New Drug Development Programme

Connaught Medical Research Laboratories

The main index of new product development at the Connaught Medical Research Laboratories is to be found in the applications for licence approval made to the Canadian Control Authorities, namely, the Health Protection Branch, Department of National Health and Welfare and to the U.S. authorities, the Division of Biologics Standards, National Institutes of Health, Bethesda, Maryland, U.S.A.

Submissions for licence approval are made in two steps. In Canada, we must obtain approval to carry out clinical trials on any prospective new drug. This involves a preclinical compliance under Section C.08.005 of the Regulations. We must submit all details of manufacture, testing, animal studies, quality control procedures and proposed clinical trial protocol together with statements from the clinical investigators who will use the product. When the clinical trials are completed satisfactorily and methods of manufacture, testing, labelling and quality control have been fully established, we then submit all these data in the form of a New Drug Submission under Section C.08.002 of the Regulations.

The collection and compilation by Connaught and review by the Control Authorities, of these data, may take anywhere from several months to several years depending upon the complexity and "newness" of the drug.

Should we wish to change any aspect of production, testing, composition, labelling, we are obliged to submit an amendment to our original Submission. Depending upon the degree of change involved, an amendment may require several months or more for approval.

Similarly, if we wish to distribute a biological product in the U.S.A. we must go through an IND (Investigational New Drug) and a New Drug licence application under the U.S. Public Health Service Regulations, Part 73.

The listing which follows comprises those products which have been developed and licensed in Canada and the U.S.A. during the last 10 years, approximately, and those which are at present at some stage of clinical evaluation for approval by Canadian authorities.

A. CANADA

1. ALG (Antilymphocyte Globulin Equine):

This equine gamma globulin is prepared by immunizing horses with adjuvanted human thymocyte membranes, absorbing hemagglutinins and antibodies to human serum proteins from the horse serum, then removing other serum proteins to yield the gamma fraction of more than 95% purity.

This experimental product received a Notice of Compliance for clinical trial on February 9, 1971, amended on August 23, 1971, for a product of greater purity.

The purpose of the trials is to compare renal graft function, in two groups of humans treated either with ALG + Imuran + Prednisone or with Imuran + Prednisone and to ascertain the efficacy of the ALG for treating auto-immune disorders.

Clinical trials on ALG are proceeding under the supervision of Dr. H.E. Taylor and the Medical Research Council.

2. Antihaemophilic Globulin (Dried, Human):

This product, no longer distributed by Connaught, was prepared from freshly drawn normal human blood or freshly frozen plasma from voluntary donors co-operating with the Canadian Red Cross. The material is Fraction I of the cold ethanol plasma fractionating process of Cohn and associates and was supplied in the freeze-dried form. The product was used for treatment of Haemophilia A in cases of uncontrolled bleeding.

The product was originally licensed for distribution in Canada on February 16, 1965.

3. B.C.G. Vaccine:

For many years, Connaught produced a liquid B.C.G. Vaccine for use in the vaccination of persons at high risk, such as nurses, physicians, social workers. This vaccine had a shelf life of only 7 days so that a more stable product was obviously needed. A freeze-dried product with a shelf life of at least two years was developed and granted licence approval on May 31, 1962.

At the present moment, collaborative work is underway with the W.H.O. to obtain their approval for the Connaught strain so that the Connaught product may compete on equal grounds with the Danish, Japanese, British and other currently available freeze-dried products.

4. Botulism Antitoxins:

The Connaught Laboratories have had a long history of involvement with the discovery and scientific study of botulism toxins, particularly types A, B and E and their corresponding antitoxins, through the work of Dr. Claude Dolman at the Western Division of the Laboratories, University of B.C. Through his help and encouragement we were able to obtain a licence for distribution of Type E Antitoxin on November 2, 1965 and for a trivalent mixture of Types A, B and E on December 14, 1966.

Stocks of these antitoxins are now held in depots in various parts of Canada under the supervision of Dr. Ernest J. Bowmer, Director, Botulism Reference Service for Canada.

5. Brinolase (Brinase, CA-7, Fibrinolytic Enzyme):

This product, a fibrinolytic enzyme, produced by fermentation at Connaught Laboratories was originally approved for general clinical experimentation on June 8, 1965. Much clinical data were accumulated.

In December 1970, a New Drug Submission was prepared limiting the application of Brinolase to local treatment of clots in extra-corporeal circulation shunts (Scribner Shunts) and in in-dwelling catheters in patients undergoing long term hemodialysis therapy. Systemic use of Brinolase is at present restricted to qualified clinical investigators.

As of February 1972, the Submission was still under review by the Health Protection Branch, Ottawa.

6. Encephalomyelitis Vaccine (Western):

Encephalomyelitis Vaccine is a formaldehyde-inactivated product prepared from a strain of Western Equine Encephalomyelitis virus, isolated in Saskatchewan in 1966. For vaccine production, the virus is grown in chick embryo cell cultures, sterilized by membrane filtration and inactivated by 1/2000 formalin at 37°C. for seven days.

The product was approved for clinical evaluation on March 19, 1971 and amended to provide for a concentration step to produce a vaccine of greater potency in February 1972. Further clinical trials will be carried out in Saskatchewan during the spring of 1972.

7. Insulins:

The Connaught Laboratories have had a long and noteworthy involvement in the production of insulin preparations of several types and uses. These have been the special interest of the Insulin Committee of the University of Toronto. Special regulations were established by the Food and Drug Authorities in collaboration with the manufacturers, both of Canada and the United States. Connaught has had to establish compliance with these Regulations before distribution was permitted. The current list of Insulin preparations offered by the Connaught Laboratories with the approximate order of their appearance or approval is as follows:-

Insulin Toronto:

- A colourless solution of zinc-insulin crystals containing the anti-diabetic principle of pancreas and having a faster and shorter effect than the modified forms of insulin later introduced.

Protamine Zinc Insulin:

- A combination of insulin and protamine to produce a product with a more prolonged blood-sugar lowering effect than that of Insulin Toronto.

NPH Insulin:

- In this product, the insulin is combined with a small amount of protamine and zinc so that the resultant material is crystalline in form. The effects of NPH Insulin are intermediate between those of Insulin and Protamine Zinc Insulin and its effect is evident over a period of about 28 - 30 hours.

Lente Insulins:

These preparations are of three types:

(i) Semilente Insulin

Insulin Zinc Suspension - Rapid.

- a sterile suspension in a buffered aqueous medium, of insulin modified by the addition of zinc in such a way that the suspended precipitate consists of amorphous material. Licenced for use April 9, 1962.

(ii) Lente Insulin

Insulin Zinc Suspension - Medium.

- a sterile suspension of crystalline and amorphous material in the ratio of approximately 7:3. Licenced April 26, 1956.

(iii) Ultralente Insulin

Insulin Zinc Suspension - Prolonged.

- A sterile suspension of crystalline insulin with not more than a trace of amorphous material. Licenced September 5, 1961.

The rationale for these three types is that their wide range of prolongation and rates of reaction enable the physician to prescribe very exactly for his patients' needs.

Sulphated Insulin:

This product is prepared from zinc-insulin crystals by chemical modification with concentrated sulphuric acid. It is useful for the control of certain Insulin resistant diabetics. Notice of Compliance for distribution in Canada was received October 7, 1965.

Insulin Neutral:

Insulin Neutral is identical to Insulin Toronto except that its pH is adjusted to a value between 7.1 and 7.4 rather than 3. The Food and Drug Authorities have required data to demonstrate efficacy and stability in chemical use.

Maleyl Insulin:

Maleyl Insulin is prepared from zinc-insulin crystals by chemical modification with maleic anhydride. It is supplied to clinical investigators as a sterile, freeze-dried product.

Following success with Sulphated Insulin in the treatment of diabetics who have developed a high level of neutralizing antibodies against insulin, it was thought desirable to prevent the development of neutralizing antibody by the induction of immuno-tolerance to insulin. Maleyl Insulin appears from animal experiments to be able to induce such tolerance.

The product was approved for clinical evaluation on November 10, 1969 and has been under clinical study since that time.

8. Liver Extract Injectable:

Liver concentrates and extracts were used many years ago for relief of pernicious anaemia. Standardization of these materials were retarded for many years until an assay was developed for the anti-pernicious anaemia principle now known as Vitamin B_{12}. Over the years, regulatory specifications were established and on February 14, 1963 Connaught obtained a Notice of Compliance for the product which is still distributed in Canada.

9. Measles Vaccine Inactivated and DPT Polio Measles Vaccine:

Following success with DPT Polio Vaccine and the need for immunization against measles, an experimental, killed measles vaccine was prepared which was later incorporated into a 5-component mixture of diphtheria and tetanus toxoids, pertussis vaccine and poliomyelitis vaccine.

A Notice of Compliance for clinical evaluation was received on June 10, 1966 and extensive trials have been carried out by the Health Department of Ontario.

10. Measles Virus Vaccine, Live, Attenuated (Dried):

Measles Virus Vaccine, Live, Attenuated as prepared by the Connaught Medical Research Laboratories is a bacteriologically sterile, freeze-dried suspension of attenuated measles virus grown in chick embryo cell cultures.

Measles Virus Vaccine, Live, Attenuated, is indicated for the active immunization of children against measles (rubeola). It does not protect against German Measles (rubella).

On May 4, 1970, a Notice of Compliance was received permitting clinical trials in Canada with a product prepared from the Edmonston B. strain of attenuated measles virus at the 25th passage. A product has now been prepared from a virus at the 48th passage and an amendment has been prepared for submission to Ottawa to obtain approval for clinical trials. Clinical evaluation is going forward on both products at La Crêche, St. Vincent de Paul, Quebec.

11. Oxytocin Injection U.S.P.:

Oxytocin is one of the active principles found in extracts of the posterior lobe of the pituitary gland. It is a polypeptide containing eight amino acids. For many years, Connaught supplied the product as an extract containing 10 U.S.P. units per ml. During this period oxytocin was synthesized by chemical means and Connaught developed its own Synthetic product. Fortunately, it was not considered a new drug subject to long clinical evaluation, but was approved for distribution on May 23, 1962. As compared to the natural extract, synthetic oxytocin has many advantages since it is a relatively pure chemical compound, free of vasopressin; hence its physiological action can be closely controlled.

12. Phenoxalid

Phenoxalid is a synthetic antituberculous drug chemically related to isoniazid. It was developed at the Connaught Laboratories where it was selected from a large number of antituberculous compounds as a drug combining marked chemotherapeutic activity with low toxicity. The product was licensed for distribution in Canada on September 22, 1961.

13. Poliovirus Live, Oral, Sabin:

An application to the Department of National Health and Welfare in 1961 resulted in a Notice of Compliance, permitting distribution of the product in Canada on February 26, 1962.

As distinct from the Salk type, Sabin Poliovirus vaccine is administered orally. It is prepared in monkey kidney tissue culture from attenuated poliovirus (Sabin) Types 1, 2 and 3 and is a sterile suspension of the Sabin polioviruses in a trivalent mixture, in 53.5% w/w sucrose solutions.

The product has enjoyed a world-wide acceptance.

Attention is now directed to the preparation of the Sabin type vaccine in human cell cultures (Diploid cells, WI-38). Production and testing methods are currently being drafted for submission to the Health Protection Branch, Ottawa, to support a Preclinical New Drug Submission. Several months of production and testing work and clinical evaluation lie ahead before approval for distribution can be expected.

14. Poliomyelitis Vaccine (Purified) - Salk:

Application for addition to the Connaught Canadian License was made April 5, 1955 by Dr. R.D. Defries. Approval was received in due course.

The presence of adventitious viruses became a matter of great concern and a method was needed to inactivate SV_{40}. Such a method was developed by C.W. Hiatt. On January 7, 1963, Connaught received approval from Ottawa for the use of this method in production of its vaccine provided the vaccine was checked over a period of six months.

The next amendment involved the development of a better preservative since over a three year period 12 contaminated vials, containing the original preservative, benzethonium chloride were returned to the Laboratories. After much searching and testing of possible preservative candidates, approval was received on September 8, 1964 for the use of 2-phenoxyethanol in Poliomyelitis Vaccine and multiple antigens containing this vaccine.

The next major advance in the improvement of Poliomyelitis Vaccine Salk involved methods of purification and concentration of the virus and methods of removal of pyrogens and virus contaminants such as SV_{40}. Approval for use of these improved methods was received on February 22, 1966.

Poliomyelitis Vaccine Salk, prepared by Connaught, was used in many parts of the world before other countries were able to prepare their own vaccine. It has also been combined with diphtheria toxoid, tetanus toxoid and pertussis vaccine for effective multiple antigens. On August 13, 1965, a report was submitted to Ottawa on the preparation and use of purified poliomyelitis vaccine in DPT Polio Vaccine and on September 27, 1965, approval was granted for all the multiple antigens referred to above.

15. Prothrombin Complex Concentrate (Human, Dried):

Prothrombin Complex Concentrate (Human, Dried) is a purified concentrate of clotting factor II, VII, IX and X prepared from pooled normal human plasma from which fibrinogen has been removed. It is dried in vacuo from the frozen state. It is supplied in vials containing approximately 250 units of factor IX. The product is indicated for use in demonstrated factor IX deficiency (Haemophelia B, Christmas Disease), in cases of uncontrolled bleeding or at a time of impending bleeding, as when surgery, including dental surgery, is contemplated. The product is also indicated for haemorrhagic disorders caused by a deficiency of factors II, VII or X.

On July 9, 1971, Connaught received approval to supply the product for clinical trial to selected investigators.

16. Rabies Vaccine (Tissue Culture Origin) - Pre-exposure:

Rabies Vaccine (Tissue Culture Origin), as supplied by the Connaught Medical Research Laboratories, is a purified, concentrated suspension of "fixed" rabies virus, adapted to and prepared in mono layers of baby hampster kidney cells and inactivated with formalin. Thimerosal is present as a preservative and aluminum phosphate is added as an adjuvant.

The product is used for pre-exposure immunization of humans, who, due to their profession, are frequently exposed to rabid animals. The vaccine does not contain any neurotissue; therefore, it is not expected to cause allergic-type post-vaccinal complications known to occur with vaccines containing high concentrations of neurotissues.

Notice of Compliance to permit distribution of the product in Canada was received from the Food and Drug Authorities on November 5, 1969, two years and seven months following the New Drug Application on April 5, 1967.

In 1966, W.H.O. recommended that booster doses should be given at 10 and 20 or more days following the last dose of an approved post-exposure vaccine. Accordingly, after some preliminary studies, Connaught prepared data for submission to Ottawa in support of the tissue culture vaccine for use as booster doses after the 14-dose Semple schedule. Submission was made on May 5, 1970, but it was not until July 16, 1971, after additional data were submitted relative to the effectiveness of the tissue culture vaccine for primary stimulus and for recall booster response, that the reviewers in Ottawa were convinced of the usefulness of the product for boostering the original stimulus of the Semple Vaccine.

17. Rh_o (D) Immune Globulin (Human):

Rh_o (D) Immune Globulin (Human), as prepared by Connaught Laboratories, is an aqueous solution of the gamma globulin fraction (Fraction II) of human venous plasma prepared by the cold ethanol fractionation procedure. Plasma used for fractionation is collected from selected

individuals who have developed antibodies to Rh positive cells arising from pregnancy or from artificial stimulation of such cells.

The preparation is used to prevent the development of Rh antibodies in women having no Rh antibodies when the development of such antibodies might cause damage to an Rh positive foetus in a subsequent pregnancy.

A New Drug Submission, dated July 18, 1968, was approved October 25, 1968.

Subsequent amendments extended the range of allowable protein content to 3.5 - 18% (September 22, 1970) and extended the expiry dating from six to twelve months (October 28, 1971).

18. Smallpox Vaccines:

For many years, Smallpox Vaccine has been prepared as a sterile suspension of the virus, propagated on the skin of a healthy calf, in 50% glycerine with 0.5% as a preservative. When kept constantly at refrigerator temperature (4°C.), the vaccine has a shelf-life of 3 months. It was, therefore, of considerable interest to produce a product of greater stability. This was achieved in the form of a freeze-dried product made from a purified elementary body suspension. Calf pulp is homogenized and centrifuged to obtain purified virus extractions which are resuspended in 0.004 M. McIlvaine's buffer. Peptone is added to a level of 5% and phenol to 0.4%. After suitable tests at this stage, the product is diluted 1 to 4 with 5% peptone solution, filled into vials and freeze-dried.

On July 31, 1964, the Food and Drug Directorate gave approval for limited distribution of this product.

The objective of a stable, dried preparation has been achieved in that the presently available product has an expiration dating of 12 months on the market following up to 24 months storage by the manufacturer when kept at 10°C. or below.

Recently, it has been demonstrated that the reconstituted product is stable for at least 90 days when kept at 4°C., even if exposed to room temperatures for up to 60 minutes.

As early as 1967, a demand developed within the W.H.O. for a Smallpox Vaccine which could be used in endemic areas of the world and which could be administered by a team of workers to large numbers of persons, sometimes under primitive conditions. The Canadian Armed Forces were also interested in such a product. The answer was to be found in a dried smallpox vaccine formulated for jet injection use. Although this product is similar in all respects to regular dried vaccine except in the matter of dilution at time of injection, the Food and Drug Authorities in Ottawa declared it to be a new drug on July 12, 1967, due to a new method of administration being involved. On February 20, 1968, a Submission was forwarded to Ottawa containing the required information on absence of

extraneous microorganisms, clinical results and serologic response. After much discussion and submission of further data, a Notice of Compliance was given on February 25, 1969.

Late in 1969 decision was reached to introduce a purification step into the process of manufacture for Smallpox Vaccine Glycerinated. This was achieved by the use of a Freon (113) extraction to remove proteinaceous cellular debris. After discussion with the Food and Drug Authorities in Ottawa agreement was obtained that the modified product was not a new drug and therefore, would only require approval for the proposed labelling and, not a New Drug Submission. Final clearance for the improved product is expected shortly.

19. T.A.B.T.D. Polio Vaccine:

Earlier in this report, reference was made to multiple antigens containing purified poliomyelitis vaccine salk. In order to satisfy a request from the Canadian Armed Forces, development was undertaken of a multiple antigen mixture containing typhoid and paratyphoid vaccines A and B, tetanus toxoid, diphtheria toxoid and polio vaccine. Experience gained in the development of DPT Polio Vaccine was brought to bear on the problem and on December 6, 1965 a Notice of Compliance was received, 2 years and 8 months after the first Submission. Since the first product did not contain purified poliomyelitis vaccine, an amendment was submitted on January 26, 1968 and approved March 25, 1968.

20. Tuberculins:

The original product used for the diagnosis and control of tuberculosis was designated as "Old Tuberculin" later shortened to "Tuberculin". It is essentially the filtrate obtained after removal of the bacilli following the growth of M. tuberculosis.

The active components in "Old Tuberculin" are the various tuberculoproteins which may vary in composition depending upon the medium used to grow the M. tuberculosis organisms and the strain of organism used. Seibert developed the original methods of separating the proteinaceous material and designated it as Purified Protein Derivative, or PPD. PPD's now used for diagnostic purposes are produced and tested according to prescribed standard methods, but some of the original PPD, known as PPD(S), still serves as the reference standard.

Connaught has developed a number of PPD preparations which have been licenced for distribution both in the U.S.A. and Canada. These products are as follows:

Tuberculin Purified Protein Derivative (PPD-Heaf):

This is a solution of PPD in 50% glycerin containing in 1 cc. PPD equivalent to 2 mg. of the International Standard. It is intended for mass screening and is administered by a multi-puncture method such as the Heaf Injection apparatus. The product was licenced for distribution in Canada on January 5, 1960.

Tuberculin Purified Protein Derivative (PPD-Mantoux):

The product for intracutaneous injection consists of dilute solutions of PPD in 4 different concentrations, 1, 5, 10 and 250 TU per test dose of 0.1 ml. These concentrations correspond to 0.02, 0.1, 0.2 and 5 mcg. of PPD per test dose. At these concentrations, PPD adsorbs to the glass of any container with which it comes in contact. Such adsorption would result in variable potencies and hence unreliable tuberculin tests. These difficulties are avoided by introducing into the solutions a small quantity of Tween 80, 0.0005%.

PPD in dilute solutions was first licenced for distribution on January 5, 1960. Since that time there have been amendments covering a change of preservative, reduction in the amount of Tween 80 used and for approval for use of a large master batch of PPD designated as CT68. CT68 is a 500 gram batch of PPD which will last for many years for the preparation of PPD solutions, thus assuring the user of a uniform product from lot to lot.

Tuberculin PPD (Mantoux):

Prepared from M. tuberculosis var. bovis (M. bovis).

- Approval for clinical testing received March 24, 1970.

Purified Protein Derivatives from Various Atypical Mycobacterial Organisms:

Approval has been received to test clinically PPD's obtained from a number of atypical mycobacteria including:

(i) M. intracellulare (Battey bacillus)
- PPD from this source has been licenced for distribution in Canada as of January 28, 1970.

(ii) M. kansasii PPD-Y.

(iii) M. scrofulacium (Gause Strain).

(iv) M. fortuitum.

(v) M. avium.

Tuberculin Active Peptide Solution:

This product is prepared from an enzymic (proteinase) hydrolysate of Tuberculin PPD made from the Johnson strain of M. tuberculosis. Approval to test this degradation product of PPD in comparison with regular PPD, PPD-S, PPD-Battey was received on February 18, 1972.

The purpose of the proposed comparison is to determine the specificity of the peptide in persons sensitized with M. tuberculosis, B.C.G. and atypical mycobacteria.

PPD in Cancer Treatment:

At the present moment there is a great deal of interest in the use of PPD to treat various forms of cancer. It is the intention to prepare an application to the Drug Authorities in Ottawa for permission to use PPD for this new purpose in doses hitherto not employed for humans.

21. Tetanus Toxoid and Diphtheria Toxoid:

Although these products have been prepared by Connaught Laboratories for many years, it is only comparatively recently that steps have been taken to introduce production changes to enable large scale production of purified materials. Such changes necessitated amendments to our Canadian licence and submission of data to demonstrate efficacy and safety. These improved products are now available to the Canadian public.

22. Vaccinia Immune Globulin (Human):

On April 5, 1971, a request was made to the Food and Drug Authorities in Ottawa to amend the Connaught product licence for Immune Serum Globulin (Human) to include Vaccinia Immune Globulin, since a small amount of suitable plasma had been obtained from the Red Cross. Notice of Compliance was received on July 22, 1971.

23. Zoster Immune Globulin (Human):

This product is prepared from plasma obtained from selected blood donors recovering from herpes zoster.

A preclinical submission made on March 29, 1971 was approved May 21, 1971.

The product is essentially available for emergency purposes.

B. U.S.A.

The distribution of Biological products in the United States is controlled by the Division of Biologics Standards, N.I.H. Both the "Establishment" and the product must be approved and yearly inspections are performed. Over many years a highly satisfactory and beneficial scientific liaison has been established between Connaught and the staff of DBS during the course of which a number of products have been licensed and a few have been distributed in the U.S.A. on a routine basis. These are:-

Diphtheria Antitoxin and Toxoid
Tetanus Antitoxin and Toxoid
Staphylococcus Antitoxin and Toxoid
Botulism Antitoxins E and A, B, E combined - Aug. 16, 1968
B. C. G. Vaccine - May 31, 1962
Tuberculin PPD (Heaf) - May 10, 1960
Tuberculin PPD (Mantoux) - June 20, 1966
Normal Serum Albumin - July 8, 1958
Poliomyelitis Vaccine (Purified) (Salk) - December 7, 1967
Smallpox Vaccines
- Glycerinated - May 13, 1969
- Freeze-Dried - Sept. 15, 1969
- Freeze-Dried for Jet Injector - Sept. 15, 1969.

Licence Applications in Progress - U. S. A.:

Rh_o (D) Immune Globulin (Human)
Tuberculin PPD (Battey)
Smallpox Vaccine (Purified) Glycerinated
DPT Vaccine Adsorbed.

J. C. W. Weber

W. R. Ashford

New Drug Office,
Quality Control Department.

JCWW/WRA/lm

March 16, 1972.