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NATIONAL LABORATORY FOR PHARMACEUTICAL QUALITY CONTROL

BY

Dr. H. Sabart
WHO Scientist

Whether or not to establish a National Laboratory for Pharmaceutical Quality Control (NLPQC) has been, for several years past, a most controversial question for many developing countries. In principle there is no doubt that to have a control is useful. In practice, it is debatable whether such a laboratory should be established regardless of the general level of technical competence in the country, whether it might not be better to make use of an inter-country laboratory serving several countries in common, and whether it is necessary to have a control at all when the foreign producer whose goods are imported has his own production control. These are the three main questions most often discussed. Different countries have given different answers, depending on their own economic and technical situations.

Clearly, a National Control Laboratory is an expensive, exacting, and at first glance non-productive organization. This legitimately leads to hesitation in the decision to establish one. Even if a clear answer cannot be given at once to these doubts, it seems likely that most developing countries will wish to have their own NLPQC either now or in the near future.

There have been many good articles, papers, and studies defining and describing the principles and nature of pharmaceutical quality control, so it is unnecessary to repeat here what has already been well said. Instead,

an attempt will be made to define the stage at which a country should consider establishing a NLPQC.

No very detailed guidance can be given since the factors vary so much from one country to another. Nevertheless, the so-called developing countries can clearly be divided into two categories:

i) those with no production of their own; and
ii) those which produce pharmaceutical preparations, even if this is done mainly from imported raw materials.

It must be unreasonable for a country which has no trace of local pharmaceutical production and imports all its preparations to think of or to plan a NLPQC. At this stage of its development it is advisable for it to import preparations from firms where adequate quality control is maintained. At a later stage, when conditions are different, there will be time enough to establish its own National Laboratory.

A country in the second category, that is, one producing pharmaceutical dosage forms from imported raw materials, is already faced with two problems:-

i) the quality control of the imported raw materials; and
ii) the quality control of the finished product.

In addition, of course, it has the task of controlling the quality of imported drugs, which should be undertaken at this point.

Both the above-mentioned requirements should be carried out as a matter of routine, together with all other in-process control measures, by the manufacturer, but there is every justification for government inspectors also to examine the processes used in the plant. During their visits the inspectors of the National Laboratory can verify the technical and scientific level of the work done, evaluate the completeness of the equipment and the qualifications of the staff, and judge any other aspects which might influence the quality of the product. In this way the National Laboratory acts as a counter-balance to the manufacturer.

The Laboratory carries out the same supervisory duties in connection with the distribution of drugs by wholesalers and retail pharmacies.

The system just described is sometimes called a two-step control; one at the level of production and distribution, and the other a super-control by the national authorities. This is the system adopted in many industrial countries, and it ensures reliable control of the quality of drugs.

Two other factors mentioned above which it is necessary to consider when deciding whether to establish a NLPQC are the state of the national economy and the availability of human resources. To put it into plain words: there should be no economic difficulties in the way of establishing, running, and steadily developing an appropriate institution.

As for human resources, a supply of qualified personnel can be obtained as soon as there is a Pharmaceutical Faculty in the country to serve as an educational base. Post-graduate training can be made available to members of the United Nations through WHO fellowships.

Developing countries usually face more problems in the supply of technicians, since they often do not possess suitable schools or courses to train this level of worker. For this reason, almost all the laboratory work has to be done by the graduates themselves, and so the output of work is low and its costs proportionately high. To remedy this situation as soon as possible, it is recommended that the graduates on the staff of the Laboratory should organize and undertake the progressive training of its technicians.

When all three of the above-mentioned conditions are met, the establishment of a NLPQC is possible, and is probably desirable as a further step in the technical progress of the country.

In order to have sufficient authority and executive power to perform its duties in relation to the production and distribution of all marketed drugs, including those imported from abroad, the NLPQC should be as close as possible to the Minister of Public Health in the organizational structure of government.

Let us now take a closer look at the desirable size and structure of a National Laboratory, and at the minimum facilities and personnel it will

need. Clearly, an elementary type of quality control could be started with almost no equipment, but it is advisable when deciding on a National Laboratory to think of all aspects of a country's needs over the next ten years. It is difficult, if not impossible, to say how big the laboratory should be, although experience in industrial countries has shown that there may be a correct relationship between the population of a country and the number of employees in its National Laboratory, in the same way as there is a relationship between the population and the number of physicians, pharmacies, hospital beds, etc., required to provide an adequate health service.

It seems safe to say that in an advanced country where drug control already exists at the manufacturing plant and regional levels, a well established and properly equipped NLPQC would be adequately staffed if the number of its employees represented about 0.001% of the population, e.g. 300 employees for a population of 30 million. This is a rough approximation, and should be regarded as a long-term aim for a well-established laboratory and not an initial requirement.

Regarding the buildings and premises needed for a laboratory, no more than planning hints can be given, owing to the complexity of the problems involved. The building should be erected in a green space with ample room for chemical, microbiological, biological, and pharmacological control laboratories, administrative offices, a library and documentation centre, a lecture hall, an animal station, a power house, garages with a service station, maintenance workshops, store-rooms, and a canteen for employees.

If the building is of more than one storey, the ground-floor should be earmarked for the pharmacological section so that it can be close to the animal house, and the top floor for the microbiological section for it to have purer air. The floor in between can be occupied by the chemical sections.

A corridor is an advantage if it is situated in the middle, with rooms of two standard sizes opening off it on both sides. The corridor can then house all the necessary ducting by which services are led into the laboratory rooms. Air-conditioning might be useful; central heating via the ceiling is considered the most up-to-date type.

The laboratory rooms themselves should preferably be for no more than two to four persons each, as in this way there is less interference and greater concentration in work, and better precautions against fire and explosion. The bigger sized rooms should be used only as laboratories; the smaller ones on the opposite side of the corridor for special and auxiliary purposes such as weighing rooms, dark-rooms, chromatographic rooms, autoclave rooms, distilling rooms, preparatory rooms, etc.

A mistake is frequently made by placing central double benches in a chemical laboratory parallel with the windows. Only by placing them at right angles to the windows can enough of the same kind of light be given to both sides of the benches. If the benches are formed of bases on castors, with the drawers and working tops fitted on separately, repairs can easily be made to the power lines. The most sophisticated laboratories are also equipped with central vacuum and air-taps in addition to the water and gas mains. New plastic materials enable the surfaces of the benches to be kept clean and undamaged by corrosive chemicals. There should be an adequate number of efficient hoods, and all the power controls should be easily accessible from outside to permit quick action in case of fire. A safety shower is an essential in a chemical laboratory. There must also be a suitable fire-proof place for the storage of bulk amounts of flammable liquids. All employees must be trained in proper safety regulations; these should be written, signed by everyone as seen and understood, and kept by the head of the laboratory. It may be useful to give here a tip about how to prevent errors when switching off all power at the end of the day. Each control should be given a small tag with a number; then, the person in charge or the last person to leave the laboratory can check that all have been turned off by following the numbers serially from No.1 to the last one. This has proved a very useful method wherever there are many controls to be checked.

The rapid development of chromatographic methods makes it necessary to have a special room for this with an efficient ventilation system. The writer of this paper thinks that it may not be out of place to mention here his opinion that the value of chromatography is often over-estimated and that it is too readily accepted as quick and adequate solution of

analytical problems. In his view it is not a satisfactory substitute for more accurate quantitative assays, although it can be a good orientation test for identity, impurity, or decomposition, and can give a semi-quantitative estimate of the active substance in a mixture, and sometimes it may be the only possible solution to a complex analytical problem.

At least two rooms should be provided with air-conditioning: that for rabbits before pyrogen testing and that for titrations, as the burettes and pipettes are calibrated for temperatures of either 20 or 25° C, and it is an inconvenience to have to make calculations for different temperatures.

In an institution like a National Laboratory it is preferable to have whole rooms as sterile boxes for microbiological work rather than mere sterile cabinets, which are only suitable for small laboratories. It is also preferable to have a separate room for the autoclaves, as this improves the safety of the employees not directly concerned with them.

Another subject it is appropriate to discuss is the equipment to be provided for a National Laboratory. There is no doubt that a great variety of apparatus can be of some use, but experience has already shown what can be of most use in the initial stage of implementing pharmaceutical control. It is necessary to define here what is meant by the initial stage. By this is meant a good degree of chemical and sterility control, and the microbiological assaying of antibiotics. The more expensive pieces of equipment which would have to be available, in addition to ordinary laboratory glassware, reagents and sundries, to ensure this degree of control, are listed in an annex to this paper.

The instruments include apparatus to perform spectrophotometric determinations in both the UV and visible regions; potentiometers to be used mostly for argentometry and nitritometry; a fluorimeter for the assay of vitamins, etc.; and a polarograph, which will enable the remaining analytical fields to be covered. In addition, a Kjeldahl Apparatus and a Micro Parr Bomb are included as indispensable for the determination of elements in organic substances. For the measurement of certain necessary physical constants for quality testing there are also included a polarimeter, a refractometer, a micro-melting-point apparatus, a disintegration tester,

a pH meter, and a K.Fischer Titrator. The more important items necessary for chromatography are a coater, an UV lamp assembly and a dryer. The remaining equipment is for general use in the chemical laboratory. In microbiological testing all the equipment mentioned is for general use except for the two items for antibiotic activity assays (the Cup Dropper and the Zone Reader).

This can be considered as giving a complete list of the more expensive items of equipment necessary to solve the great majority of analytical jobs. The acquisition of instruments, such as an IR spectrophotometer, a gas chromatograph and a flame photometer can be deferred for the time being, together with the apparatus for e.g. the pharmacological and biochemical control. Some instruments which might be considered as very important, such as a Hardness Tester or a Suppository Melting Point Tester, and others, are not included, as to begin with, simple tests with other equipment already provided can take their place. Brand names and descriptions are deliberately omitted from the list, as this paper's intention is to speak in general terms; the make and manufacturer adopted is a matter of choice, and to make recommendations here would savour of advertisement. The costs are roughly estimated to cover differences between makes and models.

As for the reference library, the laboratory would need at the start, some 500 to 600 professional books including pharmacopoeiae, pharmaceutical, chemical, microbiological, pharmacological and medical books, in addition to catalogues and lists of pharmaceutical preparations of those countries from which drugs are imported. Besides this, about 15 pharmaceutical, chemical, and microbiological periodicals should be subscribed to, by the National Laboratory to provide the most recent news on drug problems.

To start a National Laboratory it seems sufficient to have a staff of about 10 pharmacists, some 5 to 8 technicians and 6 sanitarians or auxiliary workers, one store keeper, one librarian, one or two typists, one secretary, and two microbiologists with five technicians (even untrained ones if they have good personal qualities). This number should be considered as an approximation based on experience.

The internal organization of a National Laboratory, like the other

questions discussed above is a matter of opinion and personal experience. The writer is inclined to believe that a simple division into four sections: two chemical, one microbiological and one pharmacological (biological) is both easy to manage and flexible. The director of the laboratory need communicate with four heads of sections only, thus having a small advisory group able to make decisions more quickly than a large board of section heads, where usually a big variety of only slightly different opinions are to be found. Every section can be further subdivided into laboratories with special tasks like pharmacognosy, biochemistry, antibiotics, histology, hormones, vitamins, etc.

This kind of organization ensures a balance of responsibilities among the individual section leaders, as all of them have about the same number of personnel, and at the same time allows a good transfer of information from the staff to their heads and vice versa. Having two chemical sections shows the weight of work among the various scientific fields in pharmaceutical quality control, where certainly some fifty per cent of analytical problems are solved by chemical methods. The reason is that chemical testing is done wherever possible and is usually quicker, more accurate and less expensive than biological or microbiological testing, which should be used only where chemistry cannot give a reliable or any answer. Examples of this preference in method include: activity of antibiotics, hormones, insulin, etc. Laboratories for pharmacognosy and biochemistry are included in one of the chemical sections as the determinations and evaluations made there are increasingly chemical determinations in principle.

The record-keeping system in a National Laboratory shows not only the results of analyses but also has to provide the necessary information of the quality of every preparation as found over long periods. Further records should be kept, preferably in the form of a card index, on analytical methods used or developed for testing of the received samples, so that when samples are received repeatedly the previous experience can be used. Further records on the results of inspections and on any advisory work carried out for other authorities, institutions or private persons should be available. The basic records of a NLPQC should consist

of: 1) a bound ledger for samples received, showing all basic data; 2) analytical reports; 3) bound analytical note-books; 4) card index of preparations tested; 5) card index of testing methods; 6) correspondence files; 7) inspection files, 8) card index of imported preparations; 9) card index of locally made preparations and 10) inventory files.

A further aspect to be discussed is the sampling and inspection work which is closely related to the laboratory work. Much has already been said or published about the importance of proper sampling and inspections. It is undoubtedly true that the inspection visit is the beginning of quality control, the second part of which is the analytical testing of the samples. An inspector can for instance easily see that vitamin tablets might have been contaminated by an antibiotic because their tableting had been carried out at the same time on two machines close to each other. It might have taken an analyst working in the laboratory a long time to find this out by himself. Thus the main point is that the inspector should bring all possible information and observations concerning the quality of drugs into the laboratory. More about this part of control will be found in the writer's paper entitled "Specifications and Analytical Information Obtained from the Pharmaceutical Manufacturer".

Relations between a NLPQC and other relevant institutions, be it within the Ministry of Public Health (departments for registration, licensing, production) or in the field, must be constructive and co-operative. Everyone who handles drugs is a part of a chain stretching from the manufacturer to the patient. Any and every neglect may result in undesirable effects when shortcomings are overlooked or ignored, as the control net can never be as thorough as to allow every package to be checked. Thus everybody who is in a position to discover a low quality product, whether he is the wholesaler, the pharmacist, the physician, or the inspector, must immediately take the necessary action. To establish such a collaboration requires a great deal of effort on the part of the Ministry of Public Health and the National Laboratory. The public health staff can be instructed by publications, papers during meetings, training, and other adult education media.

Finally I would like to make a few remarks which might be useful for running a National Laboratory:

There is an advantage in having analysts who in addition to their general competence can specialize for periods in one or more groups of drugs within the laboratory, so that they become experts: in vitamins, diagnostic preparations, sulfonamides, antibiotics, antihistaminics, etc. The samples to be analysed are then distributed by the head of the section to the analyst who is familiar with that group.

If later on other laboratories are established on a regional level, the NLPQC should play a leading role in instructing them methodically, so as to keep a uniform control system in the country.

From the very beginning it should not be forgotten that a Laboratory is a place with high risk of fire and health hazards. An adequate number of fire extinguishers, face shields, safety showers or fire blankets, as well as other safety aids should be available in all sections.

Allied to this question is the taking out of an insurance policy, in which the employees as well as the equipment and the building should be included.

Another very important provision frequently ignored is the declaration of one of the pharmacopoeiae as official for the country. This single act of the Ministry of Public Health would simplify every reference to quality inside and outside the National Laboratory and also facilitates the analytical work itself as it would then not be necessary to prepare the many sets of reagents prescribed by different pharmacopoeiae. For reference purposes, and especially to simplify work regarding claims, it is probably advantageous to declare official the pharmacopoeia of that country whence most drugs are imported. The so-called International Pharmacopoeia or Specifications for Pharmaceutical Preparations might be chosen in a country where there is a very great variety of imports from many different parts of the world, or later as the pattern for the establishment of a National Pharmacopoeia when the level of raw material production in the country makes this necessary.

Certainly much more could be written about a National Laboratory for Pharmaceutical Quality Control, but the purpose of this paper has been limited and therefore only those problems which the writer, well aware that the topic is a well-known one, considers worth mentioning, have been described as shortly as possible. In addition, an effort has been made to discuss those points not often shown in such detail, and to mention those not found in publications at all. It is hoped that, despite the different experiences and opinions of the participants in this seminar, and the generality of the subject matter, some useful hints and information will be found in the paper.

List of Equipment

Chemistry:

		Approximate Cost $
1.	Two Potentiometers, with possibility of ampere measurements	500.00
2.	pH meter, electronic, glass electrodes	350.00
3.	UV-Spectrophotometer	2 500.00
4.	Karl Fischer Titrator, manually operated with reagents	200.00
5.	Spectrophotocolorimeter, for visible region	500.00
6.	Polarograph, recording type	1 500.00
7.	Fluorimeter with photo-cell	500.00
8.	Polarimeter, high precision, with sodium lamp	300.00
9.	Refractometer, Abbe type	150.00
10.	Ultrathermostat Water Bath	500.00
11.	Micro Melting-point Apparatus, complete with Microscope	400.00
12.	Two Balances Analytical, precision about - 0.03mg, capacity 200g	1 600.00
13.	Torsion Balance, pre-weighing	350.00
14.	Balance, general purpose, capacity 1000g	30.00
15.	Disintegration Tester for tablets	300.00
16.	Automatic Water Distilling Apparatus, capacity about 4 litres/hour	400.00
17.	Centrifuge, table type, universal with interchangeable heads, about 3,000 r.p.m.	350.00
18.	Coater for Thin-Layer Chromatography, 10cm and 20cm plates	120.00

Chemistry (cont'd)

		Approximate Cost $
19.	Ultra-Violet Lamp Assembly, 366 nm and 254 nm wavelengths, for chromatography	200.00
20.	Dryer, hot-air blower for use in chromatography	15.00
21.	Two Drying Ovens, temperature range 30° to 300°C	700.00
22.	Electric Muffle Furnace, about 2000W, operating temp. about 1100C	300.00
23.	Two Water Baths, electrically heated, without thermostat	80.00
24.	Hot Plate Heater, 6 places, with scaffolding	90.00
25.	Micro-Kjeldahl Distillation Apparatus, with Parnass-Wagner automatic discharge	50.00
26.	Two Magnetic Stirrers, electrically heated (mainly for use with potentiometers)	360.00
27.	Two Electrothermal Heaters Multimantle, capacity 50 - 2000ml, 450W	60.00
28.	Electric Shaker, universal	240.00
29.	Refrigerator, about 14 cu. ft.	400.00
30.	Bomb, Micro Parr (for det. of halogens organically bound)	50.00

Microbiology:

31.	Refrigerator, capacity about 14 cu. ft.	400.00
32.	Microscope, binocular, with triple or quadruple nose-piece	

Microbiology (cont'd)

		Approximate Cost
33.	Automatic Water Distilling Apparatus, capacity about 4 liter/hour	400.00
34.	Centrifuge, table type, universal, interchangeable heads, 6000 r.p.m.	450.00
35.	Homogenizer, universal, small, capacity 2 - 500ml, 18000 r.p.m.	200.00
36.	Hot-Air Sterilizer, range 30 to 200°C, 1800 W	500.00
37.	Bacteriological Incubating Cabinet, 0 - 90°C	300.00
38.	Horizontal Universal Autoclave, diam. 40cm, depth 60cm, with sterilizing drums	2,200.00
39.	Thermoradiator with fan, 2000W, for the thermost. chamber	400.00
40.	Water Bath, with thermostat, 2200W, for microbiology	60.00
41.	Colony Counter, with built-in illumination, transistorized digital counting circuit	200.00
42.	Two Sterisol Lamps (germicide), Ceiling Suspension, mounted on pendula	100.00
43.	Zone Reader (for det. of antibiotics)	250.00
44.	Penicylinder Dropping Equipment, (Cup Dropper), complete, with 2000 Stainless Steel Cups (for det. of antibiotics)	350.00
	Total Cost	US $ 19,505.00