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CONSIDERATION OF DRUG EFFICACY AND SAFETY 1/

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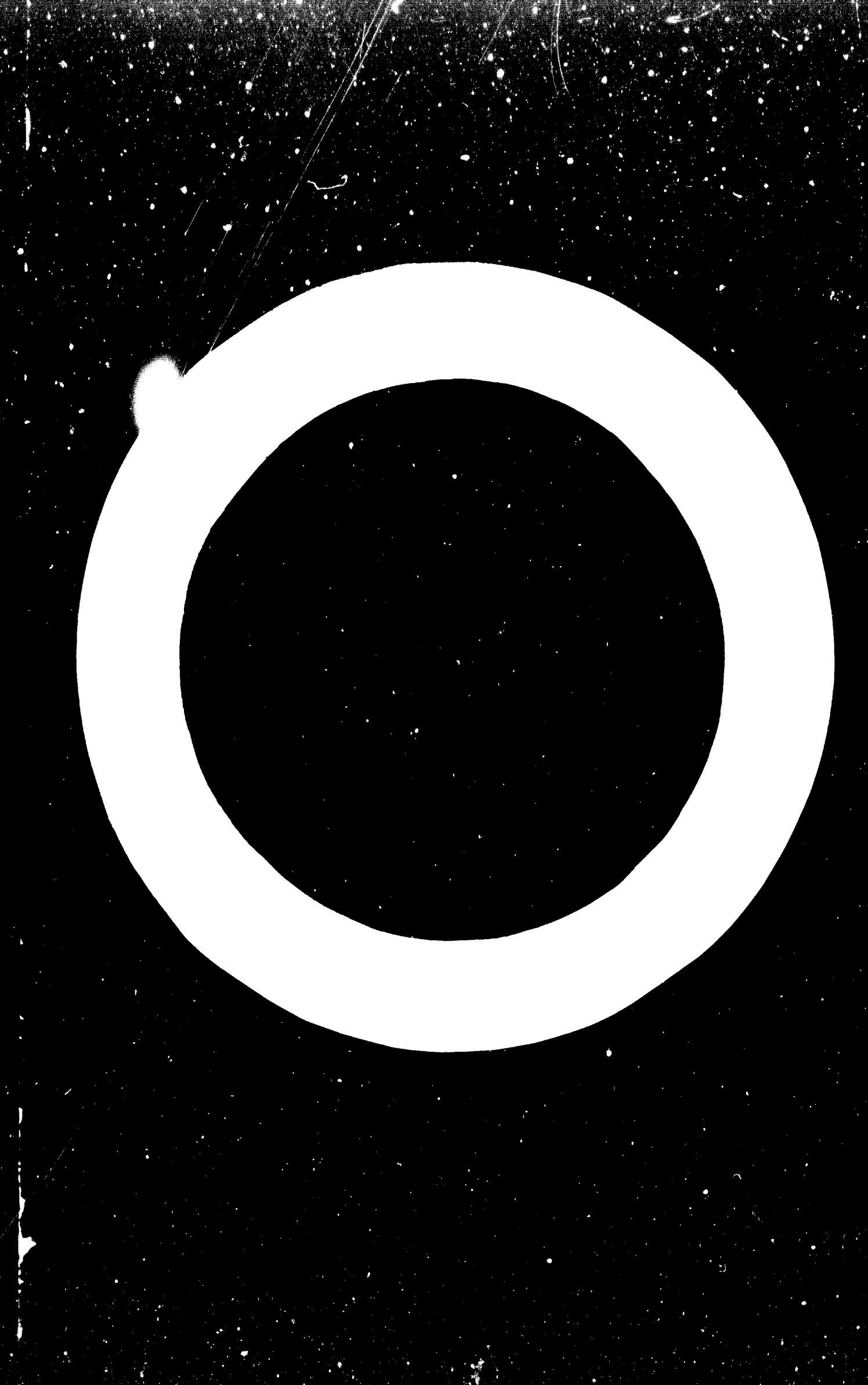

Therapeutic efficacy as well as safety of pharmaceutical products must be the concern of the manufacturer. Principles for the biological evaluation of safety and efficacy in pharmacological-toxicological laboratories, as well as in clinics and medical practice have been worked out by WHO with a view to having them accepted throughout the world.

Such principles and criteria must also be observed by manufacturers who restrict their activities to confectioning of pharmaceutical products and who are not normally involved in the biological evaluation of new drugs.

In developing countries the therapeutic methods and the conditions of drug application are often different from those in developed countries. Therefore specific problems are likely to arise in the assessment of efficacy and safety, for example:

Local factors such as nutritional habits, malnutrition, or certain genetic disorders may lead to adverse reactions which will not be observed in the country where the drug in question has been developed and tested.

So-called "traditional" drugs are not usually evaluated for efficacy and safety under modern scientific aspects; they should, however, be processed like new drugs even if national law or customs should provide certain preferences regarding the registration formalities.

Recently, serious doubts have arisen about the therapeutic equivalence of certain generic products. The therapeutic activity of such products should be checked by suitable means whenever possible.

The safeguarding of the biological standards of safety and efficacy requires close co-operation between the pharmaceutical and medical professions. The respective technical units of the WHO Division of Pharmacology and Toxicology are prepared to provide relevant information and to assist in the education and training of the necessary academic and non-academic personnel, e.g. by consultants and fellowships.

CONSIDERATION OF DRUG EFFICACY AND SAFETY

1. Responsibilities of Drug Manufacturers

The progress in the fields of drugs is affecting increasingly the contemporary societies in the highly developed countries and in the developing countries.

Each country, in its own context, is seeking to take advantage of that progress.

But, as every progress has its price, so has medical success. The term "therapeutic risk" has become familiar to all who deal with the development, manufacture, distribution and administration of effective drugs, as every act of effective therapy involves a calculated risk.

In postulating that the activity of a drug can be evaluated by objective criteria and that it must be clearly distinguishable from a placebo effect, one accepts implicitly that risk must be taken. The question which arises immediately is who is to take the risk and who the responsibility. The risk has to be taken by the patient. But since the patient is usually not in a position to evaluate the risk intelligently, this task and the related responsibility devolves on his doctor. But he in turn depends to a great extent on the working practices of the manufacturers. He trusts their seriousness regarding the drug quality control as well as the information on effectiveness and safety of their drugs. Therefore, therapeutic efficacy and safety of pharmaceutical products, must be the concern of the manufacturer.

Principles for the biological evaluation of safety and efficacy in the laboratories of the manufacturers as well as in clinics and medical practice have been worked out by WHO, with a view to having them accepted throughout the world. I shall review them briefly.

2. Biological evaluation of new drugs

2.1 Pre-Clinical Valuation, General Considerations

Newly synthetized substances are subjected to a range of tests on animals or animal preparations to ascertain any possibly useful effects for therapeutic exploitation. The principles for performance of such

research were published in 1966 by a scientific group convened by WHO 1/ The report of the Group contains collective views on generally accepted recommendations for the pre-clinical evaluation of drug efficacy and safety. To arrive at this position the group had to review the methods that are at present being used to establish the efficacy and safety of drugs, and that are laid down in several documents prepared by national groups as well as in other publications on the subject; as a result of this review it became clear that, present methods, when applied intelligently and conventionally, are useful, but do also have some limitations.

The main limitations arise from the phenomena of species-dependent differences which make extrapolation of results from one species to the other and particularly to man, difficult. There are many factors concerned with species-dependent differences, of which the most influential is the species-metabolism of drugs. The ways in which the drugs are absorbed, distributed and excreted also differs widely between species and strains. Since recently the research methodology has developed a number of techniques sufficiently sensitive for the detection of small concentrations of drugs and their metabolites in body fluids and tissues, it becomes increasingly possible to study species-dependent differences and their reflections on the transferability of results from one species to another or to man. At present the risk associated with the first and subsequent administrations of a new product to man, therefore, can be minimized but not totally excluded by rational pharmacological and toxicological studies on animals.

2.1.2 Pre-clinical studies, procedures

Pharmacological studies on animals have two aims, first to define the general pharmacological actions of the drug and, second, to estimate the intended therapeutic properties. The methods used differ according to the class of drug.

1/ Wld Hlth Org. techn. Rep. Ser. 1967, 341

Toxicological studies fall into two types: first those using single administration, so-called acute toxicity studies, and those using repeated administration, which includes short-term or sub-acute studies of less than three months' duration and second long-term or chronic studies of three to six months' duration and life-span toxicity studies. Probable teratogenic, carcinogenic, dependence producing effects and the whole question of sensitization to drugs require special studies on laboratory animals.

Biochemical studies, including studies of absorption, distribution, excretion and metabolism of a drug are of fundamental importance for the proper evaluation of the results of pharmacological-toxicological studies. Typical experiments of this type involve the administration of single or repeated doses by various routes to animals and measurement of drug concentration in body fluids and tissues. The purpose of these studies is to estimate the rate and degree of absorption and accumulation as well as the rate of disappearance from the body by metabolic breakdown, renal and other excretion. Quantitative studies of this type facilitate the extrapolation of animal data to man, disclose metabolic products with therapeutic or toxic effects, and provide the rational for development of suitable dosage regimes in animal experimentation.

Pharmacological studies, and acute and short-term toxicity tests must always be carried out in animals before a new drug is administered to man for the first time. Elaboration of some biochemical data will be of great value at that early stage of drug investigation. Long-term toxicity tests and extensive biochemical studies usually will be carried out only if it can be concluded from initial studies in man that formal therapeutic trials are justified.

2.2.1 Clinical Evaluation. General Considerations

The formulation of principles for the clinical evaluation of drugs has been undertaken by another WHO scientific group. [2] The more important considerations were:

2/ Wld Hlth Org. tech.Rep.Ser. 1968, 403

(a) In initial trials of any new agents, the investigator must be genuinely open-minded concerning the possibility that the drug is worth a trial and that it may be as good as, or perhaps better than, one or more of those already available.

(b) Adherence to ethical and human principles, as well as to economic and technical considerations, will sharply limit the number of subjects and the number and quality of organized studies in man, as compared to those on animals. Because of this, it is essential not to waste human and economic resources in carrying out scientifically inadequate studies, the validity of which will later be questioned.

(c) The clinical investigation of drugs, whether new or old, and whether used for a new action or in a new physical form or combination, has to include planned scientific studies in man of pharmacological actions, absorption, distribution, metabolism, and excretion.

(d) It is unethical to introduce into general use a drug that has been inadequately tested. The ethical programme is not solely one of human experimentation, it is also one of refraining from human experimentation; The study of comparative efficacy and toxicity of the new and standard treatments is essential. Any hazards which may arise from interaction with other drugs, domestic remedies, alcohol or food, should be considered and investigated where indicated.

(e) Even then the administration of biologically active substances to human beings will remain to be accompanied by some element of risk that cannot be avoided by the most careful and exhaustive scientific study during its pre-clinical and clinical investigation, and by careful monitoring of its adverse reactions whenever released into general medical practice.

Only general principles are offered in the report 403; the procedures applied to the testing of new drugs in man vary widely as a result of continuous improvement of the methods used, and also because facilities, attitudes and local legal regulations vary to a great extent from country to country. Any attempt to lay down rigid requirements for clinical evaluation of widely differing drugs would fail to achieve its objective and would hinder the advance of therapeutics.

2.2.2 Clinical Studies, Proceedings

Studies of new drugs in man as a rule are performed in three stages:

(a) Initial Studies include pharmacokinetic and pharmacodynamic studies on small numbers of healthy volunteers or patients, or both. Wider use in patients under close supervision occasionally may be necessary and justifiable in order to clarify whether a drug has any potential therapeutic effect or in order to obtain data on the range of dosage, patient selection etc. to allow design of a formal therapeutic trial.

(b) Formal Therapeutic Trials shall establish the formal assessment of therapeutic merits, that is of efficacy in relation to safety, and comparison with those of existing therapy, if any.

(c) After a new drug has been introduced into general medical use, it is desirable to set up a monitoring system to detect any rare adverse reactions that may not have occurred amongst the necessarily limited numbers of patients involved in formal therapeutic trials. If instances and severity of adverse reactions outweigh therapeutic benefits, the drug may have to be withdrawn.

Officially drug monitoring systems are being developed in a small number of countries only and the methods of obtaining, recording and assessing reports of adverse reactions are in an early stage of development. They require more intensive methodological research to improve their efficacy. The 15th World Health Assembly in May 1962 considered certain steps towards an international exchange of information on safety and efficacy of drugs as well as arrangements for rapid reporting of adverse drug effects. The collation and dissemination of information on adverse effects should represent the "field trial", indispensable to supplement the information obtainable from clinical trials with their inherent limitations.

Besides the problem of testing new drugs, there is a need to re-evaluate many established or commonly used drugs. Many of these have never had adequate pharmacological testing and judgements of their safety and efficacy are based as much on intuitive reasoning as on acceptable scientific evidence.

2.3 Implications of Biological Evaluation of New Drugs to Pharmaceutical Industry of Developing Countries

Which implications have those principles of biological evaluation of new drugs to the pharmaceutical industries established or to be established in developing countries? One might say that these industries, during their first years of development, will seldom have personnel and financial resources to enable them to conduct drug research comparible to that of large American and European drug companies. New compounds will rarely be introduced by them, and that therefore knowledge of the principles, which should guide such research, could seem to be of minor importance to such companies.

However, such an opinion might have to be corrected sooner or later. Manufacturers of pharmaceutical products, whatever the kind of products, will always have to be prepared for the unexpected. Even if an industry concentrates all its activities in the technocological field of drug production, it is dealing with powerful biologically active compounds or products, produced for the benefit of the majority of the sick, but inevitably harmful to some. A drug company confectioning and marketing drugs which have been biologically evaluated in the laboratories of other companies, is sharing the responsibility for efficacy and safety of such drugs with them. Such a company has to be informed on the whole impact of biological activities, whether intentional or unintentional, of those drugs. Such a company must be able and willing to inform the medical profession on those effects as completely as possible and must also be able to provide all the necessary documents on the biological evaluation of those products to governmental authorities during or after the registration procedure of those products. Therefore, companies marketing pharmaceutical products which contain ingredients investigated by others must be informed on the principles of such research and on the results referring to their products.

3. Biological evaluation of drugs in developing countries

3.2 Drug effects and environmental factors

As drug treatment and its results in developing countries are not in every respect identical to those of developed countries, one will find additional problems regarding safety and efficacy.

Deviations from the recognized compatibility of certain drugs can be expected in countries where the average body size and body weight of patients is smaller than in countries where the drugs in question have been investigated clinically in the first instance. Also, special types of adverse reactions may occur if a part of a population lives in the state of malnutrition, or carries certain genetic disorders, especially that of glucose -6- phosphat-dehydratase-deficiency.

Companies producing drugs, as well as organizations controlling their introduction into medical practice, have a responsibility to anticipate those harmful effects, and have to encourage competent scientific and legal institutions to study and prevent such events, whenever possible.

3.2 Effectiveness of "traditional" drugs

Other important problems relate to the efficacy of drugs. As there are inefficient drugs to be found in the markets of industrialized countries, they are sold in developing countries. In the latter additionally a certain number of so-called "traditional" or "indigenous" drugs are available. These drugs may be of value - though questionable - if administered in cases of harmless ailments but incompatible with the needs of the sick in cases where effective treatment is imperative. There is no reason to think that all of these newer or older drugs were ineffective in the framework of the scientific or philosophic knowledge available at the time of their introduction, but medical science has made tremendous advances during the last thirty years and this fact must be recognized by drug producers, as well as by health authorities and drug prescribers. In view of today's knowledge, many of them may be of no more use than a placebo.

3.3 Therapeutic equivalence

Producers of pharmaceutical products will be especially interested in the problems of therapeutic equivalence. This subject leads back to one point which I mentioned earlier and is presenting a fine example for the needs of close co-operation between pharmaceutical and medical science in drug research and production.

In an Editorial in JAMA (216: 1785, Nov. 18, 1968) entitled "Generic Drugs and Therapeutic Equivalence", Dale C. Friend stated: "Unless a

preparation has been proven to be as effective as the standard preparation, it should be considered as a possible source of therapeutic non-equivalence".

If this point of view is to be the prevailing one, then official Compendia in all countries must add tests of therapeutic equivalence to their standards of drug purity in order to guarantee the physician a therapeutically active drug product. Though the problem is not a new one, its urgency became enhanced by recent findings, that some brands of chloramphenicol, although of equal chemical purity, were not as therapeutically active as the original brand, possibly because of difference in crystal size or the manner in which they were tabletted. It is assumed by some experts that this may be true of many other drugs sold by different manufacturers. Examples are brands of diphenhydramine, sulfafurazole, erythromycin, tolbutamide, etc.

Pharmaceutical industries to be established in developing countries will be confronted with the problem of therapeutic equivalence right from the beginning of their activities. Their products must be controlled for identity and purity, but this precaution does not necessarily guarantee the therapeutic equivalence to standard preparations. Therapeutic equivalence could only be ascertained by the results of clinical trials.

4. Technical Assistance by WHO

This, as many other pharmaceutical and therapeutic problems to be found in developing countries, requires close co-operation between the pharmaceutical and medical professions. But not in every country will the necessary academic and non-academic personnel be available.

WHO, therefore, would like to assist - as far as its personnel and financial resources permit - inter alia in the training of technicians, students and post-graduates in [illegible] sciences.


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