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THE PRODUCTION OF STANDARDS AND REAGENTS FOR THE QUALITY CONTROL OF MEDICINES

DP/VIE/84/006

SOCIALIST REPUBLIC OF VIET NAM

Technical report: Establishment of secondary reference substances for pharmaceutical quality control in Viet Nam*

Prepared for the Government of the Socialist Republic of Viet Nam
by the United Nations Industrial Development Organization
acting as executing agency for the United Nations Development Programme

Based on the work of Ms. Monika Westermark, consultant
in Chemical Reference Substances

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United Nations Industrial Development Organization
Vienna

* This document has not been edited.

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ABSTRACT

THE STRENGTHENING OF THE STANDARD SECTION OF THE INSTITUTE OF DRUG QUALITY CONTROL.

DP/VIE/84/006/11-52

Objective:Advise the counterpart staff in the establishment and maintenance of chemical reference substances.

Duration:15 April-29 April 1990

Monika Westermark ,Director of WHO Collaborating Centre for Chemical Reference Substances ,Stockholm ,Sweden visited the National Institute of Drug Quality Control in Hanoi,Vietnam as a short-term consultant in Chemical Reference Substances to strengthen the standards unit.
During september-november 1989 two pharmacists from the Institute were trained at the WHO Collaborating Centre in Stockholm , Sweden. Discussions on analysis of reference substances performed since the training were held and analytical results followed up for ampicillin trihydrate and tetracycline hydrochloride.

A workshop was arranged titled "WORKSHOP ON CHEMICAL REFERENCE SUBSTANCES", 23-26 April 1990 were Monika Westermark gave lectures on the following topics.

*Guidelines for establishment of chemical reference substances.

*Analytical methods used in testing of chemical reference substances(two lectures)

*Certification, record keeping reperatory and GLP.

*Maintenance, storage and distribution of chemical reference substances.

22 primary International Chemical Reference Substances were donated as a start for the calibration of Vietnamese reference substances.Reports and certificates for these substances were reviewed and dicussed.

INTRODUCTION

In order to strengthen the Standards section at the National Institute of Drug Quality Control, the UNIDO (Vienna) engaged Monika Westermark as a short-term consultant to perform the duties given in the job description (Annex 1).

Monika Westermark ,Director of WHO Collaborating Centre for Chemical Reference Substances in Stockholm visited the National Institute of Drug Quality Control in Hanoi. The expert arrived in Hanoi 17 April 1990 and reported at the Institute on 18 April 1990. The activity was finished at 27 April 1990.

The following report is based on observations made during the laboratory visit and on the discussions held with the laboratory staff.
The report also includes a suggested plan for the implementation of the programme and a list of recommendations to strengthen establishment and the analytical investigations of the standards .

SECONDARY REFERENCE MATERIALS -ASSESSMENT OF PRESENT USE AND FUTURE NEEDS.

After discussions held with the laboratory staff it was evident that there is a need today in Vietnam for reference materials to be used in the daily quality control work at the Institute and to support the regional province laboratories (44 different) and the local factories. From earlier list obtained from the Institute (Annex 2) there is today a need for 38 different reference substances in various amounts from 50 to 1000 ampoules. For various reasons as high costs and the the large amounts requested existing primary reference materials as International Biological Standards ,International Chemical Reference Substances ,USP Reference Standards ,BP and EP Chemical Reference Substances cannot normally be used as working standards.
The National Institute of Drug Quality Control has therefore already started to prepare national reference substances.Today six of them are available i.e.
Ampicillin trihydrate, Benzylpenicillin potassium, Tetracycline hydrochloride, Benzylpenicillin sodium, Chloramphenicol and Phenoxymethylpenicillin. However as there exists difficulties in obtaining suitable bulk materials some of these might be too impure to be suitable as secondary standards.
A total need of 38 substansces were expressed as mentioned above they are given in Annex 2.The International Chemical Reference Substances for 22 of these (Annex 3) together with full reports and certificates were donated by the WHO Collaborating Centre for Chemical Reference Substances as a start for calibration of the secondary reference substances. The others are at the present time not available from the WHO Centre but some will be in the future and the others can be obtained from the USP,BP or EP. The present status and possible sources are given in Annex 4.
The present production of national secondary reference substances is delayed for several reasons as difficulties in obtaining sufficient quantities and satisfactory qualities of the required substances,insufficient instrumentation and instrumentation out of order with difficulties to obtain spare parts and service, shortage of dispensing areas at low humidity, lack of experience of the analytical methods used for characterization of the substances.
In the view of the consultant there is a need to establish secondary reference substances in Vietnam. However it was difficult to get a real view of the intended use of the Vietnamese reference substances .Therefore it is strongly advised that visits are planned to the provinsional laboratories and factories to see how the substances are used in real work and what type of analytical instrumentation that is available. Probably the main methods are UV-spectrophotometry and thin-layer chromatography .

II. EVALUATION OF LABORATORY RESOURCES

As the consultation was only for short time and most of the time was spent on the WORK-SHOP only a superficial survey could be made and the consultant therefore wishes to apologize for any errors and omissions in her report.

Staff
Regarding the staff qualifications the consultants impression is that the personal involved in the standards production were well qualified with good understanding of the problems involved in the use of reference materials and also from establishing in-house working standards.The list of counterpart staff involved in the work on chemical reference substances are given in Annex 5
The laboratory has already experience from regular pharmacopoeial testing of raw material working with the International Pharmacopoeia , the British Pharmacopoeia, the United States Pharmacopoeia and the Vietnamese Pharmacopoeia (a translation of the russian pharmacopoeia) as appropriate.
However it will be necessary for the staff to train more practical on analytical documentation of chemical reference substances according to the training performed in Sweden and the work-shop held in Hanoi.

B. Localities.
It is important that a laboratory involved in the preparation of chemical reference substances has air-condition and preferably also de-humified rooms for its work. As the institute is situated in old and rather unmodern localities this is a problem. However dehumidifiers were installed in most of the rooms but must also be on during nights which caused som problems due to fall in voltage and high electricity costs. It is also suggested that the laboratory has at least one large refrigerator set aside exclusively for storage of reference substances. The institute had two refrigerators combined with freezers for this purpose. As freezing is not recommended for substances containing water due to the risk of freezing out of the water and resulting in inhomogenous bulk in the future the installation of a cool-room is probably necessary if the amounts of reference substances increases.

C. Instrumentation.
As regards to analytical instrumentation most of the basic instruments required of validation of secondary reference materials are already available at the laboratory as listed in Annex 6. However some of the most important instruments were out of order this includes the infrared spectrophotometer, the ultraviolet spectrophotometer and the thin-layer densitometer. A list of spare parts that must be ordered and other instruments that will be needed in the future are also given in Annex 6.

III. DISCUSSIONS ON ANALYTICAL RESULTS FOR SUBSTANCES ON THE PROJECT LIST

Ampicillin trihydrate:Since the training in Sweden a better bulk has been obtained that is of far better quality (less than 1 % impurities) than the former (10 % impurities).Problems with the determination of water was discussed. Only Karl Fisher titration which was performed is too weak for the documentation as penicillines with high amounts of impurities can give false results.The consultant recommended loss on drying to be performed as a complement.The WHO Centre will also assist in performing

Tetracycline hydrochloride:Problems with liquid chromatographic determination of 4-epitetracycline where increasing values were obtained during the day.Stability was discussed as this is probably the main problem .in a country with high temperature as Vietnam it is of outermost importance to prepare fresh solutions when working with sensitive substances as tetracycline.

Nystatin and Rifampicin: As these substances are in work during 1990 at the WHO Centre, probably there is a possibility to perform some tests also on the Vietnamese substances as a guiding help.

IV. AVAILABILITY OF BULK.

Bulks for new reference substances have been supplied by UNIDO.At present the bulks listed in Annex 7 were available at the Institute.These are a good basis to start with .They can be calibrated against the corresponding International Chemical Reference Substance.
As this must be a long-term project it is strongly recommended to make a project plan and to concentrate on a few substances every year. A recommended working procedure is given in Annex 8.
The consultant also recommended a regular reexamination (at least every year) and calibration of existing Vietnamese standards against the corresponding ICRS.

V. WORK-SHOP

Most of the time of the consultation was spent on the "WORK-SHOP ON CHEMICAL REFERENCE SUBSTANCES" ,23-26 April 1990 where the consultant gave lectures and adviced on the following topics.
Copies of all the lectures material was given to the Institute.

*Guidelines for establishment of chemical reference substances

Most important is the working procedure for secondary standards given in Annex 8. Different types of standards as primary ,secondary,working,in-house etc, were dicussed.The intended use of the substance is very important to perform the necessary amont of work on each substance and to chose suitable purity of the bulk.

*Analytical methods used in testing of chemical reference substances (two lectures)
Typical methods used in the testing are given in Annex 9. For the Vietnamese standards the recommendation is to concentrate on analytical methods as liquid chromatography, thin-layer chromatography, UV-assays, titrations , loss on drying, Karl Fisher water determination and IR-identifications.The intended use of the substance must be the guiding principle in the choice of methods.
For special techniques which demands sensitive equipment as thermoanalysis(DSC) and thermogravimetric analysis(TGA) the WHO Centre is willing to assist in performing the analysis at this stage of the project.

*Certification ,record keeping reperatory and GLP
The importance of having all documentation for each reference substance in one file including raw data from analysis was stressed.Important detailes which should be included in a certificate were discussed.

*Mair tenance,Storage and distribution of chemical reference substances.
The importance of good storage conditions were discussed, a coolroom with low humidity is preferred.The use of a glove-box for dispensing is also useful to control humidity.
Regular stability studies is preferred instead of frequent replacement of existing batches .
A regular supply of primary reference materials i.e ICRS,USPRS ,BPCRS,EPCRS every year is necessary for the reexaminations.
If the substance under investigation is included in the document "Accelerated stability studies... (Annex 10) there is no need to perform these studies again, as this document is meant to be a guiding help.

Containers for reference substances should afford protection from moisure, light, and sometimes also oxygen. From the point of view of the stability of the substances, sealed glass ampoules are the best containers, but they suffer from certain disadvantages, notably the risk of contaminaiting the substance with glass particles when the ampoules are opened and the difficulty of re-closure. Sealed ampoules are therefore principally used only for materials that must be kept in an oxygen-free atmosphere. Most chemical reference substances, however, are conveniently supplied in re-closable containers, which should be uniform in type and size to facilitate distribution. In determining the suitability of containers for reference substances it is emphasized that their permeability to moisture is an important factor. It is suggested that small size penicillin-type vials with rubber stoppers and aluminium seals would be satisfactory containers for most of the materials that are to be established as secondary reference substances.

The packing of a batch of a reference substance into containers is a small-scale operation and is therefore conveniently done manually with the aid of a top-pan balance. Several pharmaceutical reference substances have to be packed in conditions of controlled humidity. This can be accomplished by use of a glove-box.

SUGGESTED PLAN OF ACTION TO ESTABLISH SECONDARY REFERENCE MATERIALS FOR VIETNAM

It should be realized that a programme for establishing reference materials must be a long-term project.It is suggested that the programme be started first on a small scale and that it be further expanded as further experiences has been gained and when necessary facilities in terms of equipment and training of staff has been obtained.

1.The following equipment has to be repaired if possible.If not possible (due to the age of the instrumentation) new equipment must be purchased.
IR-spectrophotometer---power supply broken
UV-spectrophotometer ----lamp out of order
TLC-scanner ----- motor out of order
For details see ANNEX 6.
It is recommended to have one person responsible for each instrumenty and to have spare parts as eg.UV-lamps in stock.Written instructions for normal use must be placed at each instrument.

2. A visit by eg. the project leader to some of the provinsional laboratories and/or factories would be of good help to the project. This is to see how the reference substances are used and to judge if the large amounts required see ANNEX 2 could be decreased as reference materials are very expensive and time-consuming to prepare.

3. A concentration on the analytical examination of the reference substances is recommended .Today two persons are busy with the dispensing and handling and only one performs the analysis .At least two persons full time engaged in performing analysis would gain the project.The dispensing is only a small part of the work.

4. In the project budget a sum must be reserved for annual aqusition of primary reference materials as ICRS ,USPRS etc,or support must be sought from WHO/UNIDO.
Reference substances should preferably be ordered as the need for them arises.Only those for which a regular demand can be foreseen should be stored in the laboratory.Established secondary standards should be subjected to annual calibration against primary reference materials.

5. Make an annual realistic plan of work with a priority list chosen from the bulks in ANNEX 7.
If some reference substances only are requested in small amounts it is probably better as an intermediary solution to use primary standards(25-50 vials can be ordered of an existing ICRS) .Review the plan every year.

6. Equipment listed in ANNEX 6 under additional equipment will be necessary if the project expands.

7. Select a committee for adoption and handling of reference substances.

8. As a second phase it is advised to arrange a more practical work-shop were persons are trained in using the different analytical techniques. Maybee staff from the regional laboratories should be included. It must be well planned and all equipment must be fit for use, and all necessary chemicals must be available at the laboratory. Some important substances on the project list could be a basis.

9. As antibiotics seems to be very important it might be necessary to strengthen the training in microbiological assays of standards at eg. the WHO International Laboratory for Biological Standards, London

ANNEX 1

dr:M.Quintero/vs
16 January 1990

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

JOB DESCRIPTION

DP/VIE/84/006/11-52

Post title Short-term Consultant in Chemical Reference Substances

Duration 2 weeks

Date required April 1990

Duty station Hanoi, Vietnam

Purpose of project The strengthening of the Standards & Reagents Section of the Institute of Drug Quality Control to increase its services to the pharmaceutical industry to provide standards, reference substances and reagents both in improved quality and increased quantity to the provincial drug quality control institutes, pharmaceutical factories and public health related institutions.

Duties

As a member of international experts assigned to the Institute of Drug Quality Control, under the Chief Technical Adviser and in collaboration with the National Project Coordinator and counterpart staff, the expert is expected to :

- Advise on the structure and management of a national reference substances unit
- Assist in drawing up guidelines for the establishment, maintenance, storage and distribution of national chemical reference substances
- Advise on certification, record keeping, documentation and specification repertory of chemical reference substances
- Recommend improved procedures for sampling, testing, labelling and stability studies of reference substances
- Conduct lectures to upgrade and extend the knowledge of local staff about chemical reference substances

The expert is expected to prepare a final report setting out his findings and recommendations

..../..

Qualifications

University Degree or equivalent in chemistry and/or pharmacy with extensive experience in the production of chromatographic absorbents

Language

English

Background information

The Government in accordance with the Development Plan, attaches great importance to local production of drugs primarily for attaining relative self-sufficiency and saving scarce foreign exchange. The pharmaceutical industry consists of one factory manufacturing pharmaceutical chemicals and 10 central formulation plants, approximately 25 % of the production being of the traditional system. The central factories, provincial production units, trading companies, depots, provincial and district services form a network of quality control laboratories at the provincial and central levels. The provincial laboratories are small- to medium-size and carry out some essential testing. The central level is directly under the control of the Ministry of Health and deals with samples which require detailed analysis through advanced techniques. The quality control network requires a continuing supply of standards and reagents.

At the top of this network, the Institute of Drug Quality Control (IDQC) heretoafter referred to as the "Institute", has been established in Hanoi in 1971, with a sub-Institute in Ho Chi Minh City (HCMC) in the South. The main functions of the Institute are:

- to control the quality of medicines (including traditional ones), their intermediates and raw materials with regard to their production, imports, exports, purchase, storage and utilization;
- to study various methods of testing, controlling and standardizing the quality of drugs such as: metrology, pharmaceutical regulations, legal chemistry, production and supply of standards and reference substances and analytical and biochemical reagents;
- to disseminate scientific and technical information; and
- to provide training in drug quality control.

ANNEX 2

Project list for the Vietnamese secondary reference standards

December 1989

	Name	Present	Projected
1 -	Ampicillin trihydrate	100 amps	1000 amps
2 -	Benzylpenicillin potassium	500	500
3 -	Benzylpenicillin sodium	250	500
4 -	Chloramphenicol	100	500
5 -	Erythromycin	100	500
6 -	Neomycin	100	100
7 -	Phenoxymethylpenicillin	500	1000
8 -	Phenoxymethylpenicillin potassium	500	1000
9 -	Rifampicin		100
10 -	Streptomycin sulfate	300	1000
11 -	Trimethoprim		100
12 -	Oxytetracycline	100	200
13 -	Tetracycline, HCl	500	1000
14 -	4-Epitetracycline, HCl	50	100
15 -	Anhydrotetracycline, HCl	50	100
16 -	4-Epianhydrotetracycline, HCl	50	100
17 -	Diazepam		50
18 -	Ethambutol		50
19 -	Prednisolone		50
20 -	Sulfadimethoxine		50
21 -	Progesterone		50
22 -	Sulfadimidin		50
23 -	Sulfadoxine		50
24 -	Sulfamethoxazole		50
25 -	Sulfamethoxypiridazine		50
26 -	Sulfanilamide		50
27 -	Tolbutamide		50
28 -	Vitamin A		300
29 -	Vitamin D		100
30 -	Vitamin E		50
31 -	ACTH		50
32 -	Insulin		50
33 -	Oxytocin		50
34 -	D-strophantin		50
35 -	G-strophantin (ouabaine)		50
36 -	Digitoxin		50
37 -	Digoxin		50
38 -	Histamine		50

ANNEX 3

International Chemical Reference Substances obtained from WHO Collaborating Centre for Chemical Reference Substances.

Name	Quantity	Control No
Ampicillin trihydrate	1 x 200 mg	274003
Anhydrotetracycline hydrochloride	1 x 25 mg	180096
Benzylpenicillin potassium	1 x 200 mg	180099
Benzylpenicillin sodium	1 x 200 mg	280047
Chloramphenicol	1 x 200 mg	486004
Diazepam	1 x 100 mg	172062
4-Epianhydrotetracycline hydrochloride	1 x 25 mg	288097
4-Epitetracycline ammonium salt	1 x 25 mg	180098
Ethambutol hydrochloride	1 x 100 mg	179081
Ouabain	1 x 100 mg	283026
Oxytetracycline dihydrate	1 x 200 mg	189142
Phenoxymethylpenicillin	1 x 200 mg	179082
Phenoxymethylpenicillin potassium	1 x 200 mg	176075
Prednisolone	1 x 100 mg	283029
Progesterone	1 x 100 mg	167033
Sulfmethoxazole	1 x 100 mg	179092
Sulfmethoxypyridazine	1 x 100 mg	178079
Sulfanilamide	1 x 100 mg	179094
Tetracycline hydrochloride	1 x 200 mg	180095
Tolubutamide	1 x 100 mg	179086
Trimethoprim	1 x 100 mg	179093
Vitamin A acetate (solution) (à 25000 IU)	1 x 5 caps	686038

Requested reference substances not yet available as ICRS (possibly available from USP, BP or EP)

Substance:	Comments:
Erythromycin	Bulk available for ICRS but not adopted yet
Neomycin	Not on project list, impurity Neomycin B-Sulfate is however
Rifampicin	Not on project list, but its impurities are available 1991
Streptomycin sulfate	Not on project list
Sulfadimethoxine	Not on project list
Sulfadimidin	Not on project list
Sulfadoxime	Not on project list
Vitamin D	Colecalciferol, Vitamin D_3 } available 1991 Ergocalciferol, Vitamin D_2 }
Vitamin E	Not on project list
ACTH	Not on project list
Insulin	Not on project list
Oxytocin	Not on project list
Histamin	Not on project list

ANNEX 5

Persons involved in the preparation of Vietnamese national chemical reference substances at the National Institute of Drug Quality Control.

Professor Doan Huy Khac
Director of the National Institute of Drug Quality Control

Madame Tran Le Sung
Head of Laboratory of Standards and Reagents

Mrs Luong Bang Phi
Head of Standards section

Mrs Hoang Thanh Mai
Pharmacist Standards Section, Analysis

Mrs Nguyen Minh Nghia
Pharmacist Standards Section

Mrs Lébich Dao
Head of analytical instrumental laboratory

Nguyen van Khang
Head of microbiology section

ANNEX 6

Observations made during laboratory visit

Premises: Laboratory building is old and unmodern. However modern equipment as dehumidifiers and refrigerators are installed. No cool-room available. No fume-hoods. No glove-box.

Equipment available: Generallly the equipment is relatively modern, but some are out of order.

Examples of available intrumentation:

IR-spectrophotometer (Pye) - out of order
UV-spectrophotometer (Pye) - out of order
Liquid Chromatographs (Hitatchi)
TLC scanner (Schimadzu) - out of order
Balances (Mettler)
GLC
Fluorimeter
Potentiometric titrator

Acquisition of the following equipment is necessary:

Spare parts for:
Infrared spectrophotometer (Pye):
Nernst supply F321 for Pye Unicam
Infrared spectrophotometer, Model SP2000 England, Purchase order K 720962/C

UV spectrophotometer (Pye):
Vale (Lamp) A2792 for detector unit of UV-Vis spectrophotometer, Model SP8000 (Pye Unicam), England

TLC scanner (Schimadzu):
Synchronous Motor Typ D-2M-60 RPM 100 V 50Hz 6W, No 17888 76-10, Japan Secvo Co-LTD for Schimadzu Anal. TLC Scanner CS-210, Japan

If not possible to repair these three instruments must be replaced by new equipment.

Acquisition of the following additional equipment would be desirable:

HPLC - equipment, if the working-load on the existing increases
Glove - box
Fume - hood
Sealing apparatus
Vials

ANNEX 7

Bulk materials obtained through UNIDO

Chloramfenicol

Digoxitin

Digoxin

Ethambutol

Histamin base

Neomycin

Nystatin

Ouabain

Oxytetracycline

Oxytocin

Prednisolone Acetate

Progesterone

Rifampicin

Vitamin E

ANNEX 8

WORKING PROCEDURE ON "SECONDARY STANDARDS"

- Estimate the amount needed
- Define the intended use
- Verify the identity
- Examine the material by a stability indicating procedure
- Standardize the material against the corresponding ICRS

ANALYTICAL METHODS FOR CHARACTERIZING AND ASSAY OF CHEMICAL REFERENCE SUBSTANCES (BULK MATERIAL)

IDENTITY

- IR spectrophotometry
- Elemental analysis
- UV spectrophotometry
- NMR
- Mass spectrometry

PURITY

- HPLC, UV, Diode Array
- TLC, densitometry
- GC
- PSA
- Thermoanalysis, DSC, DTA
- NMR
- Water, titrations, TGA, LOD

SUITABILITY

STABILITY

REFERENCES

1. Accelerated stability studies of widely used pharmaceutical substances under simulated tropical conditions
WHO/PHARM/86.529

2-3. General guidelines for the establishment, maintenance and distribution of chemical referencesubstances,
World Health Organization Technical Report
Series No. 681, 1982, pp 19-33
No. 748, 1987. p 14

4. Yearly reports from WHO Collaborating Centre for Chemical Reference Substances
Eg. WHO/PHARM/89.544