ROPES & GRAY LLP
ONE METRO CENTER 700 12TH STREET, NW SUITE 900 WASHINGTON, DC 20005-3948 202-508-4600 F 202-508-4650
BOSTON NEW YORK PALO ALTO SAN FRANCISCO TOKYO WASHINGTON, DC www.ropesgray.com

October 9, 2008

BY HAND

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Citizen Petition Concerning Approval of Follow-On Budesonide Inhalation Suspension Products (Docket No. 2006P-0073)

Dear Sir or Madam:

In light of recent developments at the Food and Drug Administration ("FDA"), I submitted information to the above-referenced docket on September 18, 2008, that relates to consideration by FDA of the June 9, 2006, citizen petition filed by our client, AstraZeneca LP ("AstraZeneca"). Since that submission, IVAX Pharmaceuticals ("IVAX") has publicly described the proposed labeling for its follow-on budesonide inhalation suspension product ("BIS"), which is currently the subject of an abbreviated new drug application ("ANDA"). Inasmuch as certain of these statements are highly relevant to FDA's consideration of IVAX's ANDA and AstraZeneca's citizen petition, I write to bring these statements to the attention of FDA and to include them in the administrative record.

Specifically, on September 23, 2008, the U.S. District Court for the District of New Jersey held a hearing on a summary judgment motion filed by IVAX in ongoing litigation involving two patents that relate to treating respiratory diseases, such as asthma, through the administration by nebulization of a budesonide composition or suspension at a frequency of not more than once per day. During this hearing, counsel for IVAX made the following statements that are of substantial relevance to FDA's consideration of IVAX's ANDA and AstraZeneca's citizen petition concerning labeling requirements for follow-on BIS products:

IVAX's public disclosure of its proposed labeling: "Ivax wants to make and sell budesonide inhalation suspension, that's what we refer to as BIS, BIS for twice daily use

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and IVAX has asked the FDA to approve ANDA No. 77519 for that purpose." (Transcript at 74, lines 9-12)

IVAX's description of the lowest effective dose in its proposed labeling: "[T]here really isn't any dispute in this case that on the IVAX label, the lowest effective dose according to that label is 0.5 [mg] administered in two 0.25 mg doses per day." (Transcript at 111, lines 4-7)

IVAX's description of a physician's reading of its proposed labeling: "We say the doctor who reads that looking at the IVAX label would see that the lowest effective dose on the IVAX label is 0.5 [mg] given in two divided daily doses. In other words, that doctor is already at the lowest effective dose based on that label. And so there is no titrating down that the doctor can do if he is following the instruction on the label because the label is instructing that the safe and effective use is the lowest safe effective use is 0.5 [mg] in two divided daily doses. So that doctor, if he's following that label, is not going to titrate down." (Transcript at 163-164, lines 21-25 and lines 1-5)

IVAX's description of its proposed labeling for once-daily use: "There is no evidence on the IVAX label that 0.25 mg once a day is a safe and effective treatment." (Transcript at 172, lines 19-20)

The foregoing statements by counsel for IVAX provide further support for the concerns expressed, and the actions requested, in AstraZeneca's citizen petition to FDA. Indeed, no matter whether the IVAX label provides for once-daily or twice-daily dosing, these statements by IVAX demonstrate that FDA cannot approve the IVAX ANDA under the FDCA and the agency's implementing regulations. 21 C.F.R. § 314.127(a)(7). If, as AstraZeneca believes, the IVAX label instructs once-daily dosing, IVAX has unambiguously stated that there is no evidence in its label to support safe and effective treatment of patients at 0.25 mg once a day. At the same time, IVAX has publicly and unequivocally stated that the lowest effective dose on its label is 0.5 mg per day given in two divided daily doses. Since the lowest effective dose of PULMICORT RESPULES®, as approved by FDA, is 0.25 mg administered once per day, FDA cannot conclude under its regulations that IVAX's follow-on BIS product would be as safe and effective as PULMICORT RESPULES. That is especially true in light of FDA's class labeling requirement for inhaled corticosteroids that calls for patients to be titrated down to the lowest effective dose once asthma stability is achieved.

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me and my client on or about September 23, 2008.

If I received or expect to receive payments, including cash and other forms of consideration (other than by virtue of our retention by our client) to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: none. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this supplemental information.

Thank you for your consideration of this information.

Respectfully submitted,

Bruce S. Manheim

Bruce S. Manheim, Jr.

Attachments: as stated.

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ASTRAZENECA, LP, et al,

Plaintiffs, CIVIL ACTION NUMBER:

-vs- 05-5142(RMB)

IVAX PHARMACEUTICALS, INC.,

Defendant.

Mitchell H. Cohen United States Courthouse
One John F. Gerry Plaza
Camden, New Jersey 08101
SEPTEMBER 23, 2008

B E F O R E: THE HONORABLE RENEÉ MARIE BUMB
UNITED STATES DISTRICT JUDGE

A P P E A R A N C E S:

MCCARTER & ENGLISH
BY: Andrew T. Berry, Esquire
Mark H. Arania, Esquire

ROPES & GRAY
BY: Denise L. Loring, Esquire
Christopher J. Harnett, Esquire
Pablo D. Hendler, Esquire
Attorneys for the Plaintiffs

STEVENS & LEE
BY: Neil C. Schur, Esquire

GOODWIN PROCTER LLP
BY: Anne Marie Hassett, Esquire
Keith A. Zullow, Esquire
Michael B. Cottler, Esquire
Attorneys for the Defendant

Theodore M. Formaroli, CSR, CRR
Official Court Reporter
New Jersey CSR # 433

United States District Court

Camden, New Jersey

THE COURT: Good morning. You may be seated.

Okay. We're this morning in the matter of AstraZeneca versus Ivax, 05-5142. Let me hear from counsel representing AstraZeneca.

09:40AM MR. BERRY: Good morning. Andrew Berry and Mark Arania from McCarter & English. With me from Ropes & Gray are Denise Loring, Pablo Hendler, Chris Harnett and Derek Kato. And from AstraZeneca is Chris Kaufman.

THE COURT: Okay, good morning. And who is going to be

09:40AM --

MS. BERRY: Within the Court's permission, Ms. Loring will do the introduction to the tutorial of the plaintiff and both Mr. Hendler and Mr. Harness will take pieces of it.

THE COURT: All right. And for Ivax?

09:40AM MR. SCHUR: Good morning, your Honor. Neil Schur from Stevens & Lee for Ivax. We have with us Annemarie Hassett from

THE COURT: That might work out perfectly.
MS. HASSETT: Yes.
THE COURT: I would like for break at 12:30. I don't want to cut you off at 12:30, I have a little bit of flexibility. Let's just take a five-minute break and then we'll get started.
DEPUTY CLERK: All rise.
(Brief Recess.)
DEPUTY CLERK: All rise.
THE COURT: Okay. You may be seated.
Okay. Ms. Hassett, whenever you're ready.
MS. HASSETT: Good morning, your Honor.
My partner and I, Mr. Zullow, will be presenting this morning. And we, on behalf of our entire team, welcome this opportunity to tell you what, from our perspective, this case is about. And I want to first tell you that when we -- the presentation that we have prepared today was done in consultation with two of our consulting experts in this case, Dr. Gene Colice, who is pulmonologist who is sitting in the court today, and Douglas Sporn, who worked the FDA for many, many years who is also in the court today.
Now, in the course of listening to AstraZeneca's presentation, what we decided to do is not repeat certain things that they discussed where our view and our statements would amount to the same. We're going to focus our attention

on areas where they may have discussed them but we have a different slant or they haven't discussed them at all. When we spoke with you at that telephone conference long ago, you said you wanted to us to present in this tutorial what this case is about, and that's what we're prepared to do today from our perspective.
Can we have the first slide, please?
What this case is about is a pharmaceutical product. Ivax wants to make and sell budesonide inhalation suspension, that's what we refer to as BIS, BIS for twice daily use and Ivax has asked the FDA to approve ANDA No. 77519 for that purpose.

Now, AstraZeneca wants to prevent Ivax from taking this product to market, and they are asking you in this litigation to issue an order that FDA final approval cannot take effect until the two AstraZeneca patents, the '603 patent and the '099 patent expire on December 23, 2018.

Ivax thinks it shouldn't have to wait that long. And the two reasons -- two of the key reasons that Ivax thinks it shouldn't have to wait that long we presented as our defenses in this case.

First, that the Ivax generic BIS, that's the product that's actually delivered to the patient, and the label for twice daily use don't infringe the AstraZeneca patents, that's one of the points that we think are a reason why we shouldn't

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have to wait for the patents to entire, at least for the '603 because it's not an issue, we have a carve out.

And the second reason is that these AstraZeneca patents are not valid and can't even fairly exclude once daily use.

These are our two defenses, non-infringement, that's the first defense, and invalidity of the patents, that's the second defense, the second statement on the slide.

Now, AstraZeneca believes that Ivax should be prevented from going to market for both these reasons. But Ivax believes that in fact both of its defenses are true, that both -- we don't infringe and both the patents are invalid. But the fact is that Ivax can make and sell its product if either one of these is true.

Now, what I'm going to do this morning is present to you information -- what Mr. Zullow and I will do this morning is present to you the support that exists for the Ivax defenses in three main areas: One is developments in the field of asthma treatment that took place before the two AstraZeneca patents were even filed, the second is a brief look at the AstraZeneca patents themselves that I will do in a more thorough look by Mr. Zullow, and third is the regulatory landscape for pharmaceutical products. And we want to focus on that in particular because we think it's critical to your understanding the question of the Ivax label and whether it infringe.

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safe and effective use on that label, the Ivax product doesn't infringe because the term "lowest effective dose" in that phrase "titrate to lowest effective dose" can only mean the lowest effective dose on the Ivax label. And since it's only a twice-daily dose, there can't be infringement.

THE COURT: Can you say that over again?

MS. HASSETT: Yes. We're saying that the label means -- a label indicating means that once-daily administration is a safe and effective use on that label and so why is it that the Ivax product doesn't infringe under that construction? If you take the language that AstraZeneca's saying is the infringing language, which is titrate to the lowest effective dose, on the Ivax label that language has to be understood as meaning the lowest effective dose on the Ivax label and that the lowest effective dose that is shown to be a

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safe and effective use on the Ivax label. And on the Ivax label, that is 0.5 milligrams administered in two 0.25 milligram doses each day. And we will discuss it in more detail this afternoon, but there really isn't any dispute in this case that on the Ivax label, the lowest effective dose according to that label is 0.5 administered in two 0.25 milligram doses per day. Okay?

THE COURT: Thank you.

MS. HASSETT: All right. Now, we think that our analysis here is correct because the kit claims all focus on -- they contain the words "label indicating," and this is the language that AstraZeneca chose when these claims were drafted and that language focuses you on the label itself. And in the context of a label for pharmaceutical product in the United States, the label as a whole standing on its own has to indicate that once-daily use is safe and effective and things outside the label aren't what you use to interpret what's on that label from the FDA. And this is why we think our analysis is correct. Again I'm telling you for this afternoon you can ignore the Ivax analysis, we're not asking you to consider that for summary judgment, but if summary judgment isn't granted and we go in to a trial, you are going to have to ultimately consider these two claim constructions and I want to tell you about them so you understand what the case is about in the broader sense.

So what's the claim construction or the claim interpretation that's offered by AstraZeneca? Well, here it is. A label indicating administration at a frequency of not more than once a day should mean a label that includes an instruction to administer at a frequency of not more than once a day. So that's their construction.

Now, I'm going to submit to you that even under that construction, Ivax doesn't infringe, and I'll talk about this this afternoon, I'm not going to get into that now, but we just want to point out a few things that we think are wrong with that construction, or that interpretation.

If you really apply it to the claim language -- and here Ivax's analysis of how that language applies as a claim interpretation on infringement, you see what's wrong with it. If you really apply it the way they say, infringement arises on the Ivax label by looking at the language "titrated to lowest effective dose." What they're telling is that language is an instruction to administer at a frequent not more than once a day because by ignoring thing that or on the label about what the safe and effective dose are, what the frequency, the effective frequency administration is, which is always twice-daily, and by ignore what the label says that the lowest effective dose is on that label, which is 0.5, they say ignore that, but they say look to things outside that label, look to what the Pulmicort Respules® says, look to what the

expert guidelines say and then take that outside information, bring it into the Ivax label, ignore what's on the Ivax label, and say oh, now we have an instruction. And we just submit that as a matter of claim interpretation as a matter of analysis. It just doesn't make sense.

In fact, it ends up being an interpretation of the claim which is now not the label itself, which is where the claim language focuses you, but label plus other information that may be potentially available to a physician.

And as a matter of claim interpretation one of the other reasons this doesn't make sense is that it completely undermines the notice function of a claim. Claims are designed to let the world know this is what we cover and we don't cover this. And by the interpretation that AstraZeneca is offering

twice daily use. But when you get to this section where I don't mention the study, now when you go look at that study, you should ignore everything on my label, pull that into my label, and now say I'm instructing you to do it once daily, I think that just isn't a rational way to interpret the construction that they're offering to you.

And so, you know, I think if we continue along -- if you have more questions on that, I'd be happy to answer them.

THE COURT: No, go ahead.

03:23PM MS. HASSETT: Now, and I guess let me just focus on this point for a moment because I think it comes up over and over again, it's going to come up in the question of titrate to the lowest effective dose. It's really the same issue. The construction that AstraZeneca has offered you, you know, appears to be a focus on the label, but in fact it's not a focus on the label, and in that sense I think, you know, it's not a correct construction. But here's the problem. It says you can find an instruction on the label by going somewhere else and pulling in that information, putting it in the label now to make that label have that instruction, and have that be an instruction, despite other things that would say that's not what you do. In other words, it says ignore what's on the label and bring in something else. And that seems to be a fundamental problem that comes up over and over again.

It's the same problem with the question of the

titrate to the lowest effective dose language, the lowest effective dose on the Ivax label. If you look at that in the confines of itself, which as even Doctor -- as I think both sides would agree is the correct way to do from the FDA's perspective, and as I think even Dr. Chipps acknowledged on the face of the Ivax label if you just look at that label, the lowest effective dose is .5 milligrams administered in two 0.25 milligram doses daily. That's what the efficacy and safety data on that label said.

03:25PM Now, if you go to the titrate to the lowest effective dose language, they're saying let's say you've got a patient who is being maintained who has gotten stabilized --

THE COURT: I'm sorry.

(Short pause)

03:25PM 15 THE COURT: Okay. Go ahead.
16 MS. HASSETT: Now, let's take the hypothetical that
17 AstraZeneca has presented to you. Patient is receiving
18 budesonide inhalation suspension .5 milligrams a day in two
19 divided daily doses and now they've reached stability and the
03:26PM 20 doctor is looking at the language on the label that says
21 titrate to the lowest effective dose. We say the doctor who
22 reads that looking at the Ivax label would see that the lowest
23 effective dose on the Ivax label is 0.5 given in two divided
24 daily doses. In other words, that doctor is already at the
03:26PM 25 lowest effective dose based on that label. And so there is no

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1 titrating down that the doctor can do if he is following the
2 instruction on the label because the label is instructing that
3 the safe and effective use is the lowest safe effective use is
4 0.5 in two divided daily doses. So that doctor, if he's
03:27PM 5 following that label, is not going to titrate down.
6 THE COURT: So, do you agree with the general
7 proposition that in looking at this it requires someone to
8 reasonably interpret it, the label?
9 MS. HASSETT: I think that the label is -- has to be
03:27PM 10 interpreted in the context of itself and what it is as an FDA
11 document, yes.
12 THE COURT: Okay. And so if there is a better way of
13 saying it, is that something that I should consider?
14 MS. HASSETT: I'm not sure I understand your
03:27PM 15 question.
16 THE COURT: Well, it seems to me there would be no --
17 when you look at recommended starting dose, for example, it
18 seems to me that it had said lowest effective dose per
19 administration, that would be more clear.
03:27PM 20 MS. HASSETT: I'm trying to understand. Lowest
21 effective dose per administration?
22 THE COURT: Well, or per frequency or whatever word
23 you want to use. But it does seem to me that looking at the
24 when it says recommended starting dose that if you titrate
03:28PM 25 down and you have .5 daily, that the only way to go is that

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effective dose and that's because there is no efficacy data
03:37PM for 0.25 given in --
THE COURT: AstraZeneca's --
MS. HASSETT: That's in AstraZeneca's label, it's not
on the Ivax label.
THE COURT: No, my question is, is there efficacy data
03:37PM that shows that it is safe and efficacious to give at 0.25
milligrams once daily.
MS. HASSETT: Well, not on the Ivax label. Now
AstraZeneca --
THE COURT: That's what I mean, in the AstraZeneca
03:37PM label.
MS. HASSETT: We actually don't -- we don't agree
that the data on the -- the clinical data reported on the
AstraZeneca label in fact supports that 0.25 once a day is a
safe and effect dose under the standard that the FDA sets. We
03:38PM don't agree that that's the case, but we don't think -- I

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mean, we don't think you need to resolve that for a question
of determining what the Ivax label is or isn't instructing,
but --
THE COURT: No, I think I do because if I'm
03:38PM understanding what you are saying is that the lowest effective
dose must be examined in the context of what the FDA
determined to be safe. Stop me when I say something wrong,
okay?
MS. HASSETT: Safe and effective.
03:38PM THE COURT: Okay.
MS. HASSETT: Yes.
THE COURT: So that's what you're saying. So what
you're saying is that according to that concept then, 0.25
twice daily has been deemed to be safe and effective by the
03:38PM FDA and therefore when you look at the FDA data you can't
titrate down to 0.25 once-daily because there is no evidence
that that's safe and effective by the FDA.
MS. HASSETT: Right. And that's correct for the Ivax
label. There is no evidence on the Ivax label that 0.25 once a
03:39PM day is a safe and effective treatment.
THE COURT: But you keep telling me that I have to
look at what the FDA has determined to be the lowest effective
dose.
MS. HASSETT: Right. On the Ivax label. On the Ivax
03:39PM label. And that is -- I mean, first of all -- and so when you

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C E R T I F I C A T E.

I, **Theodore M. Formaroli, C.S.R.**, Official United States Court Reporter and Certified Shorthand Reporter of the State of New Jersey, do hereby certify that the foregoing is a true and accurate transcript of the testimony as taken stenographically by and before me at the time, place and on the date hereinbefore set forth.

I do further certify that I am neither a relative nor employee nor attorney nor counsel of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel and that I am not financially interested in this action.

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THEODORE M. FORMAROLI, C.S.R.
Certificate No. 433
Date: September 23, 2008

United States District Court

Camden, New Jersey
