

EXHIBIT 17

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

FRITSCH ET AL.)	
)	
v.)	Interference No. 102,334
)	
LIN)	Examiner-in-Chief:
)	Marc L. Caroff

BOX INTERFERENCE

Hon. Commissioner of Patents
and Trademarks
Washington, D. C. 20231

**OPPOSITIONS OF LIN TO
37 CFR §§ 1.633 AND 1.635 Motions by Fritsch et al**

Sir:

The Senior Party Lin opposes each of the four motions which have been brought by Fritsch et al. ("Fritsch") pursuant to 37 CFR §§ 1.633 and 1.635 for the reasons presented hereinbelow. In addition, in view of the Motion I for Judgment brought by Fritsch, Lin is compelled to submit a motion in accordance with 37 CFR §1.635. Each of the Lin submissions follow at the page numbers indicated.

- A. OPPOSITION BY LIN TO FRITSCH ET AL
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- B. OPPOSITION BY LIN TO FRITSCH ET AL
MOTION II UNDER 37 CFR §1.633(a)Page 11

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- C. OPPOSITION BY LIN TO FRITSCH ET AL
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- D. OPPOSITION BY LIN TO FRITSCH ET AL
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- E. MOTION FOR JUDGMENT BY LIN ON THE
GROUND THAT THE JUNIOR PARTY FRITSCH
ET AL HAS ADMITTED HIS SOLE CLAIM 8
CORRESPONDING TO THE COUNT IS NOT
PATENTABLE UNDER 35 USC §102(b) OVER
MIYAKE ET ALPage 19

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OPPOSITION BY LIN TO FRITSCH ET AL MOTION I UNDER 37 CFR §1.633(a)

Lin submits that motion I of Fritsch et al ("Fritsch") has no merit and should be denied.

Motion I requests judgment on the ground that claims 76-83 of Lin's application S.N. 113,178, are unpatentable under 35 USC §102(b) over Miyake et al, J. Bio. Chem., Vol. 252, pgs. 5558-64 (1977).

Clearly, Miyake et al ("Miyake") does not disclose the subject matter of Lin claims 76-83. The Miyake publication relates to the purification of human urinary erythropoietin. On the other hand, claims 76-83 of the Lin application specify a non-naturally occurring polypeptide produced by recombinant DNA. It cannot be disputed that the urinary erythropoietin ("u-EPO") of Miyake is not "non-naturally occurring" nor is it made by using recombinant DNA. Miyake provides no disclosure or any suggestion whatsoever regarding either non-naturally occurring erythropoietin or the use of any recombinant procedures to make the same. Although the non-naturally occurring polypeptide claimed by Lin may (or may not) have the same amino acid sequence as human urinary erythropoietin, it differs in carbohydrate composition. The difference in carbohydrate composition is attributable at least in part to the way the non-naturally occurring polypeptide is manufactured. For example, the non-naturally occurring polypeptide claimed by Lin is made in a non-human eucaryotic host cell.

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Pages 2 through 9 of the Fritsch motions present an alleged "consolidated statement of material facts" in support of Motions I and II. These are incorporated by reference to page 13 and again at page 16, purportedly in support of motions III and IV. At page 18 of the submission, Fritsch threatens a motion for judgment if Lin fails to lodge a dispute with any of the alleged "material facts". Even a cursory review of the allegations spanning pages 2-9, 13 and 16 reveals that most are wholly non-factual and amount to no more than argumentative remarks of counsel. The few statements that are actually accurate provide no "material" support for grant of the Fritsch motions.¹ Rather than clutter this reply with specific disputations of the additional arguments of counsel which have been mischaracterized as statements of "fact", Lin attaches hereto as Exhibit 3 a brief annotated response to each of the disputed statements.

It is well recognized that u-EPO and r-EPO although structurally similar, are different because of differences in the carbohydrate moiety. (See Takeuchi et al.² and Sasaki et al.³ which were considered by the Examiner during examination of the Lin application) There has been no showing or representation by Fritsch including the

¹ Statement Nos. 3 and 11 merely quote from the record, although even statement 11 includes an argumentative footnote. Statement Nos. 14, 16 and 20 appear to accurately quote from the Cumming Declaration. Lin does not dispute the accuracy of the quotation process, but does dispute the substance of the statements quoted.

² Takeuchi et al., *J. Bio. Chem.*, Vol. 263, No. 8, 3657-3663, March 15, 1988

³ Sasaki et al., *J. Bio. Chem.*, Vol. 262, No. 25, 12059-12076, September 5, 1987

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declaration of Dr. Cumming, Genetic Institute's head of Carbohydrate Chemistry, that the average carbohydrate composition of u-EPO and r-EPO are the same.

In an attempt to overcome this obvious deficiency, Fritsch has noted statements comparing urinary EPO and recombinant EPO made by employees of Lin's assignee, i.e. Amgen, wherein the two EPOs are said to be "very similar" (Egrie et al) or "essentially the same" (Browne et al). However, this does not mean that the two EPOs are identical. To bar patentability, Section 102 requires identity of subject matter, not a generalized similarity. In the Official Action of January 24, 1989 (which was issued in response to the first response submitted by Lin in the prosecution of the '178 application) it was acknowledged by the PTO that:

"the declaration under 37 CFR 1.132 filed 12/9/88 is sufficient to overcome the rejection of claims 41, 55-57 and 61-66 based upon 35 USC 102/103..."

Of interest is the fact that the Examiner in this same Office Action recognized that Takeuchi and Sasaki teach r-EPO having differences in carbohydrate composition from uEPO.

Moreover, the question of patentability over Miyake in the sense of Section 102 was considered in depth with the Primary Examiner during prosecution of the Lin application here at issue and the Examiner correctly decided that Lin's claims 76-83 were patentable over Miyake. Fritsch has raised no new substantive points which would warrant reversing the Examiner's finding of invention over Miyake.

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Statements made by employees of Lin's assignee must be kept in the proper context. Statements made regarding the fact that a) the biological property (i.e. ability to cause bone marrow cells to increase production of reticulocytes and red blood cells), or b) immunological property (i.e. lack of production of antibodies in vivo) of recombinant EPO and urinary EPO are indistinguishable based on the criteria used to evaluate the materials are not relevant to the 35 USC § 102 issue as to the differences between r-EPO and u-EPO in carbohydrate composition. Although r-EPO and u-EPO may perform some of the same functions in the same way, structurally, in terms of carbohydrate composition, the two types are different.

Evidence that the non-naturally occurring r-EPO of Lin's claims are different in carbohydrate composition from the naturally occurring urinary material can be found in:

- (a) the Declaration of Thomas Wayne Strickland dated November 30, 1988, which shows the more acidic nature of the u-EPO isoforms compared to the r-HuEPO isoforms is due to differences in carbohydrate composition (See ¶11 thereof);
- (b) the Declaration of Thomas W. Strickland attached hereto as Exhibit 1* (referred to herein as the second Strickland Declaration and specifically ¶¶ 6 and 17.
- (c) The papers of Takeuchi et al. and Sasaki et al. noted supra.

* A photocopy of Dr. Strickland's Declaration is attached hereto since the original which was executed in California could not be forwarded to counsel in Washington in time for the filing of Lin's oppositions. The original will be submitted as soon as received by counsel.

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Any error in the Lin application regarding an assay for hexose content does not change the fact that the claimed recombinant EPO of the claims is different from Miyake's urinary EPO. The only relevant consideration is that the Lin specification does disclose a non-naturally occurring polypeptide which has a different average carbohydrate content from the urinary EPO of Miyake. The Lin application and each of its parent applications are fully enabling as to the subject matter of the Count herein. (See second Strickland Declaration ¶16) Lin's Example 10, for instance, provides a recombinant EPO that differs in this way from Miyake's urinary EPO. Thus, as stated by Dr. Strickland in his second declaration:

- ¶16. There is nothing in any of the documents referred to in paragraph 4 above that changes my opinion that recombinant erythropoietin as described and claimed by the Lin application has a different carbohydrate composition than that of the naturally occurring urinary erythropoietin.
- ¶17 Based on the disclosure of the Lin application, my work as reported in the Strickland Declaration, the exhibits hereto and my professional experience in studying the carbohydrate chemistry of rEPO and uEPO, it is my firm opinion that the average carbohydrate composition of rEPO as described and claimed in the Lin application inherently differs from the average carbohydrate composition of uEPO.

Fritsch alleges that to secure FDA approval Lin's assignee Amgen argued that recombinant EPO is the same as urinary EPO, but that before the Patent and Trademark Office Amgen argued that they are different. This is a gross mischaracterization of the actual position. There is clearly nothing inconsistent with the facts as represented by

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Lin's submissions to the FDA and PTO (see second Strickland Declaration ¶¶13, 14 & 15, Exhibit 1 hereto). The comparative data based on isoelectric focusing presented to the PTO in the Strickland declaration confirming differences between the carbohydrate composition of recombinant EPO and urinary EPO was in fact data that was submitted to the FDA (see second Strickland Declaration ¶15 and Exhibit E thereto). Even the portion of the Product License Application submitted to the FDA by Amgen (Exhibit 4 to the Fritsch motions) clearly evidences the differences in carbohydrate composition (see for example pages 0765, 0791, 0796, 0799, 0898, 0905 and 0906 of Fritsch Exhibit 4, as well as the second Strickland Declaration ¶¶13 & 14). Further, the Patent Office was well aware of similarities and differences between recombinant EPO and urinary EPO. In fact, the Patent Office originally rejected the claims of the Lin application under 35 USC §102(b) as being unpatentable in view of literature on the natural material (Miyake et al). It was from this starting point that the Patent Office determined that u-EPO and r-EPO are different under 35 USC 102(b) in view of the Strickland declaration and the art recognized differences between recombinant and urinary derived EPO. Amgen statements regarding biological properties must not be confused with statements made with regard to carbohydrate composition. Although different in carbohydrate composition, recombinant EPO and urinary EPO have the same biological property of increasing production of reticulocytes and red blood cells. If anything, this underscores the novelty and unobviousness of the r-EPO invention at issue.

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The statement in the Cumming Declaration to the effect that Strickland's use of isoelectric focusing experiments to evaluate enzymatically treated urinary and recombinant erythropoietin is inappropriate to assess carbohydrate compositions, is completely unfounded and unsupported by any facts. (See the second Strickland Declaration ¶¶8, 9 & 10) Briefly, summarized, Dr. Cumming focused on only a portion of the work relied upon by Dr. Strickland, and then, attacked the results as providing unsuitable support for Dr. Strickland's conclusions. Had Dr. Cumming accounted for all of the work, he could not have criticized the conclusions reached by Dr. Strickland. Moreover, Dr. Cumming is apparently unaware of literature which directly contradicts his statement concerning hexose composition set out in CD-9 (See second Strickland Declaration ¶13). Lastly, as can be seen in the publications listed above including analysis of material developed by Genetics Institute and manufactured by its exclusive licensee, Chugai Pharmaceutical, there is unchallenged evidence of the differences between the carbohydrate composition of the two types of EPO.

In view of the foregoing, Lin submits that the Fritsch et al Motion I should be denied.

Should the Examiner-in-Chief be of the view that the Fritsch motion cannot be denied, the party Lin, pursuant to the provisions of 37 CFR §1.639(c), requests that he be permitted to present testimony directed to the involved issues of patentability over the Miyake et al. publication. Such testimony would be in the form of depositions including

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further testimony by Dr. Strickland and possibly Drs. Egrie and Lin as necessary to establish patentability to Lin and enable the Examiner-in-Chief to deny the motion.

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OPPOSITION BY LIN TO FRITSCH ET AL MOTION II UNDER 37 CFR §1.633(a)

Motion II of Fritsch et al has no merit and should be denied.

Fritsch et al ("Fritsch") request judgment on the ground that claims 76-83 are not patentable to Lin pursuant to 35 USC §112, first paragraph. Fritsch alleges that the Lin application does not contain a written description in such full, clear, concise, and exact terms as to enable any person skilled in the art to make "a non-naturally occurring glycoprotein product of the expression in a non-human eucaryotic host cell of an exogenous DNA sequence ... and having an average carbohydrate composition which differs from that of naturally occurring human erythropoietin" in accordance with claims 76-83. Fritsch further alleges that the Lin specification "enables a man skilled in the art to make an rEPO product that is the same in average carbohydrate composition as the hEPO product disclosed in Miyake et al." Fritsch has made no showing of any data or other evidence to support these unfounded allegations.

Furthermore, the recombinant product obtained by Lin as exemplified in his disclosure (for instance, Example 10) necessarily and inherently meets the claim limitation to the effect that the recombinant product is different in terms of coverage carbohydrate composition from naturally-occurring EPO (see for example, the second Strickland Declaration ¶¶16 & 17, attached as Exhibit 1).

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Fritsch points to the hexose value given at page 65, line 18 of the Lin application, and then states that the value cannot legitimately be used to support a conclusion that recombinant erythropoietin has "an average carbohydrate composition which differs from that of naturally-occurring erythropoietin". There is no evidence of record that Lin relied upon the hexose value during prosecution of the Lin application. The last paragraph of page 65 supports this limitation as does, for instance, Example 10. Fritsch and the declarant Cumming, have apparently assumed that a single hexose value is the only basis for Lin's statement regarding carbohydrate composition. However, the facts are that recombinant erythropoietin made according to the Lin specification does have an average carbohydrate composition which differs from that of naturally-occurring erythropoietin and thus the language at issue is supported by the Lin specification regardless of the accuracy of the hexose value given at page 65.

Clearly, the second Strickland Declaration (§16) establishes that the limitation is inherent in the Lin disclosure.

In view of the foregoing, Lin submits that the Fritsch et al Motion II should be denied.

Should the Examiner-in-Chief be of the view that the Fritsch motion cannot be denied, the party Lin, pursuant to the provisions of 37 CFR § 1.639(c), requests that he be permitted to present testimony on the issue of inherency and entitlement to the benefit of the prior applications. Such testimony would be in the form of deposition testimony by Dr. Strickland and possibly Drs. Egrie, Lin and others as necessary.

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OPPOSITION BY LIN TO FRITSCH ET AL MOTION III UNDER 37 CFR §1.635

Motion III of the junior party Fritsch et al ("Fritsch") to strike the Lin application is improper on its face and should be dismissed. Manifestly, the motion has no merit and if it is not dismissed as improper, should be denied.

The motion by Fritsch is based on the unwarranted assumption that the Lin application was filed "without review of the specification or under conditions amounting to gross negligence under 37 CFR 1.56(c)(3)". In support, Fritsch contends that the Lin application "contains data so strikingly false that it is reasonable to conclude that Lin and his attorney did not read the application before it was filed or the application was filed with false data under conditions amounting to gross negligence".

The Fritsch position could not be further from the truth and has no merit whatsoever. Before commenting on this, however, it appears appropriate to note that the Fritsch motion appears to go contrary to the spirit and intent of the Commissioner's notice published October 11, 1988 at 1095 O.G. 16 as supplemented by the notice published on November 8, 1988 at 1096 O.G. 19. For this reason alone, the Fritsch motion should be dismissed as improper and inappropriate.

In any event, the Fritsch motion has no merit and should be denied for the reasons detailed below.

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The Fritsch motion is based entirely on an assay "error" in a single assay to determine the hexose value recited for recombinant EPO ("r-EPO") at page 65, lines 17-18 of the Lin application, and on the mischaracterization that those two lines of page 65 of the Lin application is the "entire enabling disclosure" for the claim limitation that the average carbohydrate of rEPO differs from that of naturally-occurring (urinary) EPO. Any error in the determination of the hexose value is of no real consequence.

The Lin disclosure is obviously not limited to page 65 for this indicated feature of the Count or the Lin claims. The Lin specification, as supported by the Strickland Declaration of November 30, 1988, as well as the second Strickland Declaration, ¶¶ 6 & 17 (Exhibit 1 hereto) provides r-EPO which has a carbohydrate composition that is different from the carbohydrate composition of urinary EPO.

Attached as Lin Exhibit 2 is a declaration by Fu-Kuen Lin confirming that he read the application before he signed the application papers. The Lin declaration also notes that he "believed all the information contained in the application to be accurate including the 15.09 value recited at page 65, line 18."

As explained fully in the Oppositions to Fritsch Motions I and II, and as noted above, the hexose value (15.09) given on page 65, whether or not it is correct, does not change the fact that the Lin specification is fully enabling in the preparation of a polypeptide which is non-naturally occurring and which has an average carbohydrate composition which differs from that of naturally occurring human erythropoietin. That value is not essential to support the noted difference between r-EPO and urinary EPO.

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In view of the foregoing, Lin submits that Fritsch Motion III should be denied.

Should the Examiner-in-Chief be of the view that the Fritsch motion cannot be denied, the party Lin, pursuant to the provisions of 37 CFR § 1.639(c), requests that he be permitted to present testimony to rebut further the unfounded allegations contained in the Fritsch motion. Such testimony would of course involve the deposition testimony of Dr. Lin and others as might be necessary to further evidence the unsoundness of the Fritsch motion.

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MOTION IV UNDER 37 CFR §1.633(a)

Motion IV of junior party Fritsch et al ("Fritsch") has no merit and should be denied.

Fritsch attacks the benefit accorded to the senior party Lin, in the notice declaring this interference, of the filing dates of applications earlier filed in the U.S. Fritsch argues that those applications fail to set forth a written description to enable a person skilled in the art to practice the invention defined by claims 76-83 of the Lin application. Fritsch reasons that the Lin applications filed earlier than Lin's immediate parent Serial No. 675,298 (i.e. Serial No. 561,024, filed December 13, 1983; Serial No. 582,185, filed February 21, 1984 and Serial No. 655,841, filed September 28, 1984) are silent on any enablement with respect to the difference in average carbohydrate composition specified in the claims. However, support for claim language does not require that the exact words be used. Support can be expressed differently or it can be inherent in a party's disclosure. Thus, while it is true that the specific claim language "average carbohydrate composition" was not included in the earlier filed Lin applications, all of the Lin applications are fully enabling for the preparation of a non-naturally occurring polypeptide as claimed including the feature of "having an average carbohydrate

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composition which differs from that of naturally occurring erythropoietin". The polypeptide made in accordance with the Lin specification inherently has the properties specified in the count. This is confirmed by the second Strickland Declaration (Exhibit 1) which states at ¶17:

"Based on the disclosure of the Lin application, my work as reported in the Strickland Declaration, the exhibits hereto and my professional experience in studying the carbohydrate chemistry of rEPO and uEPO, it is my firm opinion that the average carbohydrate composition of rEPO as described and claimed in the Lin application differs from the average carbohydrate composition of uEPO."

Lin's parent case (S.N. 675,298) has the same disclosure as the Lin application in interference and supports the Lin claims in the same way. The Lin position in this regard is set out in Lin's opposition to Fritsch Motion II and is incorporated herein by reference.

Dr. Strickland further notes in his second declaration (¶ 16) that clear support for the subject matter of the Count exists in each of Lin's prior applications, the benefit of which already has been properly accorded to Lin herein.

In view of the foregoing, Lin submits that Fritsch Motion IV should be denied.

Should the Examiner-in-Chief be of the view that the Fritsch motion cannot be denied, the party Lin, pursuant to the provisions of 37 CFR §1.639(c), requests that he be permitted to present testimony to further support the position taken by Lin herein. Such testimony would include the deposition testimony of Thomas W. Strickland and

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possibly others in order to establish that the subject matter of the count is supported inherently by each of the earlier Lin applications.

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**Motion for Judgment By Lin on the Ground That the Junior
Party Fritsch et al Has Admitted His Sole Claim 8
Corresponding to the Count is not Patentable Under
35 USC §102 (b) Over Miyake et al**

Pursuant to the provisions of 37 CFR § 1.635, Lin moves for judgment on the ground that the Junior party Fritsch et al ("Fritsch") has admitted his sole claim 8 corresponding to the count is not patentable under 35 USC § 102(b) over Miyake et al.

Fritsch asserts in his Motion I for judgment that the Lin claims corresponding to the count are unpatentable under 35 USC § 102(b) over the Miyake et al reference. While Senior party Lin strongly disagrees with the Fritsch assertions for the reasons specified in the opposition to Fritsch Motion I, Lin submits that judgment should be entered against Fritsch since the Fritsch assertion, absent any attempt to show that the basis for unpatentability does not apply to Fritsch, constitutes an admission that the Fritsch application claim corresponding to the count is unpatentable. See Guglielmino v. Winkler 11 USPQ2d 1389 (PTO BD Pat. App. and Int., 1989).

In Guglielmino the Board noted at page 1390:

The [senior] party Winkler et al, in a motion under 37 CFR 1.633(a) for judgment filed March 23, 1987, has cited the aforementioned [Ross] patent which the senior party effectively states,

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makes obvious the issue of the interference. There appears to be no reason why the senior party's representation that the issue of the interference is unpatentable to him should not be accepted at face value as an admission that he is legally barred from obtaining a patent on that subject matter. *Ex parte Grall*, 202 USPQ 701 (1978). If an applicant does not regard claims patentable to him, there is no good reason why the Patent and Trademark Office should be put to the burden of considering the question of patentability. *Slivinski v. Lane*, 1922 CD 4 (Comm'r 1922).

In awarding judgment as to the subject matter of the count in issue the Board noted at page 1391:

...Winkler's admission lies not in any specific terms of admission used by him in his motion, but in the very nature of his motion, which in effect alleged unpatentability of the subject matter of the count to the patentee. By specifically charging that [Junior party] Guglielmino's claim 1, which corresponds exactly to the count, is unpatentable over the Ross patent, it is inescapable that Winkler charged that the subject matter of the count and his own claim 15 corresponding thereto, are unpatentable.

...Winkler's failure to avoid an admission arises from the fact that in his motion charging unpatentability to the patentee he made no attempt to show that the basis for unpatentability did not apply against himself.

As in Guglielmino, Fritsch asserts that Lin's claims, including claim 76 which corresponds exactly with the count, are unpatentable over the prior art, i.e. the Miyake publication. By having made no attempt to show that the basis for unpatentability did not

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apply against himself, Fritsch has made an admission that the subject matter of the count and his own claim 8 corresponding thereto, are unpatentable to him. Under the wording of Guglielmino, judgment as to the subject matter of the count should be awarded to Lin. Clearly, as stated in Slivinski v. Lane, supra,

"If an applicant does not regard claims patentable to him, there is no good reason why the Patent and Trademark Office should be put to the burden of considering the question of patentability."

One significant factor which further warrants the relief sought by Lin, resides in the fact that, unlike Guglielmino, Fritsch cannot possibly establish prior invention over Miyake et al. Miyake et al. stands as prior art under 35 USC §102(b).

This motion should be granted and the interference terminated forthwith with judgment entered for Lin. In accordance with the requirements of 37 CFR §1.637(b), Counsel for Lin has discussed this motion with counsel for Fritsch and has been informed that the motion will be opposed.

This motion could not be brought earlier by Lin because it arises from Fritsch's Motion I.