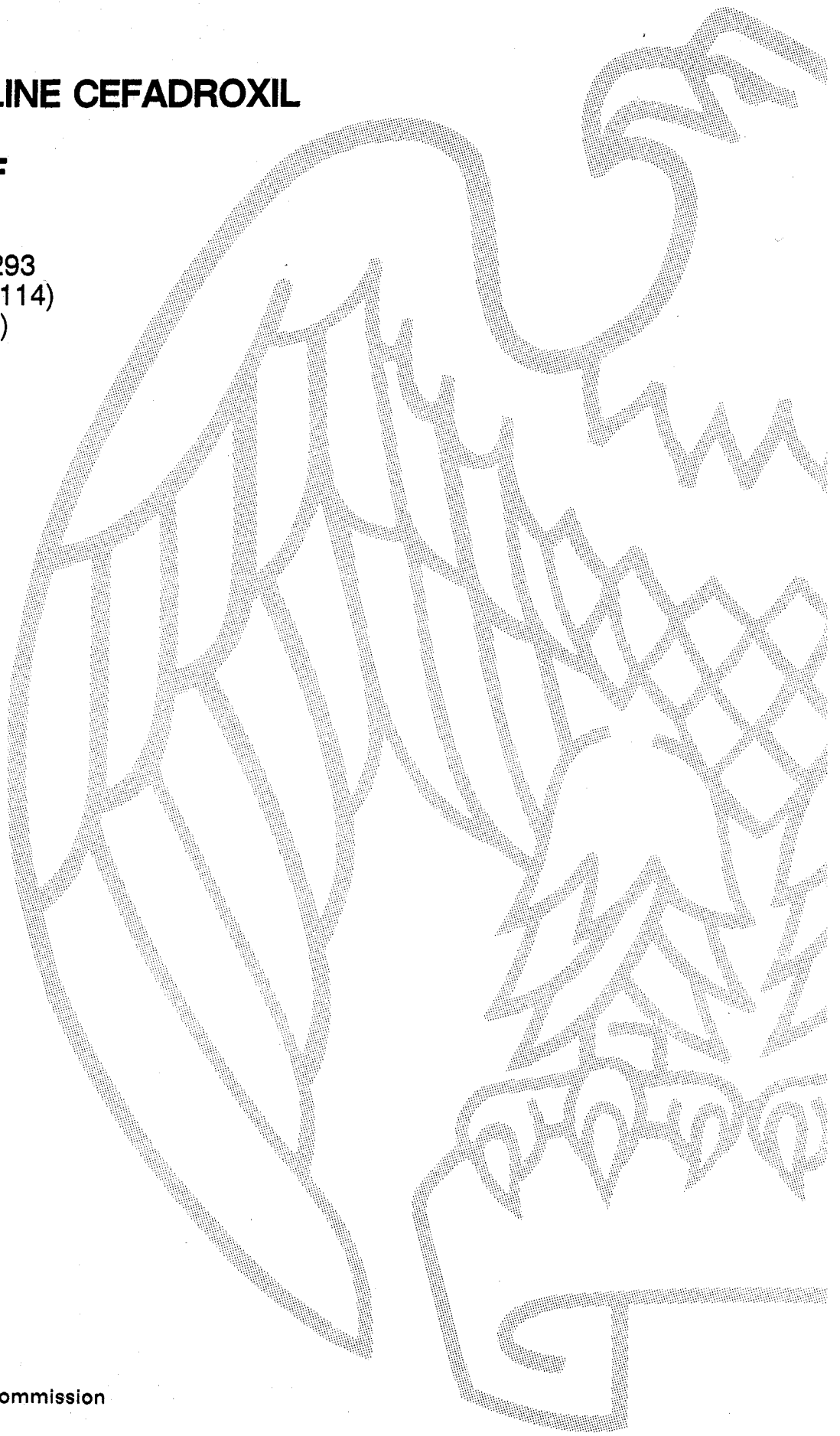
In the Matter of

CERTAIN CRYSTALLINE CEFADROXIL MONOHYDRATE TEMPORARY RELIEF PROCEEDING

Investigation No. 337-TA-293
(Decision: 54 Fed. Reg. 26114)
(June 21, 1989)



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United States International Trade Commission
Washington, DC 20436

UNITED STATES INTERNATIONAL TRADE COMMISSION

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UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, D.C. 20436

In the Matter of

CERTAIN CRYSTALLINE CEFADROXIL MONOHYDRATE
TEMPORARY RELIEF PROCEEDING

Inv. No. 337-TA-293

NOTICE OF COMMISSION DECISION TO VACATE A PART OF THE ADMINISTRATIVE LAW JUDGE'S INITIAL DETERMINATION ON TEMPORARY RELIEF

AGENCY: U.S. International Trade Commission

ACTION: Notice

SUMMARY: Notice is hereby given that the U.S. International Trade Commission has determined to vacate the part of the presiding administrative law judge's (ALJ's) initial determination (ID) on temporary relief that discusses the issue of complainant's bond. The Commission has neither modified nor vacated the remainder of the ID.

ADDRESS: Copies of the non-confidential version of the ID and all other non-confidential documents filed in connection with this investigation are available for inspection during official business hours (8:45 a.m. to 5:15 p.m.) in the Office of the Secretary, U.S. International Trade Commission, 500 E Street SW., Washington, DC 20436, telephone 202-252-1000.

FOR FURTHER INFORMATION CONTACT: Tim Yaworski, Esq., Office of the General Counsel, U.S. International Trade Commission, telephone 202-252-1096. Hearing-impaired individuals are advised that information on this matter can be obtained by contacting the Commission's TDD terminal on 202-252-1810.

SUPPLEMENTARY INFORMATION: On February 1, 1989, Bristol-Myers Company (Bristol) filed a complaint and a motion for temporary relief with the Commission alleging violations of section 337 of the Tariff Act of 1930 (19 U.S.C. § 1337) in the importation and sale of certain crystalline cefadroxil monohydrate (CCM), a prescription antibiotic medicine. Bristol alleged direct and induced infringement by respondents of Bristol's U.S. Letters Patent 4,504,657 (the '657 patent) which claims the product CCM.

Pursuant to Commission interim rule 210.24(e)(8)(53 Fed. Reg. 33061 (Aug. 29, 1988)), the Commission provisionally accepted

Bristol's motion for temporary relief at the Commission meeting on March 8, 1989. The Commission also instituted an investigation of Bristol's complaint. A notice of investigation was published in the Federal Register on March 15, 1989. 54 Fed. Reg. 10740. The notice named the following respondents: (1) Instituo Biochimico Italiano Industria Giovanni Lorenzini S.p.A. of Milan, Italy; (2) Kalipharma Inc. of Elizabeth, New Jersey; (3) Purepac, an unincorporated division of Kalipharma; (4) Biocraft Laboratories of Elmwood Park, New Jersey; (5) Institut Biochimique, S.A. of Massagno, Switzerland; (6) Gema S.A. of Barcelona, Spain.

The ALJ held an evidentiary hearing from April 24 through April 29, 1989. All respondents actively participated in the hearing. Although Commission interim rule 210.24(e)(18)(ii) (53 Fed. Reg. 49133) (Dec. 6, 1989)), invites parties to file written submissions on the issues of remedy, the public interest, and respondents' bond by the 60th day after institution, in this case by May 15, 1989, the Commission received no submissions on those issues from any party. 1/ The Commission expects that, in the future, the parties to investigations in which temporary relief is requested will file written sumissions in accordance with Commission interim rule 210.24(e)(18)(ii).

On May 24, 1989, the ALJ issued her ID denying Bristol's motion for temporary relief. On June 1, 1989, all of the parties filed written comments concerning the ID as provided for by interim rule 210.24(e)(17)(iii). Responses to the comments were filed on June 5, 1989. No government agency comments were filed.

This action is taken under authority of section 337 of the Tariff Act of 1930 (19 U.S.C. § 1337) and section 210.24(e)(17)(ii) of the Commission's interim rules (53 Fed. Reg. 49133) (Dec. 6, 1988).

By order of the Commission.

Kenneth R. Mason
Secretary

Issued: June 13, 1989

1/ Complainant Bristol included a section on respondents' bond in its comments concerning the ID which were filed on June 1, 1989. However, Bristol did not request leave for late filing of its comments on respondents' bond and so those comments were not properly before the Commission.

CERTIFICATE OF SERVICE

., Kenneth R. Mason, hereby certify that the attached NOTICE OF COMMISSION DECISION TO 'ACATE A PART OF THE ADMINISTRATIVE LAW JUDGE'S INITIAL DETERMINATION ON TEMPORARY .ELIEF was served upon the following parties via first class mail and air mail where .ecessary on June 14, 1989.

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[PUBLIC VERSION]

UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, D.C.

In the Matter of	)	
	)	Investigation No. 337-TA-293
CERTAIN CRYSTALLINE CEFADROXIL MONOHYDRATE	)	

INITIAL DETERMINATION ON MOTION FOR TEMPORARY RELIEF

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PROCEDURAL HISTORY

On February 1, 1989, Bristol-Myers Co. filed a complaint and a motion for temporary relief with the International Trade Commission alleging violations of Section 337 of the Tariff Act of 1930 as amended (19 U.S.C. § 1337) in connection with the importation of certain crystalline cefadroxil monohydrate. The complaint, as supplemented, alleged as unfair acts direct and induced infringement of U.S. Letters Patent 4,504,657.

On March 9, 1989, the Commission issued a notice of investigation that was published in the Federal Register on March 15, 1989. 54 Fed. Reg. 10740. The notice instituted an investigation to determine:

> whether there is a violation of subsection (a)(1)(B) of section 337 in the importation into the United States, the sale for importation, or the sale within the United States after importation by the owner, importer, or consignee, of certain crystalline cefadroxil monohydrate by reason of alleged direct or induced infringement of U.S. Letter Patent 4, 504,657, and whether there exists an industry in the United States as required by subsection (a)(2) of section 337.

Pursuant to Section 210.24(e)(8) of the Commission's rules, the motion for temporary relief was provisionally accepted and referred to an administrative law judge for an initial determination.

Complainant Bristol-Myers Company is a Delaware corporation with its offices at 345 Park Avenue, New York, New York 10154.

The respondents are:

1. Istituto Biochimico Italiano Industria Giovanni Lorenzini S.p.A, located at Via G. Lorenzini 2-4, 20139 Milano, Italy.

2. Kalipharma, Inc., a Delaware corporation, located at 200 Elmora Avenue, Elizabeth, New Jersey 07207.

3. Purepac Pharmaceutical Co., a division of Kalipharma, located at 200 Elmora Avenue, Elizabeth, New Jersey 07207. (This is an unincorporated division and need not have been made a separate respondent.)

4. Biocraft Laboratories, Inc., a Delaware corporation, located at 92 Route 46, Elmwood Park, New Jersey 07407.

5. Institut Biochimique, S.A., located at Via al Ponte 13, 6900 Massagno, Switzerland.

6. Gema S.A., located at Via Agusta 158, Planta 7, 08006 Barcelona, Spain.

The hearing on temporary relief commenced on April 24, 1989 and ended on April 29, 1989. All parties actively participated in the hearing.

After consideration of the testimony at the hearing, the evidence received into the record, and the briefs filed by the parties, the following findings and conclusions are made:

JURISDICTION

Finding No. 1:

The Commission has subject matter jurisdiction over this case and personal jurisdiction over all the respondents.

The Commission has jurisdiction over the subject matter of this case (which is set forth in the notice of investigation) under Section 337 of the Tariff Act as amended. The parties consented to the Commission's personal jurisdiction over them because all parties litigated the issues.

RES JUDICATA

Finding No. 2:

The issues in this case are not limited by res judicata, collateral estoppel or issue preclusion.

Under Rule 210.24(e)(15) of the Commission's Rules, an interlocutory appeal of Order No. 3 requested by respondent Kalipharma was denied. Order No. 3 denied Kalipharma's motion for summary determination, dismissal of the motion for temporary relief, and a stay of proceedings. Upon the filing of this initial determination, Kalipharma can appeal Order No. 3.

Among other things, that order stated that new evidence not before either the District Court for the Southern District of New York or the District Court for the District of New Jersey would be offered in the TEO hearing in this case. A substantial amount of new evidence has been received from all of the parties, and the evidentiary record of the TEO proceeding in this case is different from the record before either district court.

NO REASON TO BELIEVE THAT A VIOLATION OF SECTION 337 EXISTS

Finding No. 3

There is no reason to believe that a violation of Section 337 exists.

Section 337(e), 19 U.S.C. §1337(e), is a recent revision of an earlier provision relating to temporary relief. It provides that if the Commission, during the course of an investigation, determines that there is reason to believe that there is a violation of Section 337, it may direct that certain articles be excluded from entry into the United States, unless, after considering the public interest factors listed in 19 U.S.C. §1337(e)(1), it finds that such articles should not be excluded. Articles excluded by a Commission TEO order may be imported under bond determined by the Commission.

One difference between the old temporary relief proceeding and the new provision is that temporary relief proceedings are completed in even less time than they were before. In some cases this may present difficulties because the statute still requires that these proceedings be heard under the Administrative Procedure Act, and a fair hearing must be given. (A TEO hearing can be avoided if a motion for summary determination or a motion to dismiss is granted.) In this case, I believe that an opportunity for a fair hearing was made available to the parties, although the time for

presenting each party's case was limited and discovery had not been completed.

In a temporary relief proceeding, the Commission traditionally has looked first to the issue of whether there is reason to believe that there is a violation of Section 337. To make this threshold determination in a patent infringement case, the issues relating to patent validity, infringement, enforceability and domestic industry must be considered, although complainant's burden of proof in a TEO proceeding is lower than in a hearing for permanent relief. Then if it is determined that there is reason to believe that a violation of Section 337 exists, four equitable factors must be considered by the Commission before it decides whether to grant temporary relief. The four factors are (1) the likelihood of success on the merits, (2) the amount of injury that would be caused to complainant if temporary relief were not given, (3) the amount of injury that would be caused to respondents if temporary relief were given, and (4) the effect of temporary relief on the public health and welfare. The practice of balancing these four factors was derived from federal district court practice in cases involving the issuance of a temporary restraining order or a preliminary injunction.

Subsection (e)(3) of §337, added by the 1988 amendments, states that "The Commission may grant preliminary relief under this subsection or subsection (f) to the same extent as preliminary injunctions and temporary restraining orders may be granted under the Federal Rules of Civil Procedure." The legislative history indicates that this provision was intended to codify existing Commission practice in this regard. S. Rep.

No. 71, 100th Cong., 1st Sess. 131 (1987); H.R. Rep. No. 40, 100th Cong., 1st Sess. 159 (1987).

The requirement that a threshold determination be made that there is reason to believe that a violation exists is unique to the Commission. In effect, the standard for determining that there is reason to believe that a violation exists has been the same as the standard for determining whether there is a likelihood of success on the merits. If the complainant has a low likelihood of success on the merits, there will be no reason to believe there is a violation of §337. If there is no reason to believe there is a violation, then the balancing of the four factors is not reached, because the threshold test has not been met.

In contrast to this, in district court practice there is no threshold step to take before balancing the four factors. In district court, a finding that the complainant's likelihood of success on the merits is low could be counterbalanced and outweighed by findings that there is a high level of irreparable harm to complainant, and a low level of harm to respondents, and that public interest factors favor an injunction.

At the Commission, balancing the factors may never be reached if the threshold finding that there is reason to believe that a violation exists is not met.

The result is that the Commission can grant relief under similar standards as those applied by a district court (even though the remedies may differ), but it can deny relief more easily than would a district court. At the Commission, no amount of harm to complainant can compensate for an adverse finding on the reason to believe issue.

In the present case, complainant has not established a reason to believe there is a violation of §337. Respondents have proved that the presumption of patent validity ultimately is likely to be overcome by clear and convincing evidence. In this case, even if the "reason to believe" threshold were ignored and the case decided as it would have been in district court, the result would be adverse to complainant. When the factors of harm to complainant, harm to respondents, and public interest are balanced with the low likelihood of success on the merits, complainant is not entitled to preliminary relief.

Finding No. 4

There is reason to believe that the patent in issue would be infringed, if it were proved to be valid.

Respondents Biocraft and Gema admitted infringement. (Conference Tr. 84.) The Kalipharma respondents contested infringement, but their own witness testified that their product infringes. (Tr. 917.)

Finding No. 5

There is reason to believe that a domestic industry exists.

Respondents do not contend that Bristol-Myers does not have a domestic industry engaged in the manufacture and sale in the United States of cefadroxil monohydrate that falls within claim 1 of the '657 patent.

Bristol has made a significant investment in plants and equipment necessary to manufacture crystalline cefadroxil monohydrate. Bristol imports the bulk form of this product from its subsidiary in Italy, and packages it in dosage amounts in Puerto Rico. (Tr. 109.) The plant in Puerto Rico processes the product and performs quality control tests. The plant and equipment in Puerto Rico is valued at about $20 million. Bristol

employs about 375 workers in the Puerto Rico plant, and has sent more than 1,000 trained and educated medical representatives to visit doctors and physicians to explain the use and safety characteristics of crystalline cefadroxil monohydrate. (Tr. 109-110.) In addition, Bristol has a substantial investment in engineering and research related to crystalline cefadroxil monohydrate. (Tr. 51, 105.) Research and development for crystalline cefadroxil monohydrate is done only in the United States. (Tr. 108.)

Finding No. 6

There is a statutory presumption that the '657 patent is valid. Based solely on the evidentiary record in the TEO proceeding, respondents have overcome this presumption and have shown by clear and convincing evidence that the '657 patent is invalid.

The TEO record as a whole indicates that respondents are likely to prevail in demonstrating the invalidity of the patent, for the reasons stated below under "COMPLAINANT'S LIKELIHOOD OF SUCCESS ON THE MERITS." If complainant offers new evidence at the final hearing it may prevail on this issue.

BALANCING THE FOUR FACTORS

If there were reason to believe that a violation of Section 337 existed, complainant would not be entitled to temporary relief after balancing the following four factors: (1) complainant's likelihood of success on the merits, (2) immediate and substantial harm to the domestic industry, (3) harm to the respondents, and (4) the public interest.

1. COMPLAINANT'S LIKELIHOOD OF SUCCESS ON THE MERITS

Finding No. 7

> **Based solely on the evidence in the TEO record, complainant has not shown that there is a likelihood that it would succeed on the merits.**

Considering only the evidence in the TEO record, it is likely that respondents ultimately will succeed in overcoming the presumption that the '657 patent is valid by proving by clear and convincing evidence that the patent is invalid under Section 103 of the Patent Act.

If the patent were found to be valid, it is likely that complainant would succeed in proving that it was infringed. If the patent were found to be valid and infringed, it is likely that the patent would be found to be enforceable.

Finding No. 8

> **It is likely that respondents will not succeed in proving that the '657 patent is invalid under Section 102(b).**

Under Section 102(b) of the Patent Act, a person shall not be entitled to a patent if the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country more than one year prior to the date of the application for patent in the United States.

All of the respondents contend that under Section 102(b), the Garbrecht patent fully anticipates the '657 patent. (This contention is not made with respect to the Crast '741 patent.) It is not likely that respondents ultimately will succeed in showing that the '657 patent is invalid under Section 102(b).

For a patent claim to be anticipated under Section 102(b), every element of the claim must be found in a single prior art reference. The prior art reference need not teach what the anticipated patent teaches. Kalman v. Kimberly-Clark Corp., 713 F.2d 760, 772 (Fed. Cir. 1983), cert. denied, 465 U.S. 1026 (1984.) Each and every element of the claim must be described in a single prior art reference either literally or inherently. Kloster Speedsteel AB v. Crucible Inc., 793 F.2d 1565, 1571 (Fed. Cir. 1986.)

The only claim of the '657 patent is a form of crystallized cefadroxil monohydrate that has a particular X-ray diffraction profile. This is neither literally described nor claimed in the Garbrecht patent. The product claimed in the '657 patent is not inherently described in the Garbrecht patent by reading Example 7 or by reading Example 7 in the context of Garbrecht as a whole. This is illustrated by the fact that Dr. Micetich followed the procedure suggested in Garbrecht with certain modifications within the ordinary skill in the art in late 1976 and he produced a crystalline cefadroxil product, but it was not the new monohydrate claimed in the '657 patent. (See Tr. 1167, 1168, 818, 1048.)

Respondents then argue that even if the product of the '657 patent is not inherently produced by using the Garbrecht patent process, it can be produced by one who makes certain modifications in the process of the Garbrecht patent and these modifications are within the skills of one with ordinary skill in the art in late 1976. But one type of monohydrate is made when one set of modifications to the Garbrecht processes is made, and a different type of monohydrate is made when a different set of modifications is made. The single product claimed in the '657 patent

therefore is not described or disclosed in the prior art Garbrecht patent, nor is one told step by step how to make it.

Whether the cefadroxil monohydrate that was covered by claim 1 of the '657 patent could have been made by one with ordinary skill in the art who made certain modifications to processes disclosed in Garbrecht is an argument will be considered under Section 103.

It is found that the Garbrecht patent does not describe (literally or inherently) every element of the product claimed in the '657 patent, and that respondents have failed to overcome the presumption of validity of the '657 patent under Section 102(b).

Finding No. 9

It is likely that respondents will succeed in proving that the '657 patent is invalid under Section 103.

Finding No. 10

Based solely on the evidence in the record of the TEO hearing, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Finding No. 11

Based solely on the evidence in the record of the TEO hearing, claim 1 of the '657 patent would have been obvious under Section 103 of the Patent Act.

Section 103 of the Patent Act, 35 U.S.C. Section 103, reads in part as follows:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in Section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

In Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 U.S.P.Q. 459, 467 (1966), the Supreme Court required that certain factual inquiries be made before a determination of obviousness is made:

> Under Section 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

The relevant prior art includes all of the references cited in the '657 patent by the patent examiner. U.S. Patent 3,781,282 to Garbrecht (Biocraft/Gema Ex. 13), U.S. Patent 3,985,741 to Crast (Biocraft/Gema Ex. 10), U.S. Patent 4,091,215 to Bouzard, and U.S. Patent 4,160,863 to Bouzard are among the prior art references mentioned in the patent.

The prior art also includes Bristol's Crast '752 patent, which was issued in 1970 and now has expired after 17 years, covering cefadroxil in any form. The '657 patent in issue here claims only one crystalline form of cefadroxil that has a particular X-ray diffraction profile.

The principal prior art references relied upon by respondents are the Garbrecht '282 patent and the Crast '741 patent.

A. The Garbrecht patent

The Garbrecht patent discloses a process for making purified cephalosporins. (Biocraft/Gema Ex. 13.) Cefadroxil is a cephalosporin. (Tr. 211-217.)

One of the differences between the Garbrecht patent and the '657 patent is that the Garbrecht patent discloses a way to make purified cephalosporins, including crystallized cephalosporins, but it does not claim a particular crystalline form that is identified by a specific X-ray diffraction profile.

Example 7 of the Garbrecht patent describes (among other things) a process by which a cefadroxil monohydrate crystal can be recovered from a cephalosporin DMF solvate. In Example 7, an intermediate product is produced from a cephalosporin and dimethylformamide (DMF). (Biocraft/Gema Ex. 13; Tr. 663-664.) After this intermediate product is formed, Example 7 teaches that it can be "treated as in Example 1" until the compound precipitates as its DMF complex. Example 7 then teaches that the complex should be treated as in Example 5 to form a certain chemical. According to the testimony, this means to a chemist that if one treats the solvate with acidified water and heat, and follows certain instructions, a cefadroxil monohydrate can be crystallized out of the solvate. (See Tr. 227-228, 546-551.)

The '657 patent originally was rejected by the patent examiner as obvious under Section 103 of the Patent Act in the light of the Garbrecht patent. (Bristol-Myers Ex. 45 at 93-97.) After this rejection, Bristol drafted a protocol in September 1983 (which it later discussed with the patent examiner on October 4, 1983) in which Bristol discussed possible experiments that could be made to determine whether someone with ordinary skill in the art in April 1976 could have made the new cefadroxil monohydrate claimed by Bristol by following the teachings of Garbrecht and

making modifications that would have been obvious to one with ordinary skill in the art as of April 1976.

The proposed protocol prepared by Bristol's scientists and lawyers in September 1983 included one experiment (the third experiment) that would add more hydrochloric acid to the initial mixture of Garbrecht Example 1 to provide a pH in the range of 1.0-1.5 for several hours. (Biocraft/Gema Ex. 73 at 7.) It is not clear from the record whether Bristol or the patent examiner intended that this third experiment be made, but it was discussed with the patent examiner. At the time that the protocol was discussed, the patent examiner had rejected the Bouzard claim over the Garbrecht patent. Bristol was trying to persuade him that someone with ordinary skill in the art in 1976 could not have made the product of the '657 patent claim by using the teaching of Garbrecht. A significant issue before the patent examiner and Bristol was what modifications in the Garbrecht process would have been made by someone with ordinary skill in the art. (Bristol-Myers Ex. 152 at 117.) I do not think that the patent examiner intentionally would have left this issue to be decided by Bristol alone, but his comments in the file history on the tests to be made do not make it clear that the third test (adding more hydrochloric acid) would have to be made. The patent examiner stated:

> **"In addition, if Zn/HCl is known to be able to remove t-BOC, then choice C is also a reasonable option." (Bristol Ex. 45 at 117.)**

The words of the patent examiner were ambiguous. He had just discussed with Bristol this test in which additional hydrochloric acid would be added in Garbrecht Example 7. Bristol knew that additional hydrochloric acid was known to be able to remove t-BOC. (See Tr. 301, 383-

385). Was Bristol arguing that ordinary skill in the art in 1983 had drastically improved since April 1976, the claimed date of the invention, or that Bristol scientists had more than ordinary skill in the art, and others would not have known that a protecting group might be removed by hydrochloric acid? Whatever Bristol argued, Bristol scientists knew enough in 1983 to suggest the use of hydrochloric acid to test the Garbrecht patent. (Biocraft/Gema Exs. 72 and 73.)

After the first two experiments described in the protocol were carried out by Professor Micetich under the instructions of Bristol, Bristol reported the results of the tests back to the patent examiner, and he never asked that the third test be done. It is not clear why. Perhaps if he had been told that Professor Micetich's earlier tests had accomplished a partial cleavage of the second protecting group, the patent examiner would have insisted on the third test being made.

With respect to the Garbrecht patent, the issue under Section 103 is whether one with ordinary skill in the art in April of 1976 could have produced the cefadroxil monohydrate of the '657 patent (the "new cefadroxil monohydrate" or the "Bouzard monohydrate") by following the teachings of the Garbrecht patent as a whole, and modifying Example 7 of Garbrecht only to the extent that those modifications would have been within the skill of one with ordinary skill in the art at that time.

It is found that based solely on the evidence in the TEO hearing, there are no differences between the teachings of the Garbrecht patent and the '657 patent that would have prevented one with ordinary skill in the art in 1976 from making the product of the '657 patent by using the teachings of the Garbrecht patent with minor modifications that were within

the skills of one with ordinary skill in the art on the date on which complainant relies to show the date of the invention of the '657 patent, April 27, 1976. April 27 was the foreign priority date for British Patent Application No. 17028/76. (Bristol-Myers Ex. 20, see certificate of correction.) An applicant may rely upon a foreign priority date as a constructive reduction to practice to avoid a potential prior art reference. 35 U.S.C. Section 119. For the purposes of Section 103 of the Patent Act, ordinary skill in the art as used herein will refer to ordinary skill in the art as of April 27, 1976.

During the prosecution of the '657 Bouzard patent, Bristol stated:

> "Old cefadroxil monohydrate and cefadroxil trihydrate of the Weber and Berman declarations are, nevertheless, believed to be representative of the prior art since their production represented contemporaneous best efforts of chemists and pharmacists skilled in cephalosporin and penicillin chemistry to produce a pharmaceutically acceptable form for commercial use.

(Biocraft/Gema Ex. 8, page 4, lines 19-24.)

Whether work done at Bristol that was not made public should be considered to be part of the prior art if the applicant stated that it was "representative of the prior art" is not decided here. The statement made by Bristol to the PTO, however, admits that chemists and pharmacists at the time of the invention were making efforts to produce a pharmaceutically acceptable form of cefadroxil for commercial use, and old cefadroxil monohydrate was believed to be representative of these efforts. There was an incentive for one with ordinary skill in the art in 1976 to find a commercially acceptable form of cefadroxil at the time of the invention of the '657 patent.

The product claimed in the '657 patent is a specific form of crystalline cefadroxil monohydrate, an orally administered cephalosporin antibiotic sold by Bristol under the brand names DURICEF and ULTRACEF. (Staff Ex. 3 at 16.) The pertinent art (for the purposes of defining ordinary skill in the art) will be considered to be chemistry, with a specialty in the field of cephalosporins.

Many chemists working in the field of cephalosporins in April 1976 were highly skilled and had a Ph.D. degree in chemistry and a year or so of experience in the field of cephalosporins. It is found that the hypothetical person with ordinary skill in the art at that time would have been a skilled and experienced chemist. He would have had at least an undergraduate degree in chemistry and from six months to three years of experience in the field of cephalosporins. (See Tr. 992-95, 1037-1038.)

What would one with ordinary skill in the art at that time have known?

1. He would have had enough hands-on experience with cephalosporins to understand the conditions under which they would be stable. (Tr. 992.) One who understood the conditions under which cephalosporins would be stable would have been aware that the beta-lactam ring might be destroyed by certain amounts of hydrochloric acid, but he would not have known how much hydrochloric acid would be needed to destroy the beta-lactam ring. (See below.) The beta-lactam ring should not be broken because it is the means by which cephalosporins kill bacteria. (The cephalosporins kill bacteria because the beta-lactam ring is mistaken by the cell wall of the bacterium as one of its components. The substitution of the ring into the cell wall of the bacterium causes a malformation of the bacterium and destroys it.) (Tr. 247-50.)

2. One with ordinary skill in the art in April 1976 would have known from the description of the starting material in Garbrecht Example 7 that the protected cefadroxil had two protecting groups, para-nitrobenzyl and the t-BOC group. Example 1 in the Garbrecht patent would have taught him that one of these protecting groups (para-nitrobenzyl) can be removed by the use of hydrochloric acid and zinc. (Biocraft/Gema Ex. 13, col. 7, line 74-col. 8, line 4.) He would have known that hydrochloric acid alone would be enough to remove the other protecting group (the t-BOC group). (Tr. 811, 1185.) He would have known that if enough hydrochloric acid remained after the zinc had reacted with it and absorbed as much as it could, both protecting groups would be stripped away. (Tr. 798-99, 811, 1190.)

If this were not known to one with ordinary skill in the art at that time, the Garbrecht patent itself at Col. 6, lines 40-42 teaches that enough hydrochloric acid would remove both protecting groups:

> Any non-oxidizing acid can be used to provide the acid medium but hydrochloric acid is preferred. Such acid treatment also removes certain amino nitrogen protecting groups if such groups were not removed earlier in the process.

3. One with ordinary skill in the art in 1976 would have known that the two protecting groups in Garbrecht Example 7 were amino nitrogen protecting groups. If he read the Garbrecht patent he would have learned from Example 1 that he could use the treatment described in Example 1 to remove one protecting group, and that the resulting DMF solvate could be processed as described in Example 5 to make cefadroxil monohydrate.

4. It would have been clear to someone with ordinary skill in the art reading Example 7 of Garbrecht that the starting material in Example 7

has two protecting groups, and that the material in Example 1 has only one protecting group.

5. A critical fact that would have been recognized by one with ordinary skill in the art would be that Example 1 does not suggest the use of enough hydrochloric acid to remove both protecting groups in Example 7. (Tr. 811 and 1176.)

6. The question then is whether one with ordinary skill in the art would have known that he should try to add more hydrochloric acid to remove both protecting groups. Bristol argues that he would not have tried this because he would have known that hydrochloric acid could destroy the beta-lactam ring. One with ordinary skill in the art in 1976 would have known this, (Tr. 1160, 1167), but he would not have known how much hydrochloric acid was needed to destroy the beta-lactam ring. As a skilled chemist, he would have had enough experience and skill to know how to determine this by experimentation. A large number of experiments would not have been required to determine whether enough hydrochloric acid could be used to remove a protecting group without destroying the beta-lactam ring. (See Tr. 383-385.)

The Garbrecht patent itself suggests that one could add more hydrochloric acid than is taught in Example 1 without destroying the beta-lactam ring. Garbrecht teaches using acid at a pH of 1-2 on the solvate form of cephalexin and heating it to 40° to 70° C. (Biocraft/Gema Ex. 13, Col. 7, lines 28-48.)

To show that the modifications in the Garbrecht process that resulted in the new monohydrate were not obvious modifications, Bristol relies upon the efforts of Dr. Micetich to make the new monohydrate using Garbrecht and

[confidential information deleted]

Both of these efforts were unsuccessful.

Dr. Micetich had no compelling economic motive to be successful in making the new monohydrate using Garbrecht. He was working for Bristol, and Bristol wanted the new patent to issue. Nevertheless, there is absolutely nothing in the record to suggest that Dr. Micetich made less than his best efforts in doing the work he was instructed to do. The question with respect to Dr. Micetich is not whether he did what he was asked to do, but what did Bristol ask him to do. Apparently no one at Bristol-Myers suggested to Dr. Micetich that he use more hydrochloric acid, and he was not told that this procedure had been discussed with the patent examiner. Bristol had no incentive to encourage Dr. Micetich to try adding more hydrochloric acid, and the record shows that he did not do so. A second issue was raised as to whether Dr. Micetich added too much water to the solution, resulting in a weaker solution of hydrochloride. This does not matter much because apparently Example 7 would not have produced the new monohydrate unless he had added additional hydrochloride to the amount suggested in Example 1. Others who followed Example 7 literally were unable to produce the new monohydrate.

[confidential information deleted]

[confidential information deleted]

As for his experiment relating to Garbrecht Example 7, perhaps he simply gave up too soon, because of his prior experience. Professor Dunitz testified that success or failure could have depended on the amount of persistence of the person making the experiment. (Tr. 619-620.) Although undue experimentation should not be required of the person reading a patent to enable him to practice the patent, in the field of chemistry a certain amount of experimentation must be expected of the chemist reading the patent. The very process of repeating a chemical experiment that is described only in a cursory manner in a patent involves a certain amount of

guessing as to quantities and procedures to be followed. There is an assumption made by the writer that the reader is a chemist and knows what he is doing, so that every step need not be spelled out in detail. (See Tr. 1033-1034.)

[confidential information deleted]

But the weight of the evidence, at least in this TEO proceeding, is that one who was asked to reproduce Garbrecht Example 7 and who had ordinary skill in the art in 1976 would have tried to use more hydrochloric acid than that suggested in Example 1 to see if he could get rid of both blocking groups in Example 7 without destroying the beta-lactam ring.

Respondents offered compelling evidence that someone with ordinary skill in the art in 1976 would have been likely to have tried to use more hydrochloric acid if he wanted to remove both protecting groups, as suggested in Garbrecht itself, and he would have determined experimentally at what point there would be too much hydrochloric acid and the beta-lactam ring would be destroyed.

Dr. Bouzard, one of the named inventors in the '657 patent, before the invention of the '657 patent, added even more hydrochloric acid to cefadroxil solvate than would be necessary to remove both protecting groups in Example 7 of the Garbrecht patent. He added 6.45 liters of 12N HCl in 110 liters of distilled water. This resulted in a pH of .2, but Dr. Bouzard reported that the beta-lactam ring was still intact. His treatment produced the trihydrate molecule of cefadroxil. (Tr. 301-305, 383-385; Bristol-Myers Ex. 41.)

There is no evidence that Dr. Bouzard's work was made public. The published prior art, however, did teach the use of HCl to remove amino protecting groups. (Tr. 571-573; Biocraft/Gema Exs. 146 and 161.)

One with ordinary skill in the art in 1976 would have known that he should try to add more acid when reproducing Garbrecht Example 7, to see if he could add enough hydrochloric acid to destroy both protecting groups without destroying the beta-lactam ring. This is what a number of scientists did try when they were asked to repeat Garbrecht Exhibit 7.

Two scientists ([c] and Micetich) trying to repeat Garbrecht Exhibit 7 did not try this. This does not mean that they did not have ordinary skill in the art. They may have had more than ordinary skill in the art, but they did not try to do what the others tried to do in their first or second efforts to make Garbrecht Exhibit 7. It is not necessary to prove that every competent chemist acts in the same way when making an experiment to prove that a certain practice would be within the skills of a hypothetical person with ordinary skill in the art.

Dr. Farina recently tried to reproduce Garbrecht Example 7, making minor modifications. He produced the new cefadroxil monohydrate of the '657 patent. Dr. Cainelli repeated the experiment with the same results. (Tr. 919, 958, Kalipharma Ex. 1-Y; Kalipharma Ex. 58.)

The modifications made by Dr. Farina were within the skills of one with ordinary skill in the art in 1976. The most significant modification made by Dr. Farina was the addition of more hydrochloric acid to remove the second protecting group. This was suggested in Garbrecht itself. This procedure had been taught in universities teaching basic chemistry courses well before 1976. (Tr. 902-903.) Bristol suggests that Dr. Farina's

solution to the problem of reproducing Garbrecht Example 7 was too easy to be believed, especially in view of the fact that many Bristol scientists had been trying to get a better cefadroxil monohydrate for years without success, and the '657 patent invention was the result of an accident. So far, however, Bristol has not been able to prove that Dr. Farina lacked credibility, although Bristol raised a question about the accuracy of his testimony describing the product of his company. Dr. Farina has not yet had an opportunity to explain the discrepancy between his testimony and the analysis that has been made by Bristol of his company's product.

The record in this TEO proceeding does not prove whether the cefadroxil beta-lactam ring is more likely to be destroyed after it is stripped of protection, as it is in Garbrecht Example 1, than it would be in the solvate stage of Example 5. Respondents did prove that it would not have been unusual in 1976 to have experimented with greater and lesser amounts of hydrochloric acid to determine what would happen to the beta-lactam ring. One with ordinary skill in the art would have known that the cefadroxil molecule would become unstable at some point as more hydrochloric acid was used, but he would not have known at what precise point that would be, without some minor experimentation. (See Tr. 861-862, Tr. 1166.)

It is found that one with ordinary skill in the art who was trying to produce a crystallized cefadroxil monohydrate using Example 7 of the Garbrecht patent could have made the product of claim 1 of the '657 patent by making adjustments to the procedures taught in Garbrecht, adjustments that would have been within the skill of someone with ordinary skill in the art in 1976.

B. The Crast patent

The Crast patent, U.S. Patent No. 3,985,741 issued on Oct. 12, 1976, but earlier was "published under the second Trial Voluntary Protest Program on February 10, 1976." (Item 44 of the cover page, Biocraft/Gema Ex. 10.) The patent was assigned to Bristol-Myers. It described improved purification processes for certain types of products. The purpose was to obtain higher yields for commercial production and to reduce the cost of production. (Id., Col 2, lines 29-41.)

The Crast patent claims a certain process and it claims a specific solvate. Unlike the '657 patent, it does not claim a specific crystalline product that is identified by its X-ray profile.

There are no differences between the Crast patent and the '657 patent that would have prevented one with ordinary skill in the art in 1976 from making the product of the '657 patent using what was taught in the Crast patent and ordinary skill in the art. One with ordinary skill in the art is deemed to be aware of all prior U.S. patents.

One with ordinary skill in the art in 1976 who used what is taught in Example 6 of the Crast patent could have made the new monohydrate of claim 1 of the '657 patent by making only minor adjustments to the procedure, adjustments that would have been well within his skill.

Professor Just was asked by Biocraft to prepare a substantially pure crystalline cefadroxil as disclosed in the Crast '741 patent. He used the process described in Example 6 of Crast, with one modification that would have been known to a person of ordinary skill in the art in 1976, and he produced the new monohydrate. (Prehearing Conf. Tr. 38-39.) He received no special instructions other than to follow the process described in

Example 6 as closely as possible. (Tr. 411.) He was to make only those changes that he deemed appropriate to purify the product. (Tr. 402.) The only suggestion that he received was to perform the process on a larger scale. (Tr. 390.) Cefadroxil had not been produced previously in his laboratory. (Tr. 389.)

In his first attempt, Professor Just failed to make the new monohydrate. He heated the crude cefadroxil to 100° C. to dissolve it. He found that, in his experiment at least, the crude material did not dissolve in DMF. The Crast patent described the crude cefadroxil as dissolving in DMF, and the DMF solvate crystallizing out. Professor Just was not aware that at 100°, the crude cefadroxil would decompose. (Tr. 993-94.)

His next experiment was successful. Instead of mixing everything together at once as described in Example 6, he purified the DMF solvate by first treating it with water and then with methanol to make the 90% mixture of Crast Example 6. He used water because he had found in prior experiments that the solvate was soluble in water. (Tr. 425.) He testified that when he used solvents to crystallize a product he always tried to find a solvent in which the product readily dissolved and then he would dissolve it in this solvent before he added a solvent in which the product was less soluble. (Tr. 395-98.) He testified that this was standard practice (Tr. 415) and that he had been teaching it to his students since 1958. (Tr. 398-99.)

Professor Wolfe confirmed that this was a common practice; he had learned this crystallization technique in 1952 when he took his first laboratory course in organic chemistry. (Tr. 984-85.) Both Professor Wolfe and Professor Dunitz thought that it was reasonable to dissolve the

DMF solvate in water before adding the methanol solvate, and that it would have been the first thing they would have thought of doing. (Tr. 627-30.) Professor Baldwin, testifying for Bristol, stated that it was conventional to use co-solvents simultaneously or in sequence to precipitate products. (Tr. 246-47.) In at least three of the experiments upon which Crast Example 6 is based, Gottstein had dissolved the DMF solvate in water before crystallization. (Biocraft/Gema Ex. 78 at 67-69, Biocraft/Gema Ex. 68 at 4-8.) Bouzard testified that he used a number of techniques to crystallize cefadroxil from the DMF solvate, including adding water first and then the other solvents. (Tr. 321-24.)

For complainant, Dr. Baldwin pointed out that Crast Example 6 disclosed a slurry rather than a solution, and he saw no need to try to dissolve the solvate at all when reproducing Crast Example 6. But Professor Just had tried that way first, and it had not worked for him. Nothing precipitated out of the slurry. It was reasonable for Professor Just to try something else when literally following what is taught in the example does not work. As pointed out above, there was a substantial amount of testimony that chemists expect to try out a number of variations in the procedures they use when at first they are not successful, and that chemists do not expect a patent to describe every step in detail. It is assumed that the chemist knows what he is doing, and success or failure in getting a patent example to work may depend on how long and how hard you try to make it work. The patent law requires that a patent specification describe the invention in sufficient detail to enable one skilled in the pertinent art to make and use the invention (35 U.S.C. §112), but there is no requirement that the way to use the invention be spelled out in such

detail that someone without any skill in the art can practice it. There will be variations in how this rule is applied depending on the subject matter of the patent, but chemistry surely is an area in which chemists expect to have to do some experimentation in reproducing in their own laboratories an example that has been described briefly by someone else.

It is found that it would have been within the ordinary skill in the art to try adding the water first and then the methanol, especially when one had followed Crast Example 6 literally, and had found that literally following Crast Example 6 did not precipitate out a product. Professor Baldwin confirmed that Professor Just's crystallization technique was within the ordinary skill in the art. (Tr. 1141-1143.)

Dr. Ludescher later repeated Professor Just's experiment using Example 6 of the Crast patent and the slight modifications made by Professor Just. Ludescher's experiment confirmed the results of Professor Just's experiment in producing the new monohydrate. (Tr. 544.)

[c] carried out the Crast Example 6(B) procedure as written and did not produce the new monohydrate. (Biocraft/Gema Ex. 170 at 60-61.) There is no evidence that repeating Crast Example 6(B) without modifying the slurrying step will result in the new monohydrate.

It is found that respondents are likely to show that it would have been obvious for one of ordinary skill in the art in 1976 to make the crystalline cefadroxil monohydrate claimed in the '657 patent by practicing (with obvious modifications) Example 6 of the Crast patent.

C. Secondary considerations

There are secondary considerations that support respondents' side:

1. If the product of the '657 patent can be produced by one with ordinary skill in the art by using the Garbrecht or Crast teachings, then no superior properties can be claimed for the '657 patent product without begging the question of whether the same product could have been produced by the prior art.

2. Complainant has not licensed the '657 patent to anyone else, so this cannot be a secondary consideration.

3. Two lawsuits have challenged the validity of the patent. This does not suggest that the industry had great respect for the '657 patent.

There are secondary considerations supporting patent validity:

1.

[confidential information deleted]

2. Before Weber obtained the new monohydrate from the trihydrate, resulting in the '657 patent, there was a need for and motivation to prepare various commercial forms of cefadroxil, including crystalline cefadroxil monohydrate. (Tr. 308-320; Biocraft/Gema Ex. 157.) Yet a number of experienced cephalosporin chemists did not obtain the new monohydrate. Mr. Crast, the inventor of cefadroxil, did not obtain the new monohydrate. Mr. Gottstein, an experienced Bristol cephalosporin chemist, made a cefadroxil hydrate, but not the new monohydrate. Eli Lilly, which owned the Garbrecht patent, did not make the new monohydrate. (Tr. 1154-

1155.) The inventors named in the '657 patent had been working for about two years with cefadroxil before Dr. Weber accidentally obtained the trihydrate that led to the new monohydrate.

[confidential information deleted]

3. The new monohydrate has had commercial success. It can be given in doses that last longer than the old monohydrate. (Bristol-Myers Ex. 59.) Respondents have chosen to sell the new monohydrate although they are capable of making the old monohydrate that would not be covered by the '657 patent.

On balance, the secondary considerations supporting patent validity more than offset the lawsuits that have been filed to challenge the validity of the patent. The lawsuits are to be expected in connection with a patent that has this much commercial value. The secondary considerations supporting patent validity are not strong enough to overcome the strong evidence offered by the respondents in the TEO proceeding to prove that one with ordinary skill in the art at the time that the invention was made, who was trying to make a crystallized cefadroxil monohydrate by following the teachings of Garbrecht or Crast, probably would have made such a crystallized cefadroxil monohydrate on his second or third try, at least, making only minor modifications in procedure and doing nothing unexpected or unusual. The monohydrate that he would have produced would have been the new monohydrate.

While it is true that other skilled cephalosporin chemists did not do this, there was no evidence that they were trying to make Garbrecht Example

7 or Crast Example 6 work. [c] and Dr. Micetich are the exceptions. Dr. Micetich tried to reproduce Garbrecht Example 7, but his instructions from Bristol limited his experimentation.

[confidential information deleted]

Garbrecht itself, however, suggests that more hydrochloric acid could have been used without destroying the beta-lactam ring.

[confidential information deleted]

D. Seeding

Finding No. 12

Without further proof, there is little or no evidence in the TEO hearing that complainant is likely to succeed in proving that its theory of local-universal seeding is the correct explanation for the results of the recent tests that have been made to determine whether one with ordinary skill in the art, using the teaching of the prior art, would have been able to make the product claimed in claim 1 of the '657 patent in 1976.

Seeding occurs when a small number of crystals provides a substrate for further crystallization in that particular form. (Tr. 262.) It may be intentional (for example when a chemist deliberately adds crystals to a supersaturated solution so that it will crystallize in that form), or it may be unintentional, when crystals in the environment act as a contaminant, inducing crystallization in an unexpected form. (Tr. 262-263, 610-611.)

Professor Lipscomb agreed with respondents' witnesses Professor Dunitz and Professor Keizer with respect to their testimony that atmospheric seeding occurs only across small distances and that universal seeding of the whole atmosphere by the new monohydrate was implausible. (Tr. 266-267, 610-613, 1295-1296.)

Professor Lipscomb described his new theory of local-universal seeding as the seeding of the environment in a distant place when someone inadvertently carries or sends seeds of the new monohydrate to a place where those seeds were not present before. (Tr. 1296-1297.)

Bristol offered this theory as a possible explanation of why scientists are now able to make the new monohydrate using modifications of the procedures taught in the prior art Crast and Garbrecht patents. Bristol argues that until the first time that the new monohydrate was made in the trihydrate experiment leading to the '657 patent, no one could have made the new monohydrate by using what was taught in Garbrecht and Crast and what was known in the art in 1976.

In earlier litigation, Bristol had taken the position that because of seeding the old monohydrate could not be reproduced as long as the new monohydrate was in the surrounding atmosphere. Bristol's position was that the old monohydrate was unstable, and that seeding would cause the stable new monohydrate in the surrounding atmosphere to displace the unstable old monohydrate as it precipitated out of solution in crystallized form.

As a result of subsequent experiments, Bristol changed its position in this TEO proceeding. Bristol no longer contends that the new monohydrate is more stable than the old monohydrate, nor does it contend that the new monohydrate displaces the old, or is dominant over the old.

Dr. Ludescher (respondents' witness) and Dr. Schofield (a Bristol consultant) did tests that showed that the old monohydrate could coexist with the new monohydrate.

Two experiments made by Dr. Schofield proved that the new monohydrate could be produced in the first experiment, and that the Gottstein/Misco monohydrate (an old monohydrate first made by Bristol) could be made in a later experiment, proving that the new monohydrate in the atmosphere did not displace the old monohydrate. (Tr. 1128-1143, 1227-1228, 1381-1383.) (Bristol did not explain why the new monohydrate was not found along with the old monohydrate in the second Schofield experiment that produced the old monohydrate, if seeding had occurred. Nor did Bristol explain why seeding did not occur.)

Dr. Ludescher made four experiments for Biocraft, one of which repeated Professor Just's experiment, and is discussed above. The three other experiments are described here.

In the first of these experiments Dr. Ludescher produced the old monohydrate. This experiment was done in a location less than 15 miles from the laboratory in which he had previously made the new monohydrate. This was within the range of possible atmospheric seeding as described in Professor Lipscomb's local-universal seeding theory. Moreover, Ludescher used starting materials obtained from facilities where the new monohydrate had been made previously, and he took no special steps to avoid seeding. (Tr. 537.) Finally, commercial forms of the new monohydrate were available throughout Austria at the time all of these experiments were made. (Tr. 538.) There was every reason to believe that the new monohydrate was in the atmosphere and available for seeding Dr. Ludescher's

experiment, under Professor Lipscomb's theory. Dr. Tessadri, a witness for Biocraft, found that the product of the first Ludescher experiment had the same crystal structure as the old monohydrate. (Tr. 671.) It is possible that seeding had caused the new monohydrate to appear somewhere in the crystals formed, but the crystalline structure of the new monohydrate was not found by Dr. Tessadri in the sample he tested.

In his second experiment, Dr. Ludescher prepared the new monohydrate, and then two days later in the same laboratory, he prepared the old monohydrate. He took no steps to clean up the laboratory to avoid the possibility of seeding from the new monohydrate. (Tr. 539-40.) Dr. Tessadri confirmed that Dr. Ludescher had produced the new monohydrate and later the old monohydrate. (Tr. 674-75; Biocraft/Gema Ex. 151 at G-272.)

In a third experiment, Dr. Ludescher dissolved the new Bouzard monohydrate in a solvent. He then applied Bristol's procedure for making the old monohydrate, using the new monohydrate as a starting material. He was able to crystallize a mixture of the old monohydrate and the new monohydrate from the same solution. (Tr. 543.) Dr. Tessadri identified crystals of both the new and the old monohydrate, and by using an electron microscope he showed a crystal of the old monohydrate growing on a crystal of the new monohydrate. (Tr. 676; Biocraft/Gema Ex. 151, at G 282, 283 and 301-305.)

Dr. Ludescher's experiments demonstrated that both the new monohydrate and the old monohydrate were stable. They showed that a solution containing the new monohydrate could form new and old monohydrate crystals,

and that the new monohydrate would not displace the old. The old and new monohydrates could be crystallized out of the same solution.

Professor Lipscomb, after seeing the results of the Just, Ludescher and Schofield experiments, thought that it was possible that the new monohydrate displaced only the unstable trihydrate formed originally in the process described in the '657 patent that produced the new monohydrate for the first time. (Tr. 1293-1298, 1320-1324.)

It is now Bristol's position that Dr. Weber, an inventor named in the '657 patent, originally had made by accident an intermediate product, a trihydrate that was extremely unstable. This unstable trihydrate quickly changed into the new monohydrate which is stable, as is the old monohydrate. This would explain why the new and the old monohydrate can exist together. Professor Lipscomb testified that a few extremely unstable products have existed in the past that no longer can be made because they have been replaced by a more stable form. (Tr. 1320-1321; Bristol Ex. 45 at 137-139.)

Bristol now contends that the trihydrate that produced the new monohydrate the first time was unstable and cannot be reproduced as long as crystals of the new monohydrate are in the atmosphere around it. Dr. Bouzard testified that after the new monohydrate had been formed, Bristol no longer could obtain the trihydrate, even using identical procedures to those that produced trihydrate the first time. (Tr. 306-307.) Bristol's position is that the new monohydrate never could have been produced without the original Weber experiment that resulted in the trihydrate that changed into the new monohydrate, and that anyone now getting the new monohydrate from an experiment only does so because the Weber experiment originally

produced the new monohydrate from the trihydrate, and the new monohydrate now can be found in many locations and it causes the new monohydrate to be found in experiments made both in the United States and in Europe.

Bristol's seeding theory does not explain the results of all the experiments in evidence here. For example, according to Professor Dunitz (testifying for respondents), when two forms of cefadroxil, such as the old and the new monohydrate, can coexist as two different crystal modifications, they can precipitate out of a solution as mixed crystals. Seeding has no effect on the existence of these two crystals.

In another situation, one compound may take over the other compound. In this situation, seeding from the local environment may take place if a dominant (perhaps more stable) compound contaminates a solution and provides a foreign nucleus around which the crystal could form. This was described as local seeding by Professor Dunitz. (Tr. 262-266.)

Using Professor Dunitz' definition of seeding, seeding would not explain the results of Dr. Just's experiment in which the new monohydrate was formed because the new monohydrate would not displace the old. Dr. Just made minor changes in the Crast procedure of Example 6. Dr. Lipscomb testified that the Crast patent does not produce the trihydrate. (Tr. 1368.) The new monohydrate could not have displaced the unstable trihydrate or the old monohydrate. The new monohydrate therefore must not have come from seeding. If it did come from seeding, Bristol still has to explain how this occurred.

Respondents' position is consistent with the test results. They take the position that the ability to produce the trihydrate is irrelevant to the issues in the case. Respondents have proved that the old monohydrate

still can be made, and that the new monohydrate can be made now by modifying the Crast process or the Garbrecht process without going through the trihydrate stage of the Bouzard experiment on which the '657 patent is based. They have proved that the new monohydrate could have been made in 1976 by making these same obvious modifications to Garbrecht or to Crast, without going through the trihydrate stage of the first Weber experiment.

Bristol has not offered any evidence to support the theory that local-universal seeding is the source of the new monohydrate when it is made following the Crast or Garbrecht procedures. Complainant indicates that it is still discussing how to make appropriate tests to prove its theory, but that it does not expect that these tests will be completed within the next two years. (Tr. 1399, 1417, 1457-58.) It is unlikely that the evidence, whatever it is, will be available before the Commission has completed this case.

The evidence now in the record shows that the hypothetical person with ordinary skill in the art could have made the product of the '657 patent by combining modest changes within the ordinary skill in the art with the teaching in Crast or Garbrecht or both.

It is likely that respondents will succeed in proving that the '657 patent is invalid under Section 103.

E. Infringement

Finding 13

If the patent were valid, it is likely that complainant would succeed in proving that it was infringed.

The evidence shows that the product now produced by respondents falls under claim 1 of the patent. All of the respondents except Kalipharma,

Purepac, IBI and IBSA stipulated that their product was covered by the '657 patent claim. (March 21, 1989 Preliminary Conference Tr. 84.)

X-ray experts testified that the IBI product was identical to the product claimed in the '657 patent. (Tr. 934, 961.) IBI manufactures bulk crystalline cefadroxil monohydrate in Italy and sells it to IBSA. (Staff Ex. 7.) IBSA processes the bulk cefadroxil into dosage form in Switzerland and exports the resulting capsules to Kalipharma in the United States. (Id.) Kalipharma, through its Purepac division, sells in the United States the infringing crystalline cefadroxil monohydrate. (Id.)

It is likely that if the patent is found to be valid and enforceable, all the respondents will be found to infringe the patent directly or to induce its infringement.

F. Enforceability (Inequitable Conduct)

Finding No. 14

If the '657 patent were found to be valid and infringed, it is likely that the patent would be found to be enforceable.

Respondents have not carried the burden of proving that the patent is unenforceable under recent precedent in the Federal Circuit because of fraud or inequitable conduct in the Patent and Trademark Office.

Respondents failed to prove by clear and convincing evidence that Bristol-Myers had an intent to deceive. More than gross negligence must be proved. Inequitable conduct is the failure to disclose material information or the submission of false material information to the Patent and Trademark Office, with an intent to deceive. Both materiality and intent must be proven by clear and convincing evidence. Kingsdown Medical Consultants Ltd. v. Hollister Inc., 863 F.2d 867, 9 U.S.P.Q. 2d 1384, 1389

(Fed. Cir. 1988). Information may be considered to be material for various reasons. One would be if there is a substantial likelihood that a reasonable patent examiner would consider it important. J.P. Stevens & Co., Inc. v. Lex Tex Ltd. Inc., 747 F.2d 1553, 223 U.S.P.Q. 1089, 1092 (Fed. Cir. 1984), cert. denied, 474 U.S. 822 (1985).

Respondents allege that complainant acted inequitably on a number of occasions during the prosecution of the patent.

On August 7, 1978, Bristol filed a patent application including one product claim for crystalline cefadroxil monohydrate. The claim was rejected on May 4, 1979 and again on October 19, 1979 over the Garbrecht patent. The patent examiner stated that the only way to show that the product is not that of Garbrecht is to repeat Garbrecht's crystallization procedure. (Bristol Ex. 45, at 121-123.) Bristol appealed, and the Board of Appeals affirmed the rejection. On March 16, 1982, Bristol filed another third application claiming the crystalline cefadroxil monohydrate. It was in connection with this application that Dr. Micetich filed two declarations, one dated October 13, 1982, and one dated June 29, 1984.

Bristol's representations to the PTO relating to Dr. Micetich's two declarations and its failure to ask Dr. Micetich to make the third test in connection with Dr. Micetich's second group of experiments are perhaps the most important allegations of inequitable conduct.

1. In 1982 Bristol asked Dr. Micetich to make some experiments following Garbrecht Example 7 to determine whether the new monohydrate could be produced by using Example 7. On August 3, 1982, Dr. Micetich reported to Dr. Carnahan of Bristol that he had made five experiments attempting to follow Garbrecht Example 7. Dr. Micetich reported that the

removal of the t-BOC group was "at best incomplete." (Biocraft/Gema Ex. 91.)

In reporting the results of Dr. Micetich's experiments to the patent examiner, Bristol failed to disclose that Dr. Micetich had removed part of the t-BOC group. In the first declaration of Dr. Micetich dated August 31, 1982, filed with the PTO (Bristol-Myers Ex. 45, '657 prosection history, at 92), he stated that by repeating Garbrecht Example 7, he was unable to produce the monohydrate of what is now the '657 patent.

Respondents argue that Bristol should have told the examiner that the removal of one protecting group was incomplete, not that it had failed. I agree. Nevertheless, respondents fell short of proving an intent to mislead the patent examiner. After reading the first declaration, the examiner rejected the application anyway. (Id. at 93.)

2. A question was raised in connection with later work done by Dr. Micetich for Bristol following Bristol's discussion of a protocol with the patent examiner after he had rejected the claim over Garbrecht again. After this rejection, Bristol drafted a protocol discussing possible experiments that could be made to determine whether the new monohydrate could have been made using the teaching of the Garbrecht patent and ordinary skill in the art. The third test in the protocol was discussed with the patent examiner, as is shown by the file history. (Id. at 117.) Bristol must have intended, at least when the protocol was drafted, to try the third experiment in the protocol. Bristol argues that when the protocol was discussed, the examiner decided that the third test would be made only if adding more hydrochloric acid to remove a protecting group would have been known in the prior art. The record is not clear on this

point, and the conference occurred so long ago that memories of it are not trustworthy. It is not clear whether the examiner wanted this test made or if he did, whether Bristol thought that the test should be made only if in Bristol's opinion adding more hydrochloric acid was within the ordinary skill in the art at the time of the invention. I do not think that it is likely that the examiner intended to leave this determination up to Bristol alone. The record shows that Bristol did not disclose to Dr. Micetich that the third experiment should be made, but it is not clear whether Bristol thought that this is what the examiner wanted. Dr. Micetich did not make the test for Bristol, nor did anyone else at Bristol make this test. (Tr. 706.) The failure of anyone at Bristol to make the third test is surprising; it suggests that if Bristol in fact never made this test, Bristol may have feared that the test would result in production of the new monohydrate.

In the second declaration of Dr. Micetich to the PTO dated June 29, 1984, (Id. pp. 133-144), he stated that with specified modifications to the examples of the Garbrecht patent, he was unable to produce the monohydrate of the '657 patent. He described the tests that he had made, and the patent examiner could have read these tests and asked that the third test be made, if he had thought it important. He did not do so.

In his first experiments, Micetich had not used enough hydrochloric acid to remove the two protecting groups. Dr. Micetich knew that both protective groups had to be removed to get a cephalosporin, but he testified that he thought that he was supposed to duplicate Garbrecht Example 7. (Biocraft/Gema Ex. 33, Micetich deposition, at 37.) Micetich also testified that he understood that the examiner wanted him to use

"established methods," and that this was why he did not continue his experimentation. (Biocraft/Gema Ex. 33 at 71.) He used only the concentration of acid called for by Garbrecht Example 1. As found above, one with ordinary skill in the art (acting without instructions from Bristol) would have tried to use more hydrochloric acid to remove the t-BOC group, at least after he found that literally following Garbrecht Example 7 would not remove the t-BOC group or produce the new monohydrate.

Bristol later suggested to the patent examiner that adding more hydrochloric acid was one possible variation to make in Garbrecht Example 7. The third test suggested by Bristol, which was not made, called for the use of zinc and more hydrochloric acid to remove the protecting groups.

Bristol's attorney testified that he understood the examiner to say that Micetich was to perform the third test only if it would have been known to one skilled in the art. (Kalipharma Ex. 22.) If Bristol did not know what one skilled in the art would have known, it could have said so, or it could have tried to find out. Again, I do not believe that the examiner intended to let Bristol alone decide what was ordinary skill in the art, or that the examiner, once the test was described to him, would have indicated that he did not want to have it made. The examiner's record of his meeting with Bristol concerning the protocol is ambiguous at best. (Bristol-Myers Ex. 152 at 117.) Bristol wrote the protocol suggesting the use of more hydrochloric acid, and this test clearly was within the skills of Bristol's chemists.

Bristol argues that the first two tests already had produced a crystalline cefadroxil, but it was not the monohydrate of the '657 patent,

so that there was no need to go to the third test. (Kalipharma Ex. 33; Tr. 1167-1170.) There is no clear and convincing evidence that complainant failed to perform the third experiment intentionally, knowing that the examiner wanted to have the test made. There is no evidence that the tests made by Dr. Micetich were not reasonable tests as far as they went, and within the limitation of Bristol's instructions to him. Bristol's tenacious efforts to obtain the patent are in stark contrast to its meager efforts to prove to the patent examiner that obvious modifications to the Garbrecht Example 7 would not produce the new monohydrate.

3. Respondents also allege that Bristol acted inequitably in the representations that it made to the patent examiner about the disclosures made in the Garbrecht patent. Complainant may have construed the Garbrecht patent incorrectly without any intent to mislead the patent examiner. In any event, the patent examiner could interpret the Garbrecht patent himself, as he had rejected the Bouzard claim repeatedly over the prior art Garbrecht patent.

Serious questions have been raised about possible inequitable conduct on the part of Bristol before the PTO particularly in connection with the failure to make the third test, and the manner in which Bristol reported the results of some of Dr. Micetich's earlier experiments to the Patent and Trademark Office. Nevertheless, this record does not contain clear and convincing evidence of an intent on the part of complainant to mislead the PTO or to act inequitably.

2. IMMEDIATE AND SUBSTANTIAL HARM TO THE DOMESTIC INDUSTRY

Finding No. 15

In the absence of the requested temporary relief, there will be immediate and substantial harm to the domestic industry.

If validity and infringement of the patent were clearly established, immediate and irreparable harm would be presumed. Roper Corp. v. Litton Systems, Inc., 757 F.2d 1266, 225 U.S.P.Q. 345, 348-49 (Fed. Cir. 1985). Even if that were not so, the record contains evidence that imports will cause immediate and substantial harm to the domestic industry if temporary relief is not granted.

Generic competition from imports began in March 1989. (Tr. 123.) From the beginning of March 1989 through the middle of April 1989, respondents had gross sales of about [c] of imported crystalline cefadroxil monohydrate. (Staff Phys. Ex. F, Gray deposition, at 62; Bristol-Myers Ex. 2, Snyder deposition, at 129.) Complainant sold more of its cefadroxil monohydrate in March 1989 than in at least any of the preceding 13 months. (Tr. 70-71, 123-124.) By the first week of April 1989, Bristol-Myers was losing more than 16% of its crystalline cefadroxil monohydrate sales to generics, with more than $630,000 in net sales losses during the preceding month. (Bristol-Myers Ex. 61.)

Respondents have introduced their generic product at about [c] per [c] capsule bottle, while complainant charges $160.00 for the same amount. (Tr. 198.) The lower price makes the generic product attractive to consumers who want to save money and retailers who want higher profits. Since the repeal of anti-substitution laws, pharmacists may substitute generic products for brand-name products, and some states have removed the

complainant's product from Medicaid formularies. (Staff Phys Ex. F, Gray deposition, at 39; Tr. 120.)

If the sale of generics continues its present rate of growth, generic competition could cost complainant at least $45 million to $50 million in lost net sales revenue through December 1989. (Bristol-Myers Ex. 61.) Generics could capture about 50% of complainant's sales within a year and-a-half. (Tr. 44; Bristol-Myers Ex. 65 at 40-44; Staff Ex. 13 at 9-10.) The product has a shelf-life of at least two years, so sales made now by respondents could affect the ability of complainant to make sales in the future. (Staff Phys. Ex. F, Gray deposition, at 47; Tr. 197.)

As of the end of March 1989, Biocraft had an inventory of [c] bottles of [c] capsules of crystalline cefadroxil monohydrate. (Staff Ex. 5(c) at 10.) Kalipharma's inventory in late March 1989 was [c] bottles of one hundred 500mg capsules and [c] bottles of fifty 500 mg capsules, and [c] bulk product. Kalipharma also had received [c] bottles of one hundred 500mg capsules. (Staff Ex. 7(c) at 9 and 14.)

3. HARM TO RESPONDENTS

Finding No. 16

Respondents have not proved to what extent they would be harmed by the issuance of temporary relief in this case. If only an exclusion order were issued, respondents could still import under bond.

Respondents sell many pharmaceutical products, and only recently began to sell cefadroxil monohydrate. (Staff Ex. 5 at 9; Staff Ex. 7 at 8; Bristol-Myers Ex. 1; Tr. 123.) The distribution network for generic drugs (including chain drug stores and hospitals) will remain in place, regardless of whether temporary relief is granted. (Tr. 194-195.) It is not clear to what extent Kalipharma or any respondent would be injured if a

temporary exclusion order or cease and desist orders were issued in this case. It is clear that they would be injured because cefadroxil is a high profit margin product, and respondents would be losing sales on a large market share that they could expect to gain from complainant.

If a respondent wanted to import the accused products into the United States during the time that only a temporary exclusion order were in effect, it could do so under bond, but the bond could be large enough to make their sales unprofitable. See 19 U.S.C. § 1337(e)(1).

4. THE PUBLIC INTEREST

Finding No. 17

Temporary relief would have a mixed impact on the public interest, but on balance it would adversely affect the public interest.

If temporary relief were granted, there would be a mixed impact on the public interest. Prices for Bristol's cefadroxil are already high. If high bonds are set, large quantities of respondents' products might come on the market, but it is unlikely that they would be marketed at the low prices (relative to Bristol's prices) at which they are sold now. Generic cefadroxil monohydrate is currently available at a price substantially lower than Bristol's, but still at a high price per capsule. (Tr. 198-200; Bristol-Myers Ex. 2, Snyder deposition, at 36.)

If temporary relief were granted, some services that Bristol-Myers representatives have offered in the past to doctors in connection with cefadroxil would decline. Efforts of Bristol to find new uses for the cefadroxil might diminish. It is unlikely that Bristol will reduce its efforts in research because of a decline in profits on cefadroxil because a

principal source of its revenues appears to be the sale of patented products resulting from research.

Complainant is able to produce an adequate supply of cefadroxil monohydrate to meet all medical needs in the United States regardless of whether respondents import any products. If the market demand increases, complainant could increase its capacity to supply the market. (Tr. 198-199.) Even if this were not the case, other drugs compete with complainant's product to treat many of the same illnesses. (Tr. 122, 135; Bristol-Myers Ex. 59 at 2.)

Although it is in the public interest to protect valid patent rights, Eli Lilly & Co. v. Premo Pharmaceutical Laboratories, Inc., 630 F.2d 120, 207 U.S.P.Q. 719, 735-36 (3d Cir.), cert. denied, 449 U.S. 1014 (1980), at this stage in this case it does not appear likely that there is a valid patent right to protect. There clearly would be adverse economic effects on the public from the issuance of temporary relief against respondents. The public would have to pay higher prices for the generic product. A patent owner is entitled to a monopoly for 17 years on his patented product, and therefore to any price he can get, but why is it in the public interest to require respondents to charge that same high price for the generic product? In district court respondents could be required to compensate complainant directly, if it turns out that Bristol had a valid patent that has been infringed. Here, the Commission can impose a bond on respondents as the cost of importation while the case is pending, and the cost probably will be passed along to the consumer, who will continue to pay high prices during the temporary relief period, even if Bristol ultimately loses the case. Respondents can import and get a foothold in

the market, and because Bristol's profit margins are high, respondents probably can make a profit even after passing the cost of the bond on to the consumer. It is concluded that in this particular case it would not be in the public interest to grant temporary relief. Bonds might help the complainant but they would not be likely to hurt respondents very much. The loser would be the consumer.

BONDING

Finding No. 18

If temporary relief were granted, complainant should not be required to post a bond, and the bond on respondents should reflect only the difference between respondents' costs and complainant's cost in making the product.

The Commission's new rule on bonding a complainant when temporary relief is granted encourages requiring a bond and setting the bond at an amount between 10 and 100 percent of complainant's sales revenues. 53 Fed. Reg. 49120 (Dec. 6, 1988); 19 C.F.R. § 210.24(e)(1)(v). The principal purpose of Congress in changing the law on which this rule is based was to discourage frivolous motions for temporary relief. (H.R. No. 576 at 635-636; 133 Cong. Rec. S10364.)

Although complainant does not have a strong case, there is no evidence that the motion for temporary relief was frivolous. Some of the questions, for example those relating to ordinary skill in the art and to inequitable conduct, are close, and additional evidence could turn around the conclusions on these issues.

If a bond were to be required of complainant based on sales revenues, in 1988, complainant's net sales of the product were about $100 million. (Staff Ex. 9 at 3; Tr. 105.) In March of 1989, sales of the product

reached about $12.5 million. (Tr. 123.) Complainant projects that it may lose up to $50 million to generic cefadroxil monohydrate. A bond of $25 million would represent about one quarter of complainant's sales of the product last year, and about two months of sales at the current rate. Complainant's sales of the product are large, and the margin of profit is high.

A large bond on complainant in this case could discourage complainants in the future from filing frivolous motions for temporary relief. In this particular case, however, the cost of bonding complainant could be passed along to the consumer, who already is paying a high price for this drug. This adverse impact on the consumer in my opinion outweighs any deterrent effect that a large bond on complainant here would have on future complainants. Complainant should not be required to post a bond.

The size of the bond on respondents is a way to let respondents continue to import while the case is pending without allowing respondents to destroy complainant's business by undercutting complainant's prices while the case is pending. In this case, however, if the bond is large, respondents may pass most of this cost along to the public. Because Bristol's prices are so high, respondents could raise their prices and still compete with Bristol. Or respondents could keep their prices substantially lower than Bristol's and still get much of Bristol's market.

In this particular case, where profit margins are high, it is expected that respondents would post the bond and import. Without much pain they could either raise their prices closer to Bristol's price or keep their prices substantially lower than Bristol's and try to capture Bristol's market share. If the product were a small profit item so that respondents

might decide not to import rather than post a bond, a high bond on respondents might keep the product out of the United States during the period of temporary relief. Or if the products in issue were race horses or sports cars, the amount of the bond on either respondents or complainant would be unlikely to affect the public interest. Here, the cost of drugs affects the public interest. The patients whose doctors prescribe this particular drug will buy it even though competitive products for treating the same illnesses are available. In my opinion the public interest factor favors keeping respondents' bond low.

Bristol argues that a product such as cefadroxil monohydrate has a limited life, and will be replaced by another drug fairly soon. If complainant is going to make high profits on this product, it must do so now. If complainant has a valid patent on a new form of cefadroxil monohydrate it is entitled to high profits as long as the patent is valid.

Nevertheless, this does not justify a bond during the temporary relief phase of this case that would raise respondents' prices to as high as or nearly as high as complainant's monopoly prices. A bond on respondents that would equal the difference between respondents' cost to make the product and complainant's cost to make the product, exclusive of Bristol's past research costs related to this product, might be fair if there were a way to compensate complainant directly if respondents later lost the case. (This record does not contain detailed evidence on the costs of the parties in making this product.) Section 337 does not provide for the bond to be forfeited to the other side if that side wins, but damages could be sought in district court if the patent is found to be valid. In Section 337, the principal amount of the bond of the losing party may or may not be

forfeited to the Treasury, and the winning side does not recover the cost of its bond.

Any higher costs of the product that may result from bonding in this case probably will be paid for by health insurance companies, Medicare, and the uninsured consumer. This is like an indirect tax on people paying for medical care.

FORM OF TEMPORARY RELIEF

Because it is found that there is no reason to believe that there is a violation of Section 337, the issue of the form of relief, other than the discussion of bonding, is not reached.

CONCLUSIONS

It is found that there is no reason to believe that a violation of Section 337 exists because respondents have offered clear and convincing evidence that the '657 patent is invalid under Section 103 of the Patent Act, thus overcoming the presumption of patent validity. If the next issue had been reached, four factors would have been balanced in determining whether temporary relief should be granted. After balancing these four factors, the most important factor is found to be that complainant has been unable to show a likelihood that ultimately it will succeed on the merits. The motion for temporary relief is therefore denied, and the issues will be tried in the hearing on permanent relief to be held after the parties have had time for further discovery.

The pleadings record includes all papers properly filed with the Secretary. The evidentiary record in this TEO proceeding consists of all exhibits identified in Bristol-Myers Ex. 75, Biocraft/Gema Exs. 152 (except Exs. 83, 87, 121, 124, 125) and 153, Kalipharma Ex. 52, and Staff Ex. 1. In

addition the evidentiary record includes Staff Ex. 19, Kalipharma Exs. 59 and 61 , and Bristol Myers Ex. 99.

The evidentiary record also includes the transcript of the testimony at the hearing. The evidentiary record is hereby certified to the Commission.1/

Janet D. Saxon

Janet D. Saxon
Chief Administrative Law Judge

Issued: May 24, 1989

1/ Pursuant to 19 C.F.R. § 210.24(e)(17), this initial determination shall become the determination of the Commission unless the Commission modifies or vacates the initial determination within the period set forth in that section.

CERTIFICATE OF SERVICE

I, Kenneth R. Mason, hereby certify that the attached Initial Determination was served by hand upon Cheri Taylor, Esq., and upon the following parties via first class mail, and air mail where necessary, on May 26, 1989.

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