

11/1/01

Mike,

The following is a summary of the luncheon discussion between Matt Bourke, Jaeson Kaplan, Dr. Michael Reinstein, Lynn Jones RN, practice manager, and John G. Sonnenberg PH.D., executive director of the Uptown Research Institute. During the lunch meeting several concerns were raised regarding the lack of utilization of their practice in clinical studies. They also mentioned that certain members of the company have been very uncooperative and inaccessible in the discussion of the practice's concerns. Over all, they felt that there was an immense "lack of follow through" by several members of the company.

According to Dr. Sonnenberg and Dr. Reinstein, their disappointment can be put into three major categories. First, They feel that the company has "dropped the ball" by not using them in our multi-centered trials. They are the single largest users of Seroquel in the country, and they feel they can get ample enrollment in a short period of time. As an example, they were given a year to enroll a number of patients in a study for Eli Lilly, and they enrolled their number in two weeks time. They went on to say that they use Seroquel far more often in their practice, and enrolling patients for a Seroquel study would be, "A no Brainer." Dr. Sonnenberg believes there to be " in the range of one thousand patients on doses of Seroquel exceeding 800mg." "75% of the unhappiness would go away, if we could get involved in a study, even as an add-on-site."

The second area of disappointment stems from an overall lack of follow through on the part of AstraZeneca. Dr. Reinstein was very unhappy with the fact that the "Quest Study" has not been published yet. He feels that four years should have been ample time to rewrite the study, and have it published. Dr. Reinstein said that there is no help from medical writers on getting these studies published by AstraZeneca, and that our competition has a definite advantage over us in getting papers prepped and published. Dr. Reinstein also mentioned that there was a lack of help with the writing of the poster he presented at the conference in New Orleans this year.

Also included in this lack of follow through is a "Lack of cooperation by the clinical research people at AZ." In particular they mentioned Faith Yao as being "Terrible to work with". She often makes inappropriate comments such as, "You should realize that you are not the only practice," when confronted about why the office is not used for clinical studies. The practice also routinely calls Faith, to discuss issues, and often do not even receive the courtesy of a return phone call.

Their frustrations extend beyond Faith. They mentioned to us that issues with other clinical research people, including Jamie Mullen, have left them with a bad taste in their mouths. Often, Dr. Reinstein has called to find out information on the "Quest Study", and he feels like he gets the "run around". He has been told a countless number of times that the "Quest Study" was being worked on by another physician, and when he calls that

individual, he/she denies that they are currently working on it. He therefore has the impression that he is being lied to.

The final issue that the doctor has with AstraZeneca is the travel policy. Dr. Reinstein has never had to front the money for Hotels, Planes, etc with other companies. He feels that there is a lack of a centralized speakers' Bureau, and that we should take a lesson from the Canadian portion of AZ and the other companies in the industry. Dr. Reinstein was offered a meeting in Delaware with AZ, and then was told that we did not have the budget to fly him out. When he mentioned that he would like a teleconference, it was refused.

In closing, Dr. Reinstein again emphasized that Seroquel was "The best, and **most efficacious** drug available". He feels that it is "Ludicrous that Risperidone has double the market share that Seroquel does after four years on the market." Dr. Reinstein said, "Risperidone has EPS, sexual dysfunction, and is just a dirty drug." He and his colleagues feel that one of the reasons Seroquel is underutilized is a lack of clinical studies and medical information. Doctors feel that the drug does not work because they are not using the right dose. He has seen that other healthcare providers are afraid to push the dose, because there is a lack of information about the drug. Often, AZ Professional Sales Specialists from around the country call him for information about Seroquel at high doses. He would love to do a study looking at doses in excess of 800mg. Dr. Reinstein feels that AZ has the best drug, and the best representatives, but wishes the clinical side would match the research scope of companies such as Jansen and Eli Lilly.

Again, Jaeson and I are sharing with you the comments made by Dr. Reinstein and his associates at this luncheon.

Sincerely,

Matt Bourke  
&  
Jaeson Kaplan

PHONE(773)989-9868 \* FAX(773)989-9824

October 23,2001

David Brennan, C.E.O.  
AstraZeneca Pharmaceutical, U.S.A.  
1800 Concord Pike  
P.O. Box 15437  
Wilmington, Delaware 19850

Dear Mr. Brennan;

RE:Seroquel(Quetiapine)

We have been informed by several of AstraZeneca's Pharmaceutical Sales Specialist that the physicians In our practice are the largest prescribers of Seroquel In the world and we have consistently taken an active role In promoting Seroquel. We want to express our long term frustration with certain practices of your company which, we feel have limited the overall use of Seroquel. Although the use of this drug is slowly increasing we feel that this drug should have a much higher market share. It seems almost laughable that Risperdol has approximatel double the market share of Seroquel since, Seroquel has now been available for over four years has better efficacy and fewer side effects than Risperdol.

The reasons 'for Risperdol having a higher market share than Seroquel are obvious:

1. The promotion of Seroquel lacks medical direction. Janssen does far more research than AstraZeneca. Risperdol studies are of better quality and Janssen has published far more studies on their product than AstraZeneca has.
2. AstraZeneca still has not promoted an appropriate dosing strategy. When Seroquel was Initially launched in 1997, the dosing strategy was, 300mg/day. Our dosing practices and research Indicate that for a large number of patients a therapeutl dose of 1200mg/day Is needed. The perception of most psychiatrist Is that Seroquel lacks efficacy. This false perception prevents them from using it and/or using it effectively.

Daily we have encountered third pArty payers that refuse to pay for Seroquel prescriptions over 800mg/day due to the dose range listed In the P.D.R. This has made It difficult for us to appropriately treat our patients. When our physicians lecture across the country, we encounter complains from other psychiatrist who have been unable to get third party payers to pay for prescriptions over 800mg/day. More research needs to be done and submitted to the F.D.A. to increase the dose range.

**CMHS**

**COMMUNITY MENTAL HEALTH SERVICES**

**4755 NORTH KENMORE**

**CHICAGO, ILLINOIS 60640**

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**3. Functioning as a speaker for Seroquel in the United States is problematic to say the least. Unlike AstraZeneca Canada and other pharmaceutical companies the speaker must pay his airfare, hotel and other expenses. Despite numerous promises collecting our out of pocket expense and honorarium continues to, be very difficult. Complicating this further is the large number of speaking engagements that are canceled due to the Sales Representatives who scheduled the engagement being, "over budget". The speaker doesn't get reimbursed for his/her time scheduling the speaking engagement, long distance calls and faxes to the sales representative or lose revenue due to inability to replace the time slot with another revenue source at such a late date. Another major inconvenience is the lack of a coordinator for AstraZeneca in the United States. The Canadian division and other pharmaceutical companies have such a person. We must mail or fax our vitae and program description to each sales representative.**

**We feel it is time for some new leadership with this exciting product which could help so many patients. We would like to share our thoughts further with anyone in your organization that is willing to work with us to make the needed changes.**

**Sincerely,**

**Michael J. Reinstein M.D.,P.C.**

**S.C. Mohan M.D., S.C.**

**Maxim Chasanov M.D.,P.C.**

**S.A. Patel M.D.,S.C.**

**Rad Gharavi M.D.,S.C.**

**Lynne E. Jones R.N.**

**John Sonneberg Ph.D.**

Tuesday, October 30, 2001

To: L. Palczuk  
D. Beamish  
L. Lloyd-Washington  
J. Mullen  
J. Allsop (via E Mail)  
S. Maseth (via E Mail)

From: G. Tugend

Re: Letter to D. Brennan from Dr. Reinstein and colleagues, dated 10/23/01

I have attached the subject letter, a copy of which I received today. The following represents my comments but I would appreciate the opinions of Jamie, Lisa, Jeff and Sarah as well in the areas that they are familiar with.

Point 1. No doubt Janssen does significantly more research than AZ which is not surprising given the resources that Janssen provides to the #1 drug in their overall business. The fact that they were launched nearly 4 years before SEROQUEL also results in a research portfolio that is significantly more robust than ours. However, the remark about the quality of our studies is both untrue and unfair. This group is constantly demanding research grants from us but the quality of their research and poor reputation in the psychiatry community has limited our work with them to retrospective chart reviews or small pilot trials. In fact that have blatantly threatened to switch their SEROQUEL patients to Geodon (or back to Risperdol <sic> Risperdal) if they do not get research funding from AZ.

Point 2. There is really no dispute in my opinion on the comments made here. But regarding the actual dosing, we are restricted to the Prescribing Information which was based upon the registration trials which gave us the "initial target dose of 300-450 mg" and dose range of 750 mg in Study 13 and 800 mg for safety. We do have high dose and rapid titration trials planned although they will not result in a label change. Again, this group is practically demanding funding to do a SEROQUEL high dose study.

Regarding the points about claims being denied beyond 800 mg/day I would be interested in our Field Sales and Account Directors asking around to see if Zyprexa claims are denied over 20 mg/day, which is their label maximum.

Point 3. Customer has very good point, in particular regarding reimbursements and honoraria resulting from field-sponsored programs. The Marketing team has heard this on more than one occasion from customers and in fact pursued with Field PREP the possibility of out-sourcing and/or providing a person/group to handle such payments from field programs. Field PREP, who felt that the current system was adequate, did not entertain this recommendation. (Note: Payments to faculty participating in central Marketing programs such as National/Regional Ad Boards, National Speakers Updates, Satellite Symposia, etc are reimbursed by the vendor on our behalf and are not the programs referred to in this letter).

My only comment on the "time for some new leadership" is that I was personally very surprised by this letter, given that I have had several conversations with both Drs. Reinstein and Sonneberg over the past few months and without exception that have been collegial, cordial and positive in the outcome. I know that this is also the case with Jamie, Jeff and his group, and Sarah.

Please let me know if you want me to compile comments from Jamie and Lisa and respond to David and James, as well as to the customer. This customer does generate a tremendous amount of business for us and Sales, Marketing and Medical have all had significant open and honest dialog with them over the past weeks. Therefore, I am puzzled by their on-going lack of understanding, particularly as pertains to Points 1 and 2.

Thanks, Georgia

APT.  
24/6/01

CMHS  
COMMUNITY MENTAL HEALTH SERVICES  
4755 NORTH KENMORE  
CHICAGO, ILLINOIS 60640  
PHONE(773)989-9868 \* FAX(773)989-9824

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October 23,2001

David Brennan, C.E.O.  
AstraZeneca Pharmaceutical, U.S.A.  
1800 Concord Pike  
P.O. Box 15437  
Wilmington, Delaware 19850

Dear Mr. Brennan;

RE:Seroquel(Quetiapine)

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Daily we have encountered third party payers that refuse to pay for Seroquel prescriptions over 800mg/day due to the dose range listed in the P.D.R. This has made it difficult for us to appropriately treat our patients. When our physicians lecture across the country, we encounter complaints from other psychiatrist who have been unable to get third party payers to pay for prescriptions over 800mg/day. More research needs to be done and submitted to the F.D.A. to increase the dose range.

3. Functioning as a speaker for Seroquel in the United States is problematic to say the least. Unlike AstraZeneca Canada and other pharmaceutical companies the speaker must pay his airfare, hotel and other expenses. Despite numerous promises collecting our out of pocket expense and honorarium continues to be very difficult. Complicating this further is the large number of speaking engagements that are canceled due to the Sales Representatives who scheduled the engagement being, "over budget". The speaker doesn't get reimbursed for his/her time scheduling the speaking engagement, long distance calls and faxes to the sales representative or lose revenue due to inability to replace the time slot with another revenue source at such a late date. Another major inconvenience is the lack of a coordinator for AstraZeneca in the United States. The Canadian division and other pharmaceutical companies have such a person. We must mail or fax our vitae and program description to each sales representative.

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Sincerely,

Michael J. Reinstein M.D.,P.C.

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S.A. Patel M.D.,S.C.

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Lynne E. Jones R.N.

John Sonneberg Ph.D.

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**Id :** i.m.84c8bdeb6554203aecc19d7d2bd7f19e  
**CN :** SQ1ED01256558  
**Date :** Monday, December 16, 2002 8:00:00 AM GMT  
**From :** Fontana, Patricia  
**To :** McCormack, Eileen  
**Subject :** re: High Dose Seroquel Letter  
**Attachments :**  Doses\_above\_800mg.doc  
**Custodians :** McCormack, Eileen

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**From:**  
Fontana, Patricia

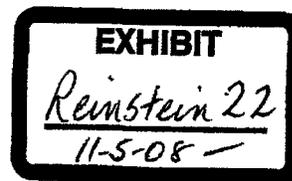
**Sent:**  
Monday, December 16, 2002 10:07 PM

**To:**  
McCormack, Eileen

**Subject:**  
re: High Dose Seroquel Letter

**Attachments:**  
Doses\_above\_800mg.doc

Hi Eileen,



Here is the final version of the High Dose Seroquel letter. Lucette has reviewed and I incorporated her changes. With respect to the Reinstein abstract, I checked a databases of letters from other countries.

None of them are using the Reinstein abstract in their letters. As previously discussed, John Tumas felt that "referring to it can lead to more questions about it (results, methodology) and would indicate that we support its findings, which we don't" This was considered a sensitive issue. I cut and pasted his comments from previous emails to refresh your memory. Let me know what you think. I am at the BPD preceptorship tomorrow so I will touch base with you Wednesday.

Patricia

Patricia,

The Reinstein/Sonnenberg poster at APA 2001 was a sensitive issue. This was an IIT that we supported, but it was determined that the investigator deviated from the protocol and his results were suspect. There were discussions with the investigator that I was not a part of and it was decided that we would not assist in poster production to try to distance ourselves from the study. Drs. Reinstein and Sonnenberg presented the results anyway, but my understanding is that AZ has chosen to ignore the study.

John

No. Referring to it can lead to more questions about it (results, methodology) and would indicate that we support its findings, which we don't.

Patricia Fontana B.Sc. B.Sc Phm

Medical Information Associate

phone (905) 804-4927

fax (905) 277-3556

email: [patricia.fontana@astrazeneca.com](mailto:patricia.fontana@astrazeneca.com)

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**Id :** i.m.7c05909efeee17a5dbe42a22aa3896a2  
**CN :** F339-E05326923  
**Date :** Tuesday, December 12, 2000 6:41:00 PM GMT  
**From :** Schilling, Ann E  
**To :** Moriarity, Sean  
**Cc :** Tumas, John A  
**Subject :** FW: Reinstein/Sonnenberg paper  
**Attachments :**  Comparative Efficacy and Tolerability of Quetiapine at High and Low Doses.doc  
**Custodians :** grpshare

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**From:**  
Schilling, Ann E

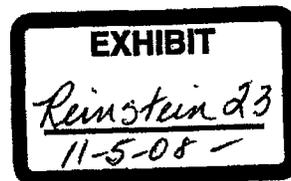
**Sent:**  
Tuesday, December 12, 2000 3:40 PM

**To:**  
Moriarity, Sean

**Cc:**  
Tumas, John A

**Subject:**  
FW: Reinstein/Sonnenberg paper

**Attachments:**  
Comparative Efficacy and Tolerability of Quetiapine at High and Low Doses.doc



Sean, Can you shed any light on the Reinstein retro trial. I think it was approved sometime last spring.

Thanks

Ann S

-----Original Message-----

From: Tumas, John A

Sent: Tuesday, December 12, 2000 10:11 AM

To: Brecher, Martin; Altman, Charles; Jones, Martin AM (PHMS); Goldstein, Jeffrey M; Richards, Adam B; Holdsworth, Debbie; Mullen, Jamie A; Schilling, Ann E; Gavin, Jim P; Zimmerman, Paul M; Leon, Ann L; Ney, Christine A; Williams-Hughes, Celeste

Cc: Yao, Faith

Subject: Reinstein/Sonnenberg paper

Importance: High

All,

Attached is a preliminary draft of a manuscript by John Sonnenberg, who works with Michael Reinstein. It is based on the IIT they are doing comparing high and low dose quetiapine. Although the basic message sounds favorable, ie there were no safety issues with the high dose (1200 mg) vs the low dose (600 mg) and there appeared to be some improvement in efficacy at the higher dose, I think this data is likely to be criticized.

Firstly, the investigator selected which patients would be in which group. Presumably, the sicker patients got the higher dose, which may explain the small difference in efficacy.

Secondly, safety was based entirely on adverse event reports, and out of 30 patients there were no reports of adverse events - a bit hard to believe, especially at 1200 mg. I don't think this will support any claims of safety.

Dr. Sonnenberg wants to submit an abstract to APA on this data. As the deadline is only a couple of weeks away, please let me know your thoughts on this as soon as you can. Even though it is an IIT, I'm not sure that we can prevent him from submitting this data if he wants to. Perhaps we can help him with some statistical support, as Faith has suggested.

Best regards,

John

cid:CHILKAT-CID-9a244b03-bedf-49ea-bc2f-de6a7fa3bfc2

Apr 03 07 11:39p

p. 4

**Unknown**

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**From:** Mullen, Jamie A  
**Sent:** Tuesday, January 25, 2005 4:24 PM  
**To:** Daniels, Stephanie  
**Subject:** RE: Reprints of Reinstein

Stephanie - This is the study. Goes to show you that if there's a huge need for data to support a message, the data will find its way out (despite our guidance to the contrary).

If you want to talk about the advice to provide Anders, I'd be happy to help you on the phone.

Jamie

-----Original Message-----  
**From:** Daniels, Stephanie  
**Sent:** Tuesday, January 25, 2005 11:30 AM  
**To:** Mullen, Jamie A  
**Subject:** FW: Reprints of Reinstein

Hi Jamie - Is the Reinstein study the one we're not supposing to be using any more??

(Interestingly, Sweden were also asking about the Nagy study earlier in the week.)

Thanks

Stephanie

-----Original Message-----  
**From:** Granö, Anders  
**Sent:** Tue 25 Jan 2005 15:23  
**To:** Daniels, Stephanie  
**Cc:** Andersson, Britt-Marie A  
**Subject:** Reprints of Reinstein

Dear Stephanie,

The study by Reinstein showing the favorable switch from clozapine to Seroquel has been very popular among Swedish psychiatrists. In fact, so popular that we have run out of copies. Do you know what the cost for further reprints would be and/or if maybe there is a "secret stash" somewhere?

Thank you in advance,

**Anders Granö**  
Brand Manager Seroquel

AstraZeneca Sverige AB  
B413 42C1 SE-151 85 Sodertälje Sweden  
Tel +46 8 553 248 58 Fax +46 8 553 278 81 Mobile **REDACTED**  
anders.grano@astrazeneca.com

EXHIBIT 5  
WIT: *Mullen*  
DATE: 11/1/07  
LINDA ROSSI RIOS

2

# **EXHIBIT 17**

**From:** Beamish, Don G  
**Sent:** Monday, November 05, 2001 10:24 PM  
**To:** Pusey, James M  
**Cc:** Tugend, Georgia L  
**Subject:** FW: Reinstein Response Letter and Backgrounder

**Importance:** High

**Attachments:** Reinstein Response.doc; Reinstein Backgrounder.doc  
James,

Georgia has spoken to Dr. Reinstein directly and has drafted the attached response to his letter. Georgia has also provided some background information that would not be sent to Dr. Reinstein. I would recommend that the letter should be sent from Georgia. I think it is important for Georgia to maintain her relationship with Dr. Reinstein and be viewed as his key contact. As I suggested in my previous memo, I also think it would be appropriate for me or someone else in a leadership role to acknowledge his concerns directly either in a phone call or in a follow up letter. Please let me know how you would like to proceed.

Don

-----Original Message-----

**From:** Tugend, Georgia L  
**Sent:** Monday, November 05, 2001 4:49 PM  
**To:** Beamish, Don G  
**Subject:** Reinstein Response Letter and Backgrounder  
**Importance:** High

November 5, 2001

Michael J. Reinstein MD, PC  
Community Mental Health Services  
4755 North Kenmore  
Chicago, IL 60640

Dear Dr. Reinstein,

I am in receipt of your in your letter dated October 23, 2001 to David Brennan. and hope to address the points you raise.

Here at AstraZeneca we are aware of the critical nature of our relationship with you and your colleagues that has been established with individuals from our Sales, Marketing, and Medical functions. We value the contribution that you, as an important customer, have made toward the success of SEROQUEL and appreciate your candid feedback to us.

Regarding your first point, there is little doubt that Janssen has funded more research in support of risperidone in the past than AstraZeneca did for SEROQUEL. This, while not ideal for us, is not surprising given that risperidone was launched nearly 4 years before SEROQUEL and that Janssen does provide significant resources to the #1 drug in their overall business. This has resulted in a rich research portfolio to date. However, like you, we recognize the excellent attributes and benefits of SEROQUEL and with its current level of success and its promise for even greater market penetration, the company has increased resources in support of its clinical development program and commercial activities so that past trends may well reverse

There really is no dispute regarding the second point you raise regarding communication of dosing issues. One of the greatest challenges SEROQUEL has faced is ensuring that the appropriate dose is used. The dosing strategy was never to limit use to 300 mg/day but because of trials submitted to the FDA for registration, the Prescribing Information contains the statements "initial target dose of 300-450 mg/day" and dose limit of 800 mg/day for safety. This led to confusion and uncertainty in the minds of some prescribers, which we have aggressively attempted to address in numerous promotional and educational programs over the past several years.

Thank you for bringing the reimbursement issue to our attention. We have confirmed that Omnicare in Chicago is denying claims beyond 800 mg/day of SEROQUEL. They apparently are doing likewise with another atypical antipsychotic. While we will work with our Account Directors and Advocacy Groups to alleviate this situation in the near term, your point to do research to obtain a higher dosing ceiling is well taken.

AstraZeneca prides itself at being a customer-focused organization and as such timely payments of honoraria and reimbursement for expenses is essential. We have put a new system in place for the payment of honoraria but we realize there is room for improvement particularly around travel and other out-of-pocket reimbursements. Likewise an AstraZeneca speaker should not be inconvenienced if a program is cancelled for reasons outside their control and we will address this with our Professional Relations and Sales Departments.

We value the contributions of leaders in Psychiatry such as yourself and appreciate our long-standing relationship with your group. And although we must balance the needs of AstraZeneca products across the entire business portfolio, please let me assure you that the company is in complete support of SEROQUEL and hope to have your continued support as well.

Sincerely,

Background: letter from M. Reinstein, et al to D. Brennan, dated Oct. 23, 2001

This group does generate a very significant amount of SEROQUEL sales for us. They run several clinics in the city of Chicago and by all accounts have over 1,000 patients on SEROQUEL. While likely not "the largest prescribers of SEROQUEL in the world", they probably are in the top 5 in the US.

Because of their patient volume they are attempting to establish themselves as a research center.

This group, in particular John Sonneberg PhD, Director of Research has been extremely persistent in recent months with demanding research from AZ. Their comments to several AZ employees suggest since they use large volumes of SEROQUEL they should by default be doing research on our behalf. They have further implied that should they not get research funding that they would switch patients currently on SEROQUEL to competitive agent(s).

Our Clinical colleagues have significant and numerous issues in past with the quality of research that this group has produced in the past. Matters such as not getting informed consent from study participants, modification of protocols without permission, etc has made the business understandably reluctant to place studies with this group. There is little confidence that Good Clinical Practices can be adhered to. Their research is often criticized by peers in Psychiatry.

However, in attempts to have a "win-win" for all, we have offered funding for projects such as retrospective chart reviews (as opposed to well-controlled, double blinded trials) that could do little harm but still demonstrate commitment to the customer. The group has not accepted this and they continue to insist on funding to do a high dose SEROQUEL trial (>1600 mg/day) that is addressed in Point 2 of their letter.

Drs. Reinstein and Chasnov are prolific speakers on our behalf and are particularly influential with prescribers outside the Chicago regional area. They get numerous speaking engagements because of their own experience and belief in the brand. (Note: they are generally held in poor regard among their peers in the greater Chicago area).

Because of their importance to our business, they have had an extraordinary amount of attention given to them. A number of AZ personnel from numerous functions have had open, honest but collegial, cordial dialog with Drs. Reinstein and Sonneberg. Contact has been with Sales, Marketing, USDD, and Scientific Commercialization at several levels, including Leadership levels within our organization. All involved have had extremely good communication internally and with the customers to address their interests. Every discussion appeared to be well received at that time. However, actions like this letter and other persistent calls demanding research continue to occur despite our attention to their group, thus disappointment with the "time for new leadership" remark.