OCCASION

This publication has been made available to the public on the occasion of the 50th anniversary of the United Nations Industrial Development Organisation.

DISCLAIMER

FAIR USE POLICY

CONTACT

Please contact publications@unido.org for further information concerning UNIDO publications.

For more information about UNIDO, please visit us at www.unido.org

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org

D00258

United Nations Industrial Development Organization

Distr.
LIMITED

ID/WG.37/9
14 January 1970

ORIGINAL: ENGLISH

Expert Working Group Meeting on the Establishment of Pharmaceutical Industries in Developing Countries

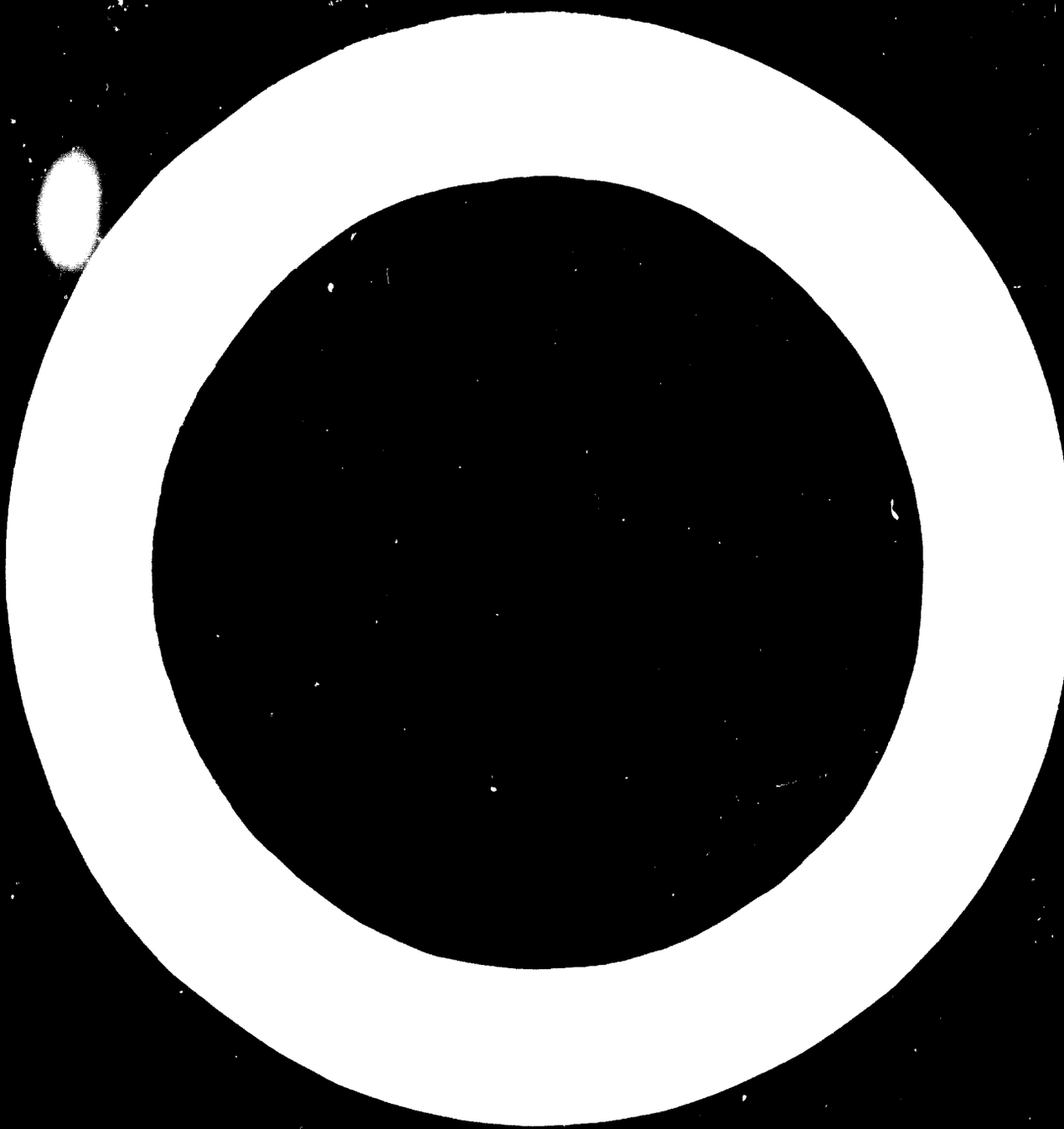
Budapest, 4 - 10 May 1969

THE DEVELOPMENT AND APPLICATION OF VETERINARY PHARMACEUTICALS 1/

by

Richard A. Huebner
Wyeth Laboratories
Athens, Georgia
United States of America

1/ The views and opinions expressed in this paper are those of the author and do not necessarily reflect the views of the secretariat of UNIDO. This document has been reproduced without formal editing.



Perspective:

For the reasonable anticipation of success, any industrial development program must begin with the essential resource of a healthy and productive populace. Health services must be provided to the people themselves and to their animals (1) to control diseases transmissible among man and other species and (2) to support animal husbandry for mankind's benefit. While the mission of medicine is to sustain and to prolong human life, the purpose of veterinary medicine is to maintain and to restore animal usefulness.

Essentially, then, consideration for the welfare of domesticated animals, other than those supported as pets, is motivated neither by altruism nor by kindness but by the self-serving demands of man. Animals contribute to us (1) nutritionally to provide food, (2) socially to provide clothing and to provide sport spectacles, (3) economically to provide motive power and to provide barter, (4) politically to provide military and police support.

Man's dominion over animals, God-granted or assumed (depending upon one's theological beliefs), results in their being herded, handled or sacrificed at our will within the restraints only of our religious or national scruples. However, because groups or species of animals may be widely dispersed over comparatively large land areas and because their temperament may be not docile, efforts at disease prophylaxis or therapy may be cumbersome or, under some circumstances, impractical. The most highly efficacious drug, chemical, antibiotic or biological product is of little value unless it can be administered properly in correct dosage to the animal patient by qualified personnel.

Approach:

I. The first step in an animal health program is clear definition of the problem in practical, realistic terms. The glory of national pride, the luxury of national state, the intoxication of egocentrism and the delusion of aggrandizement are understandable human responses but they must be quelled to avoid bias. Honest, complete and detailed answers should be obtained from reliable informants and sources for such questions as:

(1) Is there a reasonable current estimate of the animal population?
(2) Which diseases are the greatest threats?
    (a) Of which species?
    (b) What is the disease incidence?
    (c) Is the disease spread by or common to wildlife?
    (d) Is the disease truly significant or is it a sporadic but dramatic occurrence encouraging local conversation which becomes more colorful with retelling?

Because the animals' environment is an important factor, the effects of climate, topography and soil type should be considered. Nutrition, sanitation, and the control of internal and external parasites and insects are influences. Whether the animals are on free range, are restricted, or are herded in groups bears on disease incidence and transmission.

The regulation of animal movement within, through or into an area and/or quarantine measures may serve to reduce disease. In many instances they are important supportive actions for other efforts and, in some, they are the only methods that are effective. There are a few diseases for which the sole measure of repression, within the limits of current knowledge, is slaughter; action so drastic may be unacceptable to national custom or morality.

The quality, strength and caliber of the veterinary medical profession should be examined. The number of veterinarians, their geographical distribution in relation to animal population, the availability and rapidity of their transportation and intraprofessional communication bear vitally on the substantive effectiveness of veterinary service.

II. The second step is <u>definition of the goal</u> in specific and realizable fashion. "To control animal disease" expresses merely a visionary and inexact generality, granting license to frequently purposeless, often wasteful and occasionally dishonest actions.

Unlike the human hope of heaven, here the reach should not exceed the grasp. Toward each animal disease recognized previously during the first step should questions be raised: is the goal: (1) to reduce incidence? (2) to eradicate? (3) to prevent? (4) to protect?

Here the unemotional arithmetic of economics should determine the desirability and acceptability of the selected program. The prolonged treatment of chronically ill animals consumes resources that might be better applied to benefit the citizenry.

III. The third and last step in approach is the <u>search for the solution</u>. If the first two steps have been fully and carefully evaluated, many requirements should be clearly evident. Practicality should be the keynote. Not unusually, somewhat less attractive alternatives may offer more pragmatic and more readily attainable ends.

Searches of the literature offer guidance in the selection of the most effective methods and allow the avoidance of work duplication or repetition of the mistakes of others. Consultation with [illegible] experience is invaluable but final judgments must be tempered by [illegible] variations in disease occurrence and by differences in national, religious and tribal customs. Almost 400 years ago Francis Bacon, the English philosopher and author, lucidly warned "Read not to contradict and confute, nor to believe and take for granted ... but to weigh and consider." The direct extrapolation of others' strategy may bring disappointment and failure of acceptance of the chosen program.

Regulatory measures, mentioned above, may be revamped to improve their effectiveness. Where animals are herded, relatively minor revisions in

sanitation practices may reduce or eliminate sources of infection or disease vectors or fomites. Veterinary services may be redistributed or revisionally supported to provide wider and more intensive health support.

Finally, the classes of drugs and/or other pharmaceutical agents to bring about the desired animal physiological responses should be chosen. Their identity and the extent of demand will be readily determinable if the preliminary surveys have been prepared assiduously. Many substances are unstable or subject to deterioration from weather and temperature variations; thus, handling, storage, transportation and field facilities must be governed by these decisions. Too, their selection must be tempered by the capabilities of the operators; if laymen or farmers will administer them, those requiring experienced dosage techniques and those of critical toxic potential should be renounced. In some instances, the expedient of administration of drugs in the feed may offer advantages for mass therapy, but exposure of the active agents grossly to weather risks and the marked variation in feed consumption among individual animals make the benefits often more apparent than real.

Considerations:

I. To evaluate and to clarify the facets of the overall health problem, classification of diseases is helpful. As a guide (more fully described in Supplement 1) to suggested groupings:

Animal diseases of several hosts transmissible to man[1]:

(1) By direct contact:
- (a) Viral diseases = rabies, psittacosis, ornithosis, coryza, Newcastle Disease, infectious ecthyma, foot and mouth disease;
- (b) Rickettsial = Q fever;
- (c) Bacterial = anthrax, brucellosis, erysipeloid, tularemia, glanders, leptospirosis;
- (d) Fungal = ringworm, sporotrichosis, mycetoma.

(2) Through infected milk:
Tuberculosis (under intensive methods of production), brucellosis, Scarlet Fever, staphylococcal intoxication.

(3) Through meat:
- (a) Bacterial = anthrax, brucellosis, tularemia;
- (b) Animal parasites = trichinosis, tapeworm and hookworm infestations.

(4) By invertebrate vectors:
- (a) Viral = encephalitis, encephalomyelitis;
- (b) Rickettsial = typhus fever;
- (c) Bacterial = [illegible], tularemia.

The transmission of diseases in the reverse direction, from humankind to animals, constitutes another hazard. Man may transfer to lower animals his tuberculosis, pox, ringworm, scabies, Pseudotuberculosis infectiosa, poliocencephalomyelitis, pneumococcal infections (to primates); mankind was the original source of the influenza virus which now attacks swine.

The significance of diseases affecting a single or several species of

animals (on which full information is included in Supplement #2) should be determined, perhaps those:

(1) Of swine:[2]

African Swine Fever (v)* - in equatorial and southern Africa, western Europe;

Teschen Disease (v) - throughout Europe.

(2) Of cattle:

Bovine Infectious Petechial Fever (v) - in Kenya, Africa;

East Coast Fever (protozoan)(T)* - in eastern coast Africa from Kenya to Cape Province, South Africa;

Ephemeral Fever (v)(I)* - in tropical and subtropical regions of Asia, Africa, Australia;

Contagious Bovine Pleuropneumonia (mycoplasma) - in Africa, Asia, Russia, Australia;

Infectious Infertility (v) - in central and southern Africa;

Lumpy Skin Disease (v) - in central and southern Africa, Madagascar;

Malignant Catarrhal Fever (v) - throughout world, Europe, Africa;

Rinderpest (v) - in Asia, Africa.

(3) Of sheep:

Bluetongue (v)(I) - in Africa and Mediterranean area;

Contagious Agalactia (pleuropneumonia-like organism) - in southern Europe, Mediterranean area, Russia, Brazil;

Louping Ill (v)(I) - in Scotland, England, Russia;

Maltosi Sheep Disease (v)(I) - in Kenya, Uganda;

Sheep Pox (v) - in Asia, northern Africa, eastern Europe.

(4) Of cattle and sheep:

Heartwater Disease (Rickettsial)(T) - in Africa south of Sahara Desert:

Nagana (Trypanosomal)(I) - in African south of Sahara Desert except S. of Fed. and S. W. Africa;

Rift Valley Fever (v)(I) - in central and southern Africa;

Streptothricosis (fungal) - in tropical and subtropical Africa.

(5) Of cattle, sheep and swine:

Anthrax (bacterial)(I) - occurs worldwide;

Vesicular diseases (v): foot and mouth disease, vesicular exanthema, vesicular stomatitis - occur variably.

(6) Of horses:

Venezuelan Equine Encephalomyelitis (v)(I) - in Venezuela, Colombia, Ecuador, Trinidad;

African Horse Sickness (v)(I) - in southern and equatorial Africa, Middle East.

(7) Of poultry:

Newcastle Disease (v) - occurs worldwide;

Fowl Plague (v) - in Egypt, Palestine and other areas.

(* v = viral; T = tick-, I = insect-borne)

The great majority of highly infectious and readily transmissible diseases are of viral etiology wherein control depends, to a large degree, on regulatory and sanitary practices, vaccination and, rarely, the use of

certain of the antibiotics. Obviously, in most of them, prophylaxis offers the single satisfactory approach to their repression.

Predicated on extant capabilities, the status of the local veterinary medical art and of disease problems, and the needs of the practicing veterinarian for his care of individuals or groups of animal patients, decision is required on the classes of therapeutic agents (single and of multiple ingredients) believed to be most important. The costs may be approximated by basing probable demand on the disease incidence estimates and the directional efforts determined previously. Again, as examples, categories (more fully detailed, with retail costs in the United States, in Supplement 3) may include:

Analgesics	Diuretics	Antisera
Anesthetics	Fungicides	Antitoxins
Antibacterials	Hormones	Bacterins
Antibiotics	Keratolytics	Toxoids
Antidiarrheals	Lubricants	Vaccines
Antihistamines	Nitrofurans	
Anti-inflammatory agents	Ophthalmic & Otic preparations	
Antiprurities	Parasiticides (internal & external)	
Antipyretics	Sulfonamides	Nutritional
Counterirritants	Tranquilizers	Supplements

II. After the requirements have been established, (1) the effective implementation of adequate treatment and (2) the costs should be weighed together against each of the alternatives:

(1) Importation of:
  (a) Finished, packaged products,
  (b) Bulk materials for packaging and finishing,
  (c) Partially processed intermediates for further refining;
(2) Manufacture (with licenses and patent rights where required), with
  (a) Research and development program support.

The alternative most desirable for one drug or drug group may differ from that for another; it may be more desirable to import one medicinal preparation in finished packages ready for use and to manufacture some others. In some instances, for immediate use demands and to avoid planning and building delays and expenses, a special contract with a foreign supplier may offer the more pragmatic solution to the problem.

Importation of finished biological products, the least complicated procedure, occasionally may not be the most advantageous choice. Due to their mutations and to the variants of localization, several pathogenic bacteria and viri of indigenous origin serve much more satisfactorily as seed for the preparation of effective biological protective antigens.

Quite familiar are the advantages of large scale production thus, if a neighboring market exists or one may be encouraged, exportation of some products may serve to lower unit costs and, additionally, may contribute to the national economy. Enthusiasm should be tempered by reason, however; in most

instances, somewhat slower progress is a concomitant of stronger and more readily sustainable growth. Each product class should be examined against the alternatives above, similarly to the judgments reached for the local choices, to avoid overprediction of unsalable items. But there are circumstances when only by combining local and export demands can production become practical; here international agreements, or those made between organizations of two or more countries, reached before the project is undertaken, may enhance the likelihood of success.

If human product pharmaceutical facilities are functional or are planned, their expansion or extension to accommodate some veterinary preparations may be accomplished with minimal changes. With some classes of drugs, the compounds for human and for animal uses are quite similar or identical, e.g., topical applications, antibacterials, antibiotics, sulfonamides, and some biologicals as bacterins, tetanus toxoid and antitoxin. Although some of the presently operating companies began as veterinary product suppliers, they are now arms of broad line pharmaceutical manufacturers. Several corporations entered the veterinary products field, as mentioned above, by increasing their capacities at that time existent for human product preparation and marketing.

Cost control over products, whether imported or manufactured, clearly is an imperative consideration. But devotion to monetary restrictions should never overshadow the primary purpose of the entire effort which is, of course, the provision of products that are effective under the circumstances of their use. Zeal in the basic science of chemistry should not obscure the proprieties of the pharmaceutical art. The "theoretically equivalent" drug, less expensive than but chemically identical to another manufacturer's trade-mark named specialty product, may fail to be "therapeutically equivalent" pharmacologically. The formulation of drugs into various dosage forms may affect profoundly the onset, intensity and duration of physiological patient response. Therapeutic response may be modified by many factors as: (1) rate at which the active ingredient becomes available for absorption, (2) stability of the active ingredient and the excipient, (3) pressure used in tablet compression, (4) disintegration time of tablets, (5) particle or crystal size, (6) vehicle, (7) hydrogen ion concentration, (8) concentration of additives such as preservatives or stabilizing agents.[4]

Experience:

1. Research and development endeavors in the pharmaceutical industry are the most intellectually stimulating, the most glamorous and potentially the most rewarding - and the most expensive, with a high index of frustration and disappointment. R. and D. steps usually are initiated (1) within the company organization, or (2) a new use may be discovered by (a) outside clinicians, (b) an academic scientist supported by a financial grant, or (c) an outside, independent research worker. Following acceptance of the proposed new drug or of the new use for an established drug by managerial authority, further investigation proceeds through (1) chemical research (analysis or synthesis), (2) laboratory studies on pharmacology and chemotherapy, (3) pharmaceutical research and (4) clinical research.

On the average in the United States, one drug of 5,000 ultimately reaches the market after 6 years of effort and development expenditures of $7,000,000. The costs of its production then include, from raw material to final processing, an average of 250 separate control tests such as infrared, ultraviolet and visible spectrophotometry, potentiometry, polarography, X-ray, crystallography, radioactivity, etc.[5]

To provide a guide to comparative value relationships, in the United States:[6,7]

During 1965, R. and D. expenditures for ethical or prescription (i.e., excluding proprietaries and feed additives) pharmaceuticals totaled $365,000,000. of which $329,000,000. was spent for human use products. $23,000,000. for veterinary use products, while $13,000,000. was government-financed.

For 77 firms reporting, R. and D. expenditures averaged $4,270,000. on human prescription products, $295,000. on veterinary products, but the bulk of the latter amount was spent by large companies with projects of over $20,000,000. per year.

Of the total spent, therefore, 6.5% was allocated to research on veterinary products as 5.1% on pharmaceuticals and 1.4% on biologicals.

II. Total domestic sales in the United States during 1965 of human dosage forms equalled $3,000,000,000. and of bulk forms $151,000,000. Veterinary dosage form products totaled $76,000,000., of bulk $104,000,000.

During 1966, total U. S. sales volume for all veterinary products was $371,000,000. (feed additives $215,000,000., pharmaceuticals $115,000,000., biologicals $41,000,000.), a 12.4% rise over 1965's $330,000,000.

Estimated sales volume of veterinary ethical or prescription drugs has been reported as:

	U. S.	Worldwide
1967	$228,000,000.	$750,000,000.
1972 (projected)	285,000,000.	935,000,000.

or a 25-28% increase in these items alone.

All of the dollar amounts above are not comparable directly because different sources included various components (prescription drugs, bulk products, feed additives, etc.) in their calculations. However, notable is that the 6.5% of R. and D. total expenditures devoted to veterinary products approximates the 6% of total drug sales garnered by the veterinary preparations. And the continuous growth in overall demand over the years for human and veterinary pharmaceuticals and biologicals, while common knowledge, again is confirmed.

Of the multitude of veterinary drug manufacturers, large and small, some

of those with more important positions in the worldwide pharmaceutical market are:

Abbott Laboratories	Merck & Co.
American Cyanamid Co.	Norwich Pharmacal Co.
American Home Products Corp.	Chas. Pfizer & Co.
Armour Pharmaceutical Co.	Philips Electronics & Pharmaceutical Ind. Corp.
Bristol-Myers Co.	Richardson-Merrell Inc.
Cutter Laboratories	Schering Corp.
Dow Chemical Co.	Smith, Kline & French Laboratories
Farbwerke Hoechst	Squibb Beech-Nut Inc.
Imperial Chemical Industries	Upjohn Co.
Eli Lilly Co.	Syntex Corp.

Supplement #3 includes a more nearly complete listing with addresses.

III. Embarkation upon a program for the development of veterinary pharmaceuticals requires an attitudinal approach different from that which applies to drug preparations for the treatment of mankind. The similarities of the basic ingredients and procedures, and the comparative ease with which existing facilities may be expanded are undeniably advantages but they should not serve as lures alone. The differences in the goals of drug use in man and in animals, evaluated by full consideration of their overall attainable purposes and the physical limitations associated with the handling of animal patients, should be recognized clearly and measured reflectively.

The essential and most significant factor in any enterprise, but notably pertinent in drug development and production efforts, is the quality of the responsible personnel. An intellect adequate for and equal to the job demands, a sense of dedication and of responsibility, and unassailable integrity of character are the required standards by which each person involved, from administrator to bottle-washer, should be selected. In the preparation of pharmaceuticals and biologicals the use of which literally may decide life or death, whether it be human or animal, individual disinterest and carelessness are intolerable.

J. J. Servan-Schreiber, the contemporary French commentator and author, remarked recently during an address to the International Chamber of Commerce:[8]

"The general conclusion is that a model of industrial development cannot be exported as a whole. It must evolve within the special cultural, intellectual and social framework of any country or group of countries. Each society must invent its own model of development, depending on its own historical and social conditions."

\+ + + +

Bibliography:

1. Martin, E. W.: Remington's Pharmaceutical Sciences, Ed. XIII, Mack Publishing Co., Easton, Pa. 1965. Chap. 93 "Veterinary Services" (Huebner, R. A.), pp. 1735-1747.

2. Siegmund, O. H.: The Merck Veterinary Manual, Ed. III, Merck & Co., Inc., Rahway, N. J. 1967.

3. M.V.P. Red Book, 1968 Ed. (Vol. 49, No. 10), American Veterinary Publications, Inc., Wheaton, Ill., pp. 160-297.

4. Huebner, R. A.: Veterinary Drug Enchiridion. In Press 1968.

5. Anon.: Key Facts about the U. S. Prescription Drug Industry. Bull. Pharmaceutical Manufacturers Ass'n., Washington, D. C., August 1968.

6. Anon.: Industry's Contribution to Veterinary Research and Development in 1965. Jour. of the Amer. Vet. Med. Ass'n. 153 (9):1157, 1968.

7. Sherman, J. V.: Alive and Kicking. Barron's National Business and Financial Weekly, Sept. 2, 1968, pp. 11-14.

8. Anon.: Notable & Quotable. The Wall Street Journal, Dec. 27, 1968, p. 6.

N.B.: Copies of publications 1, 2 and 3 comprise supplements identically numbered.

Acknowledgments:

Appreciation is expressed: to Mr. John Hoover, Managing Editor of "Remington's Pharmaceutical Sciences" and to Mack Publishing Co. for their provision of chapter reprints supplied as Supplement #1; to Mr. John Lawson, Publications Business Manager, Merck & Co., Inc., for copies of "The Merck Veterinary Manual" supplied as Supplement #2; to Mr. Lillian Dean, Assistant Vice President, Wyeth Laboratories division of American Home Products Corp. and to American Veterinary Publications, Inc., for copies of "M.V.P. Red Book" supplied as Supplement #3.

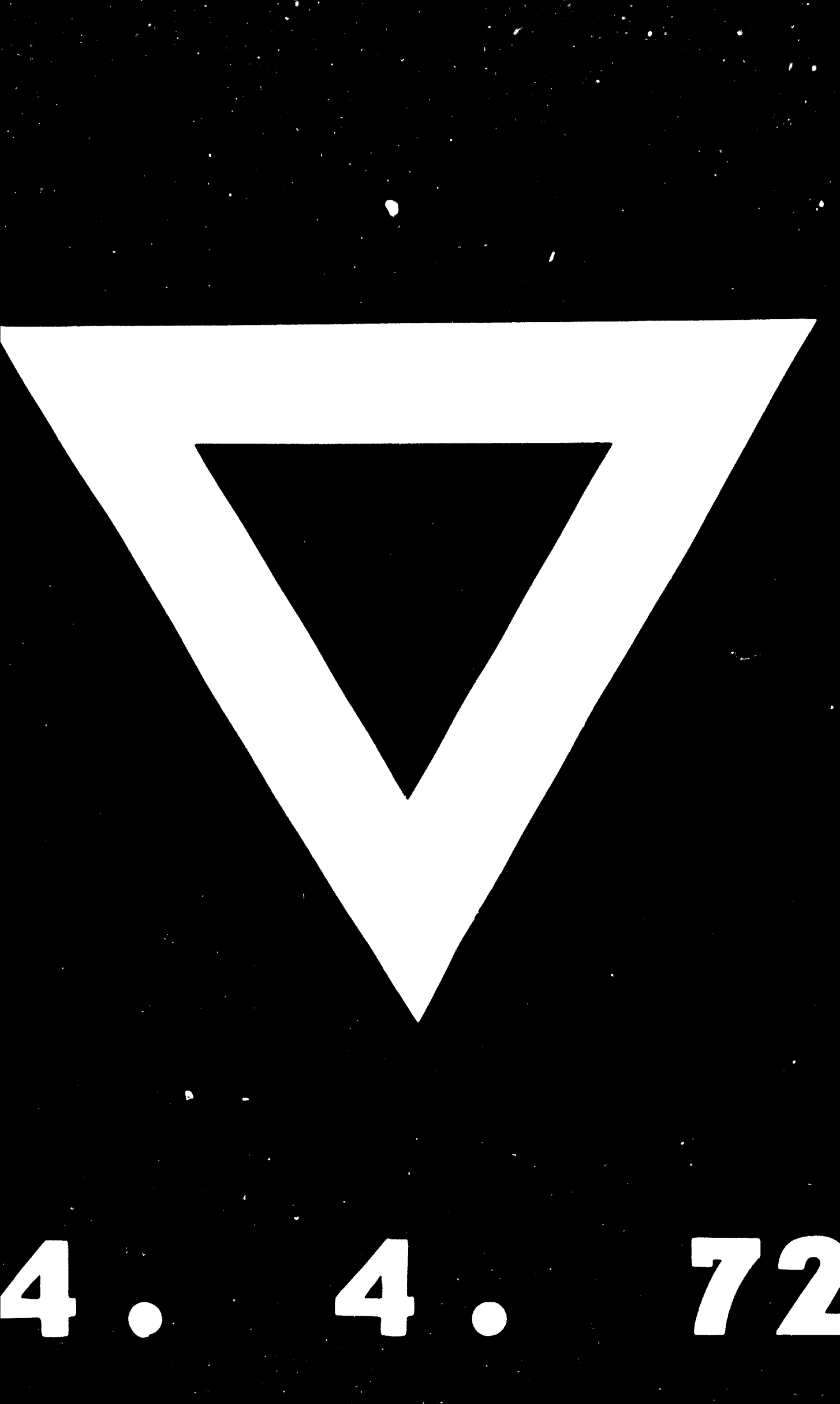
* * * *

Precis:

In broad divisions of (1) perspective, (2) approach, (3) considerations and (4) experience, the bases underlying the decision to produce veterinary pharmaceuticals, as related to general public health and to animal health, are reviewed; some disease problems and methods for their control are suggested.

Classes of veterinary prophylactic and therapeutic agents, determination of the requirements for them and approaches to meeting the requirements are offered. The economics and some potential difficulties that may be encountered are summarized from experience in the United States.

Specific support and detailed reference are provided in 3 supplements, each separate and in book form, which contain more extensive information on animal diseases, on drug formulations and their costs.


4. 4. 72