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

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PRODUCTION OF ETHAMBUTOL 1/

by

Jae Hyun Yang*

2752

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* Vice President for Research I, Korea Institute of Science and Technology (KIST), Seoul, Republic of Korea

CONTENTS

SUMMARY

In this paper a synoptical account has been presented of a project for the production of a pharmaceutical drug Ethambutol covering the entire gamut of process starting from the bench scale research followed by economic feasibility study, pilot plant test, successful transfer of technology, designing and construction of commercial plant and then eventually up to the point of normal production operation of the plant.

Through this project, it was learned that a successful completion of a research would require not only the faithful accomplishment of contractual obligations that behoove the industrial research organization involving scientific and technical aspects of the project but also demand a closely coordinated efforts of the institute and the client to provide effective solutions to all the constraints and problems that are often faced in the course of R & D activities in a developing country with all its indigenous problems.

To cite some of the major difficulties that had to be tackled with in the course of the project, which are 1) the patent dispute resulted from the foreign patent holders, 2) the troubles fomented by the domestic firms in the sales business 3) the necessity of using new starting raw material caused by the imposible supply of intermediate compound, and 4) the question of who has to take the risks on expensive pilot plant test.

These problems have all found a satisfactory solution one by one with positive government support to carry the project to a successful commercialisation.

I. INTRODUCTION

Industrial research in developing countries is in itself a most tricky undertaking involving built-in difficulties and constraints. There are, however, still greater difficulties and knotty problems to be faced in the course of implementing the research results on a commercial level. This paper is intended to provide a case study on the Ethambutol (d-ethylenediamino-di-1-butanol dihydrochloride) process that KIST has developed. The point of study is not to provide an academic account on the new method of synthesizing the Ethambutol, nor the technical explanation of engineering problems on commercial scale production, but rather is intended to explain the nature of various difficulties that were encountered from the point of bench scale research up to the eventual goal of commercialization, and how all these difficulties were overcome to carry the project to a practial reality.

The nature of difficulties in the course of commercializing the industrial research widely differs from each other depending on the field of industry such as the electronics industry, the chemical industry or the mechanical industry in view of the nonuniformity of the level of industrialization, the level of existing technology, the availability of materials and manpower, the degree of development of related industries and of the

variation in the government policies. Even in the same industrial field, the chances for success vary on each individual project depending on the nature of projects, and one of the most important considerations affecting the chances of success may be the nature of background and experiences possessed by those to whom the technology is to be transferred after completion of research.

The reasons for taking up the Ethambutol project in illustrating the case of Research, Development and Engineering are that 1) it required comparatively sophisticated synthesis route along with high level technology, 2) the existing size and structure of sales market was of a comparatively complicated nature, 3) the patent position involved a complicacy, 4) the project itself was of an integrated nature involving all the process starting from the bench scale research through pilot test and finally to the construction and operation of a commercial capacity plant, and that 5) the project may be taken as an exemplary case where a close link of cooperation was maintained not only with the project sponsor but with the government throughout the entire process of project progress.

II. BACKGROUND OF THE PROJECT

A. Pharmaceutical Industry in Korea

Largely due to the positive government support, Korea's chemical industry has achieved a remarkable development during

the past decade, and most of the basic chemical industries have grown to international scale with result of stimulating related industries in the down stream side. Accordingly, the variety of locally available chemicals has become diverse and thus a ground is beginning to be established for a rapid development of the so-called fine chemicals industry including pharmaceutical materials, agrochemicals, dyestuffs, etc.

For the moment there are some 270 pharmaceutical companies in Korea and their combined annual domestic sales proceeds are in the equivalent of US$200 million. The average annual import requirement of pharmaceutical raw materials during the recent years stands at around US$60 million. Annual increase of demands for overall pharmaceutical materials is at the rate of approximately 30% for each year up to 1975. Of the requirement, some 30% of the total materials need is being met locally.

In retrospect, there virtually did not exist pharmaceutical industry in Korea until around 1950 with foreign pharmaceuticals coming in in packaged form for local distribution. Subsequently, techniques of tabletting and capsulation has gradually been introduced for processing imported pharmaceutical chemicals, and these secondary processing techniques matched with development of packing method has shown a remarkable progress. The next stage was to process the imported intermediate compounds with one or

two last chemical step(s) to manufacture final products. In general coincidence with the time of successful completion of Ethambutol project, the pharmaceutical industry of Korea began to assume solid progress toward synthesizing the entire process starting from industrial chemicals raw material to the final products.

Some of the basic reasons that gave rise to the development of Korea's pharmaceutical industry to the point of mature industry with the synthesis capability may be enumerated as follows:

1) To multiply the steps of chemical process meant increased added value of the products, which prompted impetus for research and development of synthesizing method from raw materials for maximum profit margin.

2) The ratio of sales proceeds to the fixed investment is greater than in any other chemical industry.

3) There exists a stable domestic sales market with added potentiality for export sales.

4) The government's policy of encouraging to the development of pharmaceutical industry.

5) The industry has gradually been given a relatively easier access to the foreign technology for total synthesis process in spite of the earlier difficulty resulting from their reluctance of revealing the process. This is because

the holders of technologies realized that the technology may eventually come by through local development or that such technology may become available to the domestic industry from other competing foreign sources.

B. Government Policy for Promotion of Pharmaceutical Industry

To stimulate the desire for local development of technology and also to promote domestic fabrication of manufacturing facilities, the government is implementing various incentive measures. One of such measures is to protect the industry for a specific period of time when it is successful in producing drug material through synthesis route as compared to simple blending. Subject to the quality of end-product meeting specified criteria and when it is reasonably foreseen that the forecast product would substantially fill the domestic need and yet at reasonable prices, the government would, after due deliberations, impose a limit on importation of the same drug either in finished form or in the form of intermediate or would discourage development of the same item by other competitors for a given period of time in the interest of protecting the first producer. This means that the processors of imported materials are always exposed to the risk of losing the established market which is developed at the expense of considerable money, time and labor in the form of advertisement if they fail to start producing through chemical process development in ample time. Another form of incentive

measures, though not necessarily limited to the pharmaceutical industry, is with the financial favors. In spite of the rigid taxation policy, the cost of research goes untaxed as tax deductible expense when the research was for the development of new technologies, for development of new products and processss or for process improvement. In addition, attractive long term government loans may be available in case of factory constructions when it is built with dometically fabricated equipments.

C. Market Situation of Ethambutol

The drug which now goes in Korea by the trade name of Ethambutol was developed in advanced countries some 15 years ago for treatment of tuberculosis. The drug was initially introduced to Korea in 1968. For the first year of introduction, the amount of import was a negligible US$40,000. Since then, however, the demand for this drug has recorded a drastic increase at the rate of 50% for every year, and in 1972 the import reached a $1 million mark and further along it hit an all-time high of $5 million for 1975. The gross sales volume of this drug throughout the world is estimated to exceed $100 million.

The client who took up the Ethambutol production project in cooperation with KIST is a drug manufacturer established in 1954 and is now operating with a total employee of 900, producing some 60 different items of drug yielding a total annual sales proceeds of about US$ 20 million. In view of the government policy as

already stated above, the client firm had a reasonable prospect of dominating the existing market once they were successful in synthesizing Ethambutol. Preliminary economic study also revealed that they could produce Ethambutol at costs internationally competitive.

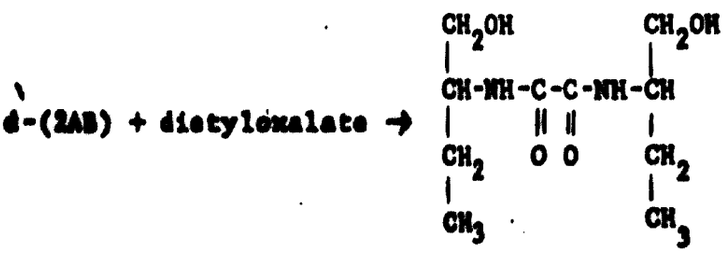
III. BENCH SCALE RESEARCH

A. Patent Dispute

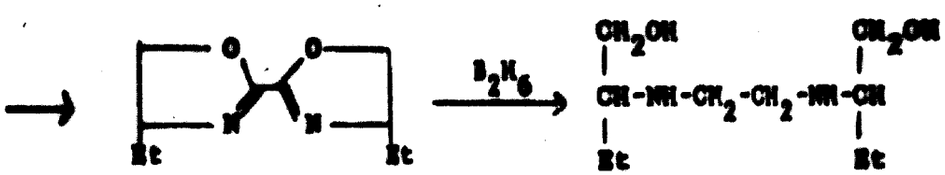
The intermediate raw material for Ethambutol synthesis, 2-amino-1-butanol, (2AB), has optical active center so that when synthesize a racemic mixture, in which contains isomers of l-and d-form in equal quantity, is obtained. D-ethambutol is produced from d-(2AB) and l-ethambutol from l-(2AB). This d-ethambutol is effective for treatment of tuberculosis while l-ethambutol can develop the side effect of eyesight impediment. Therefore, it was essential to resolve (2AB) optically to obtain d-(2AB) before proceeding with further processing steps.

At time of contract with the client firm, two foreign firms of the most advanced countries already had their patent rights registered in Korea. One of it specifies method of obtaining d-(2AB) from (2AB) by using tartaric acid and methanol, while the other is to synthesize Ethambutol by use of ethylene dichloride on d-(2AB). Neither of the two patent holders was in practice of production in Korea, but simply selling the final product to Korean dealers. Therefore, the KIST project was apparently doomed to fail unless it could successfully develop a method of economic

synthesis by a new process route. The gist was that the government would not license the production when it was involved in a patent dispute. After 2 years of research, KIST team was eventually successful in developing a new process for obtaining Ethambutol from d-(2AB) by the following process:



bis Oxalamide (OA)

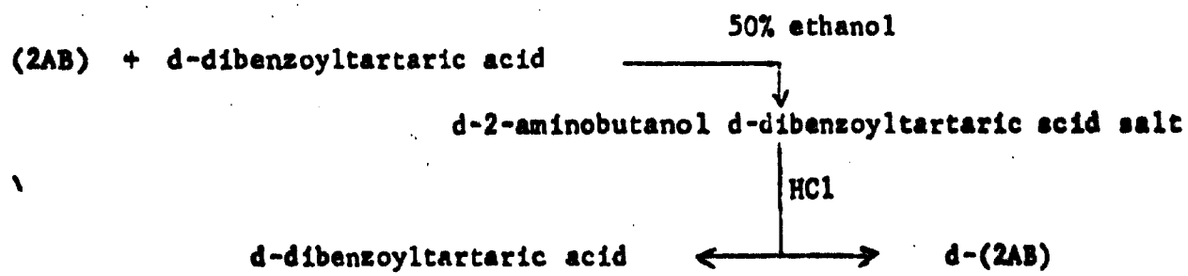


4,4'-diethyl-2,2'-bisoxaline (DO)

Ethambutol

The merit of this process was to be found in the higher yield, viz., 90% (DO) yield from d-(2AB), 90% Ethambutol yield from reducing (DO), thus obtaining a total yield of 80% as against the total yield of 65 - 70% as is claimed by the existing patent methods. From the economic consideration, the improvement of yield by 10% over the existing level had a tremendous significance in view of the costly nature of the drug that was selling for an astounding price of US$120/kg at the time when the project was in progress. Though further process improvement has subsequently

been developed on a commercial level to obtain still higher yield with less costly raw materials, the initial steps of optical resolution applied for the patent is illustrated as follows.



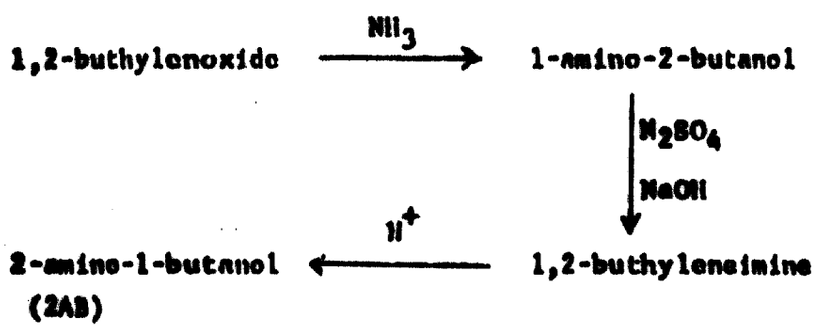
Patent rights were sought for these processes. The patent rights, however, were not granted immediately but only after some 2 years of dispute involving various law suits. The time and labor spent by research staff in the patent dispute in the meantime, however, were an irretrievable waste. The trouble was heightened by the strong challenge coming in concert from both the foreign suppliers of final product and their Korean agents who were importing the product for tabletting and sale in Korea. The favorable outcome of the final court ruling might be influenced by the fact that there were announcements of the establishment of patent rights in other countries independently on similar technology of synthesizing ethambutol from oxazoline derivative subsequent to the patent application in Korea; some 2 months later in West Germany and also 2 years later in Japan. These two foreign patents had the starting material in common with the KIST process, but only differed in reducing agent. In lieu of borohydride, one used platinum-rohdium catalyst while the other used platinum oxide and Raney nickel.

B. Choice of Starting Material

It is to be admitted that selection of chemicals for the starting material may constitute one of the most important factor affecting the final outcome of the project concerned in an industrial research. In the choice of material, 1) the initial consideration will be whether to use material externally procured or to synthesize it internally, which will involve such economic considerations as comparison of purchase prices with cost of synthesising, the financial ability of the clients to meet any additional capital investment, etc., and 2) then further considerations will be given to such other factors as corrosiveness, inflammability and boiling point of the material in order to determine the method of transportation and storage with possibility of incurring additional expenses. Still another point of consideration will be that in procurement of materials the availability itself may often suddenly become insecure or the prices may be abnormally exaggerated especially when the specific use of the material is exposed to the public.

Subsequent to the bench scale research, an economic feasibility assessment was necessary in deciding whether the project should be carried out. Throughout the world there were only one or two companies producing the basic material (2AB), who also had a complete monopoly over the primary raw material of (2AB), viz., 1-nitropropane,

and they were highly reluctant to quote on the desired material. This compelled the KIST team to embark on a second stage research to develop some other method of synthesizing (2AB) without using nitropropane. After about a year of research, new KIST process was successfully developed in which where butylene oxide is used for the starting material, which, was to be readily available from many countries. The process is illustrated as follows.



C. Contractual and Other Responsibilities

The original contract that KIST entered into with the clients clearly defined the scope of research such that; 1) the research is to develop method of synthesizing Ethambutol from (2AB), that 2) the research is to develop method which would not interfere with the existing patent held by others. Therefore, KIST would not be held responsible for any failure of commercialization for causes attributable to the failure of securing adequate supply of material, (2AB). Legal responsibilities aside, KIST could not afford the luxury of seeing the project end in a failure which

would frustrate the clients in their well meant investment in developing new product. If the project failed, regardless of the causes of failure, the fact would seriously affect the image of KIST as viewed from the industry, and this kind of disgrace to the KIST reputation might constitute a catastrophic blow to the development of KIST as a contract research organisation.

The inability of obtaining adequate supply of (2AB) prompted KIST to develop a new method of synthesising (2AB) from other material than nitropropane. Agreement was reached that KIST would use inhouse fund for the research and that when the project is successful the clients would remunerate KIST for the costs incurred in the form of a royalty at a fixed rate applicable on the sales for a given period of time. In retrospect, it may be safely asserted that one of the indomitable reasons that contributed toward successful commercialization of the project was the basic stand upheld by KIST that irrespective of the terms and conditions of the contract and regardless of the whereabouts of responsibility, the effort should be directed toward achieving final goal and whatever the bottle-necks is, KIST should find solutions as far as such bottle-necks are of the nature that could be solved on the research side.

IV. PILOT PLANT TEST

A. Risk and Expense Sharing

Results of the bench scale research were satisfactory as a whole; the optical purity problem was better than the control sample; the reproducibility was also satisfactory; the availability of all raw materials was satisfactorily established. Butylene oxide was to be imported while all other materials were locally available; and the yield of each synthesizing process was satisfactory enough to assure economic soundness.

The bench scale results are, however, not to be taken as the sole elements to be considered in designing a production plant. On the level of plant design, there were other factors that strained the nerve of all those concerned. Some of the most important considerations were; 1) the method of synthesizing Ethambutol from butylene oxide in commercial scale. 2) it was highly problematical as to whether a satisfactory yield could be assured on all multiple total synthesis steps, and 3) if a fully balanced design of reactors, distillation columns and filters could ever be achieved in order to assure total material balance. A rough budgetary estimation revealed that the overall cost involved in the pilot plant test would reach as high as somewhere around 13 times of the cost of bench scale research. Let alone the incidental problems

as enumerated above, there was to be no prior guarantee for an eventual success. It also involved possibility of incurring additional expenses when the necessity occurred for a change of designed equipments and facilities.

Such was too big a risk to be borne by the clients alone. Fortunately, the government has come to recognise the importance of the project and after a tripartite discussions involving the Ministry of Science and Technology (MOST), KIST and the clients there emerged an understanding for sharing the cost among the parties concerned. The agreement was to share the cost of pilot plant test by the respective proportions of 15% by MOST, 35% by KIST and 50% by the clients. This arrangement was to be taken as a demonstrative case of project where an integrated effort was made among the government, the industry and the research organization in a sends of sharing the risks involved and with the enthusiasm and hopes for a success of worthy project irrespective of the amount of money involved.

B. Pilot Plant Operation

A pilot plant of 10 metric tons yearly capacity was initially constructed. The plant was a product of patient and fully coordinated effort among parties whose specialities widely differed from each other; the organic chemist having little expertise in engineering and the chemical engineers having little knowledge of the synthesis method. For instance, the solid-liquid separation

will present no problem for chemist as it is to be done through common filteration procedure, however, it may require additonal data for an engineer, such as, if the required material is to be found in solid phase or in liquid phase, what is the size and physical property of precipitate, what is the viscosity of liquid, what is the required rate of filteration, and yet what are the processes to be followed before and after the separation step, because these data are to sidely affect the type and capacity of the filter. Yet, there are cases where certain information is to be taken for granted as a foregone conclusion to one party, while it would be considered as a most important information on the other.

KIST undertakes a research project jointly in cooperation with other laboratories of different fields. There may arise certain problems in the course of such cooperation in view of the fact that each individual laboratory is operating on a separate account system. The project leader is to assume entire responsibility for completion of the project, while the responsibility of laboratory management including the financial aspect lies independently with the laboratory head. When additional work load is to be assigned to the cooperating laboratories, the project leader is to be counted upon for an adequate arrangement for additional funding for the additional services out of the total project fund. In this mechanism, it may not always be an easy undertaking to achieve a complete funding equilibrium, and therefore a satisfactory completion of projects, especially when

larger projects are involved, would usually demand exercise of the sense o. cooperations coupled with the sense of certain sacrifice among parties concerned.

In the early stage of pilot plant test, the yields on different steps were generally found equal or even better than that established on the bench scale. For instance, in the step of optical isomer separation, which posed a difficult problem in the bench scale stage, the test results were much better in both the purity and the yield. Except for a few minor changes involving redesigning of distillation column and piping as were necessitated by the change of solvent used, all processes were carried out in a satisfactory manner. Due to misestimations of retention time and other minor factors on different process, it may be noted that the plant fell somewhat short of optimising the ratio of product to capital investment. It provided, however, all engineering data and reasonable confidence for designing commercial plant with improved efficiency and increased productivity.

While the project was still in progress on the bench scale, many pharmaceutical companies were clamoring to import the foreign technology of Ethambutol production with little success.

At one point after the patent dispute came to an end in favor of the project and when the construction of pilot plant was about to start, there still emerged a competing company who filed to the government an official application for introduction of foreign technology on production of Ethambutol from (2AB). Thanks to the govarnment decision to encourage the self-development of domestic technology, the approval on tha application had been withheld until the day when the pilot test was completed.

V. TECHNOLOGY TRANSFER TO THE CLIENT

It took 9 months to complete tha pilot plant from the stage of its dasign. Upon completion of initial start-up test, steps were initiated for transfer of technology to the client. The trainees of the client initially selected for technical orientation included 3 college graduates, 1 each from the respective field of chemistry, chemical engineering and pharmaceuticals, and 50 high school educatad technicians, who were to ba manned for 3-shit operation. The practice of recruiting client's personnel from the early stage of test run was from the idea to ensure an orderly transfer of know-how, yet simultaneously reducing the operation expenses on the KIST part. Inasmuch as the real merit of know-how is considered to lie not in a simple practice of operating the plant on a normal level but rathar in tha technology that would

simultaneously provide a quick remedy for any functional disorder, it was considered a best way to expose the client's people to the hazard of mistakes in order to make them truly conversant with what they were doing.

Thus the transfer of technology indicated a satisfactory progress to the extent that in the latter phase of pilot test operation the plant was running entirely on the client's force alone. Of course the test run was not without rueful mistakes. For instance, there were several occasions when prepared batches had to be wasted at the expense of tens of thousand dollars material cost. The product of test operations was put up for marketing test in order to ferret out the general reactions of consumers and the results were satisfactory.

The pilot plant started to assume routine operations in the course of approximately 6 months, and at this point the client's engineers embarked on designing and building a 35-ton capacity plant on their own. The plant production was found on a satisfactory level in general except for a minor trouble that resulted from the change in one filtering equipment from centrifugal to schiebler type. The KIST team was, and still is, deeply involved through all stage of plant operations for the dual purpose of trouble shooting and improving the yield wherever possible.

All told, some 5 years time elapsed in between the point of bench scale research and the point of normal production operation of the plant. In the meantime the structure of industry in Korea experienced an extensive change. And along with the changes in the industrial structure, the importance of R&D has come to be strongly felt upon the industry and at the same time the researchers themselves have been greatly encouraged to challenge whatever sophisticated projects with a sense of confidence built on the accumulated knowledge and experiences. In bringing about such an encouraging turn of events, the Ethambutol project may be safely asserted to have done its due part.

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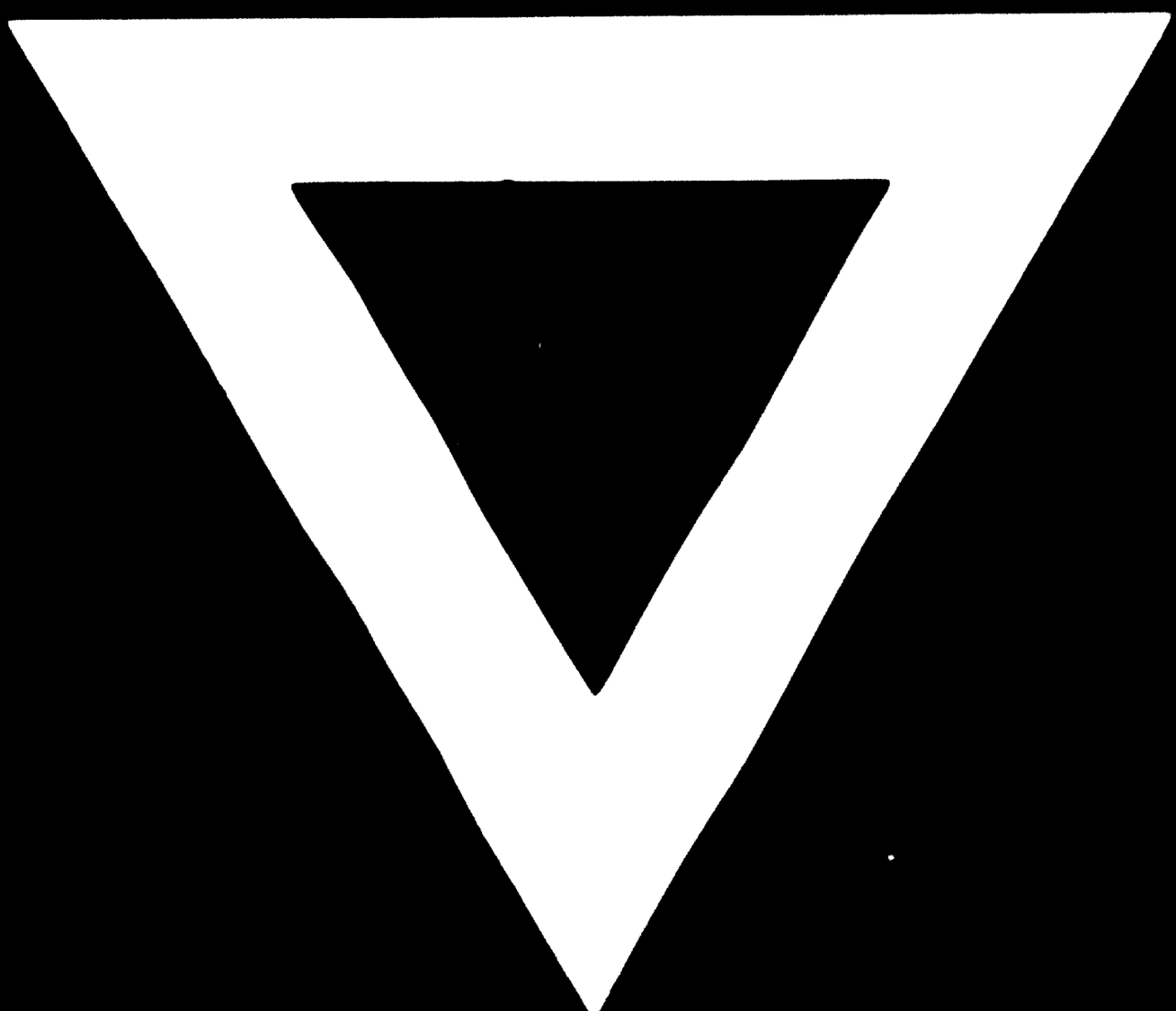

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