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ON SPECIFICATIONS FOR
PHARMACEUTICAL PREPARATIONS**

Thirty-third Report



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Geneva, 30 November – 4 December 1992

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1. **Introduction**

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 30 November to 4 December 1992. The meeting was opened on behalf of the Director-General by Dr J.F. Dunne, Director, Division of Drug Management and Policies, who drew attention to some of the major aspects of the Expert Committee's work over the previous 10 years. In so doing, he suggested that the overall objective of this work was to provide a solid foundation on which all interested Member States could build a comprehensive approach to quality assurance of pharmaceutical products. Since the previous meeting of the Committee, important changes had occurred in the world, especially in Europe. New independent states had emerged and many had joined the Organization. Dr Dunne asked the Expert Committee to bear the needs of these Member States in mind during its discussions and in recommending future action.

In May 1992, the World Health Assembly adopted resolution WHA 45.28, which requested the Director-General, *inter alia*, "to further the international harmonization of drug regulatory regimes". Dr Dunne suggested that the aim should be to build on the results of current initiatives involving the countries of the European Communities, Japan and the United States of America to the advantage of the broader constituency of WHO's Member States. He informed the Expert Committee that the administrative structure of the Division of Drug Management and Policies had been modified so as to make it better able to meet the challenges of the times. He was confident that it could provide the help needed by countries in establishing and maintaining appropriate drug regulatory systems.

2. ***The international pharmacopoeia and related activities***

2.1. **Quality specifications for drug substances and dosage forms**

The Committee was pleased to note that publication of Volume 4 of *The international pharmacopoeia*, containing additional monographs on pharmaceutical substances, excipients and dosage forms together with supporting test methods and general requirements, was expected in 1993.

The Committee considered, and recommended for inclusion in a future publication, monographs on ophthalmic drops and ointments and on suppositories, and test methods for the disintegration of suppositories and for the sterility of non-injectable preparations. It noted the progress made jointly with experts from the European Pharmacopoeia Commission on developing a test for visible particulate matter in injectable preparations.

The Committee confirmed that the requirements of *The international pharmacopoeia* should continue to be based on reliable methods widely available in small control laboratories. Such a policy is consistent with the

unique role of *The international pharmacopoeia*. However, in some circumstances, the provision of more complex methods as alternatives might be considered.

It was suggested that it would be helpful for WHO to obtain information about users of *The international pharmacopoeia* in order to ascertain more precisely by whom and for what purposes it is currently used.

2.2 Dissolution test for solid oral dosage forms: paddle method

It was agreed that, since the paddle method had been recommended for inclusion in *The international pharmacopoeia* (2), it would be helpful to supplement the description of the method (which has been harmonized with that already published in other pharmacopoeias) with additional information, especially on validation. Consultation on a draft text incorporating such information was recommended before finalization for publication in *The international pharmacopoeia*. Inclusion of other methods might be considered in the future if needed for a particular application.

Meanwhile, publication of the paddle method would permit establishment of dissolution requirements for those preparations included in the WHO Model List of Essential Drugs (1) that had been singled out previously (2) as being of particularly high priority since they were widely considered to present bioavailability problems.¹ It was agreed that the test conditions and the criteria for the acceptance of these preparations would be specified in the relevant monographs. The conditions and criteria would initially be based on existing pharmacopoeial specifications.

2.3 Therapeutic equivalence of multisource products

While the inclusion of dissolution requirements in *The international pharmacopoeia* was considered to be an important step forward, it was recognized that an *in vitro* dissolution test was only one stage in the procedure for ensuring that multisource products were therapeutically equivalent. Information on the interchangeability of conventional-release solid dosage forms from a wide range of sources, all containing the same quantity of the same active ingredient, was essential for those responsible for approving the registration of products.

It was recognized that existing national regulatory requirements varied with respect to multisource products and that a need therefore existed for global guidelines. It was suggested that WHO, among other appropriate activities, might:

- undertake a survey of national legislation and practices with regard to registration requirements, and the prescribing and dispensing in retail pharmacies of multisource products;

¹ Ampicillin, chloroquine, digoxin, erythromycin, furosemide, griseofulvin, isoniazid, levodopa, mebendazole, metronidazole, phenoxymethylpenicillin, phenytoin, tetracycline, tolbutamide.

- compile and review at regular intervals a list of drug substances that may be associated with bioavailability problems (including those of narrow therapeutic index, etc.);
- collect and compile available information on the correlation between activity *in vivo* and *in vitro* for essential drugs presenting problems (reported, for example, via drug monitoring services) of bioavailability and bioequivalence;
- develop WHO guidelines for bioequivalence studies, in the context of the WHO guidelines on good clinical practices currently in course of preparation;
- establish a policy and recommendations with regard to the role of dissolution testing in the quality control of drugs and in determining whether they are therapeutically equivalent.

2.4 **International nonproprietary names for pharmaceutical substances**

The Committee was informed of the current activities of the programme on international nonproprietary names (INNs) for pharmaceutical substances. It agreed that there was a case for increased protection of INNs, as pointed out in the fifth report of the WHO Expert Committee on the Use of Essential Drugs (1). The difficulty of establishing appropriate names for the wide range of compounds produced by biotechnology was recognized. It was agreed that wide consultation with experts from the relevant disciplines would be advisable to establish policy in this field.

The Committee noted that guidelines for the drawing of graphic formulae for pharmaceutical substances were in preparation, an area where global harmonization is needed.

3. **International Chemical Reference Substances and International Infrared Reference Spectra**

3.1 **Establishment of reference substances**

Five new¹ International Chemical Reference Substances were adopted by the Committee according to the procedure described in the thirty-second report. It was noted that replacement batches had been introduced for four² previously established Reference Substances.

The total collection now comprises 152 International Chemical Reference Substances and 13 Melting Point Reference Substances (Annex 1). The Committee took note of information concerning the International

¹ Amphotericin B, erythromycin, nystatin, rifampicin, sulfasalazine.

² *p*-Acetamidobenzalazine, ampicillin (anhydrous), ethinylestradiol, retinol (vitamin A) acetate.

Chemical Reference Substances supplied to different WHO regions and countries. It suggested that, when information was sought on the use of *The international pharmacopoeia*, as mentioned in section 2.1, those questioned should also be asked to comment on the use of reference substances.

The Committee reiterated that, as pointed out at the thirty-second meeting (3), there was a need to revise and extend the recommendations included in the "General guidelines for the establishment, maintenance, and distribution of chemical reference substances" originally issued in 1982 (4).

The Committee recommended that, for those substances where an International Chemical Reference Substance existed in parallel with an International Biological Standard (5), it should be decided on a case-by-case basis whether both reference materials were necessary. Such decisions would need to be taken jointly by the present Committee and the WHO Expert Committee on Biological Standardization. As a first step, discussions should take place between the WHO Collaborating Centre for Chemical Reference Substances, Stockholm, Sweden and the relevant International Laboratory for Biological Standards, taking into account the intended use of the relevant standards.

The Committee expressed its appreciation to the WHO Collaborating Centre for Chemical Reference Substances for its work and to the National Corporation of Swedish Pharmacies for its continued financial support for the WHO programme on International Chemical Reference Substances.

3.2 Infrared reference spectra

Further to the spectra established at the Committee's previous meeting (3), it adopted 18 additional International Infrared Reference Spectra. Those listed in Annex 2 are now available from the WHO Collaborating Centre for Chemical Reference Substances, Stockholm, Sweden. Precise instructions for the preparation of spectra are provided with each reference spectrum. A separate document including recommendations for the preparation and use of infrared spectra in pharmaceutical analysis was provisionally adopted by the Committee subject to further consultation with the participating laboratories. Once finalized, the recommendations would accompany the reference spectra. It was noted that the general interchangeability of instruments had been confirmed during the validation exercise.

The Committee emphasized that the comparison of infrared spectra by means of either a reference spectrum or a reference substance required an appropriate level of expertise.

4. **Quality control methods for medicinal plant materials**

The Committee noted the progress made in developing recommendations concerning this important aspect of control. Subject to rationalization of the terminology and to final comments from experts in the field, the Committee suggested that the recommendations should be issued by WHO.

5. **The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce**

With respect to the revised guidelines for implementing the expanded Certification Scheme published as Annex 3 of the report on the thirty-second meeting of the Committee (3), it was noted that, in May 1992, the World Health Assembly had adopted resolution WHA 45.29 in which it urged Member States *inter alia* to “issue certificates within five years in a form to be agreed in the light of experience gained in preliminary field testing”. The Committee requested that WHO and other international organizations should take every opportunity to promote the use of the Certification Scheme.

As foreshadowed in the previous report, work had been carried out on proposals for the certification of active ingredients. A significant difference between active ingredients and pharmaceutical products was that many Member States did not assess and register the former *per se*. In these circumstances, certification could only attest to the inclusion of the active ingredients in one or more finished dosage forms approved for marketing in the country concerned. The Committee agreed that, in finalizing the draft proposals in consultation with Member States, it should be stressed that certification of an active ingredient was an additional safeguard and not a substitute for analysis of the material by those responsible for the manufacture of the dosage forms.

6. **Good manufacturing practices for pharmaceutical products**

6.1 **Biological products**

Further to the publication of the revised general text on good manufacturing practices in Annex 1 of the Committee's previous report (3), it endorsed the guidelines on good manufacturing practices for biological products prepared jointly with the WHO Expert Committee on Biological Standardization (Annex 3). As emphasized in sections 1 and 2 of these additional guidelines, they are to be used only as a supplement to the main text.

6.2 Herbal medicinal products

The Committee was informed that draft supplementary guidelines on good manufacturing practices for herbal medicinal products were in course of preparation; consultations were in progress in parallel with the finalization of the recommendations on quality control of medicinal plant materials mentioned in section 4.

6.3 Process validation

The Committee noted that consultations were in progress on draft supplementary guidelines on process validation. Account would be taken of the need for the terminology to be the same as that used in pharmacopoeias and in guidelines issued by regulatory authorities.

6.4 Further developments

The suggestion that all the WHO texts on good manufacturing practices should be combined in a single indexed document was strongly supported. The Committee was pleased to note that the revised WHO guidelines were considered to be consistent in all major technical respects with those in use within the countries of the International Conference on Harmonisation (ICH), namely in the European Communities, Japan and the USA.

7. Development of globally acceptable standards for excipients

The Committee recommended that WHO should use its worldwide channels of communication to inform interested parties of the action being taken to harmonize the specifications for certain excipients in the European Pharmacopoeia, the Japanese Pharmacopoeia and the United States Pharmacopoeia. Those so informed should send any comments on the proposed harmonized specifications to whichever of the three pharmacopoeial authorities was taking the lead on the monograph in question. Once such harmonized texts were adopted by the three pharmacopoeias, the need for a monograph in *The international pharmacopoeia* or, where such a monograph existed, for its revision, could be considered.

8. Stability of dosage forms

8.1 Survey

The Committee discussed the results of the survey of products of questionable stability, which had been conducted as agreed at its thirty-second meeting (3). While the qualitative nature of the information received did not permit firm conclusions to be drawn concerning the magnitude of the problems related to the stability of the preparations

surveyed, the following important general observations were made, based on an analysis of the data provided:

1. Over half the 200 reports received related to problems encountered with formulations of only five of the 25 drug substances included in the survey (acetylsalicylic acid, ampicillin, chloramphenicol, paracetamol, and tetracycline).
2. Many of the problems had been encountered with products well before their expiry dates, sometimes within a short time of their date of manufacture (in approximately 70% of cases where shelf-life data were available, the problem had occurred when less than half the shelf-life had elapsed and in approximately 45% of cases when less than one-quarter of the shelf-life had elapsed).

The above observations together with other information from the survey pointed to the existence of intrinsically unsatisfactory formulations of certain widely used drug substances. The poor quality would appear in many cases to be due to factors other than stability.

The Committee recommended that:

- the introduction to the initial summary report prepared by the Secretariat should be revised to reflect the much broader quality implications of the problems revealed by the survey;
- this initial report should be provided in the first instance to those who had participated in the survey;
- WHO should encourage those national authorities reporting problems to take appropriate action in relation to the suppliers of substandard products;
- in continuing to monitor the quality of products in their territories, all authorities should be encouraged to pay particular attention to the five widely used preparations mentioned in point 1 above;
- the data provided by participants should be analysed further by appropriate experts;
- future WHO action should be taken in the light of this analysis together with the results of the joint WHO/UNICEF study, endorsed by the Committee in its thirty-second report, on the quality of selected products at the point of use in developing countries;
- if it is decided to conduct a further survey, the questionnaire should be revised and refined in consultation with the relevant experts.

8.2 **Guidelines on stability testing of pharmaceutical products containing established drug substances**

In response to the Committee's earlier request (2), the draft WHO guidelines on stability testing were reviewed. It was emphasized that these guidelines should be consistent with those in course of preparation within the ICH programme with respect to all technical definitions and other related issues. The focus of the WHO guidelines, however, would be on providing advice on the stability testing of formulations containing

established drug substances intended for use in the more extreme climatic conditions frequently encountered in many developing countries.

9. **Simple test methodology**

Basic tests for verifying the identity of pharmaceutical substances and their associated dosage forms have now been published (6, 7) or are in the course of development for the majority of the substances in the current WHO Model List of Essential Drugs (1). The Committee recommended that the reagents specified for use in such tests should be chosen with care with respect to both their availability and their toxicity. In response to earlier suggestions (4) that complementary tests should be developed to detect gross degradation, a thin-layer chromatographic (TLC) procedure was in the course of evaluation. The Committee agreed that, providing such a procedure was shown to be sufficiently reliable, it could be recommended for use as a basic test.

10. **Quality assurance in pharmaceutical supply systems**

Much of the advice and guidance concerning the quality of pharmaceutical products provided by WHO publications is addressed primarily to drug regulators. It is recognized, however, that many different organizations and individuals are concerned with one or more aspects of the supply of pharmaceutical products and therefore need to understand the concept of quality assurance and its application to pharmaceutical supply systems. The Committee therefore recommended that WHO should consider preparing guidelines for use by organizations and individuals involved in the supply or receipt of purchased or donated pharmaceutical products.

In this context, the Committee took note of guidelines for donors and recipients of pharmaceutical products and guidelines on drug procurement practice prepared respectively by the Christian Medical Commission of the World Council of Churches and the International Pharmaceutical Federation (8,9). These helpful documents, together with others such as the WHO document listing requirements for an emergency health kit (10), could be taken into account in developing authoritative guidance. Appropriate United Nations agencies and nongovernmental organizations should be consulted with the aim of harmonizing policies, for example on the donation of pharmaceutical products.

Within the same general context the Committee endorsed the Secretariat's proposal to develop guidelines on import procedures for pharmaceutical products. Such guidelines would be prepared in consultation with the Customs Co-operation Council, the International Narcotics Control Board and other relevant bodies. It was recognized that the point of entry of products into a country was a key step in the distribution chain. Guidance in this area would complement initiatives such as the joint WHO/UNICEF study referred to in section 8.1.

11. **Pharmaceutical production in developing countries**

11.1 **Small-scale preparation of ophthalmic (eye) drops**

In noting the document (II) containing advice on this topic produced by WHO's Programme for the Prevention of Blindness, the Committee was pleased to learn that the guidance provided on preparation and quality control was proving helpful to pharmacists in hospitals in remote areas. Local, small-scale preparation of a limited number of widely used types of eye drops was meeting an important need in the communities concerned.

11.2 **Production of hormonal contraceptives**

The Committee reviewed preliminary proposals on the production and quality assurance of hormonal contraceptives. Documents had been drafted both because of increasing pressures on several developing countries to manufacture both oral and injectable hormonal contraceptives and because WHO's Special Programme of Research, Development and Research Training in Human Reproduction was concerned about the quality of certain formulations known to it. The Committee urged that the development of such proposals should take full account of all existing WHO documentation on the quality assurance of pharmaceutical products, and in particular of the revised guidelines on good manufacturing practices (3). The Committee was concerned to avoid any suggestion that the basic principles of quality assurance and good manufacturing practice were not applicable to all pharmaceutical products. It stressed that a proliferation of guidelines dealing with different categories of pharmaceutical products should be avoided. However, to the extent that the manufacture and control of hormonal contraceptives presented particular difficulties, these could be addressed in supplementary guidelines.

Recognizing the substantial manufacturing and analytical problems associated with highly potent, low-dosage combination hormonal contraceptives, the Committee recommended that local manufacture of such products should be discouraged in the absence of well established local programmes of drug regulation and quality assurance. Special care is also required to protect workers and the environment from exposure to hormonal contraceptive agents. The Committee further recommended that national drug authorities should be encouraged to carry out post-marketing surveillance to monitor the continuing safety and effectiveness of hormonal contraceptives.

12. **Training**

The Committee was informed of various training activities that had been organized or planned since its previous meeting in December 1990 (3). These included several regional and subregional courses on administrative

aspects of drug control – and particularly on the drug registration process – organized by the German Foundation for International Development. It was agreed that, while training at international level should be continued, it would be useful if some resources could be provided to meet an important and largely unsatisfied need to support postgraduate courses and continuing education. These would provide an opportunity for topics such as the WHO Certification Scheme and the WHO guidelines on good manufacturing practices to be discussed at the national and local level.

The purpose of training, it was agreed, was not only to increase technical competence, but also to develop awareness of the tasks and responsibilities of regulatory officials, particularly with regard to quality assurance. It was also agreed that a comparable need exists in the manufacturing environment. Indeed, training packages for the authorized person in the manufacturing facility, as defined in the WHO guidelines on good manufacturing practices, are already used in some countries.

A model software package designed to support the drug registration process, developed by WHO with financial support from the German and Italian governments, was considered by the Committee to be of great potential value. This package is available in English, French and Spanish and can easily be translated into other languages. It can also be adapted to meet specific local requirements. Both the software and on-the-spot training are available to national drug regulatory authorities on application to WHO.

The Committee commended the various training activities already being carried out and confirmed the recommendations made in its previous report (3), particularly with regard to the training of laboratory technicians. Looking ahead, it underscored the need for further development of computer software packages to support the various aspects of drug regulation and control.

The need for basic training of regulators remains as high as ever, partly as a consequence of the continuing high turnover of such personnel. The losses of well qualified persons from the regulatory environment might well often be decreased at relatively low cost by the provision of more attractive career structures.

The Committee acknowledged with appreciation the generous and sustained support of training activities by the governments of Germany, Italy and Japan and by the German Foundation for International Development, the International Federation of Pharmaceutical Manufacturers Associations and the WHO Collaborating Centre for Chemical Reference Substances.

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WHO Collaborating Centre for Drug Quality Control, Therapeutic Goods Administration Laboratories, Department of Community Services and Health, Woden, Australian Capital Territory, Australia; WHO Collaborative Centre for Drug Quality Assurance, National Institute for the Control of Pharmaceutical and Biological Products, Temple of Heaven, Beijing, China; WHO Collaborating Centre for Biopharmaceutical Aspects of Drug Quality Control, Biopharmacy Laboratory, Faculty of Pharmacy, University of Clermont-Ferrand, Clermont-Ferrand, France; WHO Collaborating Centre for Stability Studies of Drugs, Regional and University Hospital Centre, Nantes, France; WHO Collaborating Centre for Drug Information and Quality Assurance, National Institute of Pharmacy, Budapest, Hungary; WHO Collaborating Centre for Quality Assurance of Essential Drugs, Central Drugs Laboratory, Government of India, Calcutta, India; WHO Collaborating Centre for Quality Assurance of Essential Drugs, The National Quality Control Laboratory of Drug and Food, Directorate General of Drug and Food Control, Ministry of Health, Jakarta, Indonesia; WHO Collaborating Centre for Chemical Reference Substances, The National Corporation of Swedish Pharmacies, Central Laboratory, Stockholm, Sweden; WHO Collaborating Centre for Quality Assurance of Essential Drugs, Department of Medical Sciences, Ministry of Public Health, Bangkok, Thailand; WHO Collaborating Centre for Drug Quality Control, State Research Institute for the Standardization and Control of Drugs, Ministry of Health, Moscow, Russian Federation.

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Unfortunately the Committee was not in a position to name all those who contributed to the development of its report but wished to extend its thanks to them for their support.

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Annex 1

List of available International Chemical Reference Substances¹

International Chemical Reference Substances are established on the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They are supplied primarily for use in physical and chemical tests and assays described in the specifications for quality control of drugs published in *The international pharmacopoeia* or proposed in draft monographs.

Directions for use and the analytical data required for the tests specified in *The international pharmacopoeia* are given in the certificates enclosed with the substances when distributed. More detailed analytical reports on the substances may be obtained on request from the WHO Collaborating Centre for Chemical Reference Substances.

International Chemical Reference Substances may also be used in tests and assays not described in *The international pharmacopoeia*. However, the responsibility for assessing the suitability of the substances then rests with the user or with the pharmacopoeia commission or other authority that has prescribed their use.

It is generally recommended that the substances be stored protected from light and moisture and preferably at a temperature of about +5°C. When special storage conditions are required, this is stated on the label or in the accompanying leaflet.

The stability of the International Chemical Reference Substances kept at the Collaborating Centre is monitored by regular re-examination, and materials that have deteriorated are replaced by new batches when necessary. Lists giving control numbers for the current batches are issued in the annual reports from the Centre and may be obtained on request.

Orders for International Chemical Reference Substances should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteksbolaget AB
Centrallaboratoriet
S-105 14 Stockholm
Sweden

Telex: 115 53 APOBOL S
Fax: 46 8 740 60 40

International Chemical Reference Substances are supplied only in the standard packages indicated in the following list.

¹ As updated at the thirty-third meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, 30 November–4 December 1992.

<i>Reference substance</i>	<i>Package size</i>
aceclidine salicylate	100 mg
<i>p</i> -acetamidobenzalazine	100 mg
acetazolamide	100 mg
allopurinol	100 mg
2-amino-5-nitrothiazole	25 mg
3-aminopyrazole-4-carboxamide hemisulfate	100 mg
amitriptyline hydrochloride	100 mg
amphotericin B	400 mg
ampicillin (anhydrous)	200 mg
ampicillin sodium	200 mg
ampicillin trihydrate	200 mg
anhydrotetracycline hydrochloride	25 mg
atropine sulfate	100 mg
azathioprine	100 mg
bendazol hydrochloride	100 mg
benzobarbital	100 mg
benzylamine sulfate	100 mg
benzylpenicillin potassium	200 mg
benzylpenicillin sodium	200 mg
bephenium hydroxynaphthoate	100 mg
betamethasone	100 mg
betamethasone valerate	100 mg
betanidine sulfate	100 mg
bupivacaine hydrochloride	100 mg
caffeine	100 mg
carbamazepine	100 mg
carbenicillin monosodium	200 mg
chloramphenicol	200 mg
chloramphenicol palmitate	1 g
chloramphenicol palmitate (polymorph A)	200 mg
5-chloro-2-methylaminobenzophenone	100 mg
2-(4-chloro-3-sulfamoylbenzoyl)benzoic acid	50 mg
chlorphenamine hydrogen maleate	100 mg
chlorpromazine hydrochloride	100 mg
chlortalidone	100 mg
chlortetracycline hydrochloride	200 mg
cimetidine	100 mg
clomifene citrate	100 mg
clomifene citrate Z-isomer (zuclomifene)	50 mg
cloxacillin sodium	200 mg
colecalfiferol (vitamin D ₃)	500 mg
cortisone acetate	100 mg

<i>Reference substance</i>	<i>Package size</i>
dapsone	100 mg
desoxycortone acetate	100 mg
dexamethasone	100 mg
dexamethasone acetate	100 mg
diazepam	100 mg
diazoxide	100 mg
dicloxacillin sodium	200 mg
dicolinium iodide	100 mg
dicoumarol	100 mg
diethylcarbamazine dihydrogen citrate	100 mg
digitoxin	100 mg
digoxin	100 mg
<i>N,N'</i> -di-(2,3-xylyl)anthranilamide	50 mg
emetine hydrochloride	100 mg
4-epianhydrotetracycline hydrochloride	25 mg
4-epitetracycline ammonium salt	25 mg
ergocalciferol (vitamin D ₂)	500 mg
ergometrine hydrogen maleate	50 mg
ergotamine tartrate	50 mg
erythromycin	250 mg
estradiol benzoate	100 mg
estrone	100 mg
etacrynic acid	100 mg
ethambutol hydrochloride	100 mg
ethinylestradiol	100 mg
ethisterone	100 mg
ethosuximide	100 mg
etocarlide	100 mg
flucytosine	100 mg
fluorouracil	100 mg
fluphenazine decanoate dihydrochloride	100 mg
fluphenazine enantate dihydrochloride	100 mg
fluphenazine hydrochloride	100 mg
folic acid	100 mg
3-formylrifamycin	200 mg
furosemide	100 mg
griseofulvin	200 mg
haloperidol	100 mg
hydrochlorothiazide	100 mg
hydrocortisone	100 mg
hydrocortisone acetate	100 mg
(-)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine	25 mg

<i>Reference substance</i>	<i>Package size</i>
ibuprofen	100 mg
imipramine hydrochloride	100 mg
indometacin	100 mg
<i>o</i> -iodohippuric acid	100 mg
isoniazid	100 mg
lanatoside C	100 mg
levodopa	100 mg
levothyroxine sodium	100 mg
lidocaine	100 mg
lidocaine hydrochloride	100 mg
mefenamic acid	100 mg
melting point reference substances (set of 13 substances with melting temperatures ranging from +69°C to +263°C)	13 × 4 g
metazide	100 mg
methaqualone	100 mg
methyl dopa	100 mg
methyltestosterone	100 mg
meticillin sodium	200 mg
metronidazole	100 mg
nafcillin sodium	200 mg
neostigmine metilsulfate	100 mg
nicotinamide	100 mg
nicotinic acid	100 mg
niridazole	200 mg
niridazole-chlorethylcarboxamide	25 mg
norethisterone	100 mg
norethisterone acetate	100 mg
nystatin	200 mg
ouabain	100 mg
oxacillin sodium	200 mg
oxytetracycline dihydrate	200 mg
oxytetracycline hydrochloride	200 mg
papaverine hydrochloride	100 mg
pheneticillin potassium	200 mg
phenoxymethylpenicillin	200 mg
phenoxymethylpenicillin calcium	200 mg
phenoxymethylpenicillin potassium	200 mg
phenytoin	100 mg

<i>Reference substance</i>	<i>Package size</i>
prednisolone	100 mg
prednisolone acetate	100 mg
prednisone	100 mg
prednisone acetate	100 mg
procaine hydrochloride	100 mg
procarbazine hydrochloride	100 mg
progesterone	100 mg
propicillin potassium	200 mg
propranolol hydrochloride	100 mg
propylthiouracil	100 mg
pyridostigmine bromide	100 mg
reserpine	100 mg
riboflavin	250 mg
rifampicin	200 mg
rifampicin quinone	200 mg
sodium cromoglicate	100 mg
sulfamethoxazole	100 mg
sulfamethoxypyridazine	100 mg
sulfanilamide	100 mg
sulfasalazine	100 mg
testosterone propionate	100 mg
tetracycline hydrochloride	200 mg
thioacetazone	100 mg
4,4'-thiodianiline	50 mg
tolbutamide	100 mg
tolnaftate	100 mg
trimethadione	200 mg
trimethoprim	100 mg
trimethylguanidine sulfate	100 mg
tubocurarine chloride	100 mg
vitamin A acetate (solution) (retinol acetate)	5 capsules ¹
warfarin	100 mg

¹ Each containing about 9 mg in 250 mg of oil.

Annex 2

List of available International Infrared Reference Spectra

International Infrared Reference Spectra are established on the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Full-scale reproductions of spectra produced from authenticated material on a suitable instrument are supplied for use in identification tests described in the specifications for quality control of drugs published in *The international pharmacopoeia* or proposed in draft monographs.

Precise instructions for the preparation of spectra are given on the label of each reference spectrum. All International Infrared Reference Spectra are distributed together with a document giving further details on the use of such spectra, entitled "General recommendations for the preparation and use of infrared spectra in pharmaceutical analysis".

Orders for International Infrared Reference Spectra should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteksbolaget AB
Centrallaboratoriet
S-105 14 Stockholm
Sweden

Telex: 115 53 APOBOL S

Fax: 46 8 740 60 40

The following International Infrared Reference Spectra are currently available from the Centre:¹

aceclidine salicylate
acetazolamide
allopurinol
amitriptyline hydrochloride
ampicillin trihydrate

benzylpenicillin potassium
biperiden
biperiden hydrochloride
bupivacaine hydrochloride

caffeine (anhydrous)
chlorphenamine hydrogen maleate
clofazimine
cloxacillin sodium
cytarabine

¹ Spectra for several other substances are still being validated and are not yet available for distribution.

dextromethorphan hydrobromide
diazepam
dicolinium iodide
dicoumarol
diethylcarbamazine dihydrogen citrate
diphenoxylate hydrochloride
erythromycin ethylsuccinate
etacrylic acid
ethionamide
ethosuximide
furosemide
gallamine triethiodide
haloperidol
hydrochlorothiazide
ibuprofen
imipramine hydrochloride
indometacin
isoniazid
lidocaine
lidocaine hydrochloride
lindane
metronidazole
miconazole nitrate
niclosamide
nicotinamide
noscipine
oxamniquine
papaverine hydrochloride
phenobarbital
phenoxymethylpenicillin calcium
phenytoin
primaquine phosphate
propylthiouracil
protionamide
pyrimethamine
sulfadimidine
sulfamethoxazole
sulfamethoxypyridazine
tiabendazole
trihexyphenidyl hydrochloride
trimethoprim
verapamil hydrochloride

Annex 3

Good manufacturing practices for biological products¹

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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.

¹ Previously published in: *WHO Expert Committee on Biological Standardization. Forty-second Report*. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 822).

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 working 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 killed 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 within 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 care¹**

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 clothing, 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).

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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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.

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3. *Laboratory biosafety manual*, 2nd ed. Geneva, World Health Organization, 1993.
4. *Quality management for chemical safety testing.* Geneva, World Health Organization, 1992 (Environmental Health Criteria, No. 141).
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