HOW CAN THE CHEMIST HELP THE PATENT LAWYER: THE PHARMACEUTICAL CHEMIST AND THE PATENT LAWYER*

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In the pharmaceutical field like the chemical field and other fields, there are many ways in which the chemist can help the patent lawyer, including accumulation of data for the specification, help at interviews with the Examiner, checking opponents' applications for adequacy and operability in interferences, etc. This calls for cooperation and team play. How best to get this all important co-operation and team play?

Possibly the German System or a modification of the German System is the answer. Under the German System, as explained to me, the law provides for the payment of money to the chemist-inventor in the event his invention is patented and is used commercially. The amount of payment -- which is over and above his basic salary, if an employee, for example, of a corporation -- is not set but is negotiated with the corporation when the invention goes commercial. With this incentive system there is little doubt but that the chemist-inventor would supply the required co-operation. If the system was modified to cut the attorney who prepared the patent in on the loot when the invention goes commercial, there is also little doubt about the required team play.

The present German System -- where the chemist-inventor alone gets the monetary reward -- however, has its disadvantages. One of these was pointed out to me by Dr. Gerhardt Irmisch of Farbenwerke Hoechst, who stated that his company was having a very difficult time getting patent attorneys for their Patent Department, as the people with the scientific background required by the Patent Department all wanted to invent, i.e., work in the laboratory where they would have a chance at the jack pot provided under the German law.

The term "jack pot" is used in its true sense and can be illustrated by the oral anti-diabetic, Orinase, sold by The Upjohn Co. under a license from Hoechst. The annual sales of this product in this country alone are rumored to run around $25,000,000.

In the pharmaceutical field, to provide a basis for cooperation and team play between the chemist-inventor and the lawyer it has been found worthwhile, if not essential, for the lawyer to educate or acquaint the chemist with the requirements of patentable subject matter in this field. This education need not be and should not be involved. There are only three basic requirements: novelty, utility and unobviousness.

Novelty.--To be patentable the subject matter, product or process, must be new--the novelty can be thin but it must be there. When a chemical compound is named in a prior publication the novelty is gone. This applies even when an investigator reports, e.g. in the J. A. Chem. Soc. that all attempts to make the compound failed. A later investigator working for say seven years, who successfully makes the compound and finds that it will cure cancer, may be entitled to a patent on the process of making the compound or even a Laskar Award or the Nobel Prize--but the compound per se is unpatentable.

The investigator finding that the compound would cure cancer, however, can under the new statute protect his discovery by obtaining a patent on the use of the compound for that purpose. This was done recently by Burroughs Wellcome & Co., in Timmis patent 2,917,432 entitled Leukemia Treatment. In this case the compound used, 1,4-dimethanesulphonyloxybutane was old, but its use in the control of a type of leukemia was new. The Timmis claim, in process form, as it must be under the statute, reads as follows:

> . . . A process for producing remissions in patients suffering from chronic myeloid leukemia which comprises administering 1,4-dimethanesulphonyloxybutane to a patient afflicted with the disease.

This type of "use process" claim, which involves the treatment of a disease, is relatively new and many lawyers initially did not believe claims of this type of much real value They present problems, which we do not have time to discuss here, but most lawyers working in the pharmaceutical field agree today that they are of value. Illustrative examples are the Hoffmann-LaRoche Fox Re-issue patent 23,947 involving the use of the old chemical compound, isonicotinic acid hydrazide, for combatting tuberculosis, and the Wisconsin Alumni Research Foundation's (WARF) Link, et al., patent 2,601,204 involving the use of the old compound 3,3'-methylenebis-(4-hydroxycoumarin), known as Dicumarol, as a blood anticoagulant for preventing additional intravascular clots, or as the medical people prefer, as a prophylaxis of further thromboembolic episodes. This is on the assumption that you are in a position for a second episode, i.e., are alive after the first coronary.

It is interesting to note that both Hoffmann-LaRoche, along with Squibb, for their work with isonicotinic acid hydrazide, and Dr. Link, for his work with Dicumarol, received Laskar Awards in the same year. It is also interesting to note that the Merck Index states that Dicumarol was first isolated from spoiled sweet clover by Link, et al. This is correct as far as isolation from clover is concerned, and it took Link, et al., seven years to complete this work, but the file history of the Link, et al., patent will show that Dicumarol was first reported in the German

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literature — with an incorrect melting point about 50° off, and with no reference to its properties or possible use. This old German reference, while it did not contribute anything worthwhile, was adequate, however, to destroy novelty, and it is for this reason that the Link, et al., patent does not claim Dicumarol per se. This patent with its process use claims is nevertheless a valuable patent and the royalties paid by the Foundation's licensees, Abbott Laboratories and Eli Lilly & Co., are substantial today.

Summarizing — as to novelty — the chemist can assist the lawyer by pointing up the novelty — and if novelty does not exist by forgetting about the subject matter patentwise.

Utility.—To be patentable the subject matter must be useful, i.e., have a use and the use must be disclosed. Here again the use can be thin—but it must be there. If the compound is an interesting intermediate of no known use but of possible use it still is not patentable. The Court of Customs and Appeals, recent 3 to 2 decision in Ciba's In re Nelson case, involving the utility of steroid intermediates, does not change this basic requirement.

The utility as noted above can be thin—that is, it does not necessarily have to be commercial or the hoped for utility in the medical field. An illustrative example is the Hoffmann-LaRoche-American Cancer Society's fluorouracil patent. This product was prepared and in tests on animals showed some anti-tumor activity. At the time the application was filed activity in humans had not been demonstrated and, as fluorouracil also has some antibacterial properties, the utility disclosed in the patent is in the antibacterial field. Recent clinical work at NIH has confirmed the animal tests and shown fluorouracil to have use in the treatment of certain types of tumors.

Another example is a new product found in animal tests to be effective against Sarcoma 180, Carcinoma 755 and in 13 other different types of tumors by Sloan-Kettering Institute for Cancer Research, and confirmed in other laboratories. In these tests, the product is reported by the Cancer Chemotherapy National Service Center to have the greatest spread in concentration required for effective action against tumors and the toxic concentration of any antitumor agent yet isolated and tested. However, as clinical data were lacking at the time the initial application was filed and, as the product had antifungal activity against ordinary air borne molds, the utility disclosed in the initial application was in the antifungal field — with special reference to its use in laboratory bacterial cultures to prevent contamination by molds. The refile application discloses the anti-tumor properties as the product was about to go under and is now under clinical test at NIH. We should have the answer, one way or the other, soon.

Still another example is coenzyme Q, reported in the literature by Dr. David Green and his associates at the Enzyme Institute at the University of Wisconsin and by Dr. Karl Folkers and his group at Merck. Coenzyme Q is an extremely interesting new type of tetrasubstituted benzoquinone. One substituent is a methyl group, two are methoxy groups and the fourth is a long unsaturated chain made of isoprenoid groups. The compound is of interest in the medical field as it in a way resembles vitamin K. The utility, however, given for coenzyme Q in the patent application, ascertainable by a look at the early issuing foreign cases, is use as a laboratory tool for assaying for the presence of or amount of succinic acid or the succinate radical. Obviously, this is not a commercial use but it is adequate to meet the utility requirement.

If the utility asserted in the application is medical, such as antitumor properties as in the above referred refile case, the therapeutic utility, including showings that the product is safe, effective and reliable for its intended purpose, must be thoroughly documented by clinical data, with medical publications by independent medical investigators being very helpful for this purpose. The reason for extensive showings here is that the Patent Office — and the Courts — recognize that some members of the public are likely to rely on the grant of a U. S. patent as certifying to the safeness, reliability and effectiveness of the patented medicine.

Summarizing — as for utility — the chemist can assist the lawyer by pointing up utility and, if no known utility exists, by forgetting about the subject matter patentwise until some utility has been demonstrated.

Unobviousness.—Even if novelty and utility are present, a patent still may not be obtained if the subject matter sought to be patented would have been obvious at the time the invention was made to a person having ordinary skill in the art. It would be well for the chemist-inventor to keep this in mind when reviewing prior publications, or what the lawyer calls, the prior art. I have seen manuscripts which review prior art publications 10-15 years old, and then state in substance that this art points to and obviously suggests the work reported in the manuscript. Assuming other investigators were not asleep at the switch, the gap of 10-15 years, or even 10 years or less, between the prior publications and the work reported in the manuscript clearly negatives obviousness, at least to a lawyer.

Summarizing, the chemist can assist the lawyer if he will point up why the subject matter sought to be patented is not obvious.

All of the above relates to factual data and the disclosure in the specification, and not the claims. Claim drafting in most instances involves technical problems with which the lawyer alone should be concerned.

My job personally has been made relatively easy by acquainting the people with whom I work with the basic requirements of novelty, utility and unobviousness noted above. In Professor Link's laboratory, for example, the graduate and post-graduate students prepare invention disclosures with detailed examples which can be dropped into the specification without change. This training should be of aid to lawyers when these students go out into industry. In the State of Michigan, Department of Health, the investigators work in the antibiotic field. After working out the form of what the Patent Office desired for a complete antibiotic specification, the invention disclosures now come to me in the form of the approved specification with complete data. This is of enormous help -- and also materially cuts down the bills.

Up to now we have been considering what the chemist should or should not do. I would like to close with a word about the lawyer who, like the chemist, has his place or position to play in the game requiring cooperation and teamwork.

The lawyer should not try to take over the chemist-inventor's job or the responsibilities of the Director of Research or attempt to run the company for management. Also, unless the lawyer can predict better than I have been able to do, the lawyer should not evaluate or especially run down the commercial aspects of the chemist's invention. This can destroy cooperation and any possible team play. I close with this illustration, where I batted zero.

When Karl Paul Link discovered warfarin, another 4-hydroxycoumarin anticoagulant, and with Ward Ross, managing director of WARF, went out to sell warfarin as a multi-dose rodenticide, I had my doubts. I was not alone—the Presidents of the two largest companies in this field went on record and said it would not work. Their doubts, like mine, were based on the critical multiple dose aspect. Let me illustrate this as follows. If a rat eats 10 mg. of warfarin at one time, there is no toxic effect. On the other hand, if a rat eats 1/10 as much—say 1-1.5 mg., over a 3-4 day period, for example, 1/3 mg. per day for 4-5 days—the rat will die. That Dr. Link was right, is clearly evidenced by the fact that WARF's licensees in the rodenticide field have paid the Foundation substantial royalties—running into the millions—and warfarin rapidly became and still is the leader in the rodenticide field throughout the world.

When Dr. Link then proposed that the sodium derivative, or salt, of the well established rat poison, warfarin, be used on humans, in the clinic, as the drug of choice for the prophylaxis of thrombo-embolic episodes—I really had my doubts. Here again I was not alone—the leading clinicians in Great Britain and some here—but not the American Heart Association—went on record, and said they would not prescribe rat poison to their patients. Once again, Dr. Link was right, and my doubts proved not to be well founded, as illustrated by the fact that the royalties paid to the Foundation for clinical warfarin sodium, are larger than those paid under the well established Dicumarol patent. Also, the warfarin sodium used in the clinic last year, 1959—if made into standard rat bait—would make 2,000,000 pounds of bait--and if this bait were eaten by rats--in the amount to kill--and no more (rats ordinarily consume an overdosage)—it would kill over 200,000,000 rats. That is a lot of dead rats, and yet there has been no report of the loss of any patient from the administration of warfarin sodium in the clinic.

Finally—as to the drug of choice—proposed by Dr. Link—if we assume that the President's physicians—President Eisenhower's doctors—after his coronary—would prescribe the best clinical anticoagulant available—then Dr. Link was right—warfarin sodium is the drug of choice.