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Geneva, 21–25 April 1997

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1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 21 to 25 April 1997. The Director-General of WHO, Dr Hiroshi Nakajima, in his keynote address to open the meeting, stressed the need for continued international support to developing countries for ensuring drug quality. In a rapidly changing world, the globalization of economic forces, the expansion of travel and trade, and the trend towards privatization, together with new technologies, changing life-styles, and demographic shifts, had immediate implications for public health. In response, WHO had been engaged since 1995 in a revision of its health-for-all strategy. The goal of health for all in the 21st century presented WHO and its partners with an unprecedented challenge. It would be of the utmost importance for WHO to maintain its normative role if it was to meet the needs and expectations of its Member States. In addition, WHO would have to concentrate its resources on targeted areas of health work: essential drugs, for example, were recognized as having a high priority. Developing countries, in particular, would need international support in assuring drug and vaccine quality. WHO's normative activities had become increasingly important to its Member States as they strived towards regional and global harmonization of standards for production, quality control, safety, certification, and trade in pharmaceuticals and biologicals. WHO guidelines and publications were thus a valuable resource for countries establishing and strengthening their own regulatory systems. The goal of the Expert Committee was to maximize the value and availability of these resources. There was an increased need for the exchange of information and for harmonization at an international level, and for the appropriate use of available technical expertise within countries.

At the World Health Assembly in 1996, concern had been expressed about persistent problems in ensuring the quality of medicines. The Assembly had urged Member States to support mechanisms for monitoring and controlling the efficacy, quality and safety of drugs. In particular, the growing incidence of production, distribution and sale of counterfeit, spurious or substandard pharmaceutical products in developed and developing countries was a matter of concern for WHO. The Assembly had also called on WHO in resolution WHA49.14 "to continue the development, harmonization and promotion of standards to enhance drug regulatory and quality control mechanisms" and "to promote vigorously the use of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce".

The Director-General informed the participants that quality assurance had been extensively discussed at the Eighth International Conference of Drug Regulatory Authorities held in November 1996 in Manama, Bahrain. Those discussions showed clearly that WHO normative guidelines were appreciated throughout the world. The Conference had also reviewed progress made in the international harmonization of regulatory requirements, and collaboration between WHO and the International Conference on Harmonisation (ICH). WHO had participated as an observer since the establishment of the ICH process in 1990. WHO's objective in doing so was to provide a bridge between the 17 countries actively involved in the ICH process and the rest of WHO's Member States. As the World Health Assembly had asserted in May 1992 in resolution WHA45.28, WHO's role was to ensure that harmonization benefited all concerned.

2. *The international pharmacopoeia* and related issues

2.1 Quality specifications for drug substances and dosage forms

The Committee received a report of a worldwide survey on the use of *The international pharmacopoeia*, and noted with satisfaction its widespread use in virtually all areas of the world. The report clearly indicated that *The international pharmacopoeia* plays a major role in defining the specifications of pharmaceutical products. It also provides a valuable tool in the quality assurance of imported products. It was suggested that manufacturers in exporting countries should be encouraged to include an indication of compliance with *The international pharmacopoeia*, wherever appropriate, in the product information, to make it easier for developing countries to check the quality of imported products.

The Committee was informed that Volume 5 of *The international pharmacopoeia* would shortly be submitted for publication. Monographs for Volume 6 were in preparation. In cases where there was insufficient information from official sources, the monographs would be prepared with the assistance of pharmaceutical manufacturers.

Texts on general methods to be included in *The international pharmacopoeia* were approved for bacterial endotoxins, the visual inspection of particulate matter and extractable volume for parenteral preparations, and guidelines on the microbial purity of pharmaceutical preparations. It was noted that revision of some pharmacopoeial monographs would be necessary to replace the test for pyrogens with

that for bacterial endotoxins. It was also suggested that guidelines for using this test might be developed. It was emphasized that the test for visual inspection of particulate matter was intended to provide a simple procedure for the independent assessment of parenteral solutions; it was not intended for use by a manufacturer for batch release purposes, which require more rigorous controls.

The Committee confirmed the need to continue to base the requirements of *The international pharmacopoeia* on reliable but simple methods widely available in small control laboratories. While recognizing the need to continue with work on new monographs, in particular to cover drugs included in the WHO Model List of Essential Drugs (*1*), both for pharmaceutical substances and dosage forms, the Committee agreed that revision of published texts was also important.

The Committee agreed that, as a matter of high priority, collaborative work should be carried out to establish dissolution requirements, details of test conditions, and acceptance criteria for the monographs previously identified as needing such requirements. It was confirmed that this selective approach was appropriate. Other aspects of dissolution testing were discussed in relation to multisource pharmaceutical products (see section 7.3).

It was suggested that monographs on important excipients in addition to the ones published in Volume 4 (*2*) should be prepared for inclusion in *The international pharmacopoeia.*

2.2 Simple test methodology

The Committee noted that a third volume to complement *Basic tests for pharmaceutical substances* and *Basic tests for pharmaceutical dosage forms* (*3*, *4*) was in the process of publication. This volume would include references to other publications and documents, including some alternative tests based mainly on thin-layer chromatography and other simple methods. Work was continuing on the development of additional simple tests.

It was stressed that the basic tests should not be regarded as suitable or intended for use only in developing countries, but should be used more widely as quick testing methods as part of the preliminary screening of suspected counterfeit, spurious or substandard pharmaceutical products at various points such as ports of entry. It was suggested that some reference should be made in *The international pharmacopoeia* to the basic tests being complementary to, but not substitutes for, pharmacopoeial tests.

The Committee noted that Volumes 1–4 of *The international pharmacopoeia* (*2*, *5*, *6*, *7*) and both publications of basic tests (*3*, *4*) had already been published in English, French and Spanish. It recommended that the possibility of publishing them in other languages, including Russian, should be explored.

3. International Chemical Reference Substances and Infrared Reference Spectra

The Committee was informed that lists of reference substances and infrared reference spectra for pharmacopoeial use were now available on the Internet, which should increase international awareness (accessible through: http://www.who.ch/programmes/dmp/docftp.htm).

3.1 Establishment of International Chemical Reference Substances

Twenty-eight new International Chemical Reference Substances[1] were adopted by the Committee according to the procedure described in the thirty-second report (*8*). It was reported that the depleted stock of benzil, a melting point reference substance, had been replaced with a new batch. The total collection now comprises 193 chemical reference substances and 12 melting point reference substances (Annex 1). The Committee was informed that, in accordance with the general guidelines for the establishment, maintenance and distribution of chemical reference substances (see section 3.4 and Annex 3) and the principles of good manufacturing practices (GMP), each International Chemical Reference Substance would now be accompanied by a signed certificate.

It was suggested that, to avoid unnecessary delays in making newly established chemical reference substances available, a procedure of approval by correspondence might be considered as an interim measure between meetings of the Committee.

The Committee expressed its appreciation to the WHO Collaborating Centre for Chemical Reference Substances for its work and to the

[1] Amidotrizoic acid, 3-amino-2,4,6-triiodobenzoic acid, benzil, betamethasone sodium phosphate, calcium folinate, chloroquine sulfate, doxorubicin hydrochloride, erythromycin B, erythromycin C, flucloxacillin sodium, fludrocortisone acetate, gentamicin sulfate, hydrocortisone sodium succinate, levonorgestrel, loperamide hydrochloride, mebendazole, methotrexate, nifurtimox, paracetamol, paromomycin sulfate, praziquantel, prednisolone hemisuccinate, prednisolone sodium phosphate, sulfacetamide, tamoxifen citrate, tamoxifen citrate *E*-isomer, testosterone enantate, toluene-2-sulfonamide.

National Corporation of Swedish Pharmacies for its continued financial support to the WHO programme on International Chemical Reference Substances.

3.2 International Infrared Reference Spectra

The Committee adopted 7 new International Infrared Reference Spectra.[1] A total of 69 spectra are now available from the WHO Collaborating Centre for Chemical Reference Substances, Stockholm, Sweden (Annex 2). The contribution of the WHO Collaborating Centre for International Infrared Reference Spectra, Zurich, Switzerland, which prepares the spectra, was acknowledged. It was suggested that consideration might also be given to the publication of the spectra separately, in reduced form, to accompany *The international pharmacopoeia.*

3.3 Use of International Chemical Reference Substances and Infrared Reference Spectra

The results of a questionnaire on the use of International Chemical Reference Substances and Infrared Reference Spectra were reported to the Committee. The majority of the answers came from national quality control laboratories (40.4%), pharmaceutical manufacturers (22.6%) and teaching and research institutions (19.8%). It was noted that the substances are mainly used as primary standards to calibrate working standards, but also to some extent directly as working standards. This probably reflects a single or infrequent use where it is not sensible to prepare a secondary standard. The Committee recommended that the WHO Collaborating Centre for Chemical Reference Substances should conduct a follow-up exercise and report on its results at the next meeting of the Expert Committee.

3.4 Guidelines for the establishment, maintenance and distribution of chemical reference substances

Revised general guidelines for the establishment, maintenance and distribution of chemical reference substances were presented with the intention of replacing the previous guidelines adopted in 1975 (*9*). Developments in advanced analytical methodology and GMP had been taken into account. The Committee adopted the guidelines, which are attached to this report as Annex 3.

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[1] Amiloride hydrochloride, beclometasone dipropionate, calcium folinate, carbidopa, dexamethasone, dexamethasone acetate monohydrate, valproic acid.

4. Quality control — national laboratories

4.1 Good laboratory practices in government drug quality control laboratories

The Committee agreed that it was time to revise the guidelines that were published in 1987 as Annex 1 to its thirtieth report (*10*). In revising the guidelines, it would be necessary to state that the document is meant for use mainly in official drug control laboratories, to avoid confusion with laboratory practices for use in toxicological and environmental laboratories. The revised guidelines would use the term "good control laboratory practices" and would make reference to any supplementary training materials that were available. The Committee encouraged the Secretariat to undertake the revision in consultation with those present at the Committee's meeting, taking account of the *Recommendations on a quality system for official medicines control laboratories* published by the Pharmaceutical Inspection Convention (PIC) (*11*).

4.2 Information on external quality assessment

The Committee recognized that national drug control laboratories, especially in developing countries, need assistance in carrying out external assessment of analytical results. Offers of assistance from well-established laboratories were welcomed and it was agreed that the experience gained by the European Official Control Laboratories and the International Pharmaceutical Federation (FIP) Section for Official Laboratories and Medical Control Services would provide a useful basis for establishing a proficiency testing service.

It was agreed that such an external quality assessment should be seen as occurring in conjunction with any ongoing internal quality assurance projects, and that the methodologies assessed should include all those used for the detection of counterfeit, spurious or substandard pharmaceuticals.

5. Good manufacturing practices

5.1 Adoption of additional guidelines

The Committee adopted two supplements to the GMP guidelines published as Annex 1 to its thirty-second report (*8*); these texts provide additional advice on the role, functions and training of the "authorized person" (Annex 4), and on the manufacture of pharmaceutical excipients (Annex 5). In adopting the guidelines on the authorized person, the Committee emphasized that this text did not

represent additional requirements in the area of GMP. It was offered as advice to manufacturers wishing to strengthen their existing quality assurance systems.

5.2 Good manufacturing practices for sterile products

Members agreed that the section of the GMP guidelines (*8*) dealing with sterile products (section 17) required revision, and offered advice to the Secretariat on a number of technical points. It was agreed that the section needed restructuring to reflect the format of the main guidelines.

5.3 Relationship between pharmacopoeial requirements and manufacturers' internal specifications

Members of the Committee generally endorsed the need to develop a document explaining the role of pharmacopoeial requirements and their place in the overall system of quality assurance. Provision of such interpretative guidance was intended to facilitate dialogue between manufacturers and regulatory authorities.

WHO might consider whether it could offer more detailed guidance on the development of manufacturers' specifications for established products, once ICH had finalized corresponding guidelines on new chemical substances and products of biotechnology.

6. Quality systems and inspection

6.1 Quality systems for GMP inspectorates

The Committee noted the draft guidelines prepared by the PIC, *Recommendations on quality system requirements for GMP inspectorates of PIC Contracting States* (*12*), and agreed that WHO guidance in this area would be helpful to complement the guidelines on inspection of pharmaceutical manufacturers. It suggested that the Secretariat should prepare a preliminary document based on that of the PIC.

6.2 Pre-approval inspection

Inspection of manufacturing premises before approval of a marketing authorization for a new medicinal product is intended to contribute to an assurance of the product quality. The Committee was pleased to note that a first draft of provisional guidelines on pre-approval inspection had been prepared, and agreed that these should be further developed. The emphasis should be on guidance relevant to inspections carried out by small- to medium-sized drug regulatory authorities, particularly for pharmaceuticals manufactured domestically.

6.3 Guidelines for inspection of drug distribution channels

In adopting guidelines for the inspection of drug distribution channels (Annex 6), the Committee recognized the need for such inspection to assure the drug regulatory authorities of the quality of medicines from the point of manufacture to their ultimate delivery to a patient. In addition, the Committee recognized the significance of appropriate advice on the detection of counterfeit, spurious or substandard pharmaceuticals (see also section 9.2).

6.4 Use of simple test methods by inspectors

The Committee recognized that simple test methods are useful tools when monitoring the quality of drugs in the distribution chain, especially in screening for counterfeit, spurious and substandard pharmaceuticals. The document *Considerations on the use of simple test methods to detect counterfeit pharmaceutical products* (*13*) was endorsed.

7. Other quality assurance topics

7.1 Compendia

The Committee took note of the progress in collating different guidelines on quality assurance adopted at previous meetings. The first volume of a combined publication (compendium) was in press,[1] and a second volume, containing material on GMP and inspection, was in preparation.

7.2 Packaging for pharmaceutical products

The Committee was informed of work being carried out on proposed guidelines on packaging components and materials used for pharmaceutical products. It considered that guidance in this area would complement other guidelines on quality control, stability and GMP. The Secretariat was encouraged to continue this activity.

7.3 Multisource pharmaceutical products

The Committee noted with satisfaction the progress that had been made in developing a system for the selection of comparator products in support of the guidance on registration requirements to establish interchangeability for multisource (generic) pharmaceutical products, published in the report of the thirty-fourth meeting (*14*). The Secre-

[1] *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Volume 1.* Geneva, World Health Organization, 1997.

tariat was encouraged to pursue this initiative, in particular concerning international comparator products, taking account of a variety of approaches under current scientific and regulatory discussion. The development of a biopharmaceutical classification system using solubility, dissolution and permeability factors might provide a useful tool to determine when *in vivo* studies were needed or not (see also section 2.1).

7.4 Guidelines for good pharmacy practice

The Committee took note of a revised version of a text on good pharmacy practice in community and hospital pharmacy settings, which takes into account the comments offered by the Committee on the initial version adopted by the FIP Congress in 1993 and reflected in its previous report. The Committee strongly supported the revised guidelines, which are reproduced in Annex 7. It recommended that WHO should assist countries in developing their own national standards for good pharmacy practice.

8. Nomenclature and terminology

8.1 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. Since it last met 230 new names have been published as proposed INNs, and 270 names have reached recommended INN status. A new edition of the cumulative list of INNs was published at the end of 1996 (*15*), and guidelines on the use and application of INNs are nearing completion. The Committee was also pleased to note that, following publication in the thirty-fourth report (*14*) of guidelines for the graphic representation of chemical formulae, a further document giving more detailed advice on drawing structures had been prepared and was available on request (*16*). This document applied to chemical entities included in both INN publications and *The international pharmacopoeia.*

8.2 Terminology

The Committee noted progress made with the compilation of a list of key terms related to drug quality assurance, together with their definitions. Subject to the additions and amendments proposed by the Committee, the Secretariat will prepare a revised document for wider circulation. In order to facilitate the receipt of comments the use of

Internet-based electronic tools was encouraged whenever possible. The usual consultation procedures will, however, continue in order to ensure optimum participation in the consultative process. The Committee emphasized the importance of taking into account ongoing activities on the international harmonization of terminology. The Committee was informed that standard terms relating to pharmaceutical dosage forms were published by the Council of Europe (*17*). It noted that WHO had established a list of terms used to describe the pharmacological action and therapeutic use of drugs (*18*), which was available in English, French and Spanish.

9. Legal aspects of pharmaceuticals

9.1 Drug regulatory legislation

The Committee endorsed the text entitled "National drug regulatory legislation — guiding principles for small national drug regulatory authorities", contained in Annex 8, which was the result of a comprehensive consultative process including meetings with experts and interested parties, and correspondence with governments and experts. It acknowledged that the legislative scheme given as an example might reflect a particular legal system, and that countries with other cultural and legal backgrounds might consider different approaches. However, it was convinced that the overall content of the scheme would be relevant to most situations. Although the Committee was aware that legal matters were somewhat outside its mainly scientific and technical expertise, it recognized that legislation was an important basis for drug regulation, and proposed wider dissemination of the guidance by means of this report.

The Committee emphasized that the text was not intended to be translated directly into national legislation, but was to be used as source documentation and adapted as necessary. While it should be of immediate value to many countries still in the process of establishing drug regulatory and legislative systems, other countries might also benefit from such a framework. The Committee recommended that drug regulatory authorities be encouraged to provide WHO with copies of newly adopted or revised legislation. These could be made available to other countries as further examples.

9.2 National implementation guidelines for combating counterfeit pharmaceuticals

The Committee noted that this issue was to be discussed at the forthcoming international workshop on counterfeit pharmaceuticals. It

recognized that advice on the strategies to be used and types of cooperation required at national and international centres was essential to combat counterfeit pharmaceutical products. The active participation of both the pharmaceutical industry and governments to prevent counterfeiting was highlighted (see also sections 6.3, 6.4 and 11.2).

10. Regulatory issues

10.1 WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce

10.1.1 *Finished pharmaceutical products*

The Committee was informed that the guidelines on the scheme relating to pharmaceutical dosage forms, as published in its thirty-fourth report (*14*), were endorsed in Resolution EB99.R21 at the 99th session of the Executive Board in January 1997, and transmitted to the 50th World Health Assembly for adoption.[1] The resolution urges Member States to implement the guidelines. Thus, importing countries should request and exporting countries should issue WHO-type product certificates as from 1 January 1998. The Committee was also informed about discussions on the scheme during the eighth International Conference of Drug Regulatory Authorities held in Bahrain in 1996. The reports given at the conference demonstrated that the use of the scheme was steadily increasing and that some regulatory authorities, including the European Medicines Evaluation Agency, were already issuing WHO-type product certificates in the revised format as published in the thirty-fourth report (*14*).

10.1.2 *Active pharmaceutical ingredients*

A status report was provided about the development of guidelines for the certification of active pharmaceutical ingredients. In the light of recent initiatives at national and regional levels to extend regulatory control to starting materials, both active ingredients and excipients, the Committee recommended that such developments should be closely followed since they would be of direct relevance to the further development of the WHO certification guidelines.

10.2 WHO model system for computer-assisted drug registration

The Committee noted that a computer-assisted system (*19*) had been developed to assist small national drug regulatory authorities to monitor their own registration activities more easily.

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[1] Subsequently adopted as WHA50.3, May 1997.

The flexible model package had been designed to accommodate a wide range of registration systems. Initial training and continued assistance in use of the model package were being developed on a regional basis.

10.3 Model guidelines for the international provision of controlled medicines for emergency medical care

The Committee was pleased to note that international agreement had been reached on guidelines (*20*) to promote the rapid provision of controlled drugs in emergencies. Some countries have already implemented these guidelines on a trial basis.

11. Training activities

11.1 Training programmes for drug regulators and related activities

The Committee was informed of the wide diversity of relevant training activities in which WHO, through its Division of Drug Management and Policies, had been involved. These activities include the following:

- Individual training in drug regulatory agencies in more advanced countries.
- Regional training seminar on the technical assessment of dossiers for marketing authorization, organized by the German Foundation for International Development (DSE).
- Seminar on quality assurance for drug regulators, organized by the International Federation of Pharmaceutical Manufacturers Association (IFPMA).
- Individual training for analysts and inspectors, offered by the IFPMA and the World Federation of Proprietary Medicine Manufacturers.
- Regional seminar on GMP, organized by FIP in cooperation with the West African Pharmaceutical Federation.
- Training in the use of the WHO model package designed to support computer-assisted drug registration.
- The 12-month Master of Science course in pharmaceutical services and medicines control, Bradford, England, targeted primarily at pharmacists working in the public sector in developing countries and also at the newly independent States of the former Soviet Union.

WHO's Regional Offices and its Action Programme on Essential Drugs are involved in training activities for drug regulators, often through the relevant WHO Collaborating Centres.

The Committee was also informed about a recently created one-year university programme on the development and international registration of medicines at the Faculty of Pharmacy of the University of Paris-Sud, France.

11.2 Training programmes for the detection of counterfeit pharmaceutical products

The Committee approved provisional guidelines for developing training programmes of inspection and examination for counterfeit pharmaceuticals (Annex 9). It recognized that a competent regulatory staff is essential for the detection and prevention of counterfeit, spurious and substandard pharmaceuticals. Education and training programmes for the detection of counterfeit pharmaceutical products must be designed and implemented efficiently and effectively within the countries' quality assurance programmes for pharmaceuticals.

12. Pharmaceuticals contaminated with diethylene glycol

The Committee discussed the cumulative incidence of diethylene glycol poisoning over the past 60 years, which has resulted in over 500 deaths of patients worldwide where glycerol contaminated deliberately or accidentally with diethylene glycol, or diethylene glycol alone, had been used in manufacturing pharmaceutical products. This continuing problem underlined the importance of ensuring quality and safety in the manufacture of medicinal products. The Committee agreed that there is no valid substitute for vigorous implementation of GMP in the production of pharmaceuticals. It proposed, however, that international measures such as special labelling and/or other identification methods for diethylene glycol should be considered, to avoid its use in the manufacture of pharmaceutical products. Moreover, the Committee recommended that WHO take active leadership in identifying ways of preventing further deaths from this cause.

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Annex 1
List of available International Chemical Reference Substances[1]

International Chemical Reference Substances (ICRS) 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. The ICRS are mainly intended to be used as primary standards to calibrate secondary standards.

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

ICRS 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 this use.

It is generally recommended that the substances should 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. It is recommended that the user purchase only an amount sufficient for immediate use.

The stability of the ICRS kept at the Collaborating Centre is monitored by regular re-examination, and any material that has deteriorated is replaced by new batches when necessary. Lists giving control numbers for the current batches are issued in the annual reports from the Centre and new yearly lists may also be obtained on request.

[1] As updated at the thirty-fifth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, 21–25 April 1997.

Orders for the ICRS should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteket AB
Produktion & Laboratorier Centrallaboratoriet, ACL
Prismavägen 2
S-141 75 Kungens Kurva
Sweden
(Telefax: +46 8 740 60 40)

The ICRS are supplied only in the standard packages indicated in the following list:

Reference substance	*Package size*	*Control number*
aceclidine salicylate	100 mg	172048
p-acetamidobenzalazine	100 mg	290042
acetazolamide	100 mg	186128
allopurinol	100 mg	287049
amidotrizoic acid	100 mg	196205
2-amino-5-nitrothiazole	25 mg	186131
3-aminopyrazole-4-carboxamide hemisulfate	100 mg	172050
3-amino-2,4,6-triiodobenzoic acid	100 mg	196206
amitriptyline hydrochloride	100 mg	181101
amodiaquine hydrochloride	200 mg	192160
amphotericin B	400 mg	191153
ampicillin (anhydrous)	200 mg	390001
ampicillin sodium	200 mg	388002
ampicillin trihydrate	200 mg	274003
anhydrotetracycline hydrochloride	25 mg	180096
atropine sulfate	100 mg	183111
azathioprine	100 mg	172060
bacitracin zinc	200 mg	192174
beclometasone dipropionate	200 mg	192175
bendazol hydrochloride	100 mg	173066
benzobarbital	100 mg	172051
benzylamine sulfate	100 mg	172052
benzylpenicillin potassium	200 mg	180099
benzylpenicillin sodium	200 mg	280047
bephenium hydroxynaphthoate	100 mg	183112
betamethasone	100 mg	183113
betamethasone sodium phosphate	100 mg	196203
betamethasone valerate	100 mg	190145
betanidine sulfate	100 mg	172053
bupivacaine hydrochloride	100 mg	289054

Reference substance	*Package size*	*Control number*
caffeine	100 mg	181102
calcium folinate (leucovorin calcium)	100 mg	194188
carbamazepine	100 mg	189143
carbenicillin monosodium	200 mg	383043
chloramphenicol	200 mg	486004
chloramphenicol palmitate	1 g	286072
chloramphenicol palmitate (polymorph A)	200 mg	175073
5-chloro-2-methylaminobenzophenone	100 mg	172061
chloroquine sulfate	200 mg	195201
2-(4-chloro-3-sulfamoylbenzoyl)benzoic acid	50 mg	181106
chlorphenamine hydrogen maleate	100 mg	182109
chlorpromazine hydrochloride	100 mg	178080
chlortalidone	100 mg	183114
chlortetracycline hydrochloride	200 mg	187138
cimetidine	100 mg	190150
clomifene citrate	100 mg	187136
clomifene citrate *Z*-isomer *see* zuclomifene		
cloxacillin sodium	200 mg	274005
colecalciferol (vitamin D_3)	500 mg	190146
cortisone acetate	100 mg	167006
dapsone	100 mg	183115
desoxycortone acetate	100 mg	167007
dexamethasone	100 mg	388008
dexamethasone acetate	100 mg	288009
dexamethasone phosphoric acid	100 mg	192161
dexamethasone sodium phosphate	100 mg	192158
diazepam	100 mg	172062
diazoxide	100 mg	181103
dicloxacillin sodium	200 mg	174071
dicolinium iodide	100 mg	172055
dicoumarol	100 mg	178077
diethylcarbamazine dihydrogen citrate	100 mg	181100
digitoxin	100 mg	277010
digoxin	100 mg	587011
N,*N*′-di-(2,3-xylyl)anthranilamide	50 mg	173067
dopamine hydrochloride	100 mg	192159
doxorubicin hydrochloride	100 mg	196202
emetine hydrochloride	100 mg	187134
4-epianhydrotetracycline hydrochloride	25 mg	288097
4-epitetracycline hydrochloride	25 mg	293098

Reference substance	*Package size*	*Control number*
ergocalciferol (vitamin D_2)	500 mg	190147
ergometrine hydrogen maleate	50 mg	277012
ergotamine tartrate	50 mg	385013
erythromycin	250 mg	191154
erythromycin B	150 mg	194186
erythromycin C	25 mg	194187
estradiol benzoate	100 mg	167014
estrone	100 mg	279015
etacrynic acid	100 mg	281056
ethambutol hydrochloride	100 mg	179081
ethinylestradiol	100 mg	291016
ethisterone	100 mg	167017
ethosuximide	100 mg	179088
etocarlide	100 mg	172057
flucloxacillin sodium	200 mg	195194
flucytosine	100 mg	184121
fludrocortisone acetate	200 mg	195199
fluorouracil	100 mg	184122
fluphenazine decanoate dihydrochloride	100 mg	182107
fluphenazine enantate dihydrochloride	100 mg	182108
fluphenazine hydrochloride	100 mg	176076
folic acid	100 mg	388019
3-formylrifamycin	200 mg	190149
framycetin sulfate (neomycin B sulfate)	200 mg	193178
furosemide	100 mg	171044
gentamicin sulfate	100 mg	194183
griseofulvin	200 mg	280040
haloperidol	100 mg	172063
hydrochlorothiazide	100 mg	179087
hydrocortisone	100 mg	283020
hydrocortisone acetate	100 mg	280021
hydrocortisone sodium succinate	200 mg	194184
(–)-3-(4-hydroxy-3-methoxyphenyl)-2-hydrazino-2-methylalanine (3-*O*-methylcarbidopa)	25 mg	193180
(–)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine (3-*O*-methylmethyldopa)	25 mg	179085
ibuprofen	100 mg	183117
imipramine hydrochloride	100 mg	172064

Reference substance	*Package size*	*Control number*
indometacin	100 mg	178078
o-iodohippuric acid	100 mg	171045
isoniazid	100 mg	185124
lanatoside C	100 mg	281022
levodopa	100 mg	295065
levonorgestrel	200 mg	194182
levothyroxine sodium	100 mg	189144
lidocaine	100 mg	181104
lidocaine hydrochloride	100 mg	181105
liothyronine sodium	50 mg	193179
loperamide hydrochloride	100 mg	194185
mebendazole	200 mg	195195
mefenamic acid	100 mg	173068
melting point reference substances		
azobenzene (69 °C)	4 g	192168
vanillin (83 °C)	4 g	192169
benzil (96 °C)	4 g	294170
acetanilide (116 °C)	4 g	192171
phenacetin (136 °C)	4 g	192172
benzanilide (165 °C)	4 g	192173
sulfanilamide (166 °C)	4 g	192162
sulfapyridine (193 °C)	4 g	192163
dicyanodiamide (210 °C)	4 g	192164
saccharin (229 °C)	4 g	192165
caffeine (237 °C)	4 g	192166
phenolphthalein (263 °C)	4 g	192167
metazide	100 mg	172058
methaqualone	100 mg	173069
methotrexate	100 mg	194193
methyldopa	100 mg	179084
methyltestosterone	100 mg	167023
meticillin sodium	200 mg	274024
metronidazole	100 mg	183118
nafcillin sodium	200 mg	272025
neamine hydrochloride (neomycin A hydrochloride)	0.5 mg	193177
neomycin B sulfate *see* framycetin sulfate		
neostigmine metilsulfate	100 mg	187135
nicotinamide	100 mg	179090
nicotinic acid	100 mg	179091

Reference substance	*Package size*	*Control number*
nifurtimox	100 mg	194189
niridazole	200 mg	186129
niridazole-chlorethylcarboxamide	25 mg	186130
norethisterone	100 mg	186132
norethisterone acetate	100 mg	185123
nystatin	200 mg	191152
ouabain	100 mg	283026
oxacillin sodium	200 mg	382027
oxytetracycline dihydrate	200 mg	189142
oxytetracycline hydrochloride	200 mg	189141
papaverine hydrochloride	100 mg	185127
paracetamol	100 mg	195198
paromomycin sulfate	75 mg	195197
pheneticillin potassium	200 mg	167028
phenoxymethylpenicillin	200 mg	179082
phenoxymethylpenicillin calcium	200 mg	179083
phenoxymethylpenicillin potassium	200 mg	176075
phenytoin	100 mg	179089
praziquantel	100 mg	194191
prednisolone	100 mg	389029
prednisolone acetate	100 mg	289030
prednisolone hemisuccinate	200 mg	195196
prednisolone sodium phosphate	200 mg	194190
prednisone	100 mg	167031
prednisone acetate	100 mg	169032
probenecid	100 mg	192156
procaine hydrochloride	100 mg	183119
procarbazine hydrochloride	100 mg	184120
progesterone	100 mg	167033
propicillin potassium	200 mg	274034
propranolol hydrochloride	100 mg	187139
propylthiouracil	100 mg	185126
pyrantel embonate (pyrantel pamoate)	500 mg	192157
pyridostigmine bromide	100 mg	182110
reserpine	100 mg	186133
retinol acetate (solution)	5 capsules[1]	791038
riboflavin	250 mg	382035

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

Reference substance	*Package size*	*Control number*
rifampicin	200 mg	191151
rifampicin quinone	200 mg	190148
sodium cromoglicate	100 mg	188140
spectinomycin hydrochloride	200 mg	193176
sulfacetamide	100 mg	196200
sulfamethoxazole	100 mg	179092
sulfamethoxypyridazine	100 mg	178079
sulfanilamide	100 mg	179094
sulfasalazine	100 mg	191155
tamoxifen citrate	100 mg	196208
tamoxifen citrate *E*-isomer	10 mg	196209
testosterone enantate	200 mg	194192
testosterone propionate	100 mg	167036
tetracycline hydrochloride	200 mg	180095
thioacetazone	100 mg	171046
4,4′-thiodianiline	50 mg	183116
thyroxine sodium *see* levothyroxine sodium		
tolbutamide	100 mg	179086
tolnaftate	100 mg	176074
toluene-2-sulfonamide	100 mg	196204
trimethadione	200 mg	185125
trimethoprim	100 mg	179093
trimethylguanidine sulfate	100 mg	172059
tubocurarine chloride	100 mg	170037
vincristine sulfate	9.7 mg/vial	193181
vitamin A acetate (solution) *see* retinol acetate (solution)		
warfarin	100 mg	168041
zuclomifene	50 mg	187137

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Annex 2
List of available International Infrared Reference Spectra[1]

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".[2]

Orders for International Infrared Reference Spectra should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteket AB
Produktion & Laboratorier Centrallaboratoriet, ACL
Prismavägen 2
S-141 75 Kungens Kurva
Sweden
(Telefax: +46 8 740 60 40)

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

aceclidine salicylate
acetazolamide
allopurinol
amiloride hydrochloride
amitriptyline hydrochloride
ampicillin trihydrate

[1] As updated at the thirty-fifth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, 21–25 April 1997.

[2] *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996, Annex 4 (WHO Technical Report Series, No. 863).

beclometasone dipropionate
benzylpenicillin potassium
biperiden
biperiden hydrochloride
bupivacaine hydrochloride

caffeine (anhydrous)
calcium folinate
carbidopa
chlorphenamine hydrogen maleate
clofazimine
cloxacillin sodium
colchicine
cytarabine

dexamethasone
dexamethasone acetate, monohydrate
dextromethorphan hydrobromide
diazepam
dicolinium iodide
dicoumarol
diethylcarbamazine dihydrogen citrate
diphenoxylate hydrochloride

erythromycin ethylsuccinate
erythromycin stearate
etacrynic acid
ethionamide
ethosuximide

furosemide

gallamine triethiodide
glibenclamide

haloperidol
hydrochlorothiazide

ibuprofen
imipramine hydrochloride
indometacin
isoniazid

lidocaine
lidocaine hydrochloride
lindane

metronidazole
miconazole nitrate

niclosamide
nicotinamide
noscapine

oxamniquine

papaverine hydrochloride
phenobarbital
phenoxymethylpenicillin calcium
phenytoin
primaquine phosphate
propylthiouracil
protionamide
pyrimethamine

salbutamol
salbutamol sulfate
sulfadimidine
sulfadoxine
sulfamethoxazole
sulfamethoxypyridazine

tiabendazole
trihexyphenidyl hydrochloride
trimethoprim

valproic acid
verapamil hydrochloride

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Annex 3
General guidelines for the establishment, maintenance and distribution of chemical reference substances

Introduction

In 1975, the WHO Expert Committee on Specifications of Pharmaceutical Preparations recommended "General guidelines for the establishment, maintenance and distribution of chemical reference substances" (*1*).[1] At that time these general guidelines were aimed at fostering greater collaboration and harmonization among various national and regional authorities responsible for collections of chemical reference substances. This aim is still relevant. The guidelines were initially drawn up for particular use by the WHO Collaborating Center for Chemical Reference Substances in Sweden, which provides International Chemical Reference Substances (ICRS). These substances are primarily intended for use with pharmacopoeial monographs included in *The international pharmacopoeia* (*2*).

It became evident that in order to meet particular national or regional pharmacopoeial requirements, it was necessary to establish chemical reference substances external to the WHO Collaborating Centre for Chemical Reference Substances. Another difficulty was to ensure prompt dispatch of the substances. Since the meticulous work of the WHO Collaborating Centre establishing the international collection would have to be duplicated in local or regional laboratories, guidelines were necessary to ensure the integrity of national or regional collections. In order to clarify the need for national and regional collections, the 1975 guidelines were reviewed and modified in 1982 (*3*). In view of refinements in pharmaceutical and analytical methods since then, the present revision was considered essential.

The purpose of having chemical reference substances is to achieve accuracy and reproducibility of the analytical results required by pharmacopoeial testing and pharmaceutical control in general. These substances are normally prepared and issued by the regional/national pharmacopoeial commission or the regional/national quality control laboratory on behalf of the drug regulatory authority. In the context of these guidelines, the general use of a chemical reference substance should be considered an integral part of a compliance-oriented monograph or test procedure used to demonstrate the identity, purity and content of pharmaceutical substances and preparations.

The establishment of chemical reference substances should be based on reports in which the results of analytical testing have been evaluated. These reports should subsequently be approved and adopted by

[1] The term *chemical reference substances*, as used in this text, refers to an authenticated uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with the properties of a product under examination, and which possesses a degree of purity adequate for its intended use.

a certifying body, normally the relevant pharmacopoeial committee or the drug regulatory authority. Such establishment can be on an international, national or regional basis. Each substance is generally established for a specific analytical purpose, defined by the issuing body. Its use for any other purpose becomes the responsibility of the user and a suitable caution is included in the information sheet accompanying a reference substance. The present guidelines are concerned with both primary and secondary chemical reference substances as defined below.

The preparation of a chemical reference substance should comply with the requirements for quality assurance systems, including principles of good manufacturing practices (GMP) and good control laboratory practices (*4–6*).

Adequate training programmes are also required. Both the WHO Collaborating Centre and other laboratories concerned with the evaluation and establishment of chemical reference substances give assistance in training, subject to the availability of resources.

Primary chemical reference substance

A designated primary chemical reference substance is one that is widely acknowledged to have the appropriate qualities within a specified context, and whose value is accepted without requiring comparison to another chemical substance.

Secondary chemical reference substance

A secondary chemical reference substance is a substance whose characteristics are assigned and/or calibrated by comparison with a primary chemical reference substance. The extent of characterization and testing of a secondary chemical reference substance may be less than for a primary chemical reference substance. This definition may apply *inter alia* to some substances termed "working standards".

Part A. Primary chemical reference substances

1. Assessment of need for the establishment of chemical reference substances

The production, validation, maintenance and distribution of chemical reference substances is a costly and time-consuming undertaking. It is therefore of great importance to determine critically whether a need for a given substance exists. Requests for new chemical reference substances usually arise when a particular approach to developing a

specification for a new substance or product has been adopted. Methods may have been proposed in a specification that require the establishment of a chemical reference substance for use as a comparative standard. Therefore, the first matter that should be assessed is whether an alternative, equally satisfactory, procedure could be adopted that does not require a comparative standard.

Analytical procedures currently used in specifications for pharmaceutical substances and products that may require a chemical reference substance are:

(a) infrared (IR) spectrophotometry, whether for identification or quantitative purposes;
(b) quantitative methods based on ultraviolet (UV) absorption spectrophotometry;
(c) quantitative methods based on the development of a colour and the measurement of its intensity, whether by instrumental or visual comparison;
(d) methods based on chromatographic separation for identification or quantitative purposes;
(e) quantitative methods (including automated methods) based on other separation techniques that depend on partition of the substance to be determined between solvent phases, where the precise efficiency of the extraction procedure might depend upon ambient conditions that vary from time to time and from laboratory to laboratory;
(f) quantitative methods, often titrimetric but sometimes gravimetric, that are based on non-stoichiometric relationships;
(g) assay methods based on measurement of optical rotation; and
(h) methods that might require a chemical reference substance consisting of a fixed ratio of known components (for example, *cis/trans* isomers, spiked samples).

2. Obtaining source material

Source material of satisfactory quality can be selected from a batch (lot) of the substance originating from the normal production process, if the purity is acceptable. Further purification techniques may be needed to render the material acceptable for use as a chemical reference substance.

The purity requirements for a chemical reference substance depend upon its intended use. A chemical reference substance proposed for an identification test does not require meticulous purification, since the presence of a small percentage of impurities in the substance often has no noticeable effect on the test.

On the other hand, chemical reference substances that are to be used in assays should possess a high degree of purity. As a guiding principle, a purity of 99.5% or higher is desirable, calculated on the basis of the material in its anhydrous form or free of volatile substances. However, where the selectivity of the analytical procedure for which the chemical reference substance is required is low, such a degree of purity may not be necessary. In making a decision about the suitability of a chemical reference substance, the most important consideration is the influence of the impurity on the attribute measured in the assay when used in a non-specific assay procedure. Impurities with physicochemical characteristics similar to those of the main component will not impair the usefulness of a chemical reference substance, whereas even traces of impurities with significantly different properties may render a substance unsuitable as a chemical reference substance.

When source material to be used as a chemical reference substance is obtained from a supplier, the following should be supplied with the material:

- Certificate of analysis with complete information as to test methods employed, values found and number of replicates used, where applicable, and relevant spectra and/or chromatograms.
- Information on optimal storage conditions required for stability (temperature and humidity considerations).
- Results of any hygroscopicity study and/or statement of the hygroscopicity of the source material.
- Results of any accelerated stability studies.
- Identification of detected impurities (by preference), and/or specific information on the relative response factor as determined in compendial methods concerning the principal component, and/or the percentage mass of the impurity.
- Updated Material Safety Data Sheet outlining any health hazards associated with the material.

For new drug substances, manufacturers should be aware that elaboration of pharmacopoeial monographs will be needed and a batch of the new substance should be set aside to be used if necessary as the chemical reference substance. It is desirable for bodies that issue chemical reference substances to provide each other with a sample of the same batch of material, even if the substance will be employed for different test methods. This will require the exchange of information

concerning the establishment process, supplier(s), availability and conditions of supply.

3. Evaluation of chemical reference substances

The suitability of a substance proposed for use as a chemical reference requires careful evaluation by the issuing body. It is necessary to consider all data obtained from testing the material by a wide variety of analytical methods. When taken as a whole, this will ensure that the substance is suitable for its intended use. The extent of the analyses required depends on the purpose(s) for which the chemical reference substance is to be employed, and may involve a number of independent laboratories.

3.1 *Use in identification tests*

For use in identification tests (IR spectrophotometry and/or chromatographic methods), a batch of good quality material selected from the normal production process is satisfactory if it is of acceptable purity. Additional purification by the supplier may be necessary. The most important check is the application of the test(s) for which the substance is intended. It is usual for at least one laboratory to apply all the tests described in the relevant monograph.

3.2 *Use in purity tests*

The characterization of a chemical reference substance used in the determination of a specific impurity is more extensive, especially when used in a limit test. If the technique employed is thin-layer chromatography (TLC) an acceptable minimum purity is recommended (normally at least 90%), but purer material may be required for liquid chromatography (LC) or gas chromatography (GC). If the proposed reference substance is being prepared or isolated for the first time, appropriate chemical and physicochemical tests, such as nuclear magnetic resonance (NMR), mass spectrometry (MS) and elemental analysis, must be applied to characterize it.

3.3 *Use in assays*

If the chemical reference substance is to be used in an assay (colorimetry, LC, GC or UV spectrophotometry), the extent of testing is very much greater. Several (a minimum of three) laboratories should collaborate in testing the proposed substance, using a variety of established and validated techniques, including the method used in the pharmacopoeial specification. The relative reactivity or relative absorbance of the impurities present must be checked when a non-specific assay method is employed, e.g. by colorimetry or UV spectro-

photometry. When a selective assay method is employed, it is particularly important to determine the quantity of impurities. In such a case, it is best to examine the proposed reference substance by as many methods as practicable including, where possible, absolute methods. For substances that are acidic or basic a titration with alkali or acid is simple, but other reactions which are known to be stoichiometric may be used. Phase solubility analysis and differential scanning calorimetry may also be employed in certain cases.

The total of the determinations of water content, organic solvents, mineral impurities and organic components should amount to 100%. For most chemical reference substances intended for assays, the content may be expressed "as is". When establishing the chemical reference substance it is therefore essential to determine the content of water and residual solvents for a non-specific assay, and also to determine the content of impurities for a selective assay.

3.4 *Use in the calibration of an instrument*

Where the chemical reference substance is to be employed as calibration material, the extent of testing is similar to that for a chemical reference substance used in assays. Several laboratories should collaborate in testing the proposed substance using a variety of techniques to check that its purity is adequate. An appropriate number of collaborating laboratories should also participate, after the reference substance has been deemed suitable, to establish a value for the essential property of the substance using an appropriate instrument.

4. Chemical and physical methods used in evaluating chemical reference substances

It is important to establish by individual testing that a substance proposed for use as a chemical reference is suitable.

The methods used to establish the suitability of such a substance fall into two broad groups: those intended primarily to identify the substance and those used to establish its purity. With most methods, the percentage purity of a chemical reference substance cannot be expressed as an absolute value if the impurities have not been identified. The quoted purity is then an estimate based upon the data obtained by the various analytical methods.

4.1 *Methods used to verify the identity of chemical reference substances*

Where a proposed substance consists of a compound whose structure has been satisfactorily defined, its identity may be confirmed by

matching the IR spectra of the substance to that of an authentic compound. Particular care should be taken when polymorphism exists (7). Other highly specific techniques, such as NMR spectroscopy, MS, or X-ray diffraction crystallography, may also be used for such comparisons. The identity of a substance that is intended to replace an established chemical reference substance of the same molecular constitution must be verified, to determine that the characteristic properties of the two specimens are identical. For this purpose it is often sufficient to compare their IR absorption spectra.

However, where no authentic specimen of the proposed substance is available for comparison, and definitive data about its properties are lacking, it may be necessary to verify its identity by applying several analytical techniques currently used to characterize new compounds. Such analytical methods may include elemental analyses, crystallographic studies, MS, NMR spectroscopy, functional group analyses, and IR or UV spectrophotometry, as well as other supplementary tests as required to establish that the proposed substance is fully characterized.

4.2 *Methods used to determine the purity of chemical reference substances*

The analytical methods to be employed in examining a substance should be considered in relation to its intended use. These analytical methods may be divided into three broad categories: those that require comparison with an external chemical reference substance (e.g. chromatographic or spectrophotometric methods), those that depend solely on an intrinsic dynamic property (e.g. phase solubility analysis and differential scanning calorimetry) and other methods.

4.2.1 *Separation techniques*

The methods used for the determination of purity should be established and validated with system suitability requirements as appropriate.

Chromatographic methods. Methods of analysis based on chromatographic separation are especially useful for detecting and determining impurities in chemical reference substances. High performance liquid chromatography (HPLC) is the most widely used chromatographic method, but TLC and GC are also used. The individual components separated by chromatographic methods may sometimes be recovered for characterization.

The selectivity of HPLC and of GC usually exceeds that of TLC. Both the first two methods also have the advantage of being readily appli-

cable on a quantitative basis, but they require more complex equipment. HPLC, employing a spectrophotometric method of detection, is of particular value in the examination of chemical reference substances intended for use in UV spectrophotometric assays. The UV wavelength of detection employed for determining the impurity content of the chemical reference substance should be chosen so that the detection responses of the substance and its known impurities are similar. When the response factors are significantly different at the optimal wavelength of detection, appropriate corrections must be made to estimate the content of impurities. LC with diode-array detection is very useful for recording the UV spectra of both the main peak and the impurities. LC with MS detection is used for identification of separated impurities as well as for the main component, and is particularly important for chemical reference substances where no other reference standards or IR reference spectra are available.

In a GC method used for an assay, as with LC, the detection responses of the known impurities are determined. Generally, GC monograph methods are of particular value in detecting and determining volatile impurities, including solvent residues, in chemical reference substances.

TLC uses apparatus that is simple and cheap; the technique is easy to carry out and is readily applicable even in the microgram range. It can separate closely related compounds, such as geometric isomers and the members of a homologous series. All the constituents of a substance submitted to chromatography appear somewhere on the chromatogram. However, some constituents may remain on the starting line, some may move with the solvent front, some may migrate at the same rate as the main component, and some may remain undetected. For this reason, the usefulness of the method may be greatly enhanced by means of two-dimensional chromatography and by using a number of different solvent systems and a variety of detection methods. In some cases the method may be used quantitatively with acceptable accuracy by using a densitometer.

Capillary electrophoresis. Capillary electrophoresis is an increasingly common method. It may be considered as complementary to LC for detecting impurities.

4.2.2 *Methods based on intrinsic thermodynamic properties*

Methods in this group measure total impurity levels in absolute terms.

Differential scanning calorimetry. This technique is used to check the presence of different polymorphic forms and to determine the total amount of solid impurities. Purity estimation is based on

determination of the heat of fusion of the sample and of the change in its melting point caused by the presence of impurities. This analytical method can be performed rapidly and with high precision. However, it is not applicable if the substance decomposes on melting. This limits its value as a general procedure for purity estimation of chemical reference substances. It is also inapplicable if solid solutions are formed.

Phase solubility analysis. The method has occasionally been used, but its value is limited and the procedure is time consuming. It may be employed to detect contaminating substances, including isomeric species, and to estimate their concentration. Some factors that may make the method inapplicable are degradation of the substance during the course of analysis, formation of a solid solution, and polymorphism in the main component.

4.2.3 *Other methods*

Spectrophotometric methods. UV spectrophotometry is occasionally used to determine purity. Since it depends upon the presence of a characteristic chromophore, it can detect impurities that contribute excessively to the absorbance value and may indicate the presence of impurities that have a negligible or distinctive absorbance.

However, the utility of the method is limited by the small number of absorption maxima in the UV range, the large numbers of compounds containing similar characteristic chromophores, and the need for an external chemical reference substance.

IR spectrophotometry may be used to identify and determine the proportions of geometric isomers. NMR spectroscopy, a powerful spectroscopic identification tool, is also occasionally useful in the determination of purity.

Titrimetric methods. Titrimetric methods provide a valuable means of confirming the identity and purity of a proposed chemical reference substance and are useful in confirming purity values obtained by other methods.

Optical rotation methods. Many chemical reference substances are optically active and the relative proportion of optical isomers can sometimes be determined by an optical rotation method, but generally such methods lack sensitivity. However, the quantitative use of these techniques is well established and can yield results of high precision, depending on the solvent and the wavelength chosen for measurement. Chiral chromatography and NMR are becoming increasingly important.

Determination of water and organic volatiles. It is essential that an accurate assessment of the moisture content and the content of volatile contaminants be made. These total values may often be obtained by drying under defined conditions that are appropriate to the proposed substance. Sometimes this may not be possible or may yield misleading results. In such cases, thermogravimetric analysis may be used to determine the water and volatile content. Alternatively, the water content may be determined by Karl Fischer titration and the content of volatile solvents by GC. Without an accurate assessment of these values at the time that other determinations are being made, judgements of the acceptability of the proposed chemical reference substance will be invalid.

5. Assignment of content

If a content is to be assigned to a chemical reference substance, it should be borne in mind that the value is based on the results of a collaborative interlaboratory programme using different analytical methods. This experimentally obtained value represents the best estimate of the true value. In general, the assignment of content for a chemical reference substance is 100% minus the content of water and volatiles, and when a substance is intended for use as an assay standard based on a separation technique the impurity content, as determined by that method, must also be subtracted. Sometimes the chemical reference substances must be dried before use, in which case the content is expressed on the basis of the dried material.

6. Handling and distribution of chemical reference substances

The handling, distribution and use of established chemical reference substances must ensure that their integrity is safeguarded and maintained throughout their period of use.

6.1 *Packaging operations*

Current GMP requirements (*5*) should be observed. The various stages in packaging chemical reference substances should be clearly defined and controlled, to avoid contamination of the sample, mislabelling of containers, or any other event which might result in mishandling or mismanagement.

Containers for chemical reference substances should protect their contents from moisture, light and oxygen and must be tested for moisture permeability. Additional measures may be necessary to ensure long-term integrity and stability. The best containers for chemical reference substances from the point of view of stability are sealed glass ampoules, but these have certain disadvantages. There is the risk

of contaminating the substance with glass particles when the ampoules are opened, and reclosure is difficult. Sealable glass ampoules are therefore principally used for substances that must be kept in an oxygen-free atmosphere. Certain other substances may require even more elaborate protection. Most chemical reference substances, however, are conveniently supplied in reclosable containers which should be uniform in type and size to facilitate distribution. The lack of permeability to moisture is an important factor in determining the suitability of container closure systems.

Before undertaking any packaging operations, the health hazards of the item to be packaged should be assessed through information sources, e.g. the Material Safety Data Sheet. Appropriate precautions should be taken to protect the person handling the chemical reference substance.

The packaging of a batch of a chemical reference substance into containers is a small-scale operation for which suitable equipment is not always available to the manufacturer of the material. Therefore, the packaging of chemical reference substances is usually undertaken by the responsible issuing body. Screw-type feeders have been constructed, but generally the packaging of chemical reference substances is carried out manually. Substances which are expensive or only available in very small quantities may have to be divided between containers in solution and then lyophilized, or evaporated to dryness.

Some chemical reference substances must be packaged under an inert gas or in conditions of controlled humidity. Therefore, the use of a glove-box or an air-tight cabinet is necessary.

6.2 *Storage*

Information about suitable storage conditions can often be obtained from the manufacturer of the source material and should be requested routinely when a new chemical reference substance is established. Theoretically, the stability of the substances should be enhanced by keeping them at low temperatures but, for substances that contain water, storage below 0 °C may impair the stability. It should also be remembered that the relative humidity in normal refrigerators or cold-rooms may be high and, unless ampoules or other tightly closed containers are used, the improvement in stability may be more than offset by degradation due to the absorption of moisture. Storage at about +5 °C, with precautions to prevent such absorption, has proved satisfactory for most chemical reference substances.

6.3 *Stability*

A chemical reference substance is an integral part of the drug specification. Thus, if the reference substance deteriorates, this will change the specification of the drug. It is therefore of the utmost importance that the stability of chemical reference substances should be monitored by regular re-examination and that they should be replaced as soon as a significant change in a property is noted.

The definition of what is a "significant change" differs according to the intended use of the chemical reference substance. Several per cent of degradation products found in a substance may not impair the usefulness of the material in identification tests. For chemical reference substances that are used in chromatographic assays, however, even small amounts of impurities may be unacceptable. When establishing a chemical reference substance, consideration must be given to its intended use and to the performance characteristics of the analytical methods in which it will be used. The tolerable degree of degradation will be different from case to case.

Laboratories in charge of collections of chemical reference substances should have a system for regular re-examination of the materials in stock. The frequency of re-testing may be modified according to the need. It must be borne in mind that the stability of a specially prepared chemical reference substance may not always be the same as that of commercial samples of the same material.

The selection of suitable analytical methods for monitoring the stability of chemical reference substances depends on the nature and intended use of the substance. A substance used solely for identification purposes will normally only require demonstration that it is still suitable for this use, e.g. that the IR spectrum is identical to that obtained during establishment. If substances are employed for other purposes, the testing must be more extensive but should use methods which are rapid and sensitive so as not to consume too much of the existing stock. It is important to check that there has been no significant uptake of moisture, which could result in degradation by hydrolysis and/or a decrease in the assigned content of the substance. Chromatography is employed extensively, as well as absolute methods such as differential scanning calorimetry where applicable. Changes in the impurity profile or purity determination usually mean that the batch must be replaced. Changes which compromise the integrity of the batch indicate it should immediately be withdrawn from use. Sometimes a batch of a chemical reference substance will discolour or otherwise change in appearance. Steps should be taken to replace this substance whether or not the results of subsequent analyses indicate

significant degradation. Such changes in physical appearance reduce the confidence of the user in the suitability of the chemical reference substance. Appropriate testing of active bulk substance should be carried out before further dispensing into vials or ampoules.

6.4 *Information to be supplied with chemical reference substances*

Labels on chemical reference substances should give the following information:

— the appropriate name of the substance: the international nonproprietary name (INN) should be used wherever possible;
— name and address of the issuing body;
— approximate quantity of material in the container; and
— batch or control number.

Where associated documents are provided they should incorporate relevant items from the list above. The following information should be given, as necessary, on the labels and/or in associated documents:

— recommended storage conditions (if special conditions apply);
— intended use of the chemical reference substance;
— directions for use (e.g. storage and handling);
— information about assigned analytical value of the chemical reference substance (needed for calculation of the results of tests in which the substance will be used);
— a disclaimer of responsibility when chemical reference substances are misused, or stored under inappropriate conditions, or used for other purposes than those intended by the issuing body; and
— health hazard information or warning in conformity with national and regional regulations or international agreements.

If analytical data are to be supplied with the chemical reference substances, it is recommended that the data provided be limited to what is necessary for the proper use of the substances in the tests and assays.

6.5 *Distribution and supply*

Distribution of chemical reference substances within the same country usually does not present problems. However, when samples are to be sent to other countries, both the sender and the receiver of the goods may encounter difficulties because of the vagaries of postal and customs regulations, e.g. the application of special procedural requirements applicable to substances under international control. Distributors of chemical reference substances waste considerable resources in seeking information on different international import

regulations, and in completing the required forms. A way of reducing such difficulties and barriers to effective distribution of chemical reference substances should be sought. There should be the minimum delay in providing the chemical reference substances to the users, and the most speedy means of transport should be chosen.

6.6 *Period of use*

Chemical reference substances do not carry an "expiry date" in the conventional sense. To avoid the unnecessary discarding of satisfactory substances, a mechanism for general control of the batch of a chemical reference substance may be used by the issuing body. If the issuing body applies stability considerations and a monitoring procedure based on its experience to its collection, this should guarantee the user of the acceptability of the chemical reference substance for its intended use.

If it is considered necessary to specify a beyond-use date, it should be stated on the label and/or on a document accompanying the chemical reference substances. Adequate shipping records should exist to enable contact with the purchaser of a batch for recall or other notification.

The storage and maintenance of unopened containers of the chemical reference substance in accordance with information provided are integral to its suitability of use. To avoid potential doubts concerning the integrity of opened containers, it is suggested that potential users obtain only the quantities of substances necessary for short-term need and obtain fresh stocks (held under controlled and known conditions) when needed. Long-term storage of substances in opened containers is to be avoided. Similarly, efforts should be made to avoid possible degradation, contamination and/or introduction of moisture during the repeated use of a substance.

Part B. Secondary chemical reference substances

The establishment of secondary chemical reference substances calibrated against a primary chemical reference substance may be desirable for various practical reasons, e.g. the latter may not be available in adequate quantities to supply all local needs. Moreover, the availability of such secondary chemical reference substances (for example, on a regional basis) would reduce the delay in receiving the reference material.

The body which establishes a secondary chemical reference substance for national/regional use should be clearly defined by the competent

drug regulatory authority. Clear documentation must exist to establish the relationship between the secondary and the primary chemical reference substance.

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Annex 4
Good manufacturing practices: authorized person — role, functions and training

This text does not constitute additional requirements in the area of good manufacturing practices (GMP). It is intended to assist manufacturers wishing to strengthen their quality assurance systems. References to ISO standards of the 9000 series are relevant primarily to manufacturers not in a position to implement full GMP requirements immediately. The reason for this may be lack of resources or a limited involvement in contractual manufacturing/testing of drugs. For such manufacturers/testing laboratories, the implementation of quality systems along the lines of ISO standards will be a step in the right direction. Manufacturers fully complying with GMP requirements may wish to adopt on a voluntary basis certain elements found in ISO standards of the 9000 series, e.g. quality manuals. Nothing in this text should be interpreted as a suggestion that drug manufacturers need external certification under ISO standards.

The GMP guidelines published by WHO[1] define the authorized person as a person (among key personnel of a manufacturing establishment) responsible for the release of batches of finished products for sale. In some other GMP guides and legal texts the term qualified person is used to describe analogous functions.

1. The role and position of the authorized person in the company

The authorized person as the overall quality controller will be a member of a team whose function includes the following major areas:

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

— implementation (and, when needed, establishment) of the quality system;
— participation in the development of the company's quality manual;
— supervision of the regular internal audits or self-inspections;
— oversight of the quality control department;
— participation in external audit (vendor audit);
— participation in validation programmes.

Although authorized persons may not have line management responsibility for many activities within this function (although they should be involved in these activities as much as possible), they must be aware of any changes that may affect compliance with technical or regulatory requirements related to the quality of finished products. When any aspect of the company's operations is not in accordance with GMP guidelines or relevant legislation in force, the authorized person must bring this to the attention of senior management. This duty should be reflected in the authorized person's job description.

The availability of an authorized person should be a prerequisite for issue of a manufacturing licence (authorization). The authorized person (as well as persons responsible for production and quality control) must be approved by the drug regulatory authority. The licence holder is obliged to inform the drug regulatory authority, or other responsible authority depending on national (regional) regulations, immediately if the authorized person is replaced unexpectedly. Such provisions will assure to a considerable degree the independence of the authorized person from the management of the company in the fulfilment of his or her duties even when under pressure to depart from professional and technical standards.

As indicated in the GMP guidelines published by WHO, in certain countries, depending on the national legislation or regulations, two authorized persons are designated: one for production and another for quality control. A company may have a complex structure, or operate at several locations, or both, and sometimes a separate authorized person may be designated who is responsible for the manufacture of clinical trial materials. Consequently it may be necessary to nominate several authorized persons, one of them having the responsibilities of the overall quality controller and the others responsible for site or branch operations. The person authorizing batch release should be independent from production activities.

The drug regulatory authority should approve the authorized person on the basis of his or her professional curriculum vitae. Authorized persons have duties not only to their employer but also to the compe-

tent authorities such as the drug regulatory authority. They should establish good working relations with inspectors and as far as possible provide information on request during site inspections.

The authorized person depends upon many working colleagues for the achievement of quality objectives, and may delegate some duties to appropriately trained staff while remaining the overall quality controller. It is therefore of paramount importance that he or she establish and maintain a good working relationship with other persons in positions of responsibility, especially those responsible for production and quality control.

2. Implementation of the quality system

Authorized persons have a personal and professional responsibility for ensuring that each batch of finished products has been manufactured in accordance with the marketing authorization, GMP rules and all related legal and administrative provisions. This does not necessarily mean that they must have directly supervised all manufacturing and quality control operations. They must be satisfied either directly or, more usually, by proper operation of quality systems, that manufacturing and testing have complied with all relevant requirements. Therefore it is recommended that the manufacturer establishes and maintains a comprehensive quality system, covering all aspects of GMP.

Useful reference material, in addition to rules and regulations on GMP, may be found in the International Standards ISO 9000 family (9000–9004). These standards describe quality systems requirements that can be used for external quality assurance purposes. The important element of these documents is a *quality manual*, describing the *quality policy* and objectives (commitment to quality) of the company, the organizational structure, responsibilities and authorities, together with a description of or references to documented quality system procedures.

Research and development activities and the transfer of results of the developmental work to routine manufacture, including original product design, formulation, processes development and validation, should observe GMP principles as guidance. Batches produced for clinical trials must follow applicable GMP. It is of vital importance that the quality of routine production batches corresponds to a specification derived from the composition of development batches. The quality and safety of a pharmaceutical product depend on the application of appropriate procedures, based on GMP, leading to a product

within the recognized specification. Standard procedures and recognized specifications cannot be separated.

3. Routine duties of an authorized person

Before approving a batch for release the authorized person doing so should always ensure that the following requirements have been met:

- The marketing authorization and the manufacturing authorization requirements for the product have been met for the batch concerned.
- The principles and guidelines of GMP, as laid down in the guidelines published by WHO, have been followed.
- The principal manufacturing and testing processes have been validated, if different.
- All the necessary checks and tests have been performed and account taken of the production conditions and manufacturing records.
- Any planned changes or deviations in manufacturing or quality control have been notified in accordance with a well-defined reporting system before any product is released. Such changes may need notification to and approval by the drug regulatory authority.
- Any additional sampling, inspection, tests and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations.
- All necessary production and quality control documentation has been completed and endorsed by supervisors trained in appropriate disciplines.
- Appropriate audits, self-inspections and spot-checks are being carried out by experienced and trained staff.
- Approval has been given by the head of the quality control department.
- All relevant factors have been considered, including any not specifically associated with the output batch directly under review (e.g. subdivision of output batches from a common input, factors associated with continuous production runs).

In certain circumstances the authorized person may be responsible for the release of intermediates manufactured on contract.

4. Education and training

The pool of expertise drawn upon for candidates for the position of authorized person may differ from country to country. The basic qualifications of a scientific education and practical experience for key personnel, including authorized persons, are outlined in the GMP guidelines published by WHO (section 10, Personnel).

Additional requirements may include subjects such as principles of quality assurance and GMP, principles of good laboratory practice as applicable to research and development as well as to quality control, detailed knowledge of the authorized/qualified person's duties and responsibilities, of International Standards ISO 9000–9004 and relationships with suppliers, principles and problems of formulation of pharmaceutical preparations, pharmaceutical microbiology, and principles and practice of sampling and testing of starting materials, packaging components and finished dosage forms. For a more detailed list of issues consult the selected references.

5. Selected references

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Annex 5
Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients

1. General considerations

These guidelines, which focus on aspects of good manufacturing practices (GMP) specific for pharmaceutical excipients, supplement the general GMP guidelines for pharmaceutical products published by WHO.[1] They also incorporate some of the concepts for quality management systems determined by the International Organization for Standardization (ISO).

Excipients significantly affect the finished product quality, in some cases making up almost the entire formulation. Many pharmaceutical excipients are used in much greater quantities in other industries, such as the food, cosmetic or industrial chemical industry. Consistency and rigour of product specifications may not be as critical in these industries as they are for pharmaceuticals, and many of the excipients used are highly variable. Therefore, a programme must be in place which will monitor these excipients and provide the necessary assurance that they meet the quality parameters for pharmaceutical manufacturing processes. The purpose of this document is to lay out some criteria which may be used to achieve this level of assurance.

The formulator of the finished dosage form is highly dependent on the excipient manufacturer to provide bulk substances that are uniform in chemical and physical characteristics. This is particularly important in the product approval process, where bioequivalence comparisons are made between clinical bioequivalence ("biobatch") production and commercial scale-up batches. To provide adequate assurance of drug product performance *in vivo*, the excipient used to manufacture commercial batches should not differ significantly from that used in biobatches. Where significant differences may be expected, additional testing by the finished dosage manufacturer may be required to establish the bioequivalence of the finished product. It remains equally important to ensure that the bioequivalence of subsequent, post-approval commercial batches of drug products is not adversely affected over time.

In general, excipients are used as purchased, with no further refinement or purification. Consequently, impurities present in the excipient will be carried over to the finished dosage form. While dosage form manufacturers may have a limited control over excipient quality

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

(i.e. by obtaining certificates of analysis and testing representative samples), the excipient manufacturer has greater control over physical characteristics, quality, and the presence of trace-level impurities in the excipient. The excipient manufacturer should perform periodic performance trend analyses of processes, and the purchaser of the material should also maintain a trend analysis of all testing done on the excipient upon receipt.

In the manufacture of excipients, the environmental conditions, equipment and operational techniques employed reflect the chemical industry rather than the finished drug manufacturing industry. In some processes chemical and biochemical mechanisms have not been fully characterized; therefore, the methods and procedures for materials accountability will often differ from those applicable to the manufacture of finished dosage forms. Many chemical processes are performed in closed systems that tend to provide protection against contamination, even when the reaction vessels are not enclosed in buildings. However, this does not preclude the introduction of contaminants from equipment, materials used to protect equipment, corrosion, cleaning and personnel.

Some excipient manufacturing processes may require observance of GMP applicable to finished drug products or bulk active ingredients because of the excipient's intended use. However, such observance is neither feasible nor necessary in many processes, particularly during the early processing steps. The requirements increase as the process progresses. At some logical processing step, usually well before the final finishing operation, appropriate GMP should be imposed and maintained throughout the remainder of the process. To determine the processing step at which these GMP should be implemented, good judgement and a thorough knowledge of the process are required. A detailed process flow should identify the unit operations, equipment used, stages at which various substances are added, key steps in the process, critical parameters (time, temperature, pressure, etc.) and monitoring points.

An excipient manufacturer should be able to identify critical or key points in the process where selective intermediate sampling and testing is necessary in order to monitor process performance. Towards the end of the process, the records should be increasingly thorough.

Significant processing steps, required to produce an excipient that meets the established physical and chemical criteria, should be identified by the excipient manufacturer. These steps can involve a number of unit operations or unit processes. Unit operations include physical processing steps involving energy transfer where there is no

chemical change of the molecule. Unit processes are those processing steps where the molecule undergoes a chemical change.

Significant processing steps include but are not limited to the following:

- Phase changes involving either the desired molecule, a solvent, inert carrier or vehicle (e.g. dissolution, crystallization, evaporation, drying, sublimation, distillation or absorption).
- Phase separation (e.g. filtration or centrifugation).
- Chemical changes involving the desired molecule (e.g. removal or addition of water of hydration, acetylation, formation of a salt).
- Adjustments of the solution containing the molecule (e.g. adjustment of pH).
- Precision measurement of added excipient components, in-process solutions, recycled materials (e.g. weighing, volumetric measuring).
- Mixing of multiple components.
- Changes that occur in surface area, particle size or batch uniformity (e.g. milling, agglomeration, blending).

Automated process controls and processing equipment are more likely to be used in an excipient plant than in a plant manufacturing finished dosage forms. Use of automated equipment is appropriate when adequate inspection, calibration, and maintenance procedures are performed. Production equipment and operations will vary depending on the type of excipient being produced, the scale of production, and the type of operation (i.e. batch versus continuous).

ISO "certification" for excipient manufacture is increasingly being required by final dosage formulators in the USA, Europe and Japan. Compliance to the International Standards of ISO 9000 series, in particular to ISO 9002, can confer greater acceptability of a supplier's excipients in world markets. There is additional value to applying the principles of ISO 9000 to excipient manufacture, since quality system measures enhance GMP. Such ISO considerations as conformance to specific customer requirements, purchase of raw materials and statistical techniques benefit both the excipient customer and the manufacturer, and strengthen the relationship between the two.

It is therefore recommended that excipient manufacturers establish and implement a formal company-wide quality policy. Management should be committed to this policy and should appoint appropriate company personnel to be responsible for coordination and

implementation of the quality system. Management should participate in the development of the company's quality policy and provide the resources necessary for development, maintenance and periodic review of such a policy and quality system. Any significant changes in the processes should be validated with respect to excipient performance. It is recommended that all pharmaceutical manufacturers and also local agents should be informed of these changes. Ideally, excipient manufacturers should not subcontract any part of their process without the explicit knowledge of the pharmaceutical manufacturer.

Safe handling instructions should be provided by the excipient manufacturer to ensure that the purchaser is adequately equipped to handle the material. This should include information on the material's toxicity and the measures to be taken upon accidental exposure. The equipment requirements for proper handling of the material should also be established.

2. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

commingling
The blending of carry-over material from one grade of an excipient with another, usually due to a continuous process.

drug master file[1]
Detailed information concerning a specific facility, process or product submitted to the drug regulatory authority, intended for incorporation into the application for marketing authorization.

model product
A product which simulates a group of similar products.

mother liquor
A concentrated solution from which the product is obtained by evaporation, freezing, and/or crystallization.

pharmaceutical excipients
Substances, other than the active ingredient, which have been appropriately evaluated for safety and are included in a drug delivery system to:

[1] This term appears to be specific to United States regulations.

— aid in the processing of the drug delivery system during its manufacture;
— protect, support or enhance stability, bioavailability, or patient acceptability;
— assist in product identification; or
— enhance any other attribute of the overall safety and effectiveness of the drug during storage or use.

3. Self-inspection and quality audits

An inspection team consisting of appropriate personnel (e.g. auditors, engineers, laboratory analysts, purchasing agents, computer experts) should participate in inspections. The operational limitations and validation of the critical processing steps of a production process should be examined, to make sure that the manufacturer is taking adequate steps to check that the process works consistently.

The excipient's end use should be identified and considered during inspection of excipient manufacturers. It is particularly important to know whether the excipient is a direct or indirect component of a drug dosage form; whether the excipient will be used in the preparation of a sterile dosage form; and whether the excipient is presented as pyrogen/endotoxin free. The excipient manufacturer is responsible for ensuring that excipients are pyrogen free if the manufacturer makes such a representation in specifications, labels or a drug master file.

A good starting point for an excipient plant inspection is a review of the following areas:

- Non-conformance, such as the rejection of a batch not complying with specifications, return of a product by a customer, or recall of a product. The cause of non-conformance should have been determined by the manufacturer, a report of the investigation prepared, and subsequent corrective action initiated and documented. Records and documents should be reviewed to ensure that such non-conformance is not the result of a poorly developed or inconsistent process.

- Complaint files. Customers may report some aspects of product attributes that are not entirely suitable for their use. These may be caused by impurities or inconsistencies in the excipient manufacturing process.

- Change control documentation.

- Master formula and batch production records. Frequent revisions may reveal problems in the production process.
- Specifications for the presence of unreacted intermediates and solvent residues in the finished excipient.
- Storage areas for rejected products.

In evaluating the adequacy of measures taken to preclude contamination of materials in the process, it is appropriate to consider the following factors:

- Type of system (e.g. open or closed). "Closed" systems in chemical plants are often not closed when they are being charged and/or when the final product is being removed. Also, the same reaction vessels are sometimes used for different reactions.
- Form of the material (e.g. wet or dry).
- Stage of processing and use of the equipment and/or area (e.g. multipurpose or dedicated).

Other factors that should be considered in evaluating an excipient plant are:

- Degree of exposure of the material to adverse environmental conditions.
- Relative ease and thoroughness of clean-up.
- Sterile versus non-sterile operations.

4. Equipment

4.1 *Use of equipment*

Many excipients are produced using multipurpose equipment. Fermentation tanks, reactors, driers, grinders, centrifuges and other pieces of equipment are readily used or adapted for a variety of products. With few exceptions such multiple usage is satisfactory provided the equipment can be adequately cleaned according to written procedures. Equipment that contains tarry or gummy residues that cannot be removed easily should be dedicated for use with these products only.

Some fermentation tanks, reaction vessels, and other equipment are not situated within a building and a considerable amount of processing occurs out of doors. Such processing is acceptable provided it occurs in a closed system.

Where temperature control is important, temperature recording devices should be used, with recording charts kept as part of the batch record.

4.2 *Cleaning programme*

Where multipurpose equipment is in use, it is important to be able to determine previous usage when investigating cross-contamination or the possibility of such contamination. An equipment cleaning and use log, while desirable and perhaps preferable, is not the only method of determining prior use. Any documentation system which clearly identifies the previous batch and shows that the equipment was cleaned is acceptable. For operations where multiple grades of the same chemical entity are processed, there must be documentation showing that the previous grade was removed. Validation data must exist to prove acceptability of the cleaning procedure.

Cleaning of multiple-use equipment should be confirmed. The manufacturer should determine the effectiveness of the cleaning procedure for each excipient or intermediate chemical used in that particular piece of equipment. The validation data required depend on the types of materials being made in the multiple-use equipment and the impact of trace contaminants on drug safety and performance. Validation data should verify that the cleaning process has removed residues to an acceptable level.

As an example, an equipment cleaning programme may include, but is not limited to, the following:

4.2.1 *Detailed cleaning procedure*

There should be a written equipment cleaning procedure that provides details of what should be done and which cleaning materials should be used. Some manufacturers list the specific solvents used for each excipient and intermediate.

4.2.2 *Sampling plan*

There should be some periodic testing after cleaning, to ensure that the surface has been cleaned to the required level. One common method is to analyse the final rinse water or solvent for the presence of the substance last used in that piece of equipment. In some cases, visual inspections may be appropriate. A specific analytical method to determinate residual substances may not always be available, but is preferred. The need for an analytical method would be based on the potential adverse effect on product quality, performance or safety.

When safety is a concern, there should be a specific analytical determination for a residual substance.

4.2.3 *Analytical methods/cleaning limits*

The toxicity of the residual materials should be considered when deciding on the appropriate analytical method and the residual cleaning limits. The residue limits established for each piece of apparatus should be practical, achievable and verifiable. The manufacturer should be able to show, with supporting data, that the residual level permitted is scientifically based. Another factor to consider is the possible non-uniformity of the residue. The level of residue found by random sampling, such as taking a swab from a limited area on a piece of equipment, does not necessarily represent the highest level of contamination.

5. Materials

5.1 *General*

In the case of labile products that may be sensitive to environmental factors such as air, light, water, heat or cold, appropriate manufacturing and storage conditions must be used to ensure product quality throughout the process.

5.2 *Starting materials*

The excipient manufacturer should verify that the supplier of starting materials and components can meet the agreed-upon requirements. This may require periodic audits of the vendor's plant if necessary. Purchasing agreements should contain data clearly describing the product ordered including, where applicable, the following:

- The name, type, class, style, grade, item code numbers or other precise identification as appropriate.
- Drawings, process requirements, inspection instructions and other relevant technical data, including requirements for approval or verification of product, procedures, process equipment and personnel.

Starting materials, including solvents and recovered solvents, are sometimes stored in silos or other large containers, making precise separation of batches difficult. Usage of such materials should be demonstrated, via inventory or other records, with reasonable accuracy.

When purchased and recovered solvents are commingled, the suitability of the recovered solvent must be demonstrated through either validation or actual testing. The purchased materials should comply with existing specifications.

Outdoor storage of starting materials (e.g. acids, other corrosive substances, explosive materials) is acceptable if the containers give suitable protection to their contents, identifying labels remain legible and containers are adequately cleaned prior to opening and use.

5.3 *Rejected and recovered materials*

Any starting material, intermediate or finished excipient not complying with specifications must be clearly identified and segregated to prevent inadvertent use or release for sale. A record of non-compliance should be maintained. All cases of non-compliance should be investigated to identify the root cause.

These materials may be:

— reprocessed/reworked to meet the specified requirements;
— regraded for alternative applications; or
— rejected or scrapped.

Occasional reprocessing/reworking of an excipient may be acceptable. However, relying on the final testing only of the reprocessed excipient to demonstrate compliance to specification is not acceptable. The quality of the reprocessed material must be evaluated and documented showing adequate investigation and demonstrating that the reprocessed excipient is at least equivalent to other acceptable excipients. When reprocessing has to be done frequently, it may be an indication that the process, work instruction or training is inadequate and needs to be adjusted or reinforced.

5.4 *Returned excipients*

Returned excipients should be identified as such and kept. If the conditions under which the products have been stored and shipped or if the condition of the container itself casts doubt on the safety, quality or purity of the excipient, the product should be destroyed, unless thorough examination, testing, or other investigation shows that the product meets the appropriate predefined standards. If returned excipient containers are reused, all previous labelling should be removed or defaced. If the containers are used repeatedly solely for the same excipient, all previous batch numbers, or the entire label, should be removed or completely obliterated.

5.5 *Storage practices*

Pharmaceutical excipients should be stored under conditions established by the manufacturer on the basis of stability data. Records should be kept of the distribution of each batch of pharmaceutical excipient, to facilitate the recall of the batch if necessary, according to written procedures.

6. Documentation

6.1 *General*

The excipient manufacturer should have a system to cover all documents and data that relate to the requirements of the quality system. Documents, and subsequent changes to the documents, should be reviewed and approved by designated personnel before being issued to the appropriate areas identified in the documents. A record should be kept of where the documents are located.

The following minimal requirements for documentation should be applied:

- To assign a unique batch number to the excipient to be released and/or certified.
- To prepare a batch record.
- To demonstrate that the batch has been prepared under GMP conditions from the processing point at which excipient GMP have been applied.
- To demonstrate that the batch is homogeneous within the manufacturer's specifications. This does not require a final blending of continuous process material, if process controls can demonstrate compliance with specifications throughout the batch.
- To demonstrate that the batch has not been commingled with material from other batches for the purpose of either hiding or diluting an adulterated substance.
- To demonstrate that the batch has been sampled in accordance with a sampling plan that ensures a representative sample of the batch is taken.
- To demonstrate that the batch has been analysed using scientifically established tests and methods designed to ensure that the product meets accepted standards and specifications for quality, identity and purity.

- To demonstrate that the batch has stability data to support the intended period of use; these data can be obtained from actual studies on the specific excipient or from applicable "model product" stability studies that can reasonably be expected to simulate the performance of the excipient.

6.2 *Specifications*

Starting material specifications should be organized to separate those tests that are routine from those that are performed infrequently or only for new suppliers. Relevant pharmacopoeial monographs, when available, provide a basis for the development of internal manufacturer's specifications.

A positive identification test uniquely applicable to the excipients should be established through analytical technology, such as infrared spectrophotometry and chromatography.

It is important that manufacturers identify and set appropriate limits for impurities. These limits should be based upon appropriate toxicological data, or limits described in national compendial requirements. Manufacturing processes should be adequately controlled so that the impurities do not exceed such established specifications.

Many excipients are extracted from or purified by the use of organic solvents. These solvents are normally removed by drying the moist excipient. In view of the varying and sometimes unknown toxicity of solvents, it is important that excipient specifications include tests and limits for residues of solvents and other reactants.

Container specifications should be established for all excipients to assure consistency in protecting the product during transport from the excipient manufacturer to the pharmaceutical producer. The specifications should not only provide for containers that maintain the stability of the product, but should also meet requirements for protection during shipping, against insect infestation, during handling, etc.

6.3 *Batch production records*

Computer systems are increasingly used to initiate, monitor, adjust and otherwise control manufacturing processes. These operations may be accompanied by recording charts that show key parameters (e.g. temperature) at suitable intervals, or even continuously, throughout the process. In other cases, key measurements (e.g. pH) may be displayed temporarily on a monitor screen, but are not available in hard copy.

Records showing addition of ingredients, actual performance of operations by identifiable individuals, and other information usually seen in conventional records, may be missing. When computers and other sophisticated equipment are employed, the emphasis must change from conventional, hand-written records to:

— systems and procedures that show the equipment and software is in fact performing as intended;
— checking and calibration of the equipment at appropriate intervals;
— retention of suitable back-up systems such as copies of the program and files, duplicate tapes or microfilm;
— assurance that changes in the program are made only by authorized personnel and that they are clearly documented and validated.

6.4 *Other documents*

Shipping and storage requirements should be established to ensure that the product reaches the manufacturer with proper quality attributes. This should be mutually agreed upon between the vendor and the purchaser and established prior to transportation of product.

Written procedures should be established and followed for maintenance of the equipment. All maintenance activities performed must be recorded; this may be in the form of a log, computer data base or other appropriate documentation, as long as the system can identify who was responsible for performing each function.

7. Good practices in production and quality control

7.1 *Change control and process validation*

Process changes may lead to changes in inherent product characteristics. Manufacturers should have a formal process change system in place, with written standard operating procedures covering such changes. Management of the change system should be assigned to an independent quality unit having responsibility and authority for final approval of process changes.

Manufacturers of excipients often produce laboratory or pilot batches. Scale-up to commercial production may involve several stages and data should be reviewed to demonstrate the adequacy of the scale-up process. Scale-up may introduce significant problems of consistency between batches. Pilot batches should serve as the

basis for establishing in-process and finished product purity specifications.

Typically, manufacturers will generate reports that discuss the development and limitation of the manufacturing process. Summaries of such reports should be reviewed to determine if the plant is capable of producing the excipient. The reports serve as the basis for the validation of the manufacturing and control procedures, as well as the basic documentation to demonstrate that the process works consistently.

A document comprising scale-up data and describing the process reactions, operating parameters, purifications, impurities and key tests needed for process control should be written. A retrospective analysis of historical data (through statistical data and process capability data analysis) as well as the previous documentation will provide a good basis for validation.

7.2 *Good practices in production*

7.2.1 *Prevention of cross-contamination*

Potential for cross-contamination should be considered in the design of the manufacturing process and facility. The degree to which cross-contamination should be minimized depends on the safety and intended use of the excipient.

The precautions taken to minimize cross-contamination should be appropriate to the conditions of the manufacturing facility and will take account of the range of materials manufactured. When the excipient product is initially recovered, it should be in a clean environment and not exposed to airborne contaminants, such as dust from other excipient or industrial chemicals. Typically, the damp product will be unloaded into clean, covered containers and transported for drying and other manipulations. These subsequent operations should be performed in separate areas or under controlled conditions because once dry, the excipient is more likely to contaminate its environment, including any surrounding products. The primary consideration is that the building and facilities should not contribute to an actual or potential contamination of the excipient.

The air handling systems at the site of manufacture should be designed to prevent cross-contamination. In dedicated areas processing the same excipient, it is permissible to recycle a portion of the exhaust air back into the same area. The adequacy of such a system of operation for multi-use areas, especially if several products are processed simultaneously, should be carefully analysed. In multi-use areas

where several products are completely confined in closed vessels and piping systems, filtration of the supply air (combined fresh make-up air and recycled air) is acceptable if the conditions are consistent with other existing regulations (e.g. environmental, safety).

In those areas where the excipient is in a damp or moistened form, such as filter or centrifuge cake, and may be exposed to room air, filter efficiencies in the supply air system as low as 85% may be adequate. In those areas where one or more of the products is being processed in a dry form, such filtration may not be enough to prevent cross-contamination. In all cases, manufacturers should be able to demonstrate the adequacy of their air handling systems.

Excipient manufacturers should have a documented programme identifying all insecticides, pesticides, rodenticides and herbicides used at the site of manufacture. Adequate measures should be taken to prevent these agents contaminating the excipients.

7.2.2 *In-process blending/mixing*

Some processes require blending or mixing. Such in-process blending is acceptable provided it is adequately documented in batch production records. Examples include:

- Collection of multiple batches or continuous accumulation of batches with defined endpoint in a single holding tank (with a new batch number).
- Recycling material from one batch for further use in a subsequent batch.
- Repeated crystallizations of the same mother liquor for better yield of crystals.
- Collecting several centrifuge loads in a single drier/blender.

Incidental carry-over is another type of in-process mixing that frequently occurs. Examples include:

- Residue adhering to the wall of a micronizer used for milling the finished excipient.
- Residual layer of damp crystals remaining in a centrifuge bowl after discharge of the bulk of the crystals from a prior batch.
- Incomplete discharge of fluids, crystals or particles from a processing vessel upon transfer of the material to the next step in the process.

These residues are usually acceptable since clean-up between successive batches of the same excipient is not normally required during

production. However, in the case of non-dedicated production units, complete cleaning procedures designed to prevent contamination that would alter the quality of the substance must be employed when changing from one excipient to another. Checking the effectiveness of these cleaning procedures may require the use of analytical testing for the substances involved.

In contrast to in-process blending and incidental carry-over discussed above, other blending operations should be directed towards achieving homogeneity of the finished excipient batch. Three areas in the processing of finished batches of an excipient which should be examined carefully and critically are:

— the final blending operation to produce the finished batch;
— the point in the process at which the batch number is assigned;
— the sampling procedure used to obtain the sample that is intended to be representative of the batch.

Blending of excipient batches to salvage adulterated material is not an acceptable practice.

Mother liquors containing recoverable amounts of excipients are frequently reused. Secondary recovery procedures for such excipients are acceptable, if the recovered excipient meets its specifications and if recovery procedures are indicated in batch production records. Secondary recovery procedures for reactants and intermediates are acceptable provided that the recovered materials meet suitable specifications.

7.2.3 *Control of microbial contamination*

The manufacture of sterile excipients for use in aseptic/sterile processing presents technical challenges. It is essential that adequately qualified and trained personnel be used to supervise and perform procedures associated with the manufacture of sterile excipients. The environment in which procedures are conducted, and the operators themselves, are significant potential sources of contamination in aseptic operations. Processes should be designed to minimize contact between excipient and the environment and operators. Those aseptic excipient operations which require considerable operator involvement must have adequate controls. Major potential problem areas include aseptic removal of the excipient from centrifuges, manual transfer to drying trays and mills, and the inability to sterilize the drier. Not all equipment currently in use can be sterilized.

The excipient manufacturer must document the cleaning of critical processing equipment such as centrifuges and driers. Any manipula-

tion of sterile excipients after sterilization must be performed as a validated aseptic process. This is particularly important for those excipients which are not further sterilized prior to packaging into final containers. In some instances, the compendial monographs may specify that an excipient which does not meet parenteral grade standards must be labelled as not suitable for use in the preparation of injectable products.

Some manufacturers of non-sterile excipients use heat, gamma radiation and other methods to reduce the microbial burden. These methods are acceptable provided the manufacturer has shown that the product meets microbial requirements and that the process is under control within the manufacturer's specifications. Any procedure should be validated in accordance with recognized international standards to demonstrate that the process will produce the intended result. Post-production treatment of excipients should not be used as a substitute for attention to microbiological control during production.

A protected environment may be necessary to avoid microbial contamination or degradation caused by exposure to heat, air or light. The degree of protection required may vary depending on the stage of the process. Often, direct operator contact is involved in the unloading of centrifuge bags, transfer hoses (particularly those used to transfer powders), drying equipment and pumps, and equipment should be designed to minimize the possibility of contamination. The sanitary design of transfer and processing equipment should be evaluated. Those with moving parts should be assessed for the integrity of seals and other packing materials to avoid product contamination.

Special environments required by some processes must be monitored at all times to ensure product quality (e.g. inert atmosphere, protection from light). If interruptions in the special environment occur, adequate evidence must be provided that they have not compromised the quality of the excipient. Such environmental concerns become increasingly important after purification of the excipient has been completed.

The environment to which the excipient may be exposed should be similar to that used in the manufacture of the final dosage form. This is especially true in the case of excipients intended for parenteral dosage forms. For example, controlled areas may need to be established along with appropriate air quality classifications. Such areas should be serviced by suitable air handling systems and there should be adequate environmental monitoring programmes. Any manipula-

tion of sterile excipient after sterilization must be performed as an aseptic process, using Class 100 air[1] and other aseptic controls.

7.2.4 *Water systems/water quality*

While drinking-water is used for many excipient processes, purified water is also widely used. Because of the well-known potential for microbial growth in deionizers and ultrafiltration or reverse-osmosis systems used to produce purified water, such systems must be properly validated and checked. Proper control methods include the establishment of water quality specifications and corresponding action levels, remedial action when microbial levels are exceeded, and adequate maintenance procedures such as regeneration and sanitation/sterilization.

Appropriate specifications for chemical and microbial quality should be established and periodic testing conducted. Such specifications will vary depending on the process and the point in the process when the water is used. For example, in some cases, if the water is used in later processing steps such as for a final wash of the filter cake, or if the excipient is crystallized from an aqueous system, the water quality standards may need to be higher than normally specified for purified water. This is particularly important where the excipient's intended use is in parenteral dosage forms. The frequency of microbial and chemical testing of purified water depends on a variety of factors, including the test results and the point in the process (e.g. final wash in centrifuge) at which such water is used.

Most purified water and water for injection systems, including reverse-osmosis and ultrafiltration systems, have the potential for endotoxin contamination. If the final excipient is supposed to be pyrogen free or sterile, or will be used in preparing parenteral products, validation of the system to control endotoxins should be conducted and routine testing of the process water for endotoxins should be performed (preferably by the LAL (*Limulus* amoebocyte lysate) method).

7.2.5 *Packaging operations*

When the programme for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups, or substitutions. Different products should

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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, Annex 1, Section 17.3 (WHO Technical Report Series, No. 823).

not be packaged in close proximity unless there is physical segregation or the use of electronic surveillance.

7.2.6 *Delivery*

The manufacturer should arrange for the protection of the product after final inspection and testing. Where contractually agreed, this protection should include delivery to destination. Distribution records should be kept.

7.3 ***Good practices in quality control***

7.3.1 *General*

The quality control unit, in addition to having the responsibility and authority to approve or reject all components, in-process materials, packaging materials and finished excipients, and to review production records, etc., should also be responsible for approving or rejecting excipients manufactured, processed, packaged, or held under contract by another company, as well as for approving or rejecting all procedures, specifications and process changes having an effect on the quality of the excipient.

7.3.2 *Control of starting materials*

All starting materials must be tested or otherwise verified prior to use. Verification should include a certificate of analysis from the supplier and, wherever feasible, an identification test. There should be clear guidance or standard operating procedures established for the approval of each starting material.

Starting materials are usually subjected to an identity test and additional testing to confirm that they meet appropriate specifications. Some starting materials may not be acceptance tested by the manufacturer because of the hazards involved or other valid considerations. In such cases, quality certification for each batch from the vendor should be on file. There should always be some evidence of an attempt by the excipient manufacturer to establish identity, even if it is only a visual examination of containers, examination of labels, or recording of batch numbers from the labels.

7.3.3 *In-process testing*

In-process inspection and testing should be performed by monitoring the process or by actual sample analysis at defined locations and times. The results should conform to established process parameters or acceptable tolerances. Work instructions should delineate the pro-

cedure to follow and how to use the inspection and test data to control the process.

7.3.4 *Quality records and retention samples*

The manufacturer should establish and maintain procedures for identification, collection, indexing, filing, storage, maintenance and availability of quality records. Quality records should be maintained to demonstrate achievement of the required quality and the effective operation of the quality system. These data should include pertinent subcontractor quality records.

All quality records should be legible and identifiable to the product involved. Quality records should be stored and maintained in such a way that they are readily retrievable, in facilities that provide a suitable environment to minimize deterioration or damage and to prevent loss. Retention times of quality records should be established and recorded. Where agreed contractually, quality records should be made available for evaluation by the purchaser or the purchaser's representative for an agreed period.

All appropriate records relating to inspection and testing must be available for review. Where the process is continuously monitored, acknowledgement must be made of this and the results of the monitoring should be available.

Reserve samples of the released excipient should be retained for one year after the expiry or re-evaluation date, or for one year after distribution is complete. Sample size should be twice the amount required to perform release specification testing.

7.3.5 *Stability studies*

Many excipient products are very stable and may not require extensive testing to check stability. The stability of some excipients may be affected by undetected changes in starting material specifications, or subtle changes in manufacturing procedures. Excipients may also be shipped in a large variety of different packaging types that can affect their stability (e.g. metal and plastic drums, bags, plastic and glass bottles, bulk tankers).

Some excipients may be similar in chemical structure to other excipients, and some may be mixtures or blends of other excipients. These excipients may be very similar to others within a product group. Minor quantitative differences of some of the components may be the only significant variation from one product to another. For these excipients, a "model product" approach to assess the stability may be

appropriate. Stability studies of this type should involve selection of several "model products" that would be expected to simulate the stability of the product group being assessed. This selection must be scientifically based. Data from stability studies of these "model products" can be used to determine the theoretical stability of similar products.

The full stability testing programme, when needed, usually contains the following features and takes into account historical data:

- The programme should be formalized in writing and ongoing studies should be reviewed at least annually.
- The programme should periodically include a sample from at least one commercial size batch.
- Stability samples should be stored in containers that approximate the primary market container. Simulations of all types of containers are not required, unless there are theoretical reasons to indicate that stability may be affected by container type.
- The samples should be stored under conditions similar to those recommended for the marketed excipient product.
- Additional samples may be stored under stress conditions (e.g. elevated temperature, light, humidity or freezing) if such conditions might reasonably be encountered during distribution and storage.
- Stability-indicating test methods should be used.
- Where stability of the excipient appears to be a significant issue in its use in pharmaceutical manufacturing, additional periodic testing of either the specific material or "model products" may have to be performed to ensure that the expected stability does not significantly change with future batches. The frequency of testing should be determined by the impact that the excipient's stability may have on its usage.

7.3.6 *Expiry/re-evaluation dating*

Conducting a stability testing programme does not necessarily mean that expiry dates must be used. Where stability testing indicates a limited shelf-life, the label should declare an expiry date or indicate the need for re-evaluation testing at an appropriate interval to assure quality at time of use.

If the need for special storage conditions exists (e.g. protection from light, heat) such restrictions should be placed on the label.

7.3.7 *Calibration of measuring and test equipment*

All measuring and test equipment identified as being part of the quality system should be properly calibrated and maintained. This includes all in-process instruments identified as critical quality instruments, as well as test equipment used in the laboratory. The control programme should include the standardization or calibration of reagents, instruments, apparatus, gauges and recording devices at suitable intervals, in accordance with an established written programme containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event that accuracy and/or precision limits are not met. Reagents, instruments, apparatus, gauges and recording devices not meeting established specifications should not be used. Computer systems used to verify that the product conforms to specifications must be audited to ensure satisfactory performance in the laboratory.

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Annex 6
Guidelines for inspection of drug distribution channels

Introductory note

The quality assurance of drugs at the level of the manufacturer is outlined in the guidelines on good manufacturing practices for pharmaceutical products (GMP) published by WHO (*1*). Compliance with these guidelines will ensure that products released for distribution are of the appropriate quality. However, if this is to be

realized in practice, it is essential that an established drug regulatory authority exists in a Member State, which complies at least with the "Guiding principles for small national drug regulatory authorities" (*2*).

In addition, the holder of a marketing authorization for a pharmaceutical product, or alternatively the (legal) person responsible for the initial marketing of a product, who ideally should be a pharmacist or a pharmaceutical company authorized to practise in the Member State, should ensure that the product is only released for distribution after it has been established that it conforms with the product specification lodged with the drug regulatory authority.

This level of quality should be maintained throughout the pharmaceutical supply system or distribution network. Basic principles of GMP are applicable to wholesale operations and (to some extent) to retail outlets. These principles may be summarized as follows:

— only authorized products are distributed;
— a quality system is in place which includes quality policy, quality management, appropriate analytical controls, self-inspection;
— personnel are quality-conscious, adequately trained and motivated;
— premises and equipment are suitable for their intended use, and kept in a good sanitary condition;
— all products are received, stored and handled appropriately (protected against contamination, cross-contamination, mix-ups, environmental factors such as heat, severe cold, moisture, light);
— all drug-related operations are performed in accordance with written procedures, are properly supervised and adequately documented; documentation ensures complete traceability of receipt of all materials, quality testing processes (if any) and shipping;
— adequate provisions exist to handle complaints, recalls, and returned goods.

At the same time, many provisions of the GMP guidelines published by WHO are clearly not addressed to wholesalers and retail pharmacies where specific rules and requirements apply. These rules are determined partly by pharmaceutical science and common sense, and partly by national (regional) regulations and standards. In this context reference is made particularly to the guidelines entitled "Good pharmacy practice in community and hospital pharmacy settings" (*3*). It follows then that the "Provisional guidelines on the inspection of pharmaceutical manufacturers" (*4*), which are directed to

government GMP inspectors, are not adequate to cover inspection in the distribution system. The present document addresses this specific issue.

These guidelines are intended for use by pharmaceutical inspectors in national drug regulatory authorities. They are therefore presented in a format that will allow for easy reference in the field. They should, however, be adapted by national drug regulatory authorities to suit their national legal requirements and available resources.

This document discusses the "simplified" situation when there is a single authority, the drug regulatory authority, where all kinds of drug inspections are located, ranging from those of drug manufacture to the inspections of pharmacies. In reality, these tasks, requiring different inspection skills are usually distributed among different (national and local) authorities.

General considerations

A comprehensive system to assure the safety, efficacy and quality of pharmaceutical products at a national level has the following elements:

- Legal: drug legislation
- Administrative:
  - drug regulatory authority with functions of product registration, licensing of manufacturers, importers and distributors (wholesale, retail and for institutional supply), inspection and independent testing of samples
  - enforcement
- Technical:
  - regulations
  - standards and norms
  - guidelines
  - independent quality control laboratory(ies)

This document focuses on one element—inspection—and in particular on inspection in the pharmaceutical supply system.

The usefulness of drugs in the treatment of ailments, diseases and disorders is well recognized and appreciated. It is also recognized that the inappropriate use of drugs can produce severe toxic effects, some of which may be fatal. National drug laws have therefore been introduced to reduce risks associated with the use, misuse and abuse of pharmaceutical preparations.

Drugs differ in the severity of their side-effects and toxicity and these differences are taken into consideration in the classification of drugs in national drug laws. Drugs may be classified into four types as follows: over-the-counter drugs, pharmacy-only drugs, prescription-only drugs and prohibited drugs.

The distribution, supply, import, export, sale, storage, advertisement and dispensing of drugs are normally regulated by national drug laws, which provide for a system of licences to be issued by a drug regulatory authority for such drug-related activities. The drug laws may identify a ministry/department/agency that would function as the drug regulatory authority as well as provide for the enforcement of the drug laws, using a system of inspections organized through an inspectorate(s).

The inspectorate advises on whether applicants and premises should be issued licences to engage in drug-related activities. The inspectorate ensures that counterfeit, spurious and substandard pharmaceutical products are not found in the national pharmaceutical supply system or outside it, and that licensed premises and authorized persons adhere to existing laws and regulations. To do this, the inspectorate gathers information on the working of the drug laws by liaising with other law enforcement agencies and health institutions, including health-care professional associations.

Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

batch
A defined quantity of any drug product processed in a single process or series of processes such that it can reasonably be expected to be uniform in character and quality.

batch number[1]
A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificate of analysis, etc.

controlled drugs
Narcotic drugs and psychotropic substances regulated by provisions of national drug laws.

[1] As defined in "Good manufacturing practices for pharmaceutical products" (*1*).

counterfeit pharmaceutical product
A pharmaceutical product which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients, with the wrong ingredients, without active ingredients, with an insufficient quantity of active ingredient or with fake packaging.

drug (pharmaceutical product)
Any substance or mixture of substances that is manufactured for sale or distribution, sold, supplied, offered for sale or presented for use in:

(i) the treatment, mitigation, cure, prevention or diagnosis of disease, an abnormal physical state or the symptoms thereof and abnormal physiological conditions in human or animal; or
(ii) the restoration, correction or modification of organic functions in human or animal.

finished pharmaceutical product
A pharmaceutical product that has undergone all stages of production and quality control, including being packaged in its final container and labelled.

good manufacturing practice[1]
Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

good pharmacy practice
The practice of pharmacy aimed at providing and promoting the best use of drugs and other health care services and products, by patients and members of the public. It requires that the welfare of the patient is the pharmacist's prime concern at all times.

over-the-counter drugs
These are drugs that can be sold from licensed dealers without professional supervision and without prescriptions. These drugs are suitable for self-medication for minor diseases and symptoms.

[1] As defined in "Good manufacturing practices for pharmaceutical products" (*1*).

pharmacist
A pharmacist is a holder of a degree or diploma in pharmacy from a recognized higher institution of learning and is registered or licensed to practise pharmacy.

pharmacy-only drugs
These are drugs authorized to be sold only in licensed pharmacies under the supervision of licensed and registered pharmacists; they may be sold without a prescription.

poison
A preparation or substance defined by a national drug law as a poison.

prescription-only drugs
These are drugs supplied only in licensed pharmacies on the presentation of signed prescriptions issued by a licensed and registered medical practitioner, licensed and/or registered dentist (for dental treatment only), and/or licensed and/or registered veterinarian (for animal treatment only), and the supply and dispensing of these drugs must be carried out by a pharmacist or under the supervision of a pharmacist. Prescription drugs are further subdivided into controlled drugs (narcotic drugs and psychotropic substances) and non-controlled drugs.

product recall
Product recall is a process for withdrawing or removing a pharmaceutical product from the pharmaceutical distribution chain because of defects in the product or complaints of serious adverse reactions to the product. The recall might be initiated by the manufacturer/importer/distributor or a responsible agency.

prohibited drugs
These are drugs with toxicity or side-effects that outweigh their therapeutic usefulness, so that public health and welfare are protected by prohibiting their production, manufacture, export, import, trade, distribution, supply, possession or use, except in amounts required for medical and scientific research. Prohibited drugs are normally determined by the national or supranational registration/licensing authority.

quality assurance[1]
Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the

[1] As defined in "Good manufacturing practices for pharmaceutical products" (*1*).

totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

quality control
Quality control covers all measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

unauthorized market (in some countries called parallel market)
The unauthorized market consists of wholesale establishments and retail outlets distributing or selling drugs without authorization from a competent authority.

1. Drug inspectors

1.1 *Qualifications*

Inspectors should normally be pharmacists who have working experience in community and/or hospital pharmacy. Where persons other than pharmacists are employed as drug inspectors, they should be adequately experienced in drug control affairs and suitably trained in inspectorate functions. The possibility of having part-time inspectors with specialist knowledge as part of inspection teams should also be considered.

The inspector should possess the following attributes:

— good knowledge of pharmacy, drugs, and poisons
— good knowledge of the laws and regulations to be enforced
— good command of technical terms and excellent communication skills
— awareness of the probable methods of using forged or false documents for transactions in pharmaceutical preparations and skill in determining the genuineness of documents presented for examination
— maturity, honesty and integrity
— responsible conduct which commands respect
— willingness to accept challenges
— ability to organize their own work with minimum supervision
— ability to assess facts quickly and take rational and sound decisions without delay

— ability to assess character and honesty of persons being interviewed
— good public relations image with key personnel/pharmacists in charge of premises while remaining firm, fair and resolute
— ability to hold discussions with company management at the completion of inspection
— ability to motivate others
— commitment to hard work and long hours
— ethical approach to any potential conflict of interest.

1.2 *Organizational aspects*

Inspectors should be embedded in an organization, usually called an inspectorate, which ensures the following aspects:

- A job description which describes the duties of the inspector.
- Proper reporting: inspectors should report either to the drug regulatory authority or to the pharmaceutical department (chief pharmacist) of the ministry of health.
- Uniformity of approach:
  (a) Regular meetings of inspectors, in which experiences on the job are exchanged, will help promote a uniform approach to inspection as well as enhance the performance of the inspectors.
  (b) Inspectors should work according to a work plan and to Standard Operating Procedures (SOPs).
  (c) Inspection reports should preferably be in three or four parts:
    (i) date of inspection and general information on the establishment inspected,
    (ii) description of the inspection activities undertaken, including analytical data of samples taken,
    (iii) observations and recommendations,
    (iv) conclusions.
  (d) Inspectors should be encouraged to submit weekly reports of work to headquarters.
- Total coverage of the country. This can be achieved by:
  (a) dividing the country into defined areas for the purpose of inspection and placing an inspector in charge of a defined area for the purpose of inspecting wholesale, community and hospital pharmacies, and clinics,
  (b) inspection of ports and border posts in a defined area.
- Total coverage of the field. The inspector will be expected to inspect establishments such as:

(a) pharmaceutical manufacturers in respect of drug distribution,
(b) pharmaceutical importers/exporters,
(c) pharmaceutical wholesalers and retailers,
(d) hospital pharmacies/clinics,
(e) ports and international border posts,
(f) drug warehouses, stores and unauthorized markets.
(*Note*: The existence of unauthorized markets for the distribution of drugs poses considerable health hazards. The inspectors should, with the assistance of task forces if necessary, investigate the extent of the unauthorized market, the types of drugs distributed and supplied, and the sources of the drugs. Where possible, unauthorized markets for drugs should be prohibited through effective inspectorate activities. Inspectors should also investigate the sources of supply of suspect counterfeit or substandard pharmaceutical products.)

- Cooperation with other agencies. The inspector will be expected to interact and cooperate with other interested parties such as:

(a) industrial, community and hospital pharmacists,
(b) management and supervisory staff of pharmaceutical establishments and hospitals,
(c) medical practitioners, dentists, veterinarians, nurses and midwives and other health workers,
(d) public analysts,
(e) ministry of justice officials and court officials,
(f) drug law enforcement officers including the police and customs,
(g) officers of port authorities, clearing agents at the ports, importers and exporters,
(h) members of the public,
(i) staff of faculties of medicine/pharmacy,
(j) foreign drug regulatory authorities.

- Independence. Inspectors should, for example, have the use of official vehicles.

- Adherence to a code of inspection.

1.3 *Methods of inspection*

The inspector uses different methods to check compliance with the national, supranational or international drug laws and regulations. Among these methods are:

- *Comprehensive/routine inspection*. This form of inspection is generally reserved for a new pharmaceutical establishment, when an

establishment is applying for permit to extend its scope of operations beyond that for which it was originally licensed, has made important changes in key personnel or is changing premises, has not been inspected for a long time (3–5 years), or when there is information (even of an informal nature) of serious lapses. Where the inspection is for a new establishment or for extension of scope of operation or because of changes in key personnel, the inspection should be announced.

- *Concise inspection.* This is reserved for establishments that have previously been inspected with a view to assessing standards of good pharmacy practice. The outcome of the inspection will help in the proper assessment of the establishment. The inspection may be unannounced.
- *Follow-up inspection.* This is normally carried out to ensure that corrective measures have been undertaken following advice and notice given during a previous inspection. Where a time limit was given for applying the corrective measures, the inspection may be unannounced.
- *Special inspection.* This is undertaken to deal with specific complaints received about lapses or non-compliance with standards of professional practice. The inspection should preferably be unannounced.
- *Investigative inspection.* This type of inspection is used to assess the performance of a new establishment whose scope of operation was previously unknown.

Any of these methods may be applied with or without prior announcement. Normally inspections should be announced but it serves a useful purpose to undertake some unannounced inspections. Follow-up, special and investigative inspections should preferably be unannounced.

Inspections should be held regularly. Premises should be inspected at least once every 12–18 months. Where contravention is often noticed, the inspection should be more frequent (e.g. every six months). For premises with a good record, less frequent inspections may be needed.

1.4 *Reference/information sources*

The reference/information sources of an inspector should include:

- Existing national and international drug laws and regulations, covering such aspects as:

— licensing
— GMP
— good distribution practice
— good pharmacy practice
— promotion of pharmaceutical products
— controlled drugs
— counterfeit, spurious or substandard pharmaceutical products.

- Codes of inspection (national and regional), where in existence.
- Codes of professional ethics.
- Health consequences of drug abuse and misuse.
- Available data on imports/exports/prohibited drugs.

2. Inspection of establishments in the drug distribution chain

2.1 *Broad objectives*

The welfare of patients and other members of the public is of prime concern in the distribution chain of drugs, either manufactured within the country or imported. Inspections of establishments are therefore undertaken to ensure:

- Protection of patients and members of the public from malpractice by distributors and suppliers of drugs.
- Adherence to the drug laws and regulations governing compounding, distribution, importation, export and storage of drugs.
- High ethical and professional standards of pharmaceutical practice.

2.2 *Establishments*

In the drug distribution chain several kinds of establishments can be distinguished:

— production sites
— storage or warehouse facilities
— establishments for the supply, sale, dispensing and distribution of drugs, such as pharmacies, hospitals, clinics, ports and stores.

2.3 *Inspections*

When inspecting these establishments the inspector uses the appropriate references. The method of inspection should be laid down in a SOP which also contains the requirements for a specific type of establishment. The inspection SOP may be in the format of a checklist (see Appendix 1 for an example applicable to most drug distribution establishments). When sampling is part of the inspection procedure, the

SOP should contain detailed guidance for the inspector; an example of this guidance is to be found in Appendix 2.

2.4 *Special categories of drugs*

When special categories of drugs are present the inspector may require a modified SOP. This situation is likely to occur with controlled drugs, pharmaceutical products moving in international commerce, or with counterfeit, spurious or substandard pharmaceutical products. For this last category an example of extra guidance is given in Appendix 3.

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Appendix 1

Checklist for inspection and the preparation of a report

Inspection applicable to all drug distribution establishments

1. ***General information***

   (a) name of establishment inspected
   (b) date of inspection
   (c) name(s) of the inspector(s)
   (d) date of last inspection.

2. ***Type of inspection***

   Comprehensive, concise, follow-up, special, investigative, announced, unannounced.

3. ***Licensing***

   (a) licensing of premises
   (b) person with supervisory role in establishments handling prescriptions and pharmacy sale-only drugs (is normally a registered pharmacist or a person so prescribed by national legislation)
   (c) personnel authorized to sell only over-the-counter drugs (licensed, where such licensing is required)
   (d) adherence to licensing provisions.

4. ***Activities undertaken on premises***

   Manufacturing, wholesale, importation, export, retail, hospital pharmacy, clinic, nursing and maternity homes.

5. ***Adequacy and suitability of premises***

   (a) premises clean, tidy and in good state of repair
   (b) premises secure
   (c) floor durable and easily cleaned
   (d) premises constructed to prevent infestation by vermin and pests
   (e) clean shelves in retail pharmacy and premises for sale of over-the-counter drugs
   (f) changing rooms and toilet available
   (g) adequacy of lighting and ventilation
   (h) appropriate layout of premises.

6. ***Warehouse/store***

   (a) adequacy and suitability of warehouse/store
   (b) warehouse/store clean and uncluttered

(c) warehouse/store inaccessible to unauthorized persons
(d) temperature and humidity control
(e) enforcement of stock rotation
(f) adequacy of shelving
(g) existence of areas for returned drugs, recalled drugs, expired drugs, and drugs in quarantine
(h) warehouse/store free from vermin and insects.

7. ***Special storage***

(a) availability of cold room storage or refrigerator for vaccines and biological products
(b) suitability of the cold storage facilities
(c) standard written procedure prepared by an appropriate national regulatory agency for the maintenance of cold chain
(d) special storage area for controlled drugs and other prescription drugs
(e) suitable and secure storage facility for controlled drugs and poisons.

8. ***Record-keeping***

(a) name and address of supplier of each drug product with date
(b) name and address of purchaser of each drug product with date
(c) supplier or purchaser licensed
(d) retention of order forms, copy of delivery notes, stores receipt and issue vouchers, and book of records (controlled drugs book/ prescription drugs book) on the premises as provided for in the drug laws
(e) accuracy of records kept.

9. ***Conditions for sale and supply***

(a) sale and supply of prescription and pharmacy sale-only drugs under the control of a registered pharmacist
(b) sale and supply prescription and pharmacy sale-only drugs effected from registered/licensed premises
(c) sale of prescription drugs on the basis of valid prescription
(d) sale and supply of over-the-counter drugs undertaken in registered premises under the supervision of a pharmacist or premises licensed for the purpose of sale and supply of over-the-counter drugs only, where such registration or licence is required by law.

10. ***Diversion of controlled drugs***

Diversion of controlled drugs prevented by examining the records and by physical examination of stock.

11. ***Returned and expired drugs***

Procedures in place for handling returned and time-expired drugs.

12. ***Product recall***

Procedures in place for recall of drugs and handling recalled drugs.

13. ***Product complaints***

Procedures in place for dealing with complaints about drugs.

14. ***Promotional activities***

Assess promotional materials for compliance with drug laws.

15. ***Personnel***

(a) person responsible for supervising sale in a wholesale/retail pharmacy is a registered/licensed pharmacist
(b) name of the pharmacist in continuous personal control noted
(c) personnel wear clean protective clothing.

16. ***Labelling of drug products and package inserts***

Check adequacy of labelling of drug and information on package inserts.

17. ***Physical examination and sampling of drugs***

Conduct physical examination of drugs in stock and take samples of drugs for quality assessment.

18. ***Reference books***

Check existence of reference books on premises, where they are required.

Specific inspection applicable to individual establishments

19. ***Importer***

(a) all drugs accompanied by import documents such as bill of lading, export authorization, product licence and batch certificate
(b) controlled drugs also accompanied by export authorization certificate or export declaration, whichever is applicable
(c) imported drugs are in original packs, except for drugs imported in bulk for repackaging and/or manufacturing drug formulations.

20. ***Retail and hospital pharmacy***

(a) compounding of drugs carried out by or under the supervision of a pharmacist

(b) quality of raw materials used in compounding complies with pharmacopoeial specifications
(c) dispensing of prescription drugs carried out by or under the supervision of a pharmacist
(d) entries of dispensed prescription drugs made in prescription book and for controlled drugs in controlled drugs book
(e) prescriptions for prescription drugs retained on premises for periods provided in the drug laws
(f) dispensed drugs labelled appropriately with name of drug, name of patient, name and address of pharmacy, clinic or hospital, instructions for using the drugs and, where appropriate, warning labels
(g) counselling of patients on use of dispensed drugs
(h) adequacy of containers for dispensed drugs
(i) personnel observe high standard of personal hygiene and wear clean protective clothing
(j) dispensing area clean, adequate and has necessary equipment
(k) walls in dispensing area easily cleaned
(l) quality of extemporaneous preparations
(m) sources of drugs sold and supplied from the pharmacy
(n) suitable cabinets for storage of controlled drugs and poisons.

21. ***Clinics, nursing and maternity homes***

(a) sources of drugs used, supplied and administered
(b) records of controlled drugs used, supplied and administered
(c) storage facilities and security for controlled drugs.

22. ***Unauthorized markets***

(a) investigate sources of drugs in the unauthorized market
(b) sample drugs for quality assessment
(c) seize drugs in the unauthorized market.

Appendix 2
Guidance on sampling

This guidance is applicable to collecting samples of drugs to be tested by the official quality control laboratory. The collection may be aimed either at assessing the quality of products on the market, in which case adequate sampling plans should apply (see, for example, "Sampling procedures for industrially manufactured pharmaceuticals" (*1*, *2*)), or at detecting substandard, spurious and counterfeit pharmaceutical products. In this case sampling shall be based on information and may involve confiscation of entire stocks to prevent further distribution. Compliance with legal procedures for sample collection, analysis and documentation is obligatory.

(a) Check that the sample is properly labelled with the following:
  (i) name of sampled pharmaceutical preparation
  (ii) batch number
  (iii) date and source of sample; the original manufacturer's label may be helpful.

(b) Check that the records contain the following:
  (i) number of samples
  (ii) types of packaging and storage conditions
  (iii) circumstances of sampling that may include suspected quality defects.

(c) Place seals on containers of the samples.

(d) Hand over one-third of the samples to the representative of the inspected establishment.

(e) Confirm in writing that samples were taken from the premises and have the confirmation countersigned by an appropriate official of the inspected establishment (see, for example, the sample receipt form in Appendix 4).

References

1. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report.* Geneva, World Health Organization, 1990, Annex 2 (WHO Technical Report Series, No. 790).

2. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials, Vol. 1.* Geneva, World Health Organization, 1997.

Appendix 3

Guidance for inspection when pharmaceutical products are suspected to be counterfeit, spurious or substandard

This section addresses specifically the situation in which the inspector suspects counterfeit, spurious or substandard pharmaceutical products to be present during an inspection. This may be during either a regular inspection or an investigation aimed at detecting such products.

1. Broad objective

The presence of counterfeit, substandard and spurious pharmaceutical products in the drug distribution channels may present a danger to public health, and it is imperative that suspect products are effectively and rapidly taken out of the distribution channels and quarantined. In order to facilitate the work of the inspector, the help of capable and experienced persons involved in the distribution of products should be obtained on a proactive basis to help identify such products.

2. Standard operating procedures

(a) A written SOP for inspectors should be drawn up and made available to them.

This SOP should include at least the following information:

(i) how the suspect product should be isolated to prevent its further distribution
(ii) the size of the samples required for testing purposes
(iii) the manner in which the samples should be taken
(iv) the record-keeping procedure to be followed in recording the details of the action taken
(v) the details which should be recorded on the receipt issued for the embargoed product and/or samples taken
(vi) the type of materials which should be used for sealing samples or for embargoing or confiscating suspect products
(vii) the names, addresses and telephone numbers of persons who should be contacted to report on the action taken
(viii) special precautions to be noted by the person initiating the sampling or seizure procedure, with particular reference to correct legal procedures to be followed
(ix) where appropriate, the manner in which the suspect product should be destroyed.

(b) Where other persons are involved in the detection of counterfeit pharmaceutical products they shall operate on the basis of a suitable SOP. In any case of suspicion of counterfeit pharmaceutical products an inspector shall be notified immediately.

3. Counterfeit products

The following applies specifically to counterfeit products:

(a) When examining a possible counterfeit pharmaceutical product the inspector shall first screen the product by looking, smelling, touching and listening to the sound of the packing and its contents. The inspector shall look for anything, in particular its labelling and packing, that makes the product look different from an original reference sample. A SOP may assist in examining the product in this way.

(b) When the organoleptic examination does not give conclusive evidence the inspector shall have a sample tested using appropriate simple screening methods, such as the basic tests recommended by WHO or a suitable thin-layer chromatography method.

(c) In addition to any full analytical testing, the drug regulatory authority of the country of origin stated on the label of the product may be asked to establish whether the product is counterfeit.

(d) Proven cases of counterfeit pharmaceutical products shall be fully documented and communicated to all other inspectors, to increase their level of expertise. Information on counterfeit products shall also immediately be made available to drug regulatory authorities of other countries concerned and to WHO.

Appendix 4
Sample receipt form

Institution/company (under inspection) .....

Address .....

.....

Date of inspection .....

Name of representative of the inspected establishment .....

Name of inspector .....

Name of the drug and description of sample .....

.....

Dosage form .....

Batch no. .....

Place sampled (warehouse, production line, packaging section, etc.)

.....

No. of samples taken (tins, packets, etc.) .....

.....	.....
Signature	Signature
Inspector	Representative of the inspected establishment

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Annex 7
Good pharmacy practice in community and hospital pharmacy settings

Background

Following the adoption of WHO's revised drug strategy by the Thirty-ninth World Health Assembly in 1986, WHO organized two meetings on the role of the pharmacist — in New Delhi in 1988 and in Tokyo in 1993 (*1*). These meetings were followed by the adoption by the Forty-seventh World Health Assembly of resolution WHA47.12 on "The role of the pharmacist in support of the WHO revised drug strategy" in May 1994.

In 1992, the International Pharmaceutical Federation (FIP) developed standards for pharmacy services under the heading "Good pharmacy practice in community and hospital pharmacy settings". These were circulated in March 1993 to WHO information officers for comments. The FIP Congress held in Tokyo in 1993 adopted this text on good pharmacy practice in the context of the Tokyo declaration on standards for quality of pharmacy services, which reads as follows:

> Standards are an important part in the measurement of quality of service to the consumer.
>
> The International Pharmaceutical Federation (FIP) in adopting international guidelines for Good Pharmacy Practice at its Council Meeting in Tokyo on September 5, 1993 believes that standards based on these guidelines should be used by national pharmaceutical organisations, governments and international pharmaceutical organisations for nationally accepted standards of Good Pharmacy Practice.
>
> The Good Pharmacy Practice guidelines are based on the pharmaceutical care given by pharmacists. The guidelines recommend that national standards are set for: the promotion of health, the supply of medicines, medical devices, patient self care, and improving prescribing and medicine use by pharmacists' activities. FIP urges pharmaceutical organisations and governments to work together to introduce appropriate standards or, where national standards already exist, to review these standards in the light of the guidelines set out in the Good Pharmacy Practice document.

The text on good pharmacy practice was also submitted to the meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations held in Geneva from 28 November to 2 December 1994. In its thirty-fourth report, the Expert Committee thanked FIP for drawing its attention to the text on good pharmacy practice. The Expert Committee welcomed the initiative in so far as it provided a basis for implementation of some of the principles embodied in resolution WHA47.12. However, the Expert Committee felt it was unable to endorse the text unless it was expanded to reflect current emphasis on the pharmacist's specific responsibility for assuring the quality of pharmaceutical products throughout the distribution chain. The Expert Committee suggested that particular attention should be paid to the current inadmissible prevalence of substandard and counterfeit products in some national markets.

The recommendations made in the thirty-fourth report of the Expert Committee are similar to comments received from governments when the text was first circulated by WHO in 1993. They have been accommodated in the text given below.[1]

Introduction

All practising pharmacists are obliged to ensure that the service they provide to every patient is of appropriate quality. Good pharmacy practice is a means of clarifying and meeting that obligation.

The role of FIP is to provide leadership for national pharmaceutical organizations which in turn provide the impetus for setting national standards[2]. The vital element is the commitment of the pharmacy profession throughout the world to promoting excellence in practice for the benefit of those served. The public and other professions will judge the profession on how its members translate that commitment into practice in community and hospital pharmacy settings.

This document is intended to encourage national pharmaceutical organizations to focus the attention of pharmacists working in community and hospital pharmacies on developing the elements of the service they provide to meet changing circumstances. It would be inappropriate for WHO or FIP to set standards or list the minimum

[1] This revised text was endorsed by the FIP Congress in September 1997.

[2] Throughout this document, the term "national standards" includes laws, regulations, standards, ordinances or other requirements enacted or promulgated by an official body at any level of government, as well as guidelines, recommendations or other pronouncements of professional organizations of pharmacy.

requirements which must be achieved in all member countries. The conditions of practice vary widely from country to country and each national pharmaceutical organization is best able to decide what can be achieved and within what time-scale.

National pharmaceutical organizations should also take action to ensure that pharmaceutical education, both pre-university and post-university qualification, is designed to equip pharmacists for the roles they have to undertake in community and hospital practice. Thus, within the necessary base of pharmaceutical sciences there must be adequate emphasis on the action and uses of medicines, there should be a reasonable introduction in the pre-university qualification course to the relevant elements of the social and behavioural sciences; and at all stages of pharmaceutical education the development and improvement of communication skills should be given due emphasis.

This document provides a framework within which each country can develop aspirations and standards that suit its situation and meet its needs.

In developing these standards, important differences between countries have to be recognized. Affluent countries usually have effective drug regulatory systems that are based on legislation. These monitor and assure the quality of industrially produced pharmaceutical products by several means: the issuance of product licences or marketing authorizations; the licensing and inspection of pharmaceutical manufacturers, wholesale and other distributors, community and hospital pharmacies and other drug outlets; and occasional quality control in a government laboratory. Many developing countries lack an effective drug regulatory system, which puts the main responsibility for the quality of pharmaceutical products on the pharmacists. These then have to rely on their own, or their pharmacists' association's, quality assessment and must make sure that they procure medicines only from reliable sources. The FIP has developed special guidelines for drug procurement (*2*).

There are numerous reports of an unacceptable prevalence of sub-standard and counterfeit pharmaceutical products in international trade. Developing countries are the ones most frequently exposed to such products which may be inefficacious or toxic and which threaten to erode confidence in the health care system. It was for this reason that in May 1994 the Forty-seventh World Health Assembly, in adopting resolution WHA47.12 on the role of the pharmacist in support of the WHO revised drug strategy, drew attention to pharmacists' responsibilities in assuring the quality of the products they dispense.

Underlying philosophy

The mission of pharmacy practice is to provide medications and other health care products and services and to help people and society to make the best use of them.

Comprehensive pharmacy service involves activities both to secure good health and to avoid ill-health in the population. When ill-health is treated, it is necessary to assure quality in the process of using medicines in order to achieve maximum therapeutic benefit and avoid untoward side-effects. This presupposes the acceptance by pharmacists of shared responsibility with other professionals and with patients for the outcome of therapy.

In recent years the term "pharmaceutical care" has established itself as a philosophy of practice, with the patient and the community as the primary beneficiaries of the pharmacist's actions. The concept is particularly relevant to special groups such as the elderly, mothers and children, and chronically ill patients, as well as to the community as a whole in terms of, for example, cost containment. While the basic concepts of pharmaceutical care and good pharmacy practice are largely identical, it can be said that good pharmacy practice is the way to implement pharmaceutical care.

The requirements of good pharmacy practice

- Good pharmacy practice requires that a pharmacist's first concern in all settings is the welfare of patients.
- Good pharmacy practice requires that the core of the pharmacy activity is the supply of medication and other health care products of assured quality, appropriate information and advice for the patient, and monitoring of the effects of use.
- Good pharmacy practice requires that an integral part of the pharmacist's contribution is the promotion of rational and economic prescribing and of appropriate use of medicines.
- Good pharmacy practice requires that the objective of each element of pharmacy service is relevant to the patient, is clearly defined and is effectively communicated to all those involved.

In satisfying these requirements, the following conditions are necessary:

- Professionalism should be the main philosophy underlying practice, although it is accepted that economic factors are also important.
- Pharmacists should have input into decisions about the use of medicines. A system should exist that enables pharmacists to report

adverse events, medication errors, defects in product quality or detection of counterfeit products. This reporting may include information about drug use supplied by patients or health professionals, either directly or through pharmacists.

- The ongoing relationship with other health professionals, particularly physicians, should be seen as a therapeutic partnership that involves mutual trust and confidence in all matters relating to pharmacotherapeutics.
- The relationship between pharmacists should be as colleagues seeking to improve pharmacy service, rather than as competitors.
- In reality organizations, group practices and pharmacy managers should accept a share of responsibility for the definition, evaluation and improvement of quality.
- The pharmacist should be aware of essential medical and pharmaceutical information about each patient. Obtaining such information is made easier if the patient chooses to use only one pharmacy or if the patient's medication profile is available.
- The pharmacist needs independent, comprehensive, objective and current information about therapeutics and medicines in use.
- Pharmacists in each practice setting should accept personal responsibility for maintaining and assessing their own competence throughout their professional working lives.
- Educational programmes for entry to the profession should appropriately address both current and foreseeable future changes in pharmacy practice.
- National standards of good pharmacy practice should be specified and should be adhered to by practitioners.

Applying good pharmacy practice

Good pharmacy practice involves four main groups of activities, namely:

— activities associated with the promotion of good health, the avoidance of ill-health and the achievement of health objectives;
— activities associated with the supply and use of medicines and of items for the administration of medicines or for other aspects of treatment (these activities may be undertaken in the pharmacy, in an institution or in a home-care setting);
— activities associated with self-care, including advice about and, where appropriate, the supply of a medicine or other treatment for symptoms of ailments that lend themselves to self-treatment;

— activities associated with influencing the prescribing and use of medicines.

In addition to these groups of activities, good pharmacy practice also encompasses:

— establishment of arrangements with other health professional communities for health promotion activities at population level, including minimization of the abuse and misuse of medicines;
— professional assessment of promotional materials for medicines and other products associated with health care;
— dissemination of evaluated information about medicines and various aspects of health care;
— involvement in all stages of clinical trials.

Setting standards for good pharmacy practice

For each of the four main elements of good pharmacy practice, national standards should be established in relation to processes and facilities. These standards should be promoted among members of the profession.

Promotion of health and prevention of ill-health

National standards are needed for:

— facilities for confidential conversation that cannot be overheard by others;
— provision of general advice on health matters;
— involvement of personnel in briefings for specific campaigns to ensure coordination of effort and consistency of advice;
— quality assurance of equipment used and advice given in diagnostic testing.

Supply and use of prescribed medicines and other health care products

Activity: Reception of the prescription and confirmation of the integrity of the communication

National standards are needed for:

— facilities;
— procedure;
— personnel.

Activity: Assessment of the prescription by the pharmacist

This activity involves therapeutic aspects (pharmaceutical and pharmacological), considerations of appropriateness for the individual, and social, legal and economic aspects.

National standards are needed for:

— information sources;
— competence of personnel;
— medication records.

Activity: Assembly of the prescribed items

National standards are needed for:

— sources of supply of medicines and other items; manufacture of medicines;
— storage;
— condition at time of supply to the patient;
— personnel involved;
— equipment required;
— facilities and workplace required;
— preparation and quality assurance of extemporaneous preparations;
— disposal of unused pharmaceutical products and pharmaceutical waste.

Activity: Advice to ensure that the patient or carer receives and understands sufficient written and oral information to derive maximum benefit from the treatment

National standards are needed for:

— facilities for confidential conversation that cannot be overheard by others;
— information sources;
— procedures to be followed and the appropriate documentation of these procedures;
— competence of personnel involved.

Activity: Following up the effect of prescribed treatments

National standards are needed for:

— procedure to be followed in regular, systematic evaluation of progress or outcomes of treatment for individual patients or for groups of patients;
— access to necessary monitoring equipment and facilities;
— quality assurance of monitoring facilities.

Activity: Documentation of professional activities

National standards are needed for:

— recording professional activities and pertinent data in a manner that allows access to comprehensive information;
— procedures for self-assessment of professional activities and quality assurance.

Self-care

National standards are needed for:

— facilities for confidential conversation that cannot be overheard by others;
— qualifications of personnel to be involved;
— ways of correctly assessing need (e.g. finding out who has the problem, what the symptoms are, how long the condition has existed, what action has already been taken, which medicines are already being taken);
— efficacy and safety of products recommended;
— timing of referral to the medical practitioner and methods of follow-up.

Influencing prescribing and medicine use

National standards are needed for:

— quality of prescribing data provided to the pharmacist;
— preparation of formularies on medicines;
— contacts with physicians on individual prescribing;
— evaluation of data on the use of medicines in medical and pharmaceutical practices;
— assessment of promotional materials;
— dissemination of evaluated information within a formal network;
— educational programmes for health professionals;
— reference sources available to the pharmacist;
— confidentiality of data relating to individual patients;
— reporting of adverse events, medication errors, defects in product quality and detection of counterfeit products.

Documentation and research

Pharmacists have a professional responsibility to document practice experience and activities and to conduct and/or participate in pharmacy practice research and therapy research.

Achieving good pharmacy practice

Specific standards of good pharmacy practice can be developed only within the framework of a national organization.

These guidelines are recommended as a set of professional goals in the interest of the patients or customers in the pharmacy. Responsibility for moving the project forward will rest with each national pharmaceutical organization. Achieving specific standards of good pharmacy practice for each nation within these guidelines may require considerable time and effort. As health professionals, pharmacists have a duty to begin the process without delay.

References

1. *The role of the pharmacist in the health care system. Report of a WHO consultative group, New Delhi, India, 13–16 December 1988 and Report of a WHO Meeting, Tokyo, Japan, 31 August – 3 September 1993.* Geneva, World Health Organization, 1994 (unpublished document WHO/PHARM/94.569; available on request from Division of Drug Management and Policies, WHO, 1211 Geneva 27, Switzerland).
2. *FIP Guidelines for drug procurement.* The Hague. International Pharmaceutical Federation, 1992.

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Annex 8
National drug regulatory legislation: guiding principles for small drug regulatory authorities

Introduction

Countries in both the developed and developing world need to fit their approach to drug regulation to their resources. All countries share the responsibility of assuring the quality, safety and efficacy of medicinal products, including biologicals.

In order to ensure the quality of pharmaceutical products, the manufacture and subsequent handling of the products — including their distribution within the domestic market and their movement in international trade — must take place under defined conditions and in conformance with prescribed standards. Medicinal products cannot

be treated like most consumer commodities. Both legislative and administrative controls must reflect the special considerations to be applied to such products.

Provision of assistance to countries with limited resources has long been regarded as a vital element of the work of WHO. In the wake of the 1985 Conference on the Rational Use of Drugs held in Nairobi, WHO embarked on the development of two key documents, the *Guidelines for developing national drug policies* (*1*), in which legislation and regulation are identified and described as the first component of a drug policy, and the "Guiding principles for small national drug regulatory authorities", which was published in 1990 (*2*) and endorsed by the World Health Assembly in 1994 (Resolution WHA47.17). Many countries have since begun to implement drug regulatory activities in accordance with these guidelines, but some still need to develop and/or update their basic drug legislation to support drug regulation. As stated in the latter (*2*):

> Small countries which have yet to introduce comprehensive legal provisions for drug regulation can draw from a diversity of national systems in determining their own requirements. None the less, problems in establishing drug control in developing countries have too often resulted from the adaptation of provisions successful elsewhere but of a complexity that precludes their effective implementation in the country of adoption. It is of paramount importance that legislation and administrative practices are attuned to available resources and that every opportunity is taken to obtain and use information provided by regulatory authorities in other countries.

The manufacture, marketing or importation of medicinal and other health care products continues to be regulated in many countries by statutory texts that are not attuned to prevailing needs or available resources, or by independent legal provisions introduced piecemeal over a period of many years. Even where there is no specific law that relates to medicinal products, there will almost certainly be some legislative provisions that apply to health care products in general. In formulating a new law, therefore, the existing provisions must be carefully considered. There should be wide consultation with interested parties, particularly those directly concerned with manufacture, importation, distribution and supply of medicinal products.

The present guidelines, with an example of a legislative scheme for medicinal products and accompanying commentary, are intended for drug regulators, those drafting legislation and parliamentarians in countries wishing to review or elaborate legal texts to regulate

medicinal products. The first draft of these guidelines was developed after an informal consultation on drug legislation for drug regulation by small national drug regulatory authorities, held in Geneva in 1993. The text was subsequently circulated for consultation and comments to members of the responsible WHO Expert Advisory Panel, to all WHO Member States through the WHO Information Officers, and to relevant nongovernmental organizations, in particular the two nongovernmental organizations representing the pharmacy profession — the International Pharmaceutical Federation (FIP) and the Commonwealth Pharmaceutical Association (CPA). The text was revised and finalized in the light of comments received, at a further informal consultation that was convened in Geneva in 1996. It should be noted that the scheme given in section 4 is an example, and countries with different cultural and legal backgrounds might consider different approaches, although the overall content of the example would still be relevant (see Appendix 1 for a provisional legislative scheme on registration of pharmacy personnel).

These guidelines are not intended to be translated as they stand into national legislations but to be used as source documentation and to be adapted as necessary. While they should be of immediate value to many countries still in the process of establishing drug regulatory and legislative systems, other countries might also profit from such a framework. As regards the latter, it must be emphasized that authorities should always be cautious about changing systems and procedures that work effectively.

Drafting national legislation: points for consideration

These guidelines are based upon and complement the "Guiding principles for small national drug regulatory authorities" published by WHO (*2*). They are intended to assist governments in formulating laws and regulations to define and control the national market in medicinal products in the interest of public health. They describe an administrative framework for a regulatory system to ensure the quality, safety and efficacy of licensed (authorized) medicinal products, and to authorize withdrawal of unsafe and/or illicit medicinal products from the market.

The advice assumes that only in exceptional circumstances will a small authority become engaged in full evaluation of all toxicological, pharmacological or clinical properties of a novel medicinal product (for example, a new chemical entity) during the regulatory assessment for marketing authorization. In most instances, the decision will be

guided by the regulatory status of the product in the country of origin on the basis of information provided through the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (*3*). However, such approval may depend on a knowledge and acceptance of the standards and competence of the drug regulatory authority of the exporting country, by the drug regulatory authority of the importing country.

Objectives

1. The objective of the drug regulatory legislation is to provide a framework for drug regulation through the establishment of a national drug regulatory authority.

2. The primary responsibility of a drug regulatory authority is to operate a system of administration and enforcement to ensure that all medicinal products subject to a drug regulatory authority control conform to acceptable standards of quality, safety and efficacy; the promotion and marketing of medicinal products is in accordance with product information as approved; the use of drugs is rational; and that all personnel, premises and practices employed to manufacture, store, distribute and sell, supply and dispense these products comply with requirements to ensure the continued conformity of the products with these standards, up to the time of usage/consumption.

3. The objectives of the drug regulatory authority can be effectively achieved only if:

(a) there is a mandatory system to license/authorize:
  (i) all medicinal products, whether locally manufactured or imported;
  (ii) all local manufacturers, importing and exporting agents, and distributors; and
  (iii) all premises and facilities used locally to manufacture, store or distribute medicinal products.
(b) all stages of manufacture and distribution of medicinal products are supervised by appropriately qualified professional staff;
(c) the licensing/authorizing system is complemented by an efficient system of inspection with access to quality control laboratory facilities;
(d) the legislation is enforceable.

4. In addition to providing for licensing/authorizing, a law on medicinal products must define the terms of reference, powers and functions of the drug regulatory authority, the powers of enforcement, and

include provision on the right to appeal or otherwise react to the decisions of the drug regulatory authority.

Scope and extent of the legislation[1]

5. The scope of the term "medicinal product" must be defined in all encompassing terms to cover pharmaceuticals, biological products (vaccines, blood products, other biologicals) and herbal products, whether for animal or for human use, including traditional medicines sold in package form (but not products harvested by traditional medicine practitioners) and products known in many countries as "pharmafoods", "nutriceuticals", or "cosmeceuticals" intended for therapeutic use. The drug regulatory authority must also determine to what extent it intends to exempt related products, such as diagnostic materials, medical devices, cosmetics, health foods and food supplements from the scope of its marketing authorizations. The legislation must state whether it includes or excludes related products. In borderline cases it may be left to the regulatory authority to decide whether a substance or preparation is considered a medicinal product.

6. The legislation must apply to all institutions and individuals, within both the public and private sectors, that are engaged in or connected with any aspect of manufacture, promotion, procurement, distribution, sale, or supply of medicinal products.

Terms of reference for the drug regulatory authority

7. The terms of reference, functions, responsibilities, powers and composition of the drug regulatory authority must be set out in the legislation. The structure, name and style of the authority will be determined essentially by precedent. In some countries with extremely limited human resources, it may be necessary for a single individual to function in this capacity. It is particularly important to designate the advisory apparatus and to define the circumstances in which its advice must be obtained.

8. The terms of reference of the authority need to be clearly set out in the law in a way that establishes its responsibilities with respect to the following functions:

(a) to require that all medicinal products manufactured in, imported into (including donations) or exported from the country conform

[1] This text uses the terms "law" and "legislation". In formulating the legal provisions, it should be noted that certain regulatory matters will be specified in the main statute (enabling or principal law, act or decree) while other matters will be addressed in subsidiary legal texts such as orders, by-laws, regulations and the like.

to established criteria of quality, safety and efficacy, and that the personnel, premises and practices employed to manufacture, promote, procure, store, distribute and sell such products comply with defined codes of practice and other requirements;

(b) to require continued conformity of medicinal products with such standards until their delivery to the end-user;

(c) to require that medicinal products are imported, manufactured, exported, stocked, sold, distributed or otherwise dealt with by duly authorized persons;

(d) to grant or refuse, after due assessment, licences/authorizations for medicinal products, whether locally manufactured or imported, and whether destined for the national market or for export;

(e) to inspect and license/authorize all domestic manufacturing premises, importing agents, wholesalers, distributors, clinics, hospital dispensaries, retail pharmacies and other outlets where medicinal products are sold;

(f) to sample and test finished medicinal products released into the distribution chain to ensure their compliance with approved specifications;

(g) to monitor and review the implementation of the legislation; and

(h) to ensure that advertising and marketing are in accordance with product information approved by the drug regulatory authority.

Structure of the drug regulatory authority

9. In order to discharge its duties effectively, the drug regulatory authority must function within an administrative and legal environment that assures its independence of action and its access to effective channels of communication. Procedures should be laid down giving the mechanism by which members and staff of the authority are appointed, their terms of reference and duration of office. Legislative provisions need to be supplemented or complemented by administrative procedures designed to safeguard the independence, integrity, effectiveness and impartiality of the authority. For instance, administrative or disciplinary rules should specify that members and staff should not be involved in any activity that is liable to create a conflict of interest. To maintain the independence of the authority, responsibilities for regulation of medicinal products should be administratively and operationally separated from activities concerned with their procurement or distribution.

10. The authority must exercise its powers independently and impartially. Lawful and *bona fide* activities and decisions must

be protected by conferring relevant empowerment(s)/immunities on staff and others working for the authority. Conversely, provision must exist to enable affected parties to obtain relief or redress in accordance with national law. The legislation should contain a clause on the confidentiality of sensitive commercial data.

11. The conditions of service, remuneration and working arrangements must be such that vested interests cannot exert any undue influence over staff or others working for the authority.

Products, personnel, facilities and practices that are subject to regulation

12. Regulatory controls should extend to all medicinal products on the domestic market as well as those destined for export. As most developing countries rely mainly on imports to meet their drug requirements, it is important that not only the imported medicinal products themselves, but also the procedures involved in promoting, importing, storing, distributing or selling them, are regulated by law. Countries with domestic manufacturing capabilities need to ensure that regulations provide safeguards for the quality of starting materials imported or obtained locally, either through a licensing process or as part of good manufacturing practices (GMP).

Issuance of definitive product authorization/licence and transitional provisions

13. In countries without a comprehensive system in place for the regulation of medicinal products, legislation provisions must be formulated for:

— authorizing/licensing of all products proposed for marketing after the "appointed date" for the licensing system;
— transitional arrangements to ensure that products on the market before the appointed date can continue to be marketed, within the regulatory system;
— the subsequent review and full registration of products authorized under the transitional provisions; and
— the regulation of renewal of the product authorization/licence after lapse of the period for which the licence is being issued.

Product licensing/issue of marketing authorizations

14. The legislation should establish the legal framework under which applications to market medicinal products are submitted to the drug regulatory authority, and the procedure for the assessment of applications and the granting or refusal of marketing authoriza-

tions. The assessment should be based on defined criteria for safety, quality and efficacy. The legislation should place the onus on the applicant to provide information and data necessary for this assessment.

15. The legislation should provide for regulations determining the amount of licensing/authorizing and renewal fees.

Transitional arrangements

16. A procedure is proposed in the "Guiding principles for small national drug regulatory authorities" (*2*) in which an inventory is drawn up of all medicinal products on the market before an appointed date. These products have the status of being "provisionally authorized/licensed" until such time as full authorizations/licences are granted. Depending on the timing of the implementation and the availability of information on medicinal products in circulation, the inventory can be established by:

— including requirements under the legislation that manufacturers, importers and distributors of medicinal products who intend to continue to manufacture, promote, import, distribute and sell medicinal products after the appointed date must submit specified information on those products to the regulatory authority, before the appointed date;
— compiling the inventory on a more "informal" basis, from available information (price lists, publications, etc.) and data supplied voluntarily by companies.

In either case the information should be collected in a form suitable for entry into a computerized database such as the computerized drug registration system developed within WHO. This will enable the inventory of products to be organized and sorted for subsequent review (see Appendix 2).

Review of provisionally authorized/licensed products

17. The legislation should establish a framework for the review and assessment of provisionally authorized/licensed products, for full registration under the product authorization procedures for new products. The timetable for the review should be determined by administrative procedures, as the pace at which these assessments can be undertaken will depend on available resources. Priorities for the review of provisionally authorized/licensed products should normally be determined by therapeutic class and based on health-related priorities established within the national drug policy or national health framework/policy.

18. The legal mandate to request the submission of applications for re-registration of medicinal products marketed prior to the appointed day should be embodied in the legislation, but details of the format and content of applications are, again, best dealt with in regulatory guidelines, to allow greater flexibility.

Authorizing/licensing of manufacturers, importers, exporters, distributors and retail outlets

19. Organizations engaged in the manufacture, promotion, import, export, distribution, sale or supply of provisionally registered or licensed medicinal products must meet prescribed criteria or requirements regarding facilities, personnel and practices, intended to ensure the quality of the product up to the time of usage/consumption. These criteria and requirements must be specified in law. In addition to numerous resolutions of WHO's governing bodies, several texts developed under the aegis of the Organization offer guidance on the elaboration of such criteria and requirements (see Appendix 2).

Enforcement

20. The administrative capacity of the drug regulatory authority must be complemented by an effective inspectorate, suitably trained and mandated to monitor compliance with the legislation. To achieve this it is necessary to liaise with other relevant law enforcement offices attached to related government agencies or authorities, and in some countries it may also be necessary to enlist the services of these law enforcement offices. In this case, the law must contain provision to confer appropriate authority on such offices to exercise statutory powers under the law governing medicinal products.

21. Provision must exist requiring manufacturers to recall unsafe, defective or inappropriately labelled medicinal products from the market and destroy them, to suspend manufacture if facilities or operations are found to be below standard, and to cease unethical promotion activities.

22. The emergence in recent years of counterfeit and other illicit products within domestic and international markets has imposed an extra dimension on the work of regulatory authorities and inspectors. It has also created a need for enhanced collaboration between regulatory authorities, licence holders, customs officials and law enforcement authorities, and for greater vigilance by all persons involved with the manufacture, distribution and sale of medicinal products. Consideration should now be given to legal provisions that facilitate timely and efficient exchange of information between the

parties concerned, both nationally and internationally, to counteract illicit trade.

Penalties

23. The law must provide a range of specific penalties and other measures to deter violations of provisions of the legislation. Provision for the right to appeal, or other measures to react to the decisions of the drug regulatory authority, should be included.

Monitoring and evaluation

24. A legislative text containing the above provisions lays the basis for an important administrative system. It is advisable, therefore, for the text to contain provision for overseeing and reviewing the operation of the system. The drug regulatory authority should thus have as one of its tasks the preparation of general and thematic reports, at periodic intervals, on the implementation of the law. These reports should, *inter alia*, underline deficiencies and weaknesses in the system and propose remedial action. Statutory provision requiring such reports to be tabled before the legislative assembly will ensure that they receive due attention.

Defining the scope of the marketing authorization procedure for medicinal products

This section complements the "Guiding principles for small national drug regulatory authorities" published by WHO (*2*).

The formulation of laws and regulations to define and control the national market in medicinal products is discussed elsewhere. In this section the scope of the application of the authorization/licensing system is discussed, with particular reference to finished medicinal products.

The prime objective of every national drug regulatory system is to ensure the safety, quality and efficacy of medicinal products. For administrative and judicial purposes a precise definition of "medicinal product" must be established in the national drugs legislation. This definition commonly reflects the usage for which the product is intended, e.g. "medicinal purpose" (see paragraph 5, p. 106).

In turn, "medicinal purpose" must be defined. Any such definition will refer to the treatment and prevention of disease, but — in order to include products such as contraceptives and anaesthetic drugs — the meaning is commonly extended in a more arbitrary sense to

include diagnosis of a disease or a physiological condition, and modification of a physiological function.

Safe and effective use of a medicinal product depends not only upon its innate biological activity, but also upon the judgement, knowledge and qualifications of the person responsible for supplying, selling, prescribing, or administering it, and on the evaluation by the national drug regulatory authority. Products must be classified subject to international conventions concerning narcotics and psychotropic substances. Furthermore, each medicinal product should be classified according to whether it is:

(a) available only on the authority of a doctor, dentist or veterinary surgeon — prescription-only medicines; or
(b) available under the supervision of a pharmacist only from a registered pharmacy — pharmacy-only medicines; or
(c) available from retail outlets other than under the supervision of a pharmacist.

The terms of reference of a national drug regulatory authority are typically directed to regulation of the distribution, sale, supply and promotion of medicinal products, not to regulating the practice of medicine. However, decisions taken by the drug regulatory authority will no doubt influence prescribing behaviour and may contribute to rational use of drugs.

The drug legislation should include exemptions from the authorization/licensing provisions, for extemporaneous dispensing and small-scale production carried out by or with the order of appropriately qualified practitioners (pharmacists, physicians, veterinarians and registered practitioners of other named systems of medicine). Safeguards covering quality assurance and limits on quantities should be included. Special provision is included in many drug acts to regulate the range of medicinal products that practitioners other than registered practitioners are legitimately allowed to use. Such provisions have been developed in many countries for herbal products and homoeopathic products in particular.

Every regulatory authority faces the difficulty of determining whether particular "borderline" products are "medicinal products" within the meaning of the drug legislation. Tonics, food supplements, medicinal soaps and shampoos and other topical preparations for which medicinal therapeutic claims are made are examples of these products. Sufficient flexibility should be preserved in drafting the legislation to enable specific classes of products to be subject to or specifically

excluded from the requirement for registration. The drug regulatory authority may be given statutory power to decide in borderline cases whether a product is medicinal or not.

Administrative coordination

Determining the scope of the marketing authorization will be strongly influenced by existing administrative arrangements. It is particularly important to recognize that a department of veterinary services or one dealing with traditional medicine practices may administratively oversee services without exercising regulatory control over the products used within the specific discipline. Before any decision to extend regulatory action to products relevant to these or other departments is contemplated, there is a need for interdepartmental consultation and coordination to determine any required legislative change, with a view to defining the products to be subjected to legal controls, the parameters of the proposed jurisdiction, the required regulatory powers and the associated responsibilities. The mechanics of exercising controls must be discussed and mutually agreed upon. There must be a clear demarcation of responsibilities and access to effective channels of communication. The administrative and technical competence of the ministries, departments, agencies or authorities must be respected at all times; issues of possible duplication or conflict of interest must be clarified as soon as possible.

Several legislative and administrative strategies exist to ensure closer and effective coordination between all concerned parties. Provision should be made, for instance, for prior consultation with such parties before the authority considers regulatory action. Representation of such interests on the authority itself is another possible option. The authority may even establish a sub-committee (e.g. a sub-committee on medical devices) with the mandate of assessing a particular type of product for regulatory action.

Availability of data

For the assessment of certain products, particularly those used in traditional medicine, often only limited data are available. When evaluating such products great care should therefore be exercised. The onus is on the applicant to provide the data required by the authority with respect to quality, safety, efficacy and registration status in other countries. Regulatory agencies may, however, require additional information about ingredients or the availability of similar medicinal products in other countries. Access to published sources of information is needed and authorities may also solicit the cooperation

of drug regulatory authorities in other countries willing to share available data, subject to existing rules of confidentiality. WHO also has an important role to play in coordinating the supply of information from its own sources and through its information officers.

The revised WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce covers medicinal products both for human use and for use in food-producing animals. Experience to date suggests that its extension to cover a group of veterinary medicines has facilitated the work of authorities. The rationale underlying the Certification Scheme is equally applicable to all health-related products. By legislation, the concept of a certificate provided for by the existing scheme can be extended to cover all or selected health products.

Technical competence

In view of the technical nature of the work involved in the regulation of medicinal products, the drug regulatory authority should employ appropriately qualified scientific staff. In addition the authority should be able to enlist the assistance of professionals who might have specialist knowledge about some of these products. Through contact with other authorities, guidance can be obtained on technical issues which require more detailed expertise. For the purposes of marketing authorizations the legislation may provide for the recognition of a medicinal product which possesses a marketing authorization in a named state.

In an increasingly interdependent world, schemes of mutual support and cooperation will provide the basis for establishing systems to ensure the quality, safety and efficacy of as many health-related products as possible.

Example of a legislative scheme for regulating medicinal products

General considerations

The structure of the example legislative scheme is based on certain assumptions. Most small developing countries have only a few qualified health professionals and are thus compelled to assign a variety of functions and responsibilities to every available official. This is in contrast to the situation in developed countries, and even in developing countries with adequate human resources for health, where there is always a group of officials — often operating within a hierarchical structure supported by advisers and committees — entrusted with regulatory responsibilities for different health care products or prod-

ucts with health implications such as drugs, food, devices, herbal medicines, cosmetics, pesticides, chemicals, narcotics, etc.

In the regulatory arena, it is customary to work through institutional mechanisms such as boards, committees or commissions consisting of several professionals. In countries without any regulatory system in place, members of a newly created mechanism will normally have to function almost on a day-to-day basis until most of the preliminary work is completed. With only a handful of qualified health professionals available to attend to all the functions in the ministry of health and even in the hospitals, it will be difficult for some small developing countries to ensure that such boards or committees will even have a quorum. Even if such boards or committees are created, it may well be that one or two officials will have to undertake most of the routine work.

This legislative scheme envisages the establishment of a drug regulatory authority or of a medicinal products board. The latter mechanism is particularly appropriate for those countries which are able to assign a sufficient number of personnel to serve on such a board. In this event, provision can be made for the appointment of a secretary to the board.

The scheme applies only to "medicinal products" (hereafter referred to as medicinal products or products). However, there is flexibility to extend the scheme to cover other health-related products, if so desired. It may well be that some countries wish to extend the same (or similar) control regimes to other products such as devices, herbal medicines, food and cosmetics, with a few additional provisions and regulation-making powers.

The drug regulatory authority or the board will be the authority in charge of the day-to-day implementation of the law. The legislative scheme provides for the creation of a small advisory committee to give guidance on general or specific policy and other related issues. The nature and composition of the board and the advisory committee depend essentially on the expertise that is available in the country and that can be mobilized for the purpose. For this reason, the size, composition and other details are not specified in the scheme itself, but left to be addressed in the regulations.

The control system provided for by the legislative scheme is structured around an "inventory" of the medicinal products available in the country. Regulation is not possible unless there is the information on available products (i.e. imported and/or manufactured) shortly after the law has come into operation.

The first step towards regulation of medicinal products is essentially the compilation of the inventory. Manufacturers and importers can be required, by law, to transmit to the drug regulatory authority or the board relevant information concerning the products placed on the market on or before a particular date (appointed date), as may be specified in an official publication such as the gazette. Notification will have the effect of "provisional authorization/registration" for the product. Notified products will be listed in an inventory which will be published or made available for public inspection. After the appointed date, a medicinal product for which information has not been provided and which does not have the status of being provisionally authorized/registered may not be imported or manufactured without the written permission of the drug regulatory authority or the board, thus facilitating control over the medicinal products currently on the market.

Provisionally authorized/registered medicinal products listed in the inventory will be subjected to a rapid screening process, primarily to secure the withdrawal of those products that do not meet standards of quality, safety and efficacy. The definitive assessment of provisionally authorized/registered medicinal products will be planned in accordance with established priorities.

New products (i.e. those not provisionally authorized/registered) may be imported or manufactured only with the prior written permission of the drug regulatory authority or of the board. Products which are the subject of applications after the appointed date for import or manufacture will be subjected to technical assessment before authorization/licence is granted.

While the proposed legislative scheme is primarily concerned with the control of medicinal products that are being imported or manufactured or sought to be imported or manufactured, the scheme provides for control of products for export as well.

Modern information technology, using desk-top computers, will facilitate the recording, updating and retrieval of information and entries (see Appendix 2). In the not too distant future it should be possible to access regulatory information provided by selected regulatory authorities and by relevant international organizations such as WHO.

As regulatory decisions affect the parties involved in manufacture, import, export or distribution, the legislative scheme provides for a right of appeal to the minister or to another administrative authority against any decision of the drug regulatory authority or the board.

The minister or such other authority may, upon considering the facts of the case, decide to affirm, modify, or rescind the decision of the drug regulatory authority or the board, or to refer it back to the drug regulatory authority or the board for reconsideration. The right of appeal to the minister or to another administrative authority is an administrative safeguard, as an aggrieved person will always have the right to appeal to a court of law, in accordance with the general laws of the country. As the decision of the minister or of such other authority will be subject to scrutiny, subject to applicable legal principles, the minister or the authority will be expected to exercise an unbiased perspective based on sound policy, scientific knowledge and the particular facts of the case. Courts of law are not normally concerned with technical decisions determined by those with the necessary scientific or technical experience and skills.

Critical to the success of the approach on which this legislative scheme is based is maximum use (through the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce) of regulatory information concerning individual medicinal products available through drug regulatory authorities. Regulatory information disseminated by WHO will also be of value here (see Appendix 2).

Besides regulating medicinal products, the legislative scheme may also regulate — through an authorization/licensing system — those who manufacture, import, export, store, dispense or distribute medicinal products. The scheme provides for regulations to specify who may be eligible for authorizations/licences and the procedures for applying for such authorizations/licences.

The legislative scheme contains only the minimum or basic provisions which a law must contain to provide a sound legislative basis for regulating drugs or medicinal products. In adapting this law to suit individual needs and circumstances additional provisions may have to be included. The provisions of the legislative scheme will be in addition to those already contained in other legislation dealing with health practitioners, such as medical practitioners and pharmacists. (See Appendix 1 for an example of a legislative scheme concerned with the registration of pharmacy personnel.)

Due to constitutional or administrative legal principles, the laws and regulations of some countries do not necessarily apply to the state or public sector, unless there is specific provision to the contrary. Even if they do apply, sometimes they are not as strictly followed as in the private sector or by the general public. This legislative scheme provides for the state or the public sector to be bound to the same extent

as the private sector or the general public. There is no scientific basis for exempting medicinal products procured or manufactured by or on behalf of the state or the public sector from regulatory and control regimes.

Potential value of the scheme

The basis on which the legislative scheme is structured is of particular value to small national drug regulatory authorities, with limited human and other resources, for a number of reasons:

- The scheme requires an inventory of medicinal products on the market to be compiled, and places the burden of providing the necessary information on importers, manufacturers and exporters. After the appointed date, a medicinal product for which the necessary documentation has not been submitted may not be imported, manufactured or exported without the written permission of the drug regulatory authority or the board, thus facilitating supervision of the movement of medicinal products on the market.
- The inventory can be compiled using a small desk-top computer with a software program tailor-made for the purpose.
- After the appointed date, the drug regulatory authority or the board can decide on the type of regulatory action to be taken for any individual medicinal product or group of medicinal products, bearing in mind the country's national drug policy and health care needs, and the nature of the regulations covering the product in other countries that have comprehensive systems in place for the assessment and regulation of medicinal products. The scheme provides for a system of "provisional authorization/registration" for medicinal products for which information was provided on or before the appointed date, and a system of product licensing for medicinal products proposed for import, manufacture or export after the appointed date. Provisionally authorized/registered medicinal products must qualify for product licences/marketing authorizations after evaluation, or may have to be withdrawn from the market if so decided by the drug regulatory authority or the board. The process for such evaluation has to be phased in as small national drug regulatory authorities without trained personnel or adequately equipped laboratories will find it difficult to undertake the assessment and registration of drugs following the same procedures as countries where regulatory systems have evolved over many decades and which are able to rely on qualified personnel for the assessment of medicinal products.

- The scheme is flexible enough to permit provisionally authorized/registered medicinal products to remain on the market until such time as a decision is taken to prohibit or otherwise regulate them, thus preventing any sudden or artificial shortages. This approach is preferred to those which do not permit any medicinal products to be marketed unless authorized, registered or licensed since personnel constraints will not permit the speedy assessment of medicinal products. Under the scheme the market will be gradually regulated through a process of assessment leading to product registration or withdrawal of the provisionally registered status. As described in section 2.2 of the "Guiding principles for small national drug regulatory authorities" (*2*), entitled "Screening of provisionally registered products", the initial screening process must be rapid to secure the withdrawal of products which, on the basis of a review of their ingredients and indications, are judged not to meet admissible standards of safety, quality and efficacy. This must be followed by the phased-in definitive assessment of all provisionally authorized/registered products according to priority. Applications for products which are to be imported, manufactured or exported for the first time after the appointed date will be assessed at the same time.
- In addition to screening individual medicinal products, or groups of medicinal products, the legislative scheme provides for regulatory action of a general nature. Through regulations or orders provision can be made for compliance with good manufacturing standards; the use of the WHO Certification Scheme on the Quality of Pharmaceuticals Moving in International Commerce; compliance with International Nonproprietary Names (INNs) for pharmaceutical substances, labelling and advertising requirements, etc.

Model legislative text and commentary

The text of the commentary is set in italics.

Part A. Administration

1. There shall be established a drug regulatory authority which shall comprise pharmacists, physicians and others.

In order to discharge statutory functions and exercise statutory powers effectively, it is important that the office of the drug regulatory authority should be accorded high visibility within the official structure and be staffed by suitably qualified professionals. This includes not only the provision of attractive terms of employment and salary structures, but also access to effective and speedy channels of communication to those in authority, while safeguarding, at all times, the independence of the

office. Under ideal circumstances, the person who functions as the officer of the drug regulatory authority [or the secretary of the board] should no longer be involved in drug procurement functions; but where this is not possible, because of staffing constraints, every precaution must be taken to ensure that the two functions of drug regulation and drug procurement are kept distinct and separate.

When appointing the officer(s) of the drug regulatory authority [or members of the board] and of the advisory committee, one issue which must be addressed is conflict of interest. It is important to ensure that regulatory responsibilities are discharged without fear or favour.

In relation to medicinal product regulation and procurement, it must be emphasized that such products should be considered a special category; appropriate administrative regulations, including tender or import procedures, must guarantee the independence of those entrusted with regulatory as well as procurement functions.

2. The functions of the drug regulatory authority shall, *inter alia*, be:

(a) to require all medicinal products manufactured in, imported into or exported from the country to conform to prescribed standards of quality, safety and efficacy, and that the personnel, premises and practices employed to manufacture, promote, procure, store, distribute and sell such products comply with defined codes of practice and other requirements;
(b) to require continued conformity of medicinal products to such standards until their delivery to the end-user;
(c) to require that medicinal products are imported, manufactured, exported, stocked, sold, distributed or otherwise dealt with by duly authorized persons;
(d) to grant, after due assessment, authorizations/licences for medicinal products, whether locally manufactured or imported, and whether destined for the national market or export;
(e) to cancel the authorization/registration of, or cause to be recalled from the market, medicinal products the continued use of which may be detrimental to public health;
(f) to maintain an inventory of provisionally authorized/registered medicinal products;
(g) to publish lists of provisionally authorized/registered medicinal products and of products with marketing authorizations from time to time, for public information;
(h) to ensure that dossiers for marketing authorization of medicinal products are kept up to date by the applicants and to approve alterations/changes thereto;

(i) to inspect and license/authorize all manufacturing premises, importing agents, wholesalers, distributors, hospital dispensaries, pharmacies and retail outlets;
(j) to sample, analyse and otherwise test finished medicinal products released into the distribution chain, to ensure their compliance with labelled specifications;
(k) to monitor the market for the presence of illegal/counterfeit medicinal products;
(l) to ensure that the promotion and marketing of medicinal products is in accordance with product information as approved by the drug regulatory authority;
(m) to approve the use of unregistered/unauthorized medicinal products for clinical trial purposes or for compassionate use and to regulate clinical trials on medicinal products;
(n) to disseminate information on medicinal products to the health professions in order to promote their rational use;
(o) to collect authorization/registration and application and renewal fees;
(p) to monitor and review the implementation of the legislation;
(q) to advise the minister on matters concerning control and authorization/registration of medicinal products;
(r) to amend the rules and regulations as deemed necessary to keep pace with time demand(s).

This section lists some of the more important functions of the drug regulatory authority. Additional functions can be added to this catalogue.

3. The drug regulatory authority shall appoint such other officers as may be necessary to assist it (or the board) to perform duties and to exercise powers under this Law. Such officers shall be known as "authorized officers".

For purposes of inspection, supervision and monitoring, the drug regulatory authority [or board] will need the assistance of other officers. The number and type of officers needed depend essentially on the profile of the pharmaceutical industry. However, it is important that the human resources needed to implement the Law are duly taken into consideration in the health resources planning process.

4. The minister shall, in consultation with the drug regulatory authority, appoint a medicinal products advisory committee to advise the drug regulatory authority on any general matter concerning the implementation of the technical aspects of the Law or with regard to any specific medicinal product.

It is envisaged that the committee will provide guidance on technical/scientific as well as administrative matters. As there are significant differences between countries in the availability of pharmacologists, medical practitioners and pharmacists who can be considered for appointment to a committee of this nature, the legislative scheme does not address issues such as composition, size, quorum, working procedures and other aspects. Committee members should be free from conflict of interest. These are matters to be regulated by way of regulations promulgated under the Law. The representative of the drug regulatory authority should be an ex-officio member; ideally, such an officer should serve as the secretary of the committee as well.

Part B. Provisional registration/marketing authorization and inventory of medicinal products

5.1 The drug regulatory authority shall, by order published in the gazette [variant: or through other means of notification], require manufacturers, importers and exporters of medicinal products to notify the drug regulatory authority of such particulars as are specified in the order concerning the medicinal products which such manufacturers, importers, or exporters wish to continue to manufacture, import, export or sell after such date (hereafter referred to as the appointed date) as is specified in the order.

5.2 Medicinal products for which a notification has been received by the drug regulatory authority on or before the appointed date shall be listed in the provisionally authorized/registered medicinal products inventory (hereafter referred to as the inventory), and until granted a product licence/marketing authorization or ordered by the drug regulatory authority (or board) not to be manufactured, imported, exported or sold, such products shall have the status of provisionally authorized/registered medicinal products.

5.3 After the appointed date no person shall import, manufacture, export or sell a medicinal product not listed in the inventory without the prior written permission of the drug regulatory authority unless a product authorization/licence has been granted in respect of such product under section 6 of this Law.

5.4 The inventory, the format of which may be laid down in regulations, shall be made available for inspection at such place and at such times as specified by the drug regulatory authority in an order published in the gazette or one or more newspapers as may be specified in the regulations.

5.5 The inventory shall be revised accordingly as and when provisionally authorized/registered products listed therein have been granted a

product authorization/licence under section 6.1, or the drug regulatory authority has ordered under section 6.3 that any such provisionally authorized/registered medicinal product should not be manufactured, imported, exported or sold from such date as is specified in the order.

This section provides for a system of provisional authorization/registration for medicinal products which are being manufactured, imported, exported or sold from a specific date, and which will be continued to be manufactured, imported, exported or sold even after that date (appointed date).

Medicinal products which are notified on or before the appointed date will be listed in a provisionally authorized/registered medicinal products inventory. The scheme envisages this inventory as well as a register. The latter is for medicinal products which have been granted a product licence/marketing authorization. The procedure for screening provisionally authorized/registered products, as well as new applications for other medicinal products, is contained in section 6.

For a provisionally authorized/registered medicinal product, the drug regulatory authority may decide one of two things: either to grant a product licence/marketing authorization, or to phase out or ban its manufacture, import, sale or export. In either event, the product will be deleted from the inventory. If a product licence/marketing authorization is granted, it will be entered in the register of medicinal products for which a product licence/marketing authorization has been granted (see section 9).

At some point — depending on the pace at which the screening process can proceed — the inventory will cease to exist, as all products which had the provisionally authorized/registered status would have been screened and either granted a product licence/marketing authorization or eliminated from the market.

Section 14 makes it an offence to manufacture, import, sell or export a product unless it has a marketing authorization or is deemed to be provisionally authorized/registered.

A renewal process will be established at regular intervals for those products which show satisfactory performance in the market and comply with regulations.

Part C. Screening of products and issuance of product licences/ authorizations

6.1 In accordance with the national drug policy and the country's health-care needs, and in relation to considerations of product

quality, safety and efficacy, the drug regulatory authority shall decide whether a provisionally authorized/registered product, or a product which is not listed in the inventory but for which an application for its manufacture, import, export or sale has been filed after the appointed date, should be granted a product licence/marketing authorization.

6.2 The drug regulatory authority may at any time call upon any manufacturer, importer or exporter to furnish such information as is required in order to enable a provisionally authorized/registered product, or a product proposed for manufacture, import or export after the appointed date, to be evaluated and assessed.

6.3 The drug regulatory authority may at any time, after scientific evaluation, determine that an authorized/registered product should not be eligible for a product authorization/licence and that such product should not be manufactured, imported, sold or exported, either with immediate effect or from such date as is specified in an order made by the drug regulatory authority.

6.4 Upon an order made under subsection 6.1 or 6.3 taking effect, the inventory shall be accordingly revised with respect to the entry for the relevant product.

This section deals with the factors to be taken into account in screening medicinal products (either those which are provisionally authorized/registered or for which a new application has been made for manufacture, import, export or sale) and the procedures to be followed in granting a product licence/marketing authorization.

7. Any manufacturer, importer or exporter who fails, without valid reason, to furnish such particulars within the stipulated time-limit, or within an extended time-limit as may have been granted by the drug regulatory authority, shall not be entitled to manufacture, import, sell or export the medicinal product from such date as is specified by the drug regulatory authority in a communication addressed to the manufacturer, importer or exporter.

This section addresses the situation where a manufacturer, importer or exporter has not submitted the particulars and data necessary for the product to be screened.

8. In determining whether a product licence/marketing authorization should be granted or not, the drug regulatory authority shall consult the medicinal products advisory committee, relevant authorities and health professionals, and may take into account regulatory information from other countries and relevant international organizations.

This section addresses the consultative process that must take place when products are being screened.

The drug regulatory authority may wish to consider how a particular medicinal product has been regulated in other countries. Product licences/marketing authorizations may be subject to various terms and conditions relating to:

— *manufacture*
— *import*
— *export*
— *marketing*
— *distribution*
— *prescription*
— *use*
— *labelling*
— *packaging*
— *pricing*
— *advertising/promotion or*
— *conditions of sale.*

The legislative scheme assumes that drug regulatory authorities in small countries should make the maximum use of regulatory information available in the public domain. Such information is available through a number of sources such as the WHO Certification Scheme on the Quality of Pharmaceuticals Moving in International Commerce (the WHO Certification Scheme); the authorities of countries with advanced drug regulatory systems; the World Health Organization; and drug-related commercial as well as non-commercial publications (e.g. national formularies; drug compendia; medical journals).

Appendix 2 describes the various publications and services that have been developed specifically to support drug regulatory authorities.

9. The drug regulatory authority shall maintain a register of medicinal products for which marketing authorizations have been issued and shall make the register, or extracts from it, available at such place and at such times as specified by the drug regulatory authority in an order published in the gazette or one or more newspapers as may be specified in the regulations.

This section provides for a register to be maintained of medicinal products for which product licences/marketing authorizations have been granted. This register will eventually replace the inventory as all provisionally authorized/registered products are screened.

10. Regulations made under this Law shall specify the terms, conditions, and validity of product licences/marketing authorizations, the

format of the register, and the particulars to be furnished to obtain a product licence/marketing authorization for provisionally approved/authorized products or for products not listed in the inventory, and other requirements, including the payment of fees, for applications for a product licence/marketing authorization.

This section provides for regulations to be made on matters relating to licences/marketing authorizations and the register. The use of modern technology such as computers facilitates the compilation, updating and printing of the inventory and the register. WHO has developed a model package for computer-assisted drug registration which can be adapted to develop such inventories or registers and even to the issuing of licences/marketing authorizations (see Appendix 2).

11.1 The drug regulatory authority may revoke or suspend the marketing authorization for importation, manufacture, sale or exportation of a medicinal product if it appears or there is reason to suspect that the conditions for the licence are no longer being fulfilled.

11.2 The drug regulatory authority may vary the provisions of the marketing authorization provided it is satisfied that such a variation does not adversely affect the safety, quality or efficacy of the medicinal product.

11.3 The order of the drug regulatory authority may specify how the order is to take effect, particularly with regard to recalling the product from the market and the procedures, if any, for notifying health professionals and the public.

11.4 An applicant (licence/marketing authorization holder) shall not deviate from the particulars submitted in the drug registration dossier unless authorized by the drug regulatory authority. A formulation or other error pertaining to a medicine shall be immediately reported to the drug regulatory authority. An adverse drug event reported to a licence/marketing authorization holder shall be conveyed to the drug regulatory authority by the licence holder within three days of the initial report.

This section empowers the regulatory authority to take prompt action to withdraw a product from the market when such a course of action is warranted by public health considerations.

12.1 Any manufacturer, importer or exporter who is aggrieved by an order made by the drug regulatory authority (see sections 11.1–11.4) may appeal to the minister/authority, in writing, within two weeks from the date of the order.

12.2 On receipt of an appeal the minister/authority may decide whether or not the drug regulatory authority should be directed to rescind, suspend, vary, modify, reconfirm or reconsider the order against which the appeal has been lodged.

This section provides for administrative relief, prior to institution of action in a court of law in accordance with the country's legal and judicial system. Provision for administrative relief in the first instance is important, as litigation is generally protracted, costly and inconvenient to all parties concerned.

Part D. Other activities requiring authorization/licensing

13.1 On or after such date as is specified in a notice published in the gazette or in any official publication as may be specified in the regulation, a person carrying on a business of manufacturing, importing, exporting, compounding, storing, dispensing, selling, supplying or otherwise distributing medicinal products must possess a valid authorization/licence in order to carry out that activity.

13.2 The licensing authority shall maintain a register of pharmacies. An application for registration of pharmacy premises under this section must be made in accordance with regulations issued by the minister.

13.3 The particulars to be furnished by applicants for an authorization/licence, their qualifications and suitability, and the terms, requirements and conditions under which such authorizations/licences may be granted, shall be specified by the drug regulatory authority in regulations made under the Law.

13.4 Any person aggrieved by a decision of the drug regulatory authority may appeal, within two weeks of the notification of the decision of the drug regulatory authority, to the minister/authority.

13.5 On receipt of an appeal the minister/authority may decide whether or not the drug regulatory authority should be directed to rescind, suspend, vary, modify, reconfirm or reconsider the order in respect of which the appeal has been lodged.

Parts B and C were concerned with medicinal products, whereas Part D deals with individuals, companies, firms, hospital clinics or dispensaries, pharmacies, etc., who need a licence/authorization to engage in various activities.

There is a right of appeal to the minister/authority against any decision of the drug regulatory authority. Provision for administrative relief in

the first instance is important, as litigation generally tends to be protracted, costly and inconvenient for all parties concerned.

Part E. General provisions

14. It shall be an offence under this Law for any person to manufacture, import, sell or export a product after the appointed date unless such product at the time of manufacture, import, distribution or export has the status of a provisionally authorized/registered medicinal product under section 5.2 or has received a product licence/marketing authorization under section 6.

This section deals with the situation in which a product which is neither provisionally authorized/registered nor covered by a product licence/marketing authorization is manufactured, imported, distributed, sold or exported after the appointed date.

15. After such date as is specified under section 13.1 of the Law, it shall be an offence for any person to engage in any of the activities mentioned in that section, unless this person holds a valid authorization/licence granted by the drug regulatory authority or is otherwise legally entitled to engage in any such activity.

This section deals with the situation in which a person engages in an activity mentioned in section 13 without a licence or legal right (under another law).

16.1 No person shall manufacture, import, export, compound, store, sell, promote or distribute a medicinal product:

(a) that is unfit for use in humans or in animals;
(b) that is adulterated;
(c) that contains any natural or added deleterious substance which renders it injurious to health;
(d) that has been manufactured, prepared, preserved, packaged or stored for sale under insanitary and/or unfavourable conditions; or
(e) that has been labelled, packaged or promoted in a manner that is false, misleading, deceptive or likely to create an erroneous impression regarding its source, character, value, quality, composition, potency, merit or safety.

16.2 No person shall manufacture, import, export, distribute, sell, supply or use any counterfeit starting materials.

16.3 No person shall manufacture a medicinal product using any counterfeit starting materials or without taking reasonable measures

to ensure that the starting materials used in the manufacture of such medicinal products are not counterfeit or of suspect quality.

16.4 No manufacturer, importer, exporter, distributor, pharmacist, health practitioner, health worker or other person shall manufacture, import, export, compound, prepare, promote, sell, supply, obtain, display, dispense or otherwise distribute, for a fee or by way of sample or gift, any medicinal product which is a counterfeit or known or suspected to be a counterfeit.

This section is of a general nature aimed at ensuring that only medicinal products which meet acceptable standards are marketed.

One potential problem area in implementing this provision is the lack of quality control facilities where products could be tested and verified in small developing countries. Through cooperative arrangements with neighbouring countries with good quality control facilities, however, it should be possible to have products tested there. Participation in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce also provides an opportunity for quality defects to be investigated.

17. Where any standard is prescribed for any medicinal product, no person shall label, package, sell, offer for sale, distribute or promote any such medicinal product which does not conform to such standard in such a manner that makes it likely to be mistaken for the medicinal product for which the standard has been prescribed.

The applicable standards will have to be specified in the regulations.

18.1 The drug regulatory authority or any authorized officer shall have the power to visit and inspect any manufacturing plant, processing unit, business establishment, warehouse, office, or any premises used for or in connection with the manufacture, import, export, distribution, storage, sale, supply, dispensing or use of any medicinal product, to take samples of any medicinal product or of any substance, and to examine records or other documents relating to any medicinal product.

18.2 No person shall refuse to permit the drug regulatory authority or any authorized officer to enter and inspect or take samples or documents.

18.3 An inspector may at any reasonable time and on production of his or her certificate of authority enter any premises:

(a) for the purpose of ascertaining whether there is or has been any contravention of the legislation;

(b) generally, for the purpose of discharging his or her functions under the legislation.

18.4 An inspector may:

(a) inspect the premises, any article and any document for the purposes of the legislation;
(b) seize any substance, article or document which he or she has reasonable cause to believe to be a substance, article or document in which or by means of which an offence under the legislation is being or has been committed.

"Premises" for the purposes of this section includes any premises, ship, aircraft or vehicle. "Premises" does not include a private residence.

It will be useful to develop a plan of action, with appropriate checklists and guide, to enable authorized officers to conduct inspections.

19. Any person who contravenes or fails to comply with any provision of this Law or any regulation or any order made under this Law shall be guilty of an offence, and on conviction shall be liable to a fine between ..... and ..... or imprisonment for a term not exceeding ..... months/years, or both; in the case of a continuing offence, to a fine not exceeding ..... for every day or part of a day during which the offence has continued.

The minimum and maximum penalties (imprisonment and/or fine) must be determined in line with the penalties generally prescribed by other laws currently in force in the country.

The need for "deterrent penalties" must be carefully balanced against the risk of "overkill". Too high a penalty, particularly one entailing mandatory jail sentences, for instance, can lead to lax enforcement and will be counterproductive in the long run. On the other hand, products like medicinal products need to be manufactured and handled with great care; any deliberate or negligent departure from established standards and norms can result in otherwise avoidable mortality and morbidity. The ubiquitous problem of counterfeit drugs has reinforced the need for severe penalties for certain types of violations involving deliberate or fraudulent behaviour.

20. The provisions of this Law shall extend to all persons, in both the public and private sectors, engaged in manufacturing, importing, exporting, compounding, storing, distributing, promoting, selling or in any other way dealing with medicinal products.

In some countries express statutory provision is required in order for a law to apply to the state or to the public (government) sector. It is

important that regulatory controls apply to all medicinal products, irrespective of who is responsible for their manufacture, import or export, distribution or sale.

21. Regulations shall be made for all or any of the matters for which the Law provides for regulations to be made and, in particular, for the following purposes:

(a) Prohibiting, limiting, restricting, or imposing conditions on, either generally or in relation to: (i) a particular medicinal product; (ii) the manufacture, import, export, compounding, dispensing, administration, sale or supply of medicinal products; (iii) printed packaging material, package leaflets and data sheets/ product information, promotion to health professionals, advertising to the general public and conduct of marketing practices.
(b) Withdrawing medicinal products from sale or distribution.
(c) Prescribing the standards to be followed in the manufacture, storage, sale, supply, dispensing and distribution of medicinal products.
(d) Classifying medicinal products for purposes of regulating importation, manufacture, compounding, prescribing, dispensing, selling, storage and distribution.
(e) Regulating persons entitled to import, manufacture, compound, export, store, prescribe, dispense or sell medicinal products.
(f) Prescribing the terms, conditions, procedures and time-limit for the issuance of licences/authorizations under Parts C and D of the Law and the forms, fees, particulars and records necessary for applications for licensing and grounds for suspension, cancellation or withdrawal of licences/product authorizations.
(g) Regulating the composition and terms of reference of the medicinal products advisory committee and/or board of medicinal products.
(h) Granting exemptions from the requirement of a product licence/ marketing authorization for imports of medicinal products required for a named patient or to meet a public health emergency.
(i) Designating laboratories and analysts for the purposes of conducting analyses and submitting reports.
(j) Regulating the licensing/authorizing and licensing/authorization renewal fees in order to support the drug regulatory functions.
(k) Prescribing any regulation in matters pertaining to this Law.
(l) Regulating clinical trials on medicinal products.
(m) Regulating drug donations.
(n) Regulating the obligation to report on drug adverse reactions.

(o) Regulating the obligation to report on product variations such as quality or manufacturing change.

There are a number of sections which provide for regulations to be made. This catalogue is in addition to the matters referred to in those sections.

Part F. Interpretation

22. The legislation should include an interpretation of terms which may be used in a special context. In the model text given here, terms which might need interpretation include:

"Appointed date" means the date specified under section 5.1 of the Law.

"Inventory" refers to the listing of provisionally registered/authorized medicinal products under section 5.2 of the Law.

"Medicinal product" means any medicine intended for human or veterinary use, presented in its finished dosage form or as a starting material for use in such dosage form, as defined in paragraph 5, p. 106 (see also p. 111).

"Minister" means the minister responsible for matters relating to medicinal products.

"Person" includes an individual as well as a body corporate, partnership or association of persons, and establishments such as hospital pharmacies, clinics, and health centres storing or distributing medicinal products.

"Provisionally authorized/registered" is used in relation to a medicinal product which has been listed in the inventory under section 5 of the Law and which has not been screened for purposes of a product licence/marketing authorization under sections 6 and 9 of the Law.

"Register" means the register of medicinal products for which a product licence/marketing authorization has been issued in terms of sections 6 and 9 of the Law or the register of persons, i.e. the pharmacist and pharmacy assistant.

"Sell" means to sell for cash or on credit or by way of exchange, whether by wholesale or retail; "sale" shall have a corresponding meaning.

The above are some of the more important terms used in the legislative scheme which need to be defined, but other terms may also require definition. The WHO text on Good manufacturing practices for phar-

maceutical products (see Appendix 2) contains a number of definitions of terms such as "manufacture" which can be included, after adaptation if necessary, in the definition section.

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Bulgaria
Degree No. 109 of 17 April 1995 promulgating the Law on Medicaments and Pharmacies with Regard to Human Medicine

(see also *International digest of health legislation*, 1996, **47**(1):56–60, Bulg. 96.1)

Estonia
Medicinal Products Act of 19 December 1995

Ghana
The Pharmacy Act, dated 30 December 1994

(see also *International digest of health legislation*, 1996, **47**(1):63, Ghana 96.2)

Latvia
Law on Pharmaceutical Activities of 27 April 1993

(see also *International digest of health legislation*, 1995, **46**(2):220, Lat. 95.1)

Malawi
Drug Act of 1988

Myanmar
Drug Law of 30 October 1992

Republic of Korea
The Pharmaceutical Act, as amended up to 7 January 1994

(see also *International digest of health legislation*, 1995, **46**(3):352, ROK 95.1)

Sierra Leone
Pharmacy and Drug Act of 1988

Appendix 1
Provisional legislative scheme for registration of pharmacy personnel

In order to assist countries to update existing laws or to draft new ones, this document offers a provisional legislative scheme on registration of pharmacy personnel. The text and provisions should be adapted to suit national conditions, requirements and situations.

1. No person shall practise as a pharmacist unless his or her name has been registered as a pharmacist by the licensing authority by virtue of this Law.

2. An applicant for registration as a pharmacist must:

(a) hold a pharmaceutical qualification granted by a university or institution of equivalent standing;
(b) have practised the pharmaceutical profession for a period of not less than two years;
(c) be in good health and have no police record;
(d) fluently speak and read the national language and possibly others;
(e) pass such an examination as the minister may consider necessary.

3. Except as is provided by this Law, no person other than a person registered as a pharmacist shall:

(a) conduct and administer a registered pharmacy;
(b) in the course of any trade or business prepare, mix, compound or dispense any medicinal product or poison except under the supervision of a pharmacist; or
(c) assume, take, exhibit or in any way make use of any title, emblem or description reasonably calculated to suggest that he or she is registered as a pharmacist.

For the purpose of subsection (c) of this section the use of the word "pharmacist" or "chemist" or "druggist" or any similar word or combination of words shall be deemed to suggest that the owner of the business on those premises is, or purports to be, a registered pharmacist.

4. No person shall practise as a pharmaceutical technician or as an assistant in pharmacy unless he or she has obtained registration as a pharmaceutical technician or assistant in pharmacy by the licensing authority by virtue of this Law.

5. An applicant for registration as a pharmaceutical technician or assistant in pharmacy must:

(a) hold a recognized certificate as a pharmaceutical technician or assistant in pharmacy;
(b) have practised within the pharmaceutical profession for a period of not less than two years in a pharmacy under the supervision of a pharmacist;
(c) be in good health and have no police record;
(d) fluently speak and read the national language and possibly others;
(e) pass such an examination as the minister may consider necessary.

6. The applications for registration under sections 2 and 5 of this Law must be made in accordance with the regulation issued by the minister.

7. The licensing authority shall maintain a register of pharmacists and technicians or assistants in pharmacy.

8. Pharmacists and technicians or assistants in pharmacy must perform their duties in accordance with the ethics of the pharmaceutical profession and in particular must:

(a) at all times act in the interest of the patient;
(b) uphold the honour and dignity of the pharmaceutical profession and not bring the profession into disrepute;
(c) at all times have regard to the laws and regulations applying to medicinal products and pharmaceutical practice, and maintain a high standard of professional conduct;
(d) respect the confidentiality of information acquired in the course of their professional practice;
(e) offer services to the public in premises which reflect the professional nature of pharmacy.

9. The minister shall by regulation establish a pharmaceutical practice committee ideally comprising:

(a) a pharmacist chairman appointed by the minister;
(b) three registered pharmacists;
(c) two registered technicians or assistants in pharmacy;
(d) one lay member.

10. The pharmaceutical practice committee shall:

(a) advise the minister on any matter relating to the pharmaceutical profession and the practice of pharmacy;
(b) ensure the maintenance of high standards of practice and conduct among pharmacists and technicians or assistants in pharmacy and promulgate codes of conduct;
(c) set standards of education and training, where appropriate, for pharmacists and/or technicians.

The pharmaceutical practice committee may regulate its own procedure.

11.1 The minister shall by regulation establish a disciplinary committee to inquire into the conduct of a registered pharmacist or registered technician or assistant in pharmacy whom it is alleged has been convicted of a criminal offence or is in breach of any of the provisions of section 8 of this Law.

11.2. The disciplinary committee shall ideally comprise:

(a) a chairman with a legal background, appointed by the minister;
(b) two registered pharmacists;
(c) one registered technician or assistant in pharmacy.

No member of the pharmaceutical practice committee shall be a member of the disciplinary committee.

11.3 The disciplinary committee shall, after inquiry, have power:

(a) to issue a reprimand/warning to a registered pharmacist or registered technician or assistant in pharmacy;
(b) to adjourn an inquiry with conditions;
(c) to recommend to the minister that the name of a registered pharmacist, a registered technician or assistant in pharmacy be suspended or removed from the respective register;
(d) to regulate its own procedure.

12. The minister, by regulation, may fix fees for the initial registration of pharmacists, technicians or assistants in pharmacy, and pharmacies. Annual fees may also be payable to retain the names of pharmacists, technicians or assistants in pharmacy, and pharmacies on the respective registers.

13. Any person who contravenes section 1, 3 or 4 of this Law shall be guilty of an offence and liable to a fine not exceeding [amount to be specified].

Appendix 2

Guidelines, documents and other regulatory instruments established by WHO to support drug regulatory authorities

Over the years WHO has issued many technical and administrative guidance documents that bear direct relevance to drug regulation, such as:

- Guiding principles for small national drug regulatory authorities (*1*)
- Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (*2*)
- Guidelines on import procedures for pharmaceutical products (*2*)
- Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (*2*)
- Provisional guidelines on the inspection of pharmaceutical manufacturers (*3*)
- Good manufacturing practices (GMP) for pharmaceutical products (*3*)
- Good manufacturing practices for biological products (*4*)
- Guidelines for the assessment of herbal medicines (*2*)
- Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology (*3*)
- Guidelines for good clinical practice (GCP) for trials on pharmaceutical products (*5*)
- Use and protection of recommended International Nonproprietary Names for pharmaceutical substances (*6*, *7*, *10*)
- Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms (*2*)
- Ethical criteria for medicinal drug promotion (*8*)
- Model List of Essential Drugs and Eighth Report of the WHO Expert Committee on the Use of Essential Drugs (*9*)

WHO also fosters exchange of information among drug regulatory authorities, and the following four WHO publications are particularly

helpful for worldwide regulatory information. The WHO *Pharmaceuticals newsletter*, published monthly, contains notifications received from WHO Member States on the regulation of human and veterinary drugs and medical devices, and also provides information on the surveillance of marketed products. The quarterly *WHO drug information* contains a section on "Regulatory matters" dealing with individual drugs subjected to regulatory action. Another quarterly, *International digest of health legislation*, reproduces important regulatory texts adopted by WHO Member States and geo-political groupings such as the EU. The *Essential drugs monitor* reports on current developments and new publications. The *Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments* published annually by the United Nations is another good source of information. As the introduction to the 1991 *Consolidated list* states: "It constitutes a tool which helps Governments to keep up-to-date with regulatory decisions taken by other Governments and assists them in considering the scope for eventual regulatory action. It enables government agencies which review applications for product registration to ascertain easily restrictive regulatory decisions made in other countries. It complements and consolidates the information produced within the United Nations system, including the World Health Organization's quarterly bulletin WHO Drug Information and its Pharmaceuticals Newsletter . . .". Countries with developed systems of drug registration or with similar social and health-care structures can be requested to provide information as to the availability of certain drugs on their markets, and the terms and conditions subject to which such drugs are being imported, manufactured, marketed or exported.

The revised *WHO Certification Scheme on the Quality of Pharmaceuticals Moving in International Commerce* enables importing countries to request the following types of documents which will provide more information with regard to any product in the country of export:

— Certificate of a Pharmaceutical Product;
— Statement of Licensing Status of Pharmaceutical Product;
— Batch Certificate.

The Certificate of a Pharmaceutical Product requires the following information to be furnished by the designated regulatory authority in the country of export:

— the proprietary name (if applicable) and dosage form;
— active ingredient(s) per unit dose (together with a qualitative listing of other ingredients contained in the dosage form);

— particulars of product licence and of product licence holder (or particulars of applicant for certificate if the product is not licensed to be placed on the market for use in the country of export);
— if the product is not licensed to be placed on the market for use in the country of export, the reason why such authorization is lacking (not required/not requested/under consideration/refused);
— particulars concerning inspection of the manufacturing plant in which the dosage form is produced;
— approved product information and technical summary.

The Statement of Licensing Status, on the other hand, indicates only whether or not the products listed in the certificate are licensed to be placed on the market for use in the country of export. This Statement is essentially intended for use by importing agents who are required to screen bids made in response to international tenders.

Upon request, WHO assists countries with a standardized approach to the computerization of drug regulatory data, for example, processing marketing authorizations and maintaining product lists. Under preparation are additional software products to help in the management of information related to monitoring of imports/exports, reporting on psychotropic and narcotic drugs, and samples in a drug quality control laboratory.

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Annex 9
Provisional guidelines for developing training programmes: inspection and examination of counterfeit pharmaceuticals

1. General remarks

1.1 *Introduction*

Counterfeit pharmaceuticals may be a serious risk to public health. It is the responsibility of governments to ensure that counterfeit pharmaceuticals are taken off the market and their sources found and eradicated. This should be a part of an overall quality control system. Clearly, expertise in drug inspection and drug examination is required. These guidelines are intended to be used to train relevant staff.

The detection and prosecution of criminals who market counterfeit pharmaceuticals have several stages. First of all, suspect products have to be traced. The drug, sampled according to an established procedure, should undergo defined physical or organoleptic examination by the drug inspector. If the results indicate that the drug formulation may be a counterfeit product, then at least some chemical tests must be repeated to confirm the necessity for further analysis. Drugs are then analysed by simple tests, including thin-layer chromatography. If these tests do not provide conclusive evidence and the drug is still considered to be a possible counterfeit, then a compendial procedure is required.

Throughout the investigation, it is assumed that a chain of custody has been established, i.e. the correct procedures were followed before the drug was received for analysis by the laboratory. This ensures that the results of these examinations are reliable and will be accepted as valid in future steps, e.g. prosecution of the supplier of the counterfeit pharmaceuticals. The final results shall be submitted to the appropriate official in the drug regulatory authority.

Section 2 describes the training necessary for inspectors. Section 3 describes training in the design and implementation of a specific programme for the screening of counterfeit pharmaceuticals. There are several common requirements for both inspection and chemical testing, and these are included as items in the training programmes for

inspection and examination of counterfeit pharmaceuticals. It is assumed that the trainers are already suitably experienced to perform the required inspection, examination and training. The two-tiered approach of the training programme should include training of trainers, who in turn educate those who need to be trained in drug inspection and examination. The main focus of these guidelines, however, is the training of the trainees.

The practical issues to be considered in the organization and implementation of the programme are described in Appendix 1.

Each country must develop its own strategy, appropriate for its situation, the availability of an institutional framework, and its professional and economical resources. Ideally it should be prepared by the country's drug regulatory authority in consultation with all major parties involved in the manufacturing, importation, distribution, sale, prescribing and use of legitimate drugs.

1.2 *Requirements and goals of the training programmes for inspection and examination*

The requirements for the programme may be defined by the fact that an effective approach to the detection and prevention of counterfeit pharmaceuticals requires professional competence of the personnel, motivation, and awareness of the problems.

The ultimate goals of the programme should be:

— to raise the morale of professionals involved in drug inspection and examination;
— to establish a control system to prevent the flow of counterfeit pharmaceuticals into the legitimate distribution channel.

These goals cannot be achieved without the concerted effort of other programmes concerned with improvement of the pharmaceutical infrastructure. In order to ensure the quality, safety and efficacy of drug products accessible to the target population, a secured and satisfactory drug distribution system is required.

1.3 *Prerequisites*

The primary prerequisite for any programme combating pharmaceutical counterfeiting is the existence of an established drug regulatory authority in the country, which complies with the "Guiding principles for small national drug regulatory authorities" (*1*). That implies the availability of at least the following:

- A legal framework. The legislation is also expected to cover criminal activity in relation to the manufacture, import, distribution, sale

and dispensing of counterfeit pharmaceuticals. The act of counterfeiting should be an offence such that the inspector of drugs, the police and other investigating agencies are all able to take action. The law should also provide for deterrent punishments.

- A system requiring:
  (a) licensing/authorization of manufacturers, importers, distributors, retailers, pharmacies;
  (b) registration/marketing authorization of drugs;
  (c) proper labelling.
- Adequate professional staff and resources within the drug regulatory authority.

2. Training programme for inspection

2.1 *Course objectives*

The aim of this course is to provide trainees with:

— an awareness of methods for the detection of counterfeit pharmaceuticals;
— an understanding of the difference between counterfeit and substandard pharmaceuticals;
— the ability to evaluate the test data;
— the ability to distinguish between normal and suspect pharmaceuticals on the basis of physical aspects;
— the ability to identify reports of adverse effects or lack of efficacy that might result from the use of counterfeit pharmaceuticals;
— the ability to justify their actions in the legal context of detection and prosecution including the prosecution of offenders, independently, if so authorized, or by the appropriate authority;
— an awareness of methods of making the legitimate distribution system secure, e.g. by a system of warranty or, for international trade, by compliance with the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (*2*);
— a knowledge of how to share information, coordinate and collaborate with all concerned in combating counterfeit pharmaceuticals.

2.2 *Types of training*

The training of inspectors consists of conveying theoretical and background information by lectures and discussion of case studies. Furthermore, the training course should contain practical examples and field work. Training will also cover the organoleptic inspection of products, including examinations of products when available.

2.3 *Educational background of trainees and trainers*

This training is aimed at inspectors, preferably with some experience in the inspection of drugs. Guidance as to what level of experience is expected can be found in the "Guidelines for inspection of drug distribution channels" (*3*). Training covering counterfeit pharmaceuticals should be included in all basic training courses for inspection.

The trainer should be experienced, have full knowledge of general and official inspection methods, and should be able to conduct and design, when necessary, the training programme for the trainee. Other characteristics include:

— previous experience with detection and prosecution procedures;
— an appreciation of the inspector's role in the legal system for combating counterfeit products;
— an understanding of the difference between counterfeit and sub-standard pharmaceuticals;
— knowledge of the latest statistics on the prevalence of counterfeit pharmaceuticals in the country, if possible;
— knowledge of relevant quality standards;
— thorough overall knowledge of the subjects to be taught.

2.4 *Course programme items*

The following items should be included in the course; the actual content of each item will depend on the prior experience of the trainees:

— overview of relevant legislation;
— national drug regulatory systems, inspection and quality control;
— drug distribution systems;
— illegal distribution channels;
— types of counterfeit pharmaceuticals encountered;
— general characteristics of various dosage forms, such as active ingredient to excipient ratio in tablets, capsules, ampoules, powder for injection, ointments, creams, etc.;
— factors leading to the manufacture and sale of counterfeit pharmaceuticals (e.g. profit);
— measures to detect counterfeiting (e.g. checking records of distributors and measurement of various physical properties of the product, labelling features, packaging materials and packaging of various drug forms);
— methods of market surveillance for detection of counterfeit pharmaceuticals at the import, manufacture, distribution and sales levels, based on intelligence services and visual examination of samples;

— organizing sample collection;
— sample and test report handling;
— preparation for prosecution by:
  (a) investigation of cases to identify the suspect persons responsible for the offence;
  (b) collection of legal evidence for proceedings in the courts;
  (c) maintaining a system of security of evidence including persons and case property;
— prosecution of offenders;
— proper follow-up of the cases;
— development of a network of informants;
— education about the system to ensure distribution and sale only of legitimate products in the market, e.g. system of warranty;
— familiarization with the methods of information sharing, coordination and collaboration with all concerned in combating counterfeiting, including other inspectors, health professionals, and representatives of the pharmaceutical industry, police and other investigating agencies at the national, and where necessary, at the international level;
— relations between the pharmaceutical inspectorate and other law enforcement agencies, such as customs, police, health inspectorate, veterinary inspectorate, legal departments;
— relations with drug manufacturers at home and abroad;
— relations with WHO, including reporting to and being informed by WHO, through the national drug regulatory authorities;
— reference data in books or electronic form (e.g. Internet);
— security aspects;
— record-keeping, the importance of properly documented standard operating procedures, including description of samples according to a defined model;
— preparation of official reports.

Course programme items may vary according to the specific requirements of each country. Further guidance may be found in the "Guidelines for inspection of drug distribution channels" (*3*).

2.5 *Duration of training course*

The duration of the course depends on the local situation. A typical course may last one week.

2.6 *Reiterative training*

Refresher courses should be regularly organized and attended. Country demand would determine the frequency of these courses.

2.7 *Assessment*

Continuous assessment will be conducted during the programme.

2.8 *Certificate*

An appropriate certificate should be issued on satisfactory completion of all parts of the programme.

2.9 *Evaluation of the programme*

Evaluation is an important component of any such activity, particularly since the occurrence and nature of counterfeiting differ from country to country. This may result in changes in the activities of inspectors. Therefore, a refresher course could be of a different nature, if so indicated by evaluation.

3. Training programme on examination

3.1 *Course objectives*

The aim of this course is to provide trainees with:

— an awareness of the importance of examining suspect pharmaceuticals in order to facilitate the inspector's decision whether or not to act;
— sufficient knowledge and skills to examine counterfeit pharmaceuticals;
— an understanding of the difference between counterfeit and substandard drugs;
— knowledge of the value and limitations of techniques for rapid examination, and the ability to make rational decisions about their use;
— the ability to justify legal action in the context of detection and prosecution.

3.2 *Types of training*

Theory and practice involving examination of drugs.

3.3 *Educational background of trainees and trainers*

Previous or formal training of trainees is not absolutely required for the examination of drugs, but former training would be advantageous. Preferably, trainees should meet the following criteria, according to country requirements:

— knowledge of and competence in selected laboratory techniques, such as using a weighing balance and carrying out volumetric measurements, and the ability to perceive differences in colours;
— reading and writing skills to facilitate adequate record-keeping;

— an understanding of the need and the willingness to work as a team and to share information.

The trainer should be experienced and have full knowledge of general and official analytical methods. Furthermore, he or she should be able to conduct and design, when necessary, the training programme. Other characteristics include:

— an appreciation of the role of chemical testing in the legal system for combating counterfeit products;
— an understanding of the difference between counterfeit and sub-standard drugs;
— knowledge of the latest statistics on the prevalence of counterfeit pharmaceuticals in the country, if possible;
— knowledge of relevant quality standards;
— knowledge of characteristics of various dosage forms;
— thorough overall knowledge of the subjects to be taught.

3.4 *Course programme items*

The following items should be included in the course; the actual content of each item will depend on the prior experience of the trainees:

— overview of relevant legislation;
— national drug regulatory systems, inspection and quality control;
— drug distribution systems;
— illegal distribution channels;
— types of counterfeit pharmaceuticals encountered;
— general characteristics of various dosage forms, such as active ingredient to excipient ratio in tablets, capsules, ampoules, powder for injection, ointments, creams, etc.;
— sampling methods;
— reference substances and working standards: importance and maintenance;
— reference data in books or electronic form (e.g. Internet);
— security aspects;
— record-keeping, the importance of properly documented laboratory work including description of samples;
— preparation of official reports;
— relations with WHO.

After demonstration of the techniques to be used, trainees should practise with an adequate number of known dosage forms, preferably including capsules, tablets, injectable preparations and ointments. Trainees will then test unknown samples, report on their work and

draw conclusions as to whether the samples are counterfeit or require additional analysis. The results will be compared with previously determined data and will be discussed in the group.

In the course, the trainee will be taught to perform various examinations including:

— examination of labelling features, packaging materials and packaging of various drug forms;
— measurement of various physical properties of the product;
— thin-layer chromatography (see Appendix 2);
— other specifically selected examination procedures.

3.5 *Duration of course*

Duration of the course depends on the local situation. A typical course would take about 10 days, consisting of:

— introduction (1–2 days)
— theory (1–2 days)
— practical work in the laboratory and field, if necessary on various dosage forms (4 days)
— preparation of a summary and reporting (2 days).

3.6 *Reiterative training*

Refresher courses should be regularly organized and attended. Country demand would determine the frequency of these courses.

3.7 *Assessment*

Continuous assessment will be conducted during the programme.

3.8 *Certificate*

An appropriate certificate should be issued on satisfactory completion of all parts of the programme.

3.9 *Evaluation of the programme*

Evaluation is an important component of any such activity, particularly since the occurrence and nature of counterfeiting differ from country to country. This may result in changes in the activities of inspectors. Therefore, a refresher course could be of a different nature if so indicated by evaluation.

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3. Guidelines for inspection of drug distribution channels. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report.* Geneva, World Health Organization, 1999, Annex 6 (WHO Technical Report Series, No. 885).

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[1] See footnote on p. 151.

Appendix 1

The practical issues of organizing and implementing the programme

Getting started

1. ***Establish a core group for organizing the training programmes***
   - Organize the core group for planning and implementing the education programme. The group may be organized by health authorities, or by nongovernmental organizations or joint enterprises.
   - Establish roles and responsibilities for all participants in planning and implementation.

2. ***Develop the profile of what is required and estimate the output of the programme***
   - Construct the profile of the required system of national or local drug distribution in terms of the characteristics of both professionals and the general public.
   - Collect data regarding the target professionals.
   - Assess the overall performance of the target professionals.
   - Identify the extent of the responsibility of the target professionals in combating counterfeit pharmaceuticals.
   - Identify what the professionals need to improve their performance in combating counterfeit pharmaceuticals, and prioritize according to the available resources.
   - Identify the "end products" to be achieved by the training programme.

3. ***Plan the curriculum according to the need***
   - Develop a survey of the needs.
   - Identify sources of data and other resources.
   - Prepare a plan (who, where, when) for collecting data.
   - Collate information.

4. ***Assess the facilities and staff available***
   - Assess the available teaching staff, equipment and facilities in institutions for training.
   - Determine whether additional staff and equipment will be needed to meet the objectives and provide the curriculum as planned.

5. ***Work with other concerned parties***

- Identify institutions, groups and persons in the community with whom to collaborate.
- Share information with these institutions, groups and persons in order to encourage collaboration in the programme.
- If there are not enough resources available in the target area, find resources outside the area.

6. ***Select the target groups***

- Identify the target professionals and select the core groups for whom the programmes will be most effective.
- Ensure that the distribution of participants in the training programme is balanced in terms of disciplines and regions.

Initiating implementation

1. ***Secure financial support***

- Investigate potential and existing internal and external sources of financial support for the programme.

2. ***Gather materials for a curriculum***

- Contact institutions, agencies and other organizations with experience and expertise in the pharmaceutical training fields, including WHO and its collaborating centres.

3. ***Make arrangements for the trainees***

- Arrange accommodation and travel for the trainees, if necessary.

4. ***Recruit teaching staff***

- Contact and recruit suitable teaching staff.
- Arrange their accommodation and travel, if necessary.

5. ***Establish a positive image for the goal of the programme***

- Identify core trainees who understand the meaning of the programme and support it.
- Obtain early support by key persons.

6. ***Deal with barriers***

- Attempt to overcome resistance to the programmes (e.g. reluctance to take up the issue of counterfeit pharmaceuticals).

Selected further reading

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Appendix 2
Thin-layer chromatography and its application

There are many reasons why thin-layer chromatography (TLC) should be the mainstay method of drug analysis:

— it can be used for identification or for qualitative analysis and semi-quantitative determination;
— it is easy to use (after training) and rapid;
— analyses are reproducible;
— results are reliable and accurate (high specificity and selectivity, no interference from excipients);
— results can be further improved by the application of selected detection reagents, which produce certain colours on reaction with the components of the dosage forms;
— it is relatively inexpensive;
— it is not labour intensive;
— plates can be coated by the analysts if necessary, e.g. silica gel can be made to different thicknesses for certain analyses;
— endpoints (eluted components) are easy to detect visually;
— the results (R_f, R_r values and colours) are easily included in a suitable database;
— it should be possible to develop a TLC kit to simplify drug analysis by TLC;
— multi-component preparations containing up to two or three components may be analysed.

Some of the disadvantages of TLC are:

— the volatility of solvents must be considered when choosing solvent systems for use in certain climates;
— some solvents are potentially hazardous to health and the environment; thus care should be taken in their selection (e.g. chloroform, benzene, ether).