LABORATORY CONTROL OF BIOLOGICAL PRODUCTS
IN LATIN AMERICA

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Special hazards are attached to the manufacture, control, and use of biological drugs (vaccines, antisera, and analogous preparations). The first section of this article outlines general control measures needed to assure the safety and effectiveness of these drugs. The second describes recent progress by the Governments of Latin America in improving the way these control measures are applied.

Introduction

Ensuring correct manufacture of any drug, whether it is a biological or a pharmaceutical, involves three levels of control. These may be classed as (a) in-process controls, (b) internal controls, and (c) national controls. Naturally, control tests at all levels must be performed carefully by properly qualified scientists or by persons under their direct supervision. The general types of controls may be described as follows:

In-process Controls

To ensure that the end-product is safe and effective, each step in its production must be carefully controlled. This means that correct and effectively written instructions for making each preparation are needed. These must clearly specify the steps to be followed, and must spell them out in great detail. The written instructions should also specify the various control tests needed, such as tests of pH, viability, sterility, antigenicity, etc. Then, during production, the actual details of production and control activity should be carefully written down, so as to ensure the existence of a permanent record. The technician or scientist who has performed the work should sign or initial each step.

It is particularly important that details of the control tests be recorded—regardless of whether they are carried out during production or after the manufacturing process is complete. For example, safety test records should clearly indicate the type and number of test animals used, their weight and sex, the volume of inoculum, and the results (including loss of weight, illness, or death). Sterility test records should show the number of vials used, the amount of biological product tested, the type of medium and the amount of inoculum employed, the temperature and time of incubation, and the results. Potency test records should likewise include all relevant details. Simply recording the results of tests as “satisfactory” is not an acceptable procedure.

Internal Controls

These control activities are carried out by a section that is separate from the manufacturing section but which is part of the same company or laboratory. It is important that the head of such a section report to a director who is not associated with manufacture. This is to ensure independence of action, thereby reducing the possibility of undue pressures being brought to bear for the release of lots that are of either marginal or doubtful quality.

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1 Also appearing in Spanish in the Boletín de la Oficina Sanitaria Panamericana, 1975.
2 PAHO/WHO Regional Adviser on Biological Products.
In general, this internal control section is or should be responsible for quality control of all raw materials entering the plant before they are given to the production section. It must therefore run quality control tests on such materials as chemical ingredients, media, glassware, rubber stoppers, labels, etc. Naturally, this section will also be responsible for the testing and release of all final products. Such release will be based on the results of safety, sterility, and potency tests, as well as on completion of proper labeling and any other production measures required. Here again, it is essential that all the test procedures be written out clearly and in great detail. The protocols, which should also be spelled out in detail, must be signed or initialed by the responsible worker. Only when all of these steps have been carefully followed, and only when the product has passed all the tests, should any lot be released. Such release of a lot should be accomplished by means of a written form signed by either the section chief or his authorized alternate. Releasing a lot by telephone or by word of mouth is not an acceptable procedure.

**National Controls**

In addition to the foregoing controls, independent tests and other control procedures should be performed by an external laboratory as a final check on the safety and quality of a given drug. No manufacturer, no matter how advanced, should be required to serve as the final judge of his own products.

The most efficient way of ensuring the proper type of external control is to establish a well-staffed and highly capable National Biologics Control Laboratory and to enact strong, effective laws that will enable this laboratory to perform its assigned role. That is, the national laboratory must have a sufficiently strong position and a sufficiently capable staff so as to be entirely responsible for its own actions. The laws authorizing its activities should therefore be written in such a way as to be effective and to ensure that there will be little or no political interference. However, in the enactment of these laws it has to be appreciated that the final authority is the Minister of Health of the country concerned and that the national control authority is acting as his agent.

A scientist from the United States Food and Drug Administration’s Bureau of Biologics (Division of Bacterial Products) uses an amino acid analyzer to conduct chemical tests on vaccines.

The establishment and development of a National Biologics Control Laboratory can be a difficult and time-consuming process. Figure 1 shows the skeletal outline of an organizational structure for a laboratory of this kind. It has been drawn up in such a way as to allow for progressive development, starting with the simpler tests and proceeding to more difficult ones. The simpler tests, including ones for sterility, viability, safety, and pyrogenicity, are shown at the left side of the chart. These require relatively few personnel (though the personnel must be
FIGURE 1 - A suitable organizational chart for national biological drug control facilities, showing the minimum numbers and types of scientific personnel required to conduct various classes of tests.

The functions of the National Biologics Control Laboratory are not limited to testing samples and reviewing protocols, which of course it must do. In fact, the most effective method for controlling the production of a biological drug is repeated and rigid inspection of the production laboratories by highly qualified and specially trained inspection officers. In such inspections a laboratory's general appearance, the quality of its personnel, its cleanliness, and the adequacy of its cleaning procedures are all assessed. The inspectors also carry out a detailed investigation and review of such things as written production and control instructions, test protocols and test suitability, sterilization procedures and records, aseptic facilities and techniques, methods for controlling labels and the labeling process, and many other activities and procedures. Naturally, the officer conducting such an inspection must be a senior scientist who is knowledgeable about drug manufacturing processes and who is thoroughly familiar with all the control test procedures involved.

Biological Drug Control in Latin America

Today about 21 government-owned or government-supported laboratories in 14 Latin American countries are manufacturing biological drugs. In some the standards of manufacture are very high—so high, in fact, that the Pan American Health Organization has been recommending them for training purposes. In other laboratories, however, the standards have varied from mediocre to poor.

It is of some concern that not a single country in Latin America has instituted the three previously mentioned levels of control. Practically all the manufacturing laboratories practice some sort of in-process control, and from time
to time most of them have had their products tested externally. The results obtained with products such as smallpox, rabies, and BCG vaccines have generally been good. The results obtained with other products have ranged from excellent to poor.

PAHO has sought to assist in upgrading the manufacture of biologicals in Latin America by placing special emphasis on control. That is because only through adoption of the best available control techniques can continually satisfactory end-products be assured.

This approach has already met with some success. At least two countries have decided to institute all three levels of control and are close to achieving that goal. Six others have made plans to establish testing facilities along the lines previously indicated (see Figure 1) and are in the process of implementing these plans.

Acting in an advisory capacity at the specific invitation of Member Governments, PAHO has visited all of the government biologics manufacturing laboratories in Latin America. At the time of these visits, it appeared that none of the laboratories could meet all the requirements of the rigid inspections carried out in countries with well-established national control laboratories. In some cases the changes required were minor and have since been made. However, the lack of inspection by qualified officers had noticeable effects, even in the better laboratories.

In general, it is hard to overstate the importance of proper inspections. Not only do they provide laboratories with useful advice, but the knowledge that an inspector may pay an unannounced visit at any time helps stimulate the manufacturer into ensuring that his laboratories are always in top condition.

In our reports to the health ministries of the countries concerned, one of the strongest recommendations made was that each country with facilities for manufacturing biologicals should establish a strong National Biologics Control Laboratory. Such a laboratory would of course carry out all the essential controls on imports as well as on domestically produced material. (In many countries the amount of biologicals imported may exceed the quantity manufactured locally.)

To date, most of our efforts at PAHO have been directed toward development of national biologics control laboratories in those countries of Latin America that already have government laboratories producing biological products. The reason for this is that such countries have a ready supply of scientists with some training and experience in this very difficult field, who can be drawn on to provide the nucleus of a staff for the control laboratory.

It would be ideal, of course, if all countries had effective national biologics control laboratories, whether or not they manufactured biological products. But even those countries experienced in producing biologicals have encountered great difficulties, and these difficulties would be even greater for non-manufacturing countries. There is no reason, however, why the latter countries should not have as a long-range goal the establishment of some type of national laboratory control over biological products. Many countries that do not have government manufacturing facilities do have agencies for controlling pharmaceutical preparations. Consideration might be given to having such laboratories conduct some of the simpler tests, such as those for sterility, pyrogenicity, and toxicity. Such steps, however, should be undertaken with great caution, and only after seeking and receiving expert advice; for these drugs, as noted above, present special problems and hazards, and poor or improper controls could do more harm than good.

Before closing, it is imperative that attention be drawn to a key point. In a number of countries, the national control laboratories are separated administratively from the national control authority. Where such a situation exists, it is essential that the two organizations act in unison so as to ensure that the results obtained in the national control laboratory give rise to swift and effective action.

Finally, it should be emphasized that a national biologics control laboratory that can perform accurate control testing and can carry out effective inspections provides much-needed
health insurance that every country with the requisite resources and personnel should have. To carry out its functions properly, this laboratory requires strong and enforceable laws authorizing and supporting its activities. Without such laws it will be unable to act effectively. Conversely, laws by themselves will have little value without a capable national laboratory to enforce their provisions. Both the laws and the laboratory are vital if biological products are to be properly controlled and their quality improved.

SUMMARY

The manufacture of safe, effective biological products in sufficient quantities to protect the entire population presents many problems in Latin America. The best way of ensuring such production would be to establish thorough control testing mechanisms.

Ideally, no regulatory program should be considered complete without three tiers of controls: "in-process" production controls; "internal" controls by the manufacturer that monitor the production section; and "national" controls by the government that monitor the manufacturer. Although the standards maintained by some biologicals manufacturing centers in Latin America are very high, no country has yet established a full-fledged three-level control system of this kind. However, two countries have decided to employ such a system and are now close to achieving that goal.

Perhaps the most essential facility in any national control program is the National Biologics Control Laboratory. This laboratory must be effectively organized, properly staffed, and backed by strong implementing legislation enabling it to perform its assigned tasks. In the past, lack of such a facility has created serious problems for biologicals manufacturing efforts in Latin America. Aware of this, a number of countries are now in the process of setting up and developing effective national laboratories of this kind.