Commentary: Standardization and Quality Control in State-sponsored Biologicals Production

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In the Netherlands, state-sponsored "biologicals" production has developed historically as an integral part of a state-sponsored mass-immunization scheme against specifically designated communicable diseases. The immunizations are offered on a free-of-charge basis to each generation of newborn babies.

The State immunization programme against smallpox, diphtheria, tetanus, pertussis, poliomyelitis and measles is not compulsory; parents can freely decide whether they will present their babies at the clinics of local public health services. Public health nurses in local health centres have good contact with mothers in their districts, encouraging 90 percent or greater acceptance of the full course of 4 injections. Convocation and registration of the newborn is performed through the local register; regional or district public health organizations administer the immunizations.

Booster-injections are given at school age.

Vaccination against rubella is offered to girls 12 and 13 years of age.

Rabies and BCG vaccination are supplied on an individual basis in cases of exposure. For therapeutic and prophylactic purposes, preparations of specific immunoglobulins are stock piled and delivered at cost. Therapeutic substances of human origin, such as blood and blood products, fall under separate legislation (Blood-products Act 1962).

The Rijks Instituut voor de Volksgezondheid (National Institute of Public Health) is organized as a directorate immediately under the Minister of Health and Environmental Protection. It is responsible for the production, distribution, and supply of biologicals for the State immunization programme. The directorate for public health is in charge of the organization and conduct of the programme. Commercially-produced vaccines have sometimes been used temporarily when the State programme had to be started and the products of the institute were still under development. In these cases, the institute selected and bought vaccines on behalf of the government.

Before the Minister decides to include or to delete immunization against a disease in the State programme, advice is sought from the National Health Council, the scientific advisory body for the government, founded by the Health Act and in existence since 1901. Recently this Council advised removal of smallpox vaccination from the programme. The Smallpox Vaccination Act was recalled on 28 November 1975.

The results of the immunization programme are very satisfactory: Smallpox, diphteria, pertussis, and poliomyelitis are at zero-level; tetanus is very rare and appears only in people above the age of 25 (the systematic vaccination programme started in 1952). The costs of the programme are relatively low: 3 guilders per inhabitant per year—1 guilder for the biologicals and 2 guilders for the costs of the public health services. For comparison the per capita national income amounts to 15,000 guilders per year.

Before commenting further on the standardization and quality control of the state production of biologicals, it is necessary to describe

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how the Netherlands controls imported or nationally produced biologicals (based on existing legislation, the Law on Sera and Vaccines, 1927, together with bylaws and subsequent regulations). The fundamental control principles are:

1. No biological may be produced without a license from the Minister of Health and Environmental Protection, nor may one be imported or distributed without a license from the National Control Authority.

   No licenses are granted or recalled without advice of the National Health Council.

2. No biological can be distributed without preliminary examination by the National Control Authority.

   This procedure is performed in two stages:

   a) Acceptance or rejection of the presented biological on the basis of a detailed registration documentation. This step is in conformity with stage 6 "Application for marketing" indicated in the paper of Dr. Perkins in this Conference. In such registration documentation, the National Control Authority must find proof that the development has gone through the 5 preceding stages described in that paper and is in accordance with national requirements.

   b) Release for distribution of each locally-produced or imported lot of an accepted biological, after examination of specimens or production protocols of that specific lot by the State Control Laboratory under the National Control Authority. The Chief of the State Control Laboratory satisfies himself that the lot of the biological under examination complies with the registration documents accepted by the National Control Authority and, where appropriate, with the requirements drawn up by the Ministry.

3. Requirements for biologicals can be laid down and published by the Ministry.

   It is customary—but not legally compulsory—for the Minister to seek advice from the National Health Council before publication of requirements. In practice, the requirements advised in reports of the WHO Expert Committee on Biological Standardization form the basis of such requirements. In other cases, requirements of national or regional origin have served this purpose (NIH, European Pharmacopea, and others).

4. Under exceptional circumstances, the Minister can authorize an immediate importation of biologicals without either a license from the National Control Authority or an examination by the State Control Laboratory.

   This is in agreement with the concept of a *National Control Laboratory for Biological Substances* published in annex 3 of the 22nd Report of the WHO Expert Committee on Biological Standardization (Technical Report Series 1970, number 444).

   The release and distribution of biologicals only after examination of each lot by the State Control Laboratory implies inevitably the introduction of a partial responsibility of the government with respect to the quality and innocuity of those products. The primary responsibility rests upon the producer.

   The National Control Authority also has power to agree to distribution of a biological for research purposes and for clinical evaluation. In such case, however, the user must sign a declaration that he is aware that he bears the full responsibility for possible untoward consequences from use of his product. The National Control Authority can prescribe conditions under which the distribution of such biologicals is permitted.

Under this rule, the importation of corynebacterium parvum vaccines for the treatment of cancer has recently been accepted for some clinicians working together in a clinical evaluation group under the direction of the Netherlands Cancer Institute.

The National Control Authority is an independant executive committee, nominated in conformity with the Law on Sera and Vaccines by the President of the National Health Council. It consists of 5 members:
the Director (chief-inspector) of health, the Director (chief-inspector) of pharmaceutical products, a University professor for microbiology, a University professor for virology (influenza specialist), and—as chairman—the Director General of the Rijks Instituut.

The State Control Laboratory is located in the Rijks Instituut. The chief of this Laboratory reports directly to the National Control Authority. The results and conclusions of his examinations of lots of biologicals presented for release are binding and cannot be overruled.

Influenza vaccines and some other bacterial vaccines are produced in the Netherlands by private industry. Commercially-produced biologicals from other countries are regularly imported and available to the medical profession.

Commercially-produced and state-produced biologicals are handled in the same way under the existing law. There is only one exception: For historical reasons there is as yet no examination by the State Control Laboratory of lots of yellow fever vaccine produced in Amsterdam (Koninklijk Instituut voor de Tropen).

Returning to the subject of standardization and quality control of state-produced biologicals, it will be clear that the Director General of the Rijks Instituut is fundamentally in the same position as other manufacturers (non-governmental and governmental) inside and outside the Kingdom of the Netherlands. Before a new vaccine developed in the Rijks Instituut can be accepted for distribution in the State immunization programme—the Rijks Instituut is not primarily engaged in the development or manufacturing of biologicals for the general market or for exportation—it has to go through the same series of experimental stages of laboratory, animal, and human testing and evaluation as described in Dr. Perkins' paper.

The format and composition of the registration documents to be placed before the Director General of the Institute and before the chairman of the National Control Authority are the same. Independent examination by the State Control Laboratory of each lot of biologicals to be distributed to the regional and district public health organizations is not different either.

The Chief of the State Control Laboratory appreciates the advantages of the location of his laboratory in a manufacturing institute. This relates especially to the need of the National Control Authority to receive regular reports on the inspection of premises and staff and the evaluation of methods of good manufacturing practice. Such inspections and evaluations can also be performed for manufacturers within national boundaries but are impractical abroad. In those cases, he must rely on licenses and other documents issued by the governments or the National Control Authorities of the countries in which the products are produced.

In conclusion, the question can be asked as to whether state-sponsored production like that in the Netherlands is preferable to commercially produced biologicals. My answer is that there is no principal or fundamental difference. Both systems, adequately controlled by the producer and by the authorities, can work perfectly well. Nevertheless, my contention is that the need to serve a particular state-sponsored immunization programme has doubtlessly stimulated the development of biologicals which are precisely adapted to the programme which calls for:

a) combination of several antigens in one in-

jection: diphtheria, tetanus, pertussis, and poliomyelitis;

b) optimal purification and dosage of antigens in order to reduce the number of injections and boosters;
c) maximum stability of antigens under practical conditions; and
d) minimal amount of untoward reactions, closely controlled by systematic surveillance.

The Netherlands government will not hesitate to make available the scientific experience and practical know-how acquired during this challenging process for future developments in the prevention of diseases at the national and international level through vaccination.