamination and to take account of the comfort of personnel working in protective clothing. Buildings shall be in a good state of repair. The condition of the buildings should be reviewed regularly and repairs carried out when and where necessary. Special care should be exercised to ensure that building repair or maintenance operations do not compromise products. Premises should provide sufficient space to suit the operations to be carried out, allowing an efficient flow of work and effective communication and supervision. All buildings and rooms shall be clean and sanitary at all times. If rooms intended for the manufacture of biological substances are used for other purposes, they shall be cleaned thoroughly and, if necessary, sanitized before the manufacture of biological substances is resumed. Areas used for processing animal tissue materials and microorganisms not required for the current manufacturing process and for performing tests involving animals or microorganisms must be separated from premises used for manufacturing sterile biological products and have completely separate ventilation systems and separate staff.

4.5 If certain products are to be produced on a campaign basis, the layout

and design of the premises and equipment shall permit effective decontamination by fumigation, where necessary, as well as cleaning and sanitizing after the production campaign.

4.6 Seed lots and cell banks used for the production of biological products should be stored separately from other material. Access should be restricted to authorized personnel.

4.7 Live organisms shall be handled in equipment that ensures that cultures are maintained in a pure state and are not contaminated during processing.

4.8 Products such as lulled vaccines, including those made by rDNA techniques, toxoids and bacterial extracts may after inactivation be dispensed into containers on the same premises as other sterile biological products, providing that adequate decontamination measures are taken after filling, including, if appropriate, sterilization and washing.

4.9 Spore-forming organisms shall be handled in facilities dedicated to this group of products until the inactivation process is accomplished. For Bacillus anthracis, Clostridium botulinum and Clostridium tetani, strictly dedicated facilities should be utilized for each individual product. Where campaign manufacture of spore-forming organisms occurs in a facility or suite of facilities, only one product should be processed at any one time.

4.10 Dedicated facilities and equipment shall be used for the manufacture of medicinal products derived from human blood or plasma.

4.11 All containers of biological substances, regardless of the stage of manufacture, shall be identified by securely attached labels. Cross-contamination should be prevented by adoption of some or all of the following measures:

- processing and filling in segregated areas;
- avoiding manufacture of different products at the same time, unless they are effectively segregated;
- containing material transfer by means of airlocks, air extraction, clothing change and careful washing and decontamination of equipment;
- protecting against the risks of contamination caused by recirculation of untreated air, or by accidental re-entry of extracted air;
- using "closed systems" of manufacture;
- taking care to prevent aerosol formation (especially by centrifugation and blending);
- excluding pathological specimens sent in for diagnosis from areas used for manufacturing biological substances;
- using containers that are sterilized or are of documented low "bioburden".

4.12 Positive-pressure areas should be used to process sterile products, but negative pressure is acceptable in specific areas where pathogens are

processed. In general, any organisms considered to be pathogenic should be handled w i t h specifically designed areas under negative pressures, in accordance with containment requirements for the product concerned.

4.13 Air-handling units should be dedicated to the processing area concerned. Air from operations involving pathogens shall not be recirculated and, in the cases of organisms in a group above Risk Group 2 (*3*), shall be exhausted through sterilizing filters that are regularly checked for performance.

4.14 Specific decontamination systems should be considered for effluent when infectious and potentially infectious materials are used for production.

4.15 Pipework, valves and vent filters shall be properly designed to facilitate cleaning and sterilization. Valves on fermentation vessels shall be completely steam-sterilizable. Air-vent filters shall be hydrophobic and shall be validated for their designated use.

4.16 Small stocks of substances that have to be measured or weighed during the production process (e.g. buffers) may be kept in the production area, provided that they are not returned to the general stocks. Otherwise, dry materials used to formulate buffers, culture media, etc. should be weighed and put into solution in a contained area outside the purification and aseptic areas in order to minimize particulate contamination of the product.

5. Animal quarters and care[1]

5.1 Animals are used for the manufacture and control of a number of biological products. Animals shall be accommodated in separate buildings with self-contained ventilation systems. The buildings' design and construction materials shall permit maintenance in a clean and sanitary condition free from insects and vermin. Facilities for animal care shall include isolation units for quarantine of incoming animals and provision for vermin-free food storage. Provision shall also be made for animal inoculation rooms, which shall be separate from the postmortem rooms. There shall be facilities for the disinfection of cages, if possible by steam, and an incinerator for disposing of waste and of dead animals.

5.2 The health status of animals from which starting materials are derived and of those used for quality control and safety testing should be monitored and recorded. Staff employed in animal quarters must be provided with special clothg, changing facilities and showers. Where monkeys are used for the production or quality control of biological products; special consideration is required, as laid down in the revised Requirements for Biological Substances No. 7 (Requirements for Poliomyelitis Vaccine (Oral)) *(5)*.

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[1] General requirements for animal quarters, care and quarantine are given in reference 4

6. Production

6.1 Standard operating procedures shall be available and maintained up to date for all manufacturing operations.

6.2 Specifications for starting materials should include details of their source, origin and method of manufacture and of the controls applied, in particular microbiological controls, to ensure their suitability for use. Release of a finished product is conditional on satisfactory results being obtained in the tests on starting materials.

6.3 Media and cultures shall be added to fermenters and other vessels under carefully controlled conditions to avoid contamination. Care shall be taken to ensure that vessels are correctly connected when cultures are added.

6.4 If possible, media should be sterilized in *situ.* In-line sterilizing filters for routine addition of gases, media, acids, alkalis, defoaming agents, etc. to fermenters should be used where possible.

6.5 Careful consideration should be given to the validation of sterilization methods.

6.6 When an inactivation process is performed during manufacture, measures should be taken to avoid the risk of cross-contamination between treated and untreated products.

6.7 A wide variety of equipment is used for chromatography; in general such equipment should be dedicated to the purification of one product and should be sterilized or sanitized between batches. Problems of decontamination and purification may arise through repeated use of the same equipment at the same or different stages of processing. The life span of columns and the sterilization method shall be defined. Particular care should be given to monitoring microbial loads and endotoxins.

7. Labelling

7.1 All products shall be clearly identified by labels. The labels used must remain permanently attached to the containers under all storage conditions and an area of the container should be left uncovered to allow inspection of the contents. If the final container is not suitable for labelling (for example a capillary tube), it should be in a labelled package.

7.2 The information given on the label on the container and the label on the package shall be approved by the national control authority.

7.3 The label on the container shall show:

- the name of the drug product;
- a list of the active ingredients and the amount of each present, with a statement of the net contents, e.g. number of dosage units, weight or volume;

- the batch or final lot number assigned by the manufacturer;
- the expiry date;
- recommended storage conditions or handling precautions that may be necessary;
- directions for use, and warnings and precautions that may be necessary;
- the nature and amount of any substance used in the preparation of the biological product that is likely to give rise to an adverse reaction in some recipients;
- the name and address of the manufacturer or the company and/or the person responsible for placing the drug on the market.

7.4 The label on the package shall, in addition to the information shown on the label on the container, show at least the nature and amount of any preservative or additive in the product.

7.5 The leaflet in the package should provide instructions for the use of the product, and mention any contraindications or potential adverse reactions.

8. Lot processing records (protocols) and distribution records

8.1 Processing records of regular production lots must provide a complete account of the manufacturing history of each lot of a biological preparation, showing that it has been manufactured, tested, dispensed into containers and distributed in accordance with the licensed procedures.

8.2 A separate processing record should be prepared for each lot of biological product, and should include the following information:

- the name and dosage of the product;
- the date of manufacture;
- the lot identification number;
- the complete formulation of the lot, including identification of seed or starting materials;
- the batch number of each component used in the formulation;
- the yield obtained at different stages of manufacture of the lot;
- a duly signed record of each step followed, precautions taken and special observations made throughout the manufacture of the lot;
- a record of all in-process control tests and of the results obtained;
- a specimen of the label;
- identification of packaging materials, containers and closures used;
- a dated signature of the expert responsible for approving the manufacturing operations;
- an analytical report, dated and signed by the responsible expert, showing whether the lot complies with the specifications described in the standard operating procedure registered with the national control authority;
- a record of the decision regarding the release or rejection of the lot by the quality-control department and, if the lot is rejected, a record of its disposal or utilization.

8.3 The records shall be of a type approved by the national control authority. They shall be retained for at least two years after the expiry date of a lot or batch of a biological product and be available at all times for inspection by the national control authority.

8.4 Records must make it possible to trace all steps in the manufacture and testing of a lot, and should include records of sterilization of all apparatus and materials used in its manufacture. Distribution records must be kept in a manner that permits rapid recall of any particular lot, if necessary.

9. Quality assurance and quality control

9.1 The quality-assurance and/or quality-control department should have the following principal duties:

- to prepare detailed instructions for each test and analysis;
- to ensure adequate identification and segregation of test samples to avoid mix-up and cross-contamination;
- to ensure that environmental monitoring and equipment validation are conducted as appropriate for evaluating the adequacy of the manufacturing conditions;
- to release or reject raw materials and intermediate products, if necessary;
- to release or reject packaging and labelling materials and the final containers in which drugs are to be placed;
- to release or reject each lot of finished preparation;
- to evaluate the adequacy of the conditions under which raw materials, intermediate products and finished biological preparations are stored;
- to evaluate the quality and stability of finished products and, when necessary, of raw materials and intermediate products;
- to establish expiry dates on the basis of the validity period related to specified storage conditions;
- to establish and, when necessary, revise control procedures and specifications; and
- to be responsible for the examination of returned preparations to determine whether such preparations should be released, reprocessed or destroyed; adequate records of the distribution of such preparations should be maintained.

9.2 A manufacturer's quality-control laboratory shall be separated from the production area and ideally should be in a separate building. The control laboratory should be designed and equipped and of such a size as to be a self-contained entity, with adequate provision for the storage of documents and samples, preparation of records and performance of the necessary tests.

9.3 In-process controls play a specially important role in ensuring the consistent quality of biological products. Tests that are crucial for quality control but that cannot be carried out on the finished product shall be performed at an appropriate stage of production.

9.4 Performance of all qualitative and quantitative tests mentioned in the specifications for starting materials may be replaced by a system of certificates issued by the producer of the starting material, provided that:

- there is a history of reliable production,
- the producer is regularly audited, and
- at least one specific identity test is conducted by the manufacturer of the final product.

9.5 Samples of intermediate and final products shall be retained in sufficient amount and under appropriate storage conditions to allow the repetition or confirmation of a batch control. However, reference samples of certain starting materials, e.g. components of culture media, need not necessarily be retained.

9.6 Certain operations require the continuous monitoring of data during a production process, for example monitoring and recording of physical parameters during fermentation.

9.7 Special consideration needs to be given to the quality-control requirements arising from production of biological products by continuous culture.

Authors

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Annex 2
Guidelines for national authorities on quality assurance for biological products

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Model certificate for the release of a lot or lots of a biological product 46

1. Scope

This document describes measures for assuring the safety and efficacy of biological products intended for use in humans. Its aim is to provide general guidelines for national health authorities on quality assurance for biological products, except those used solely as *in vitro* diagnostic agents. The concepts and principles have been harmonized with those of the Requirements for Biological Substances and other related sets of recommendations published by WHO *(1)*.Though it is difficult to provide a set of guidelines applicable to all national situations, an attempt has been made to cover a range of possibilities; the principles on which this document is based may assist in the development of national guidelines.

2. Introduction

Since the publication by WHO in 1981 of a document entitled "The national control of vaccines and sera" (*2*), it has become apparent that it would be helpful to provide updated guidance for countries wishing to develop or improve quality-assurance procedures for biological products. In addition, technological developments in the production of biologicals and the availability of new analytical methods for determining their quality

have made evident the need for a further revision of the Requirements for Biological Substances No.1 (General Requirements for Manufacturing Establishments and Control Laboratories), published in 1966 (3). The present guidelines reflect the decision to combine parts of these two documents into a single text.

National regulatory authorities have the duty to ensure that available pharmaceutical products, whether imported or manufactured locally, are of the required quality. This is particularly difficult for biological products, the quality of which cannot be established entirely by tests on the material in the final container. The national authority has the responsibility to confirm that the manufacturer is adhering to the approved standards of good manufacturing practice and to national and other requirements for manufacture and quality control specific to the product. The mechanism by which national authorities confirm the assurance of quality provided by the manufacturer may depend on the resources available and whether the product is manufactured locally or imported.

In general biological products are distinguished from other drugs by being derived from living organisms (ranging from normal or genetically modified microorganisms to humans), and frequently have a complex molecular structure. They require special quality considerations because of the biological nature of: (a) the starting materials, and/or (b) the manufacturing process, and/or (c) the test methods needed to characterize batches of the product.

Recognizing these difficulties and the need for international harmonization of quality standards, WHO, largely through its Biologicals unit, has a number of activities related to the quality assurance of biological products used for the diagnosis, prevention and treatment of diseases. These include: (a) publishing in the WHO Technical Report Series the reports of expert groups, which may include documents such as this one that constitute requirements or guidelines for use by national authorities; (b) organizing the distribution of International Standards and other reference materials for biological substances, which allow the characterization and assay of products in terms of internationally accepted units; (c) providing advice on the preparation of national reference materials; (d) advising and assisting Member States in the establishment and functioning of structures for national control purposes, e.g. by organizing visits by experts and assisting with programmes of training and research in relation to these activities; and (e) arranging scientific meetings to provide an up-to-date and scientifically valid consensus on topics relating to quality assurance that are generally applicable to Member States throughout the world.

Developments in biological products have been extremely rapid in recent years, and the potential of such products for improving health care on a global scale is immense. There is an urgent need to match technological advances with appropriate mechanisms for assuring the quality of the products.

3. General considerations

The quality, safety and efficacy of a biological product are the prime responsibility of the manufacturer; however, the national health authority of each Member State is responsible for establishing procedures for assuring that biological products intended for use in the country are of adequate quality, safety and efficacy. This responsibility should have a firm statutory basis backed by legislation. Marketing approval for a biological product should be granted by a national control authority (NCA), which should also be responsible for continued post-marketing monitoring. In carrying out these activities, the NCA should make use of expert committees and technical advisers, and have access to laboratory facilities.'

Individual Member States should have written standards, both general and product-specific, for biological products available for use in their countries. These should be based on contemporary standards, such as those available from WHO, and harmonized as far as possible with those of other Member States. For newly developed products, WHO, national and pharmacopoeia1 requirements may not have been developed and the NCA will need to agree on specifications with the manufacturer on a case-by-case basis.

In countries where biological products are manufactured, the NCA should have appropriate expertise to evaluate the adequacy of the manufacturer's establishment and facilities, starting materials, production processes, control-test procedures and product specifications, to determine whether they meet international and/or national requirements. These control activities should be fully independent of those of the manufacturer; ideally the national laboratory facilities should form a single administrative unit designated as the national control laboratory (NCL). The NCL may be administered directly by, or on behalf of, the NCA.

In countries where biological products are not manufactured, alternative approaches may be acceptable for assuring the safety and efficacy of these products (see section 8). However, an approval process limited to a mere listing of facilities and products would not be considered adequate.

In view of the complexity and cost of certain resources needed for control testing, it may be unavoidable in certain cases to share such resources with the manufacturer or an academic institution, or to rely on the resources of an NCL in another Member State.

National control authorities should, whenever appropriate, exchange information on safety issues, within the constraints of confidentiality, in accordance with the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (4).

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[1] In this document reference is made only to the role of the NCA with respect to biologicals; in practice it is to be expected that the NCA will have responsibility for all pharmaceutical products.

4. Structure of a national control authority for biological products

In countries where biological products are manufactured, the health authorities should establish and maintain a competent NCA and NCL. It is recommended that the NCA should make use of independent expert advisers and advisory committees with appropriate expertise and have access to testing facilities, such as those of the NCL, to support decision-making. In some instances a multinational or regional structure may be more efficient.

4.1 *Personnel*

The personnel of the NCA and the NCL should include person(s) qualified and experienced in the control of biological products and experts in all appropriate disciplines. The qualifications and experience of the staff at all levels should be appropriate to the review and control activities required for the range of biological products to be controlled. It is advantageous for the director of the NCL to report directly to the director of the NCA.

Contact between NCA and NCL personnel and scientists working in related fields will be beneficial for exchanging ideas and discussing techniques, problems and analytical results.

All staff of the NCA and NCL should receive suitable training through active training programmes, covering both the technical and the administrative aspects of control procedures.

Encouragement of research activities within the NCL will both lead to the development of better control methods and help the laboratory to retain an interested, efficient and highly qualified staff.

4.2 *Administration*

The NCA should have established procedures for the receipt and review of manufacturers' submissions and for testing samples provided in support of applications. On completion of the review procedures, which include the evaluation of detailed reports (see sections 5 and 6), the NCA issues a notice of approval or disapproval to the manufacturer. It may also issue notices of suspension or revocation of approval. Consideration should be given to making available appropriate legal expertise in support of this activity.

The NCA should maintain adequate filing and archiving facilities, such that all submissions, evaluations, records and correspondence are available and kept up to date. Attention should be given to the need to maintain commercial confidentiality.

The NCA and NCL should possess, or have access to, library facilities appropriate to their fields of activity. The documents available should include: current national and international requirements for products that

are manufactured locally, relevant international requirements for biological substances, and other relevant specifications and recommendations published by WHO or other bodies.

4.3 *Good manufacturing practices (GMP) inspectorate*

The NCA should have access to suitably qualified inspectors who are independent of manufacturers. The purpose of inspections will be to ensure compliance of each manufacturer's facilities and procedures with the principles of GMP as described in WHO publications *(5,* 6) and with the requirements and/or conditions for the approval for the product concerned. Guidelines are available for conducting inspections of manufacturers of both drugs and biologicals (7). Reciprocal arrangements for international inspection such as those of the Pharmaceutical Inspection Convention of the European Free Trade Association *(8)* may be used, as may the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (4).

5. Procedures for approval of manufacturers and products

Approval or licensing of a manufacturing establishment for production of biological products should be granted only if the manufacturer complies with the principles of GMP *(5,* 6), as confirmed by inspection.

Approval or licensure of a given biological product will be given by the NCA when it is satisfied that the product conforms to the relevant national and/or international requirements, including the manufacturer's specifications applicable to the product. In order to evaluate the safety and efficacy of a biological product, the NCA should review the following detailed information before granting an approval.

5.1 *Information on the manufacturing establishment*

The manufacturer should provide sufficient information to demonstrate compliance with the principles of GMP *(5,* 6), including the existence of adequate quality-assurance systems. Plans, diagrams, flow charts and texts may be used to convey the necessary information in relation to (but not limited to):

- personnel:
  - qualifications and experience,
  - organization and reporting relationships,
  - training schedules and recording systems;
- location and construction of the buildings used for manufacture and control;
- flow of raw materials, personnel and manufactured product through the facility;
- animal facilities;
- air, water and steam systems and power supply;
- drainage and effluent systems;

- segregation of operations;
- lists of major equipment;
- maintenance schedules for equipment and building services;
- cleaning schedules;
- quality-assurance and quality-control procedures;
- storage and quarantine facilities and procedures for:
  - raw materials,
  - packaging materials,
  - in-process and bulk materials,
  - final product;
- validation procedures;
- documentation and record-keeping systems;
- labelling and packaging facilities and procedures;
- recall and retrieval procedures.

To be certain that the buildings, facilities, personnel, procedures and practices comply with the description in the licence application, the NCA should arrange for the inspection of the manufacturer before granting the licence. The inspector(s) selected should be independent of the manufacturer and have sufficient expertise to conduct a meaningful review, in accordance with section 4.3, of the GMP system in use (including buildings, facilities, procedures, personnel and quality assurance).

5.2 *Information on the product*

The manufacturer should provide sufficient information to demonstrate the safety and efficacy of the product as manufactured and controlled in the establishment described above. The NCA should request from the manufacturer a critical evaluation of the procedures adopted for manufacture and control of the product and of preclinical and clinical studies relevant to its proposed use. The submission should include the following details, if appropriate:

- source materials (e.g. microorganisms, blood/plasma donations, cells/cell substrates, pollen), including their specifications and the tests used to demonstrate compliance with the specifications;
- raw materials and packaging materials, including their specifications and the tests used to demonstrate compliance;
- methods of manufacture, including a description of seed-lot and cell-substrate systems used, together with in-process, bulk and final product specifications and the tests employed to demonstrate compliance;
- demonstration of consistency of manufacture, which normally comprises the results of tests on a minimum of three satisfactory and consecutive production batches of a size corresponding to that contemplated for routine production;
- any proposal for reprocessing of the product;
- stability studies undertaken to justify the proposed validity period for the product under the indicated storage conditions;

- labels and package inserts;
- documentation used in the manufacturing and control procedures, including standard operating procedures and protocols containing details of production and quality-control testing;
- reports of preclinical studies;
- clinical trial data;
- a list of countries in which the product is approved for use.

The nature and extent of pre-licensing testing undertaken by the NCA should reflect any particular quality-assurance considerations relevant to the product; as a minimum, the NCA should undertake tests to evaluate its safety and efficacy. It may also perform chemical, physical and biological tests additional to those specified in national or international requirements.

6. The national control laboratory

The size of facilities and number of staff of the NCL will depend on the nature and extent of the quality control required. Some guidance is available in the *Manual for the design, equipping and staffing of facilities for production and quality control of bacterial vaccines (9)*.

6.1 *Laboratory testing and evaluation*

The NCL (or equivalent) should be able to perform all necessary tests on samples of source materials and of intermediate, bulk and finished products. This will require specialized facilities and equipment. If the NCL is on a site where biological products are manufactured, national control activities should be independent of control activities associated with manufacture or production.

The NCL's responsibilities should include some or all of the following activities:

- provision of advice to the NCA on technical matters relevant to the approval of products and manufacturing establishments;
- evaluation of manufacturers' preparative and analytical procedures, standard operating procedures: validation experiments and batch protocols;
- pre-licensing control testing of samples of batches, in particular for ascertaining consistency of production, as well as testing for batch release;
- evaluation of shelf-life specifications and expiry dates of final lots on the basis of the manufacturer's thermal stability tests and stated conditions of storage, and experimental verification of stability;
- development, evaluation: establishment and implementation of testing procedures and release criteria;
- review of reports of quality defects in distributed material, retesting if appropriate, and provision of advice on whether the preparations should remain on the market or be withdrawn;

- undertaking of research in relation to the above activities (which may involve collaboration with manufacturers).

In order to fulfil its responsibilities, the NCL should have the authority to demand appropriate samples (e.g. of starting materials, intermediate products and finished biologicals) from manufacturers. The samples should be properly labelled and portions should be kept for future reference.

The control laboratory should maintain adequate analytical records of all samples examined, including:

the results of tests performed, including original observations and calculations, relating to compliance with the established specifications;
- the date and signature(s) of the person(s) who performed the quality-control tests; and
- a final review, with a dated endorsement of the final decision by a responsible person.

6.2 *Establishment of national reference materials for biological substances*

WHO has published guidelines on the preparation, characterization and establishment of international and other reference materials (*10*), and a list of International Standards, International Reference Reagents and International Reference Preparations is available **(11).**

It may be desirable for appropriate national (secondary) reference materials, calibrated against international reference materials, to be established by the NCL and made available to manufacturers. However, a multinational or regional approach to the establishment and supply of secondary reference materials may be more efficient. The secondary reference materials should be used in the routine laboratory testing of biological products. Their use permits the expression of *potency* in International Units, and in some cases they may be useful in confirming the *identity* of biological products.

6.3 *Other activities of the national control laboratory*

The NCL, or the laboratories providing the services of an NCL, should devise effective internal control measures to permit the evaluation of their reliability in performing all tests. The inclusion of reference preparations and coded replicate samples in test procedures, simultaneous independent testing, and routine checks on the sensitivity and calibration of instruments are necessary as part of good laboratory practice for the NCL. The NCL should, if possible, participate in collaborative studies with other NCLs and other relevant laboratories to enhance its expertise.

7. Post-licensing monitoring of products

7.1 *Product release*

At the time a product is approved, the NCA should decide whether controls involving the NCA are to be applied to release of batches of the product. This decision will be influenced by the nature of the product. Controls will usually be imposed on complex products and on those obtained by complex manufacturing procedures. The control system may involve the following activities and may be reviewed and revised once satisfactory and consistent production has been demonstrated:

7.1.1 Testing of samples of intermediate, bulk or final product, to confirm compliance with the requirements and agreed specifications. The nature and frequency of the tests to be carried out are decided by the NCA.

7.1.2 Evaluation of the manufacturer's protocols for manufacture and control of each batch. Examples of model summary protocols are annexed to the individual Requirements for Biological Substances published by WHO. The critical review of batch protocols by the NCA is a most important part of the control of biological products. The information provided should make it possible to review the manufacture and testing of each batch of a particular product, including all required in-process controls and control tests on final products, to confirm compliance with the approved specifications.

7.2 *Inspections*

Periodic inspections of the manufacturing facility should be carried out on behalf of the NCA to assure continued compliance with GMP and with the specifications established for the product at the time of approval. Records of complaints and reports of adverse reactions should be examined.

7.3 *Post-marketing surveillance*

The procedures described in sections 7.1 and 7.2 above do not preclude the need for a post-marketing sampling and surveillance system. Countries should establish a national system for the post-marketing surveillance of biological products. Clinicians and other health workers should be encouraged to report to manufacturers and NCAs unexpected adverse events occurring after administration of biological products. The manufacturers and the NCAs should assess these reports and, in consultation with each other, attempt to evaluate their significance. This assessment may require the testing of products already released and inspection of production and control facilities. If an imported product is associated with adverse reactions, the manufacturer and, where appropriate, other NCAs and WHO should be notified.

Guidance for operating a monitoring system for adverse reactions is provided in a report published by the Council for International Organizations of Medical Sciences (12).

7.4 *Recall and revocation*

NCAs should have a system for enforcing the recall of batches, revoking approvals, and communicating such decisions to users and to the NCAs of any countries importing the product.

7.5 *Approval of manufacturing changes*

Any significant change to the manufacturing establishment, source materials, production process, quality-assurance procedures, product specifications or labelling should have the prior approval of the NCA.

7.6 *Approval of new indications*

NCAs should require that significant proposed changes in product indications or use be submitted by manufacturers for evaluation and approval.

8. Procedures for approval of imported products

The national authorities of countries wishing to import biological products could simplify the licensing formalities, and reduce the need for testing, by accepting certificates, issued by the responsible authorities in the country of manufacture, stating that the quality of the product meets a certain standard. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (4) and GMP texts *(5, 6)*, with the inclusion of the procedures described in this section, provide a suitable basis for such a mechanism. For the purpose of this Certification Scheme, "biological product" refers to a product presented in its finished dosage form and to the bulk material that is processed to produce this dosage form.

8.1 *Participating Member States*

Each Member State participating in the Certification Scheme should communicate to WHO the name and address of the department of its NCA dealing with biological products and, if appropriate, any significant reservations relating to its participation. WHO would then notify all other Member States.

Exporting Member States participating in the Certification Scheme should ensure that:

- approval of biological products is subject to appropriate control testing by the NCA to assure safety and efficacy, and adequate facilities are available for such testing;
- the manufacturer conforms to requirements for GMP and quality assurance of biological products as recommended by WHO, or to equivalent national standards;
- the NCA conducts appropriate inspections, including, for example, examination of records and samples, to ensure that manufacturers conform to these requirements;
- the inspectors in the service of the NCA have appropriate expertise.

Exporting Member States participating in the Certification Scheme should, whenever possible, ensure that International Nonproprietary Names (INN) are used on certificates and for labelling the biological product.

8.2 *Certification of products*

Biological products exported under the Certification Scheme should be certified by the NCA of the exporting Member State by means of certificates to be sent to the NCA of the importing Member State. The importing Member State would then either License the product or make licensing conditional on the submission, and approval, of supplementary data.

The issue of certificates for a biological product would be subject to the conditions set by the NCA of the exporting Member State. Certificates would, however, be expected to state that:

- the product is approved for use within the exporting Member State (if not, the reason should be given); and
- the manufacturing establishment in which the product is produced is inspected at suitable intervals to check that the manufacturer conforms to the principles of GMP (*5*, *6*) and quality assurance (as defined in the present guidelines).

For many biological products, certification on an individual lot basis is necessary because of the difficulty of controlling starting materials and ensuring that batch-to-batch variation is within acceptable limits.

Suggested model certificates for biological products are given in Appendices 1 and 2.

8.3 *Requests for additional information*

Additional information may be requested by the NCA of the importing Member State from the NCA of the exporting Member State. This information may be provided directly by the NCA, or through the manufacturer, and may include:

- details of the implementation of requirements for GMP and quality assurance of biological products;
- information on control tests performed on the product by the NCA of the exporting Member State;
- the names and functions of the persons officially designated to sign release certificates for individual batches of the product;
- copies of all documentation and labels that are supplied with the product on packaging materials and package inserts and that have been approved by the NCA in the exporting Member State, together with the date(s) on which such approval was accorded.

Information on general and specific standards for quality assurance of the biological product to be exported may also be requested if so required by

the legislative provisions of the importing Member State. The consent of the manufacturer to the provision of such information should be obtained by the NCA of the exporting Member State.

8.4 *Reporting of defects and adverse reactions*

Defects may occur in the quality of biological products imported under the Certification Scheme. If they are considered to be of a serious nature by the importing country, and are not attributable to local conditions of storage and transport, the NCA of the importing country should notify the NCA of the exporting Member State and provide the relevant data. Adverse reactions of unexpected severity or frequency should also be notified to the NCA of the exporting country. Similarly, if the NCA of the exporting Member State discovers quality defects or receives reports of unexpected adverse reactions, it should inform the NCA of the importing Member State of any action taken.

8.5 *Procedure for testing imported biological products*

Countries wishing not to rely solely on the certification scheme described in sections 8.1–8.4 may consider implementing an abridged version of the system of control applicable to the NCA of the country of manufacture, as described in sections 4–7. The system may include a review of information on the manufacturing establishment (as described in section 5.1) and on the biological product to be imported (as outlined in section 5.2), in order to assess its safety and efficacy. If adequate facilities and personnel of appropriate expertise are available, pre-licensing testing may be performed as described in section 7.1.1, although intermediate samples may not be available. Additionally, the NCA of the importing country may, if necessary, perform control tests on the biological product on a batch-to-batch basis, to obtain assurance regarding safety and efficacy, including the possibility of defects occurring during shipment.

Authors

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11. *Biological substances: International Standards and Reference Reagents 1990. Geneva, World Health Organization, 1991.*

12. *International reporting of adverse drug reactions. Final report of the CIOMS Working Group. Geneva, Council for International Organizations of Medical Sciences. 1990.*

Appendix 1

Model certificate of approval of a biological product[1]

Name and dosage form of product: _____

Manufacturer and/or, when applicable, person responsible for placing the product on the market: _____

_____

Address(es): _____

_____

It is certified that:

☐ This product has been authorized to be placed on the market for use in this country.[2]

Number of licence and date of issue (if applicable):'

_____

_____

The enclosed documents constitute the complete text of all labelling and prescribing information authorized for use in this country.'

or

☐ This product has not been authorized to be placed on the market for use in this country for the following reasons:

_____

_____

It is also certified that (a) the manufacturing plant in which the product is produced is subject to inspections at suitable intervals, and (b) the manufacturer conforms to requirements for good manufacturing practices[3] and other relevant requirements published by WHO, in respect of products to be sold or distributed within the country of origin or to be exported.

Name of designated authorized person (typed) _____

_____ _____

(Signature of designated authorized person) (Place and date)

---

[1] This certificate is intended to define the status of the biological product and its manufacturer in the exporting and manufacturing country. it is issued by the competent national authority in the exporting country in response to a request by the cornpeteni national authority in the importing country. It may be required by the importing country at the time of the first importation and subsequently if confirmation or updating is required. The certificate is intended to be product-specific, since confusion will inevitably arise if information relating to different products, or even different dosage forms of the same product, is attached to the same certificate; whenever possible, International Nonproprietary Names (INN) or national nonproprietary names should be used.

[2] Deiete as appropriate.

[3] Good msnufacturing practices for pharmaceutical products. In: WHO Experr Committee on Specifications for Pharmaceutical Preparations. Thirty-second Report. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 823), Annex 1; Good manufacturing practices for biological products. In: WHO Expert Committee on *Biological* Standardization. Forty-second Report. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 822), Annex 1.

Appendix 2

Model certificate for the release of a lot or lots of a biological product

The following biological product _____, produced by _____[1] in _____,[2] whose lot numbers appear on the labels of the final containers, meets all national requirements (_____[3]) and is manufactured in accordance with the requirements for good manufacturing practices[4] and (if applicable) the product-specific requirements published by WHO.

Lot number	Expiry date
_____	_____
_____	_____
_____	_____
_____	_____

As a minimum this certificate is based on examination of the manufacturing protocol.

Address of the National Control Authority or Laboratory _____

_____

_____

Name of the Director of the National Control Authority or Laboratory (or representative)

_____

Signature _____

Date _____

[1] Name of manufacturer.

[2] Country.

[3] Reference to appropriate document.

[4] Good manufacturing practices for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second Report. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 823), Annex 1; Good manufacturing practices for biological products. In: WHO Expert Committee on Biological Standardization. Forty-second Report. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 822), Annex 1.

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Annex 3
Guidelines for assuring the quality of monoclonal antibodies for use in humans

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Introduction

Unlike conventional polyclonal antibodies, monoclonal antibodies are homogenous products secreted by immortalized B lymphocytes that are cloned and expanded in continuous cell lines. Such cell lines may be cultivated for the stable secretion in large quantities of antibodies of defined specificities. Monoclonal antibodies produced in this way are available for a variety of clinical purposes such as anti-tumour therapy, immunomodulation (e.g. to prevent graft rejection) and passive immunization, as well as for in *vivo* diagnosis and preparative procedures for the manufacture of biologicals. They are currently obtained from murine or human cells.

Murine monoclonal antibodies are obtained from murine hybridomas produced by fusion of B lymphocytes from immunized mice or rats with murine myeloma cells.

For human monoclonal antibodies, a major difficulty has been the generation of human hybridoma cell lines of acceptable stability. It is also difficult in most cases to obtain antigen-primed human B lymphocytes suitable for fusion. In view of this, several alternative strategies have been devised for the production of human monoclonal antibodies. They include:

- fusion of human B lymphocytes with a murine myeloma or hybrid human–murine myeloma cell line;
- fusion of human B lymphocytes with a human lymphoblastoid cell line;
- transformation of human B lymphocytes with Epstein–Barr virus (EBV; human (gamma) herpesvirus 4);
- fusion of an EBV-transformed human B-lymphocyte line with a mouse myeloma cell line.

Scope

The requirements set out below are intended to apply to murine and human monoclonal antibodies for use in humans, including *in vivo* diagnosis and *ex vivo* (extracorporeal) treatment. It is recommended that monoclonal antibodies intended for use in the preparation of biological products to be used in humans should also meet these requirements, except for those relating to the final product (section A.4.5); however, validation of the purification process employed after the step when monoclonal antibodies are used during preparation of the biological product may diminish this need. This document is not concerned with the production of monoclonal antibodies by recombinant DNA techniques, such as "humanized antibodies, nor with monoclonal antibodies to be used for *in vitro* diagnostic purposes.

General considerations

An important consideration for the clinical use of monoclonal antibodies is that of potential microbial contamination, especially by viruses. While murine cells can harbour a range of viruses, murine hybridoma cells usually contain only A-type and C-type endogenous retroviruses, which are thought unlikely to be pathogenic for humans. A cell line that expressed any virus capable of infecting human cells would be acceptable only in exceptional circumstances for use in preparing monoclonal antibodies.

Other important considerations for the clinical use of monoclonal antibodies relate to the presence of potentially oncogenic residual cellular DNA, the possible undesired immunological reaction of the antibody with human tissues, and the induction of antibodies in the recipient against immunoglobulins or other proteins present in the product. Antibodies induced in the recipient may result in adverse reactions and limit the duration of effective therapy. It is, in any case, desirable to minimize the quantity of heterologous protein contaminants administered to the patient, for example by using for fusion purposes a parental myeloma cell that does not synthesize immunoglobulins.

Each of the following sections constitutes a recommendation. The parts of each section that are printed in type of normal size have been written in the form of requirements, so that, if a health administration so desires, these parts as they appear may be used as definitive national requirements. The parts of each section that are printed in small type are comments and recommendations for guidance.

Should individual countries wish to adopt these guidelines as the basis of their national regulations concerning monoclonal antibodies, it is recommended that modifications be made only on condition that they are shown to ensure at least an equal degree of safety and potency of the product. The World Health Organization should be kept informed of the action taken.

While the guidelines set out below should be considered generally applicable, individual products may present particular quality-control problems. The production and quality control of each product must therefore be given careful individual consideration, any special features being taken fully into account. Furthermore, the guidelines for a product must reflect its intended clinical use. Different requirements might justifiably apply, for example, to a product to be used in a life-threatening condition.

Part A. Manufacturing guidelines

A.1 Definitions

A.1.1 *International name and proper name*

The international name of products shall be the officially assigned nonproprietary or generic name; the proper name shall be the translation of the international name in the language of the country of origin, followed by the designation of the immunological specificity. The name shall be restricted to preparations that satisfy the requirements formulated below.

A.1.2 Descriptive definition

A.1.2.1 Murine monoclonal antibodies

Murine monoclonal antibodies are antibodies obtained from murine hybridomas produced by fusion of B lymphocytes from immunized mice or rats with murine myeloma cells.

A.1.2.2 Human monoclonal antibodies

Human monoclonal antibodies are antibodies produced by human B lymphocytes immortalized through transformation with EBV or other techniques.

A.1.3 *Terminology*

A.1.3.1 Animals

Murine: Belonging to the Muridae family, which includes mice and rats.

A.1.3.2 Seed lot system

Original cell line: The cell line produced or acquired by the manufacturer, on which the production of the master cell bank is based. The history of the original cell line (including details of parent cells, immunogens and fusion or immortalization methods) should be recorded whenever available.

Master cell bank: Homogeneous cell suspension derived from the original cell line. It is stored frozen in the vapour phase above liquid nitrogen in aliquots of uniform composition, one or more of which are used for the production of the manufacturer's working cell bank.

Manufacturer's working cell bank (MWCB): A quantity of cells of uniform composition, derived from one or more containers of the master cell bank and stored frozen in the vapour phase above liquid nitrogen in aliquots, one or more of which are used for production purposes.

A.1.3.3 Methods of production

In vivo production: Method based on the injection into the peritonea1 cavity of mice or rats of cells derived from the MWCB by *in vitro* cell culture. After a suitable incubation period, ascitic fluids are harvested by abdominal puncture. The procedure used to collect ascitic fluid should be adequately described in a standard operating procedure.

In vitro production:

(a) Batch system: Method of production in which the cell-culture fluid(s) from the production vessel(s) is/are harvested on a single occasion. The maximum number of passages or population doublings of cells of the MWCB is approved by the licensing authority.

(b) *Continuous cell-culture* system: Method of production in which the cell-culture fluid(s) from the vessel(s) used for the last passage is/are harvested on multiple occasions. The maximum number of passages or population doublings, the maximum incubation period for the last passage, and the maximum number of single harvests are approved by the licensing authority.

A.1.3.4 *Production stages*

Single *harvest:* Filtrate obtained from one batch of cell cultures seeded (in vivo or in vitro), incubated and harvested together.

Bulk harvest: Homogeneous pool of single harvests (e.g. filtrates of ascitic fluids or of supernatants of cell cultures) that are processed together in a single manufacturing run.

Purified bulk: Product after purification of a bulk harvest is complete. It is used in the preparation of the final bulk.

Final bulk: The homogeneous preparation present in a single container from which the final containers are filled either directly or through one or more intermediate containers.

Finalproduct: Finished product that is formulated and dispensed into final, sealed containers which hold the liquid or freeze-dried product in its final dosage form.

Final lot: A collection of sealed final containers that have been filled from a single container in a single continuous working session, are uniform in their contents, and are homogeneous with respect to the risks of contamination during filling and freeze-drying.

A.1.3.5 *Adventitious agents*

Contaminating microorganisms of cell cultures or ascitic fluids: including bacteria, fungi, mycoplasmas and viruses.

A.2 Reference materials

Part of a lot that has been fully characterized and evaluated in studies in humans shall be kept as an "in-house" reference material under conditions that maintain its stability for use in assays of subsequent lots; this is of particular importance if international reference materials are not available. The criteria for establishing manufacturers' reference materials shall be approved by the national control authority.

In cases where monoclonal antibody preparations have a short validity period (e.g. certain radiolabelled monoclonal antibodies), the reference material may consist of an unlabelled immunoglobulin material.

A.3 General manufacturing requirements

Manufacturing and control methods shall comply with "Good manufacturing practices for pharmaceutical products" (1), "Good manufacturing practices for biological products" (2) and the revised Requirements for Biological Substances No. 27 (Requirements for the Collection, Processing, and Quality Control of Blood, Blood Components, and Plasma Derivatives) (3).

A.3.1 *General procedure(s) for generating hybridomas and producing monoclonal antibodies*

Methods used for lymphocyte isolation, fusion of myeloma cells and lymphocytes, immortalization of lymphocytes, selection of hybridomas and screening of antibodies shall be recorded.

A.3.1.1 Material used for immunization

The material used for the generation of immune lymphocytes should be defined. If the immunogen is derived from a human source, relevant clinical data on the donor should be recorded.

A.3.1.2 Immune parental cells

Wherever possible, the source of the immune parental cells shall be documented. For murine monoclonal antibodies, information on the animal strain shall be provided, including its specific-pathogen-free (SPF) status; the animals used for immunization should, whenever possible, be SPF.

In the case of human monoclonal antibodies, all data relevant to possible viral infections of the human donors of the immune parental cells should be available. The donations employed should be screened for potential viral contamination, as a minimum in accordance with current requirements for blood donations (3).

A.3.1.3 Immortalization procedures

If myeloma cells are used, they should be fully described, with details including their source, name and characteristics.

Human B lymphocytes are usually immortalized by infecting them with EBV; however, this procedure alone cannot always ensure stability, and subsequent fusion with a myeloma may be required.

If EBV is used for immortalizing human B lymphocytes, its origin and characteristics should be clearly specified.

It is preferable to use immortalizing cells that do not synthesize immunoglobulins.

Test for bacteria, fungi and mycoplasmas. Before being fused or immortalized, cells should be tested according to the revised Requirements for Biological Substances No. 6 (General Requirements for the Sterility of Biological Substances) (4) or by a method approved by the national control authority, and should be found negative for bacterial, fungal and mycoplasmal contamination.

A.3.2 ***Seed lot system***

The manufacture of monoclonal antibodies shall be based on a seed lot system, which should be described in detail. Information on the establishment, characterization and cloning of the original cell line used to establish the master cell bank shall be provided. If feeder layers are used, their origin and the SPF status of the source animals should be recorded.

A.3.3 ***Master cell bank***

The following tests shall be performed on the master cell bank.

A.3.3.1 *Identity test for the product*

The immunological specificity of the monoclonal antibody derived from the master cell bank, i.e. its capacity to react with the target antigen and its isotype and Light-chain composition, shall be established.

A.*3.3.2 Tests for bacteria, fungi and mycoplasmas*

The master cell bank shall be tested for bacterial, fungal and mycoplasmal contaminants as specified in section A.3.1.3.

A.3.3.3 *Test for viruses*

The master cell bank shall be tested for viral contamination by inoculation of cell cultures in which a wide range of viruses can be detected; primate cells shall be included. The cell bank shall also be tested on suckling mice, adult mice, guinea-pigs and embryonated hens' eggs *(5)*.

Testing in suckling mice may not be feasible when the hybridoma cell line is extremely tumorigenic in mice,

Other methods, such as those involving immunochemical procedures, electron microscopy. molecular hybridization, and the polymerase chain reaction, are also useful for detecting viral contamination.

Appropriate tests should be performed for the presence of non-infectious complete viral genomes.

Murine monoclonal antibodies. The master cell bank shall be tested for the viruses Listed in Appendix 1 by, for example, the method of antibody production in mice (MAP) or antibody production in rats (RAP) or a method of at least equivalent sensitivity.

Tests for murine retroviruses (including the S+L– and XC tests) shall be carried out.

The master cell bank shall not be used for manufacture if any of the viruses of Appendix 1, List 1 are found. The presence of other murine viruses does not automatically preclude use of the cells, provided that adequate inactivation or removal of these viruses is demonstrated through validation of the process employed.

Human monoclonal antibodies. Tests on the master cell bank to detect expression of infectious viruses are of particular importance, especially if the cells have been transformed by EBV, and should be performed whenever possible.

The master cell bank should be tested for viral contamination by inoculation of cells into cultures of virus-free lymphoblastoid cell lines.

The master cell bank shall also be tested with a sensitive marker for the following viruses: hepatitis B virus, human immunodeficiency virus types 1 and 2, human T-cell lymphotropic virus types 1 and 2, human (beta) herpesvirus 5 (human cytomegalovirus), EBV and human herpesviruses 6 and 7, which may be able to infect, productively or latently, the lymphocytes used to produce the hybridoma.

The expression of biologically active EBV in the master cell bank may be acceptable if the production process is shown to remove or inactivate EBV.

Tests to demonstrate the absence of murine viruses shall also be performed, unless any possible contamination with murine viruses can be excluded.

A.3.3.4 Test for undesired immunological reactions

The product derived from the master cell bank shall be tested at least once to show the absence of undesired reactivity with appropriate tissues, as listed in Appendix 2.

A.3.4 Manufacturer's working cell bank

If the MWCB is prepared in a manufacturing facility different from that where the master cell bank was established, the full testing regime described in section 3.3 shall be carried out.

It shall be shown to the satisfaction of the national control authority that the MWCB is stable with respect to its ability to maintain the identity of the antibody secreted. This stability should be established by studies on samples of monoclonal antibody from cells cultivated under conditions that reproduce or mimic the production process, for a number of passages or population doublings approved by the national control authority.

However, when a replacement MWCB is derived from the same master cell bank as that used for preparing the first MWCB (which has been found to be satisfactory) and the production conditions have not otherwise changed, the tests for stability mentioned in the previous paragraph and the tests mentioned below for identity and absence of viral contaminants may be omitted.

A.3.4.1 *Identity test for the product*

The immunological specificity of the monoclonal antibody, i.e. its capacity to react with the target antigen and its isotype and light-chain composition, shall be established, except in the case defined at the end of section A.3.4.

A.3.4.2 *Test for bacteria, fungi and mycoplasmas*

The MWCB shall be tested for bacterial, fungal and mycoplasmal contaminants as specified in section A.3.1.3.

A.3.4.3 *Viral contaminants*

Samples of cells shall be tested for viral contaminants as described in section A.3.3.3, except in the case defined at the end of section A.3.4.

A.3.5 *Production processes*

All processing of cells shall be done either in an area where no cells other than those directly required for the process are handled, or under conditions that prevent cross-contamination.

The production system shall be well defined and documented. For all production systems it shall be shown that successive cultures or successive harvests yield identical products. Data provided to the national control authority for release purposes should include information on yields.

Single harvests shall be obtained aseptically, pooled and purified by methods described in a standard operating procedure. Criteria for harvesting, rejecting, terminating and storing cultures shall be defined by the manufacturer and approved by the national control authority. Antibiotics of the β-lactam type shall not be used at any stage in the production process.

A.3.5.1 *Production from mouse ascitic fluid*

If substances other than pristane are used to pretreat mice to facilitate the growth of hybridomas, they shall be approved by the national control authority. The mice shall come from SPF-monitored colonies and in particular shall be free from the viruses mentioned in List 1, Appendix 1. If mice are found to be contaminated with viruses mentioned in List 2, Appendix 1, the final product may be accepted only if the purification process is shown to eliminate the Infecting virus(es).

A.3.5.2 Production from in vitro cell cultures

Only cell cultures derived from the MWCB shall be used for production.

Details to be provided to the national control authority include the cell-culture system used, the cell doubling time, the number of subcultures, the duration of subcultivation, the incubation temperature and, in the case of continuous cell culture, the maximum number of single harvests and the maximum duration of incubation of the last culture.

If serum is included in the medium used for the production of cell cultures, it shall be tested to show its freedom from bacteria, fungi, and mycoplasmas as indicated in section A.3.1.3. Each batch of serum shall be of certified origin and shall be tested for the absence of viral contaminants. Test results provided by the supplier of the serum may be sufficient if the tests are performed according to validated and well documented procedures. Serum of bovine origin shall come from herds certified by the appropriate authority to be free from bovine spongiform encephalopathy.

A.3.6 Validation of procedures for purifying monoclonal antibody

The effectiveness of the overall purification process for the monoclonal antibody shall be demonstrated. The following validation studies shall be performed in areas other than those dedicated to production.

If a viral genome sequence has been found in the master cell bank, the product may be used on condition that the purification process is validated for its capacity to reduce the content of viral subgenomic fragments in the final product to a level undetectable by hybridization.

A.3.6.1 Validation of procedures for removing contaminating cellular DNA

Until it has been proved that quantities of DNA larger than 100 pg per single human dose do not cause harmful effects, the purification procedures shall be shown to result in final products whose DNA content does not exceed that level.

> The advantage of using a monoclonal antibody preparation containing more than 100 pg of residual cellular DNA per human dose may sometimes outweigh the theoretical risk; such situations should be examined by the national control authority on a case-by-case basis.

When monoclonal antibodies are to be used for long-term treatment, the risks of repeated exposure to DNA should be balanced against the beneficial effects of the proposed treatment.

Validation studies for the removal of cellular DNA should be performed by spiking source materials with known large amounts of representative DNA. At each purification step, the product should be tested for the content of DNA. On the basis of the overall reduction obtained in DNA content (the "reduction factor"), a calculation shall be made of the highest expected amount of DNA per single human dose (or diagnostic intervention) in the final product and, in the case of multiple injections, of the highest expected amount of DNA per full treatment.

A.3.6.2 Validation of procedures for removing viruses

Both the crude material before purification and subsequent fractions obtained during the various purification stages should be spiked with appropriate amounts of different viruses. The removal or inactivation of these test viruses should be determined.

An important part of designing a validation study is determining which viruses, "relevant" or "model", should be used.

"Relevant" viruses are those that are known, or likely, to contaminate the source material or products used in the production process. The purification and/or inactivation process shall be shown to remove or inactivate such viruses or similar viruses. Cell lines derived from rodents usually contain endogenous retroviral particles, which may be infectious (C particles) or non-infectious (intracisternal A particles); it is therefore necessary to validate the capacity of the purification process to remove murine retroviruses from monoclonal antibody preparations obtained from such cells, for instance by using a murine leukaemia virus. When human cell lines secreting monoclonal antibodies have been obtained by immortalization of B lymphocytes by EBV, it is necessary to check the ability of the purification process to remove EBV by studies with a suitable herpesvirus.

There may be cases where "relevant" viruses do not have a wide range of physicochemical properties, or where spiking with "relevant" viruses is too hazardous; in such cases validation should be performed with "model" viruses, although the presence of such viruses in cell cultures used for monoclonal antibody production may be unlikely. Preference should be given to viruses that display significant resistance to physical and/or chemical agents. Reduction factors obtained for such viruses provide useful information on the ability of the production process to remove and/or inactivate viruses in general. Suitable "model" viruses capable of resisting a range of physicochemical agents could include:

- SV40 (*Polyomavirus* maccacae 1), human poliovirus 1 (Sabin) or another small, non-enveloped virus;
- a parainfluenza or influenza virus and a murine retrovirus (or another medium-to-large enveloped RNA virus);
- a herpesvirus (e.g. human (alpha) herpesvirus 1 or a pseudorabies virus) or another medium-to-large DNA virus.

A.3.6.3 Validation of procedures for removing impurities

Additives present in the media (for example sera, serum substitutes, and substances used for digestion, purification, coupling and increasing ascitic-fluid production) should be removed during purification. This should be demonstrated by specific validation studies.

A.4 Production control

A.4.1 *Bulk harvest*

Every bulk harvest shall be tested for freedom from bacterial, fungal and mycoplasmal contamination as specified in section A.3.1.3. Harvests that are contaminated shall not be used for production.

Every bulk harvest shall be tested on a primate cell line and shown to be free from detectable viruses.

In addition, every bulk harvest of monoclonal antibodies produced from ascitic fluid shall be tested for the murine viruses listed in Appendix 1. If viruses listed in Appendix 1, List 1 are detected, the harvests shall not be used for production.

A.4.2 *Purified bulk*

The purified bulk shall pass the tests for absence of bacterial and fungal contamination as specified in section A.3.1.3. In addition, the following tests shall be performed on either the purified or the final bulk.

A.4.2.1 *Test for components other than those secreted by the cell line or the hybridoma*

A test shall be performed for any auxiliary substance that has been used to facilitate the growth of the hybridomas or the production of antibodies. The results shall be shown to be compatible with the maximum amount of substance per single human dose of the final product as authorized by the national control authority.

A.4.2.2 *Test for residual* DNA

A suitable test shall be performed for residual cellular DNA. The result shall be compatible with the authorized maximum amount per single human dose of the final product.

A.4.2.3 *Test for contaminating viruses*

If bulk harvest from mouse ascitic fluid was contaminated with viruses from List 2, Appendix 1, a test for the absence of such contaminating viruses shall be performed.

A.4.3 *Final bulk*

If a preservative is added to the final bulk, its concentration shall have been shown to have no deleterious effect on the monoclonal antibody and to cause no unexpected adverse reactions in humans. The preservative and its concentration shall be approved by the national control authority. Phenol shall not be used as a preservative.

The following tests shall be conducted on the final bulk.

A.4.3.1 *Test for identity*

The monoclonal antibody shall be tested for its isotype composition and for its immunological reactivity with the target antigen.

A.4.3.2 *Test for bacteria and fungi*

Each final bulk shall be tested for bacterial and fungal contamination as specified in section A.3.1.3.

A.4.3.3 *Test for purity*

The degree of purity of the monoclonal antibodies shall be determined by chemical and immunological methods. The monoclonal antibodies shall

also be tested for potential contaminants or additives (e.g. leachable components from chromatography columns, antibiotics, reagents), which shall not exceed levels approved by the national control authority. The tests shall include, but not be limited to, the following.

Test for distribution of molecular size. Generally, not less than 95% of the immunoglobulin present should be in form of molecular monomers and dimers. Any departure from this limit requires justification. Separate additional limits shall be set for the content of dimers, polymers and fragments.

If the monoclonal antibody is not an imrnunoglobulin G, the test for distribution of molecular size shall be approved by the national control authority.

Isoelectric focusing. The product, together with the reference material, shall be examined by isoelectric focusing; after staining (for example with silver), the two preparations shall be compared and it shall be demonstrated that there is no significant difference.

This test may be replaced by chrornatofocusing

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). The product, together with the reference material, shall be examined by SDS-PAGE under reducing and non-reducing conditions; after staining (for example with silver), the two preparations shall be compared and it shall be demonstrated that there is no significant difference.

Test for protein content. The total protein content shall be determined by ultraviolet spectrophotometry, or any other suitable method.

A.4.4 *Filling and containers*

The requirements concerning filling and containers given in "Good manufacturing practices for pharmaceutical products" (*1*) and "Good manufacturing practices for biological products" (2) shall apply.

A.4.5 *Final product*

Samples shall be taken from each final product for the following tests.

A.4.5.1 *Test for identity*

The monoclonal antibody in a labelled container from a labelled final package shall be tested for both its isotype composition and its immunological reactivity with the target antigen. The result shall meet the product specification.

A.4.5.2 *Test for potency*

The biological activity of the monoclonal antibody shall be determined by either an *in vivo* or an *in vitro* test in comparison with the reference material. The test shall be approved by the national control authority and the result shall meet the product specification.

A.4.5.3 *Test for pyrogenicity*

The product shall be tested for pyrogenicity as described in *The internationalpharmacopoeia* (6) or the national pharmacopoeia. The dose to be injected and the criteria for passing the test shall be approved by the national control authority.

> The national control authority may allow the replacement of the pyrogenicity test by the LAL (*Limulus* amoebocyte lysate) endotoxin test after five consecutive batches have been successfully tested by the two methods.

A.4.5.4 *Test for bacteria and fungi*

The product shall be tested for bacterial and mycotic contaminants as specified in section A.3.1.3.

A.4.5.5 Test for abnormal toxicity

Each final lot shall be tested for abnormal toxicity by the intraperitoneal injection of one human dose, but not more than 1 ml, into each of five mice (weighing 17-22 g) and injcction of not more than 5 ml into each of two guinea-pigs (weighing 250-3508). The test shall be approved by the national control authority. The final product shall be considered innocuous if the animals survive for at least seven days without showing signs of abnormal intoxication.

A.4.5.6 *Test for protein content*

The total protein content shall be determined by ultraviolet spectrophotometry or another suitable method. Values shall be within limits that have been shown by the manufacturer to be suitable and have been approved by the national control authority.

A.4.5.7 *Test for residual moisture*

If the product is freeze-dried, the average residual moisture in a representative sample of each final product shall be determined by a method accepted by the national control authority. Values shall be within limits that have been shown to be suitable and have been approved by the national control authority.

A.4.5.8 *Test for pH*

An appropriate test for pH shall be carried out, if applicable after reconstitution of the product, and the result shall meet the product specifications.

> The method described in The international pharmacopoeia (6) is suitable for determining the pH.

A.4.5.9 *Test for preservative*

If a preservative has been added, its concentration shall be determined and shown to be in agreement with the value stated on the label, which has been approved by the national control authority.

A.4.5.10 Inspection of final containers

Each container of each final product shall be inspected visually and those showing abnormalities of the container or its contents shall be discarded.

A.4.6 *Records*

The requirements given in "Good manufacturing practices for pharmaceutical products" *(1)* shall apply.

A.4.7 *Samples*

The requirements given in "Good manufacturing practices for pharmaceutical products" **(1)** shall apply.

A.4.8 *Labelling*

The requirements on labels and leaflets given in "Good manufacturing practices for pharmaceutical products" (1) and "Good manufacturing practices for biological products" (2) shall apply, with the addition of the following.

The labels on the containers shall include the following information:

- for liquid products: volume and protein concentration;
- for freeze-dried products: protein amount.

The label on the carton or the leaflet accompanying the product shall include the following information:

- type of source material;
- conditions of temperature recommended during transport and storage.

The statements concerning storage temperature and expiry date appearing on the label shall be based on experimental evidence and shall be submitted for approval to the national control authority.

A.5 Distribution and shipping

The requirements given in "Good manufacturing practices for pharmaceutical products" (1) shall apply.

If the product is to be exported, a copy of the official national release document (see section B.2) shall be provided by the manufacturer upon request by the importer.

> The purpose of the certificate is to facilitate the exchange of monoclonal antibody preparations.

A.6 Stability test and validity period

A.6.1 *Stability test*

Tests shall be conducted before licensing to determine how stable the product is over the proposed validity period; final containers from at least

three final lots, preferably derived from different bulks and stored under the conditions recommended to the user, shall be tested for molecular size distribution, potency, residual moisture, protein content, pH, preservative and container appearance at the end of the proposed validity period. The product shall pass these tests.

It is useful to conduct accelerated-degradation tests for these variables on one or more final lot. A suitable method for conducting such tests on biological products has been described by Kirkwood (7).

If applicable, the mean percentage loss of potency determined at the end of the validity period for the three final lots stored under the recommended conditions shall be compared with that/those determined by accelerated-degradation tests.

A.6.2 *Validity period*

The validity period is determined by the results of the stability tests referred to in section A.6.1.

When changes are made in the production procedure that may affect the stability of the product, further stability studies shall be conducted to determine the validity period of the new product. In such a case, the national control authority may agree to the new validity period being based on the results of accelerated-degradationtests.

Part B. National ntr g

B.1 General

The general conditions for national control authorities contained in the "Guidelines for national authorities on quality assurance for biological products" *(8)* should apply.

In addition, the national control authority should:

- approve the methods for producing the monoclonal antibody;
- approve the criteria for establishing manufacturers' reference materials;
- approve the tests for extraneous agents and for total protein;
- approve the tests for preservatives and for agents used for purification or during other stages of manufacture;
- approve the test for distribution of molecular size (if the monoclonal antibody is not an irnmunoglobulin G);
- approve the tests for determining the potency of the monoclonal antibody and define the acceptable range of estimated mean values and the fiducial limits;
- approve the dose to be injected and the criteria for passing the pyrogenicity test;
- approve the concentration of preservative permitted in the final product;

– approve the degree of purity of the final product;
– approve the validity period;
– approve the statements concerning storage temperature and expiry date appearing on the label;
– satisfy itself with the data gathered for ensuring therapeutic effect and safety in humans.

The national control authority should be satisfied that the results of all tests, including those done for validating the process of manufacture, are satisfactory and that consistency of production and testing have been established.

B.2 Release and certification

Monoclonal antibodies shall be released only if they fulfil the requirements of Part A.

A statement signed by the appropriate official of the national control authority shall certify whether the final lot of monoclonal antibody in question meets all national requirements as well as Part A of these requirements. The certificate shall state the lot number (number appearing on the labels of the containers), the number under which the lot was released and the expiry date. An example of a suitable certificate is given in Appendix 3. A copy of the official national release document shall be provided by the national control authority upon request by the manufacturer.

If the product has a very short validity period (e.g. radiolabelled antibody), a national certificate may not be required for the release of each final product.

Authors

The first draft of these guidelines was prepared by Dr H. J. M. van de Donk, National Institute of Public Health and Environmental Protection, Bilthoven, Netherlands, who acknowledges having consulted for this purpose the following documents:

1. Standard registration document on monoclonal antibodies (National Control Laboratory, Netherlands, 1988).
2. Points to consider in the manufacture and testing of monoclonal antibody products for human use (Thomas Hoffman, Chairman, Hybridoma Committee [HFN-838], Office of Biologics Research and Review, USA, 1987).
3. Considerations for the standardization and control of the new generation of biological products (National Institute for Biological Standards and Control, England).
4. Notes to applicants for marketing authorizations on the production and quality control of monoclonal antibodies of murine origin intended for use in man (Committee for Proprietary Medicinal Products, Working Party on Biotechnology and Pharmacy, Belgium, 1987).

5. Notes to applicants for marketing authorizations on the production and quality control of human monoclonal antibodies intended for use in man (Committee for Proprietary Medicinal Products and Biotechnology/Pharmacy, Ad Hoc Working Party, Belgium, 1990).

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1. Good manufacturing practices for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second Report. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 823), Annex 1.

2. Good manufacturing practices for biological products. In: WHO Expert Committee on Biological Standardization. Forty-second Report. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 822), Annex 1.

3. Requirements for the Collection, Processing: and Quality Control of Blood, Blood Components, and Plasma Derivatives (Requirements for Biological Substances No. 27, revised 1988). in: WHO Expert Committee on Biological Standardization. Thirty-ninth Report. Geneva, World Health Organization, 1989 (WHO Technical Report Series, No. 786), Annex 4.

4. General Requirements for the Sterility of Biological Substances (Requirements for Biological Substances No. 6, revised 1973). In: WHO Expert Committee on Biological Standardization. Twenty-fifth Report. Geneva, World Health Organization, 1973 (WHO Technical Report Series, No. 530), Annex 4.

5. Requirements for Continuous Cell Lines Used for Biologicals Production (Requirements for Biological Substances No. 37). In: WHO Expert Committee on Biological Standardization. Thirty-sixth Report. Geneva, World Health Organization, 1987. (WHO Technical Report Series, No. 745), Annex 3.

6. The international pharmacopoeia, 3rd ed. Vol. 1, General methods of analysis. Geneva, World Health Organization, 1979.

7. Kirkwood TBL. Design and analysis of accelerated degradation tests for the stability of biological standards. III. Principles of design. Journal of biological standardization, 1984, 12:215–224.

8. Guidelines for national authorities on quality assurance for bioiogical products. In: WHO Expert Committee on Biological Standardization. Forty-second Report. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 822), Annex 2.

Appendix 1

Possible viral contaminants in hybridomas of murine origin

An asterisk (*) denotes a virus capable of replicating in vitro in cells of human and monkey origin.

1. Viruses for which there is evidence of capacity for infecting humans or primates

Hantaan virus*
Lymphocytic choriomeningitis virus (LCMV)*
Rat rotavirus*
Reovirus type 3*
Sendai virus (murine and human parainfluenza virus type 1)*

2. Viruses for which there is no evidence of capacity for infecting humans

Ectromelia (mousepox) virus*
K virus (Polyomavirus muris 2)
Kilham rat virus (KRV)*
Lactic dehydrogenase virus (LDH)
Minute virus of mice (MVM)
Mouse adenovirus (MAV)*
Mouse cytomegalovirus (MCMV; murid (beta) herpesvirus 1)*
Mouse rotavirus (EDIM, epizootic diarrhoea of infant mice)*
Murine hepatitis virus (MHV)
Murine poliovirus (Theiler's encephalomyelitis virus, GD7)
Pneumonia virus of mice (PVM)*
Polyomavirus muris 1
Rat coronavirus (RCV)
Retroviruses (murine)*
Sialodacryoadenitis virus (SDAV)
Thymic virus (murid herpesvirus 3)
Toolan virus (H-1)*

Appendix 2
Human tissues that should be considered for immunohistochemical investigations of the reactivity of monoclonal antibodies

Tonsil, thymus, lymph node
Bone marrow, blood cells
Lung, Liver, kidney, bladder, spleen, stomach, intestine
Pancreas, parotid, thyroid, parathyroid, adrenal, pituitary
Brain, peripheral nerve
Heart, striated muscle
Ovary, testis
Skin

The tissues tested may vary with the immunological specificity of the antibody and its proposed use.

Appendix 3

Model certificate for the release of monoclonal antibodies[1]

The following lots of monoclonal antibodies _____[2] produced by _____[3] in _____,[4] whose numbers appear on the labels of the final containers, meet all national requirements,[5] and comply with Part A of the "Guidelines for assuring the quality of monoclonal antibodies for use in humans"[6] (if applicable, revised 19__, addenda 19__), "Good manufacturing practices for pharmaceutical products"[7] and "Good manufacturing practices for biological products".[8]

Lot no.	Expiry date	Lot no.	Expiry date
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

As a minimum, this certificate is based on examination of the manufacturing protocol.

The Director of the National Control Laboratory (or Authority as appropriate):[9]

Name (typed) _____

Signature _____

Date _____

[1] To be provided by the national control authority of the country where the monoclonal antibody has been manufactured, on the request of the manufacturer.

[2] Indicate the specificity of the monoclonal antibody.

[3] Name of manufacturer.

[4] Country.

[5] If any national requirements are not met, specify which one(s) and indicate why release of the lot(s) has nevertheless been authorized by the National Control Authority.

[6] WHO Technical Report Series, No. 822, 1992, Annex 3.

[7] WHO Technical Report Series, No. 823, 1992, Annex 1.

[8] WHO Technical Report Series, No. 822, 1992, Annex 1.

[9] Or his or her representative.

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Annex 4

Requirements for antimicrobic susceptibility tests: I. Agar diffusion tests using antimicrobic susceptibility discs (Requirements for Biological Substances No. 26, addendum 1991)

As part of these Requirements (revised 1981[1]), the Expert Committee on Biological Standardization at its thirty-third meeting[2] adopted a revised list of codes used to identify antimicrobials contained in susceptibility test discs. The list of codes was again revised at subsequent meetings of the Expert Committee[SG] to incorporate additions, deletions and changes in nomenclature. During the period since the last revision, further requests have been received by the WHO Secretariat for allocation of codes for new antimicrobial substances. The new entries that have been agreed should be incorporated into the existing list by making the following further additions to Part A, section 1.6 of the Requirements?

aspoxicillin	APX
cefbuperazone	CFB
cefdinir	CDR
cefetecol	CCL"
cefteram	CEM
ceftibuten	CTB
danofloxacin	DFX
flomoxef	FLO
habekacin	HAB
isepamicin	ISP
micronomicin	MCR
rokitamycin	ROK
temafloxacin	TMX

* This name and code replace those of "cefcatacol, CTL, which were published in the forty-first report of the Committee.

[1] WHO Technical Report Series. No. 673, 1982, p.144.
[2] WHO Technical Report Series, No. 687, 1983: p.175.
[3] WHO Technical Report Series, No.745, 1987, p.111.
[4] WHO Technical Report Series, No. 771, 1988, p. 211.
[5] WHO Technical Report Series, No. 800, 1990, p.180.
[6] WHO Technical Report Series, No.814, 1991, p. 71.

Full list of codes allocated

In view of the Expert Committee's decision no longer to annex lists of these codes to its reports (see pp.6–7 of the main report), a full updated list is given here for reference. Corrections, changes in spelling (generally to conform with recommended INNs) and additions made since publication of the revised list of codes in 1983[2] are noted in the right-hand column. Dates refer to approval by the Expert Committee rather than publication.

Antimicrobial	Code	Comment
actagardin	AG	
alafosfalin	AF	
amikacin	AN	
amoxicillin	AMX	
amoxicillin/clavulanic acid	AMC	1985[3]
amphotericin B	AB	
ampicillin	AM	
apalcillin	APL	1985[3]
aspoxicillin	APX	1991
astromicin	AST	was astromycin
avilamycin	AVI	
azithromycin	AZM	1990[6]
azlocillin	AZL	
aztreonam	ATM	
bacitracin	B	
bambermycin	FL	1985,[3] was flavomycin
bekanamycin	BK	
benzylpenicillin	P	
betamicin	BT	was betamycin
bicozamycin	BCZ	
brodimoprim	BDP	
butoconazole	BUT	1990[6]
carbenicillin	CB	
carumonam	CAR	1987[4]
cefacetrile	CAC	
cefaclor	CEC	
cefadroxil	CFR	
cefalexin	CN	
cefaloridine	CD	
cefalotin	CF	
cefamandole	MA	

[1] WHO Technical Report Series, No. 673, 1982, p.144.
[2] WHO Technical Report Series, No.687, 1983, p.175.
[3] WHO Technical Report Series, No.745, 1987, p.111.
[4] WHO Technical Report Series, No.771, 1988, p. 211.
[5] WHO Technical Report Series, No. 800, 1990, p.180.
[6] WHO Technical Report Series, No.814, 1991, p.71.

Antimicrobial	Code	Comment
cefapirin	CP	
cefatrizine	CTZ	1990[6]
cefazedone	CZD	
cefazolin	CZ	
cefbuperazone	CFB	1991
cefdinir	CDR	1991
cefepime	FEP	1987"
cefetamet	CAT	1990 (approved but unpublished)
cefetecol (was cefcatacol)	CCL	1991 (was CTL 1990[6])
cefetrizole	CZL	was cefetrizol
cefixime	CFM	1987[4]
cefmenoxime	CMX	
cefmetazole	CMZ	
cefminox	CNX	1987[4]
cefodizime	CDZ	1989[5]
cefonicid	CID	
cefoperazone	CFP	
ceforanide	CND	
cefotaxime	CTX	
cefotetan	CTT	
cefotiam	CTF	
cefoxitin	FOX	
cefpimizole	CFZ	1989[5]
cefpiramide	CPM	1990[6]
cefpirome	CPO	1989[5]
cefpodoxime	CPD	1989[5]
cefprozil	CPR	1990[6]
cefradine	CED	
cefroxadine	CRD	
cefsulodin	CFS	
cefsumide	CSU	
ceftazidime	CAZ	
cefteram	CEM	1991
ceftibuten	CTB	1991
ceftizoxime	CZX	
ceftriaxone	CRO	
cefuroxirne	CXM	
cetocycline	CTO	
chloramphenicol	C	
chlortetracycline	CH	
ciclacillin	CI	
cinoxacin	CIN	
clarithromycin	CLR	1990[6]

[1] WHO Technical Report Series, No. 673, 1982, p.144.
WHO Technical Report Series, No.687, 1983: p.175.
WHO Technical Report Series, No.745, 1987, p.111.
WHO Technical Report Series, No. 771, 1988, p. 211.
WHO Technical Report Series, No. 800, 1990, p.180.
WHO Technical Report Series. No. 814, 1991, p. 71.

Antimicrobial	Code	Comment
clavulanic acid	CLA	1985[3]
clindamycin	CM	
clotrimazole	CTR	
cloxacillin	CX	
colistin	CS	
danofloxacin	DFX	1991
demeclocycline	DM	
dibekacin	DKB	was debecakin
dicloxacillin	DX	
doxycycline	DO	
econazole	EC	
enoxacin	ENX	1985[3]
epicillin	EP	
epiroprim	EPP	
erythromycin	E	
ethambutol	EB	1985[3]
ethionamide	EA	1985[3]
fleroxacin	FLE	1990[6]
flomoxef	FLO	1991
flucloxacillin	FU	
flucytosine	FCT	1987[4]
flumequine	UB	
fosfomycin	FOS	
fosmidomycin	FMD	was fosfidomycin
framycetin	FY	
furaltadone	AL	
furazolidone	FR	
fusidic acid	FA	
gentamicin	GM	
habekacin	HAB	1991
hetacillin	H	
imipenem	IPM	1985,[3] was imipemide
isepamicin	ISP	1991
josamycin	JM	

[1] WHO Technical Report Series, No. 673, 1982, p.144.
[2] WHO Technical Report Series, No.687, 1983, p.175.
[3] WHO Technical Report Series, No.745, 1987, p.111.
[4] WHO Technical Report Series, No. 771, 1988, p. 211.
[5] WHO Technical Report Series, No. 800, 1990, p.180.
[6] WHO Technical Report Series, No. 814, 1991, p. 71.

Antimicrobial	Code	Comment
kanamycin	K	
kitasarnycin	LU	1985,[3] was leucornycin
latarnoxef	MOX	
lincomycin	L	
lividomycin	LV	
lomefloxacin	LOM	1989[5]
rnecillinam	MEC	
meropenem	MEM	1989[5]
mesulfarnide	MES	
rnetacycline	MC	
rnethenamine	M	1985,[3] was methenamine mandelate
meticillin	ME	
metioprim	MTP	
metioxate	MXT	
rnetronidazole	MTR	
mezlocillin	MZ	
miconazole	MCZ	
micronomicin	MCR	1991
mikarnycin	MI	
rniloxacin	MIL	
minocycline	MNO	
nafcillin	NF	
nalidixic acid	NA	
natamycin	NT	
neomycin	N	
netilmicin	NET	
nifuroquine	NIF	
nifurprazine	NP	
nitrofural	FC	1985,[3] was nitrofuzone
nitrofurantoin	FT	
nitroxoline	NI	
norfloxacin	NOR	
novobiocin	NB	
nystatin	NY	
oleandomycin	OL	
ornidazole	ORN	1987':
oxacillin	OX	
oxolinic acid	OA	
oxytetracycline	OT	

[1] WHO Technical Report Series, No. 673, 1982, p.144.
[2] WHO Technical Report Series, No. 687, 1983. p.175.
W H O Technical Report Series, No.745, 1987, p.111.
[4] WHO Technical Report Series, No. 771, 1988, p. 211.
[5] WHO Technical Report Series, No. 800, 1990, p.180.
[6] WHO Technical Report Series, No. 814, 1991, p. 71.

Antimicrobial	Code	Comment
paromomycin	PM	
pentisomicin	PIM	was pentisomycin
pentizidone	PTZ	
pheneticillin	PH	was phenethicillin
phenoxymethylpenicillin	PV	
pipemidic acid	PI	
piperacillin	PIP	
piridicillin	PRC	
piromidic acid	PIR	
plauracin	PL	
polymyxin B	PB	
primycin	PRM	
pristinamycin	PT	
propicillin	PR	
propikacin	PKA	
ribostamycin	RI	
rifamide	RM	
rifampicin	RA	
rifamycin	RF	
rifapentine	RP	
rokitamycin	ROK	1991
rosoxacin	ROS	
roxithromycin	RXT	1985[3]
sarmoxicillin	SRX	
sisomicin	SIS	
spectinomycin	SPT	
spiramycin	SP	
streptomycin	S	
sulbactam	SB	
sulbactam/ampicillin	SAM	1987[4]
sulbenicillin	SBC	1985[3]
sulconazole	SUC	1990[6]
sulfacitine	RE	1985[3]
sulfadiazine	SD	
sulfadimethoxine	X	
sulfadimidine	SDM	
sulfafurazole	I	
sulfamazone	SZO	
sulfamerazine	SM	
sulfamethizole	SZ	
sulfamethoxazole	SMX	

[1] WHO Technical Report Series, No. 673, 1982, p.144.
[2] WHO Technical Report Series, No. 687, 1983, p.175.
[3] WHO Technical Report Series, No. 745, 1987, p.111.
[4] WHO Technical Report Series, No. 771, 1988, p. 211.
[5] WHO Technical Report Series, No. 800, 1990, p.180.
[6] WHO Technical Report Series, No. 814, 1991, p. 71.

Antimicrobial	Code	Comment
sulfamethoxazole/trimethoprim	SXT	
sulfamethoxypyridazine	SX	
sulfametomidine	MT	was sulfamethomidin
sulfametrole	SL	
sulfamonomethoxine	MO	1985,[3] was sulfamethoxine
sulfaphenazole	PZ	
sulfasuccinamide	SNA	
sulfathiazole	ST	
sulfisomidine	D	
sulfomyxin	TS	1985,[3] was thiosporin
sulfonamides	SSS	
talisornycin	TA	
talmetoprim	TLP	
teicoplanin	TEC	1985[3]
temafloxacin	TMX	1991
temocillin	TEM	
terizidone	TZ	
tetracycline	TE	
tetroxoprirn	TET	
thiamphenicol	TP	
ticarcillin	TIC	
ticarcillin/clavulanic acid	TCC	1985[3]
tilbroquinol	TBQ	
tiliquinol	TQ	
tiodonium chloride	TDC	
tioxacin	TXC	
tobramycin	TM	
tosufloxacin	TFX	1990[6]
trimethoprim	TMP	
tylosin	TI	
vancomycin	VA	
virginiamycin	VG	

[1] WHO Technical Report Series, No. 673, 1982, p.144.
[2] WHO Technical Report Series, No. 687, 1983, p.175.
[3] WHO Technical Report Series, No. 745, 1987, p.111.
[4] WHO Technical Report Series, No. 771, 1988, p. 211.
[5] WHO Technical Report Series, No. 800, 1990, p.180.
W H O Technical Report Series: No. 814, 1991, p. 71.

Codes listed in alphabetical order

AB AF AG AL AM AMC AMX AN APL APX AST ATM AVI AZL AZM

B BCZ BDP BK BT BUT

C CAC CAR CAT CAZ CB CCL CD CDR CDZ CEC CED CEM CF CFB CFM CFP CFR CFS CFZ CH CI CID CIN CLA CLR CM CMX CMZ CN CND CNX CP CPD CPM CPO CPR CRD CRO CS CSU CTB CTF CTO CTR CTT CTX CTZ CX CXM CZ CZD CZL CZX

D DFX DKB DM DO DX

E EA EB EC ENX EP EPP

FA FC FCT FEP FL FLE FLO FMD FOS FOX FR FT FU FY

GM

H HAB

I IPM ISP

JM

K

L LOM LU LV

M MA MC MCR MCZ ME MEC MEM MES MI MIL MNO MO MOX MT MTP MTR MXT MZ

N NA NB NET NF NI NIF NOR NP NT NY

OA OL ORN OT OX

P PB PH PI PIM PIP PIR PKA PL PM PR PRC PRM PT PTZ PV PZ

RA RE RF RI RM ROK ROS RP RXT

S SAM SB SBC SD SDM SIS SL SM SMX SNA SP SPT SRX SSS ST SUC SX SXT SZ SZO

TA TBQ TCC TDC TE TEC TEM TET TFX TIC TL TLP TM TMP TMX TP TQ TS TXC TZ

UB

VA VG

X

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Annex 5
Laboratories approved by WHO for the production of yellow fever vaccine

This list supersedes Annex 10 in WHO Technical Report Series, No. 771, 1988.

Bio-Manguinhos
Oswaldo Cruz Foundation
Rio de Janeiro
Brazil

Central Research Institute
Kasauli
Himachal Pradesh
India

Connaught Laboratories Inc.
Swiftwater, PA
USA

CSL Limited
Parkville
Victoria
Australia

Federal Vaccine Production
Virology Laboratory
Yaba
Lagos
Nigeria

Institute of Poliomyelitis and
Viral Encephalitides
Moscow
Russian Federation

National Institute for Virology
Sandringham
South Africa

Pasteur Institute of Dakar
Dakar
Senegal

Pasteur Merieux Sera and Vaccines
Lyon
France

Robert Koch Institute
Berlin
Germany

The Wellcome Research Laboratories
Beckenham
Kent
England

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Annex 6
Biological substances: International Standards and Reference Reagents

A list of International Biological Standards, International Biological Reference Preparations, and International Biological Reference Reagents is issued as a separate publication.[1] Copies may be obtained from appointed sales agents for WHO publications or from: Distribution and Sales, World Health Organization, 1211 Geneva 27, Switzerland.

The Expert Committee made the following changes to the previous list.

Additions

Antisera

Anti-poliovirus serum Types 1, 2 and 3, human	Type 1: 25 IU/ampoule Type 2: 50 IU/ampoule Type 3: 5 IU/ampoule	Second International Standard 1991

This substance is held and distributed by the International Laboratory for Biological Standards, National Institute for Biological Standards and Control, Potters Bar, Herts., EN6 3QG, England.

Antigens

Rabies vaccine	16 IU/ampoule	Fifth International Standard 1991
Rabies virus PM-glycoprotein	10 IU/ampoule	First International Standard 1991
Rabies virus PM-ribonucleoprotein	135 IU/ampoule	First International Standard 1991

These substances are held and distributed by the International Laboratory for Biological Standards, State Serum Institute, 80 Amager Boulevard, Copenhagen, Denmark.

[1] Biological substances: International Standards and Reference Reagents, 1990. Geneva, World Health Organization, 1991.

Blood products

Alpha-thrombin, human	100 IU/ampoule	First International Standard 1991

This substance is held and distributed by the International Laboratory for Biological Standards, National Institute for Biological Standards and Control, Potters Bar, Herts., EN6 3QG, England.

Endocrinological substances

Calcitonin, human	17.5 IU/ampoule	Second International Standard 1991
Calcitonin, porcine	0.8 IU/ampoule	Second International Standard 1991
Thyroxine-binding globulin	30 IU/ampoule	First International Standard 1991
Tumour necrosis factor alpha, human	40 000 IU/ampoule	First International Standard 1991

These substances are held and distributed by the International Laboratory for Biological Standards, National Institute for Biological Standards and Control, Potters Bar, Herts., EN6 3QG, England.

Discontinuation

Vitamin D	Bottles containing approximately 6 g of a solution of vitamin D_3 (INN = colecalciferol) in vegetable oil (1000 IU/g)	Second International Standard 1949

An International Unit of Vitamin D is widely taken to be equivalent to the activity in 25 ng of pure colecalciferol.

This substance was held and distributed by the International Laboratory for Biological Standards, National Institute for Biological Standards and Control, Potters Bar, Herts., EN6 3QG, England.

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Annex 7
Requirements for biological substances and other sets of recommendations

The specification of requirements to be fulfilled by preparations of biological substances is necessary in order to ensure that these products are safe, reliable, and potent prophylactic or therapeutic agents. International recommendations on requirements are intended to facilitate the exchange of biological substances between different countries and to provide guidance to workers responsible for the production of these substances as well as to others who may have to decide upon appropriate methods of assay and control.

Recommended requirements and sets of recommendations concerned with biological substances are formulated by international groups of experts and are published in the Technical Report Series of the World Health Organization,' as listed here.

Requirements

1. General Requirements for Manufacturing Establishments and Control Laboratories
   Revised 1965, TRS **323** (1966)
   Replaced by "Good manufacturing practices for biological products", TRS **822** (1992) and "Guidelines for national authorities on quality assurance for biological products", TRS **822** (1992)
2. Requirements for Poliomyelitis Vaccine (Inactivated)
   Revised 1981, TRS **673** (1987)
   Addendum 1985, TRS **745** (1987)
3. Requirements for Yellow Fever Vaccine
   Revised 1975, TRS **594** (1976)
   Addendum 1987, TRS **771** (1988)
4. Requirements for Cholera Vaccine
   Revised 1968, TRS **413** (1969)
   Addendum 1973, TRS **530** (1973)
5. Requirements for Smallpox Vaccine
   Adopted 1966, TRS **323** (1966)
6. General Requirements for the Sterility of Biological Substances
   Revised 1973, TRS **530** (1973)

'Abbreviated here as TRS

7. Requirements for Poliomyelitis Vaccine, Oral
   Revised 1989, TRS **800** (1990)

8.& Requirements for Diphtheria, Tetanus, Pertussis and Combined
10. Vaccines
   Revised 1989, TRS **800** (1990)

9. Requirements for Procaine Benzylpenicillin in Oil with Aluminium Monostearate
   Revised 1966, TRS **361** (1967)
   Discontinued 1989, TRS **800** (1990)

11. Requirements for Dried BCG Vaccine
   Revised 1985, TRS **745** (1987)
   Amendment 1987, TRS **771** (1988)

12. Requirements for Measles Vaccine (Live)
   Revised 1987, TRS **771** (1988)

13. Requirements for Anthrax Spore Vaccine (Live, for Veterinary Use)
   Adopted 1966, TRS **361** (1967)

14. Requirements for Human Immunoglobulin
   Adopted 1966, TRS **361** (1967)
   Replaced by Requirements No. 27

15. Requirements for Typhoid Vaccine
   Adopted 1966, TRS **361** (1967)

16. Requirements for Tuberculins
   Revised 1985, TRS **745** (1987)

17. Requirements for Influenza Vaccine (Inactivated)
   Revised 1990, TRS **814** (1991)

18. Requirements for Immune Sera of Animal Origin
   Adopted 1968, TRS **413** (1969)

19. Requirements for Rinderpest Cell Culture Vaccine (Live) and Rinderpest Vaccine (Live)
   Adopted 1969, TRS **444** (1979)

20. Requirements for *Brucella abortus* Strain 19 Vaccine (Live, for Veterinary Use)
   Adopted 1969, TRS **444** (1970)
   Addendum 1975, TRS **594** (1976)

21. Requirements for Snake Antivenins
   Adopted 1970, TRS **463** (1971)

22. Requirements for Rabies Vaccine for Human Use
   Revised 1980, TRS **658** (1981)

23. Requirements for Meningococcal Polysaccharide Vaccine
   Adopted 1975, TRS **594** (1976)
   Addendum 1980, TRS **658** (1981)

24. Requirements for Rubella Vaccine (Live)
    Adopted 1976, TRS **610** (1977)
    Addendum 1980, TRS **658** (1981)

25. Requirements for *Brucella melitensis* Strain Rev. 1 Vaccine (Live, for Veterinary Use)
    Adopted 1976, TRS **610** (1977)

26. Requirements for Antimicrobic Susceptibility Tests
    I. Agar Diffusion Tests Using Antimicrobic Susceptibility Discs
    Revised 1981, TRS **673** (1982)
    Addendum 1982, TRS **687** (1983)
    Addendum 1985, TRS **745** (1987)
    Addendum 1987, TRS **771** (1988)
    Addendum 1989, TRS **800** (1990)
    Addendum 1990, TRS **814** (1991)
    Addendum 1991, TRS **822** (1992)
    Discontinued 1991, TRS **822** (1992)

27. Requirements for the Collection, Processing, and Quality Control of Blood, Blood Components and Plasma Derivatives
    Revised 1988, TRS **786** (1989)

28. Requirements for Influenza Vaccine (Live)
    Adopted 1978, TRS **638** (1979)

29. Requirements for Rabies Vaccine for Veterinary Use
    Adopted 1980, TRS **658** (1981)

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32. Requirements for Rift Valley Fever Vaccine
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