21 Page(s) Withheld

cc: NDA 20929
Div. File
HFD-570/Purucker
HFD-570/Anthracite
HFD-570/Meyer
HFD-570/Chowdhury
HFD-570/trout

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Rd initial by: Purucker/1-6-2000

MINUTES

TROUT

INDUSTRY TELECONFERENCE MINUTES

Astra
NDA 20-929
Pulmicort Respules (budesonide inhalation suspension)
September 17, 1999

FDA REPRESENTATIVES

Ray Anthracite, Medical Reviewer
Bob Meyer, Division Director
Mary Purucker, Medical Reviewer
Gretchen Trout, Project Manager

SPONSOR REPRESENTATIVES

Frank Casty, Global Medical Leader
Eric Couture, Regulatory Liaison Director
Mario Cruz-Rivera, Pulmicort Respules Program Leader
Donna Dea, Respiratory Therapeutic Area Regulatory Leader
Robert Monaghan, Senior Regulatory Project Manager
Karen Walton-Bowen, Biostatistics Project Team Leader

BACKGROUND: The Division requested this teleconference to have further discussion on Astra's June 16, 1999, submission requesting revisions to the pediatric written request. (See minutes of July 27, 1999, teleconference for previous discussion).

Astra stated that following the previous teleconference they spoke with 8-10 investigators about the study proposal, and the investigators validated what Astra had stated previously (that they can recruit 60 patients total over a 12 month period). The Division stated that we also had additional discussion following the teleconference and while we still want an efficacy trial, we are willing to compromise on the number of patients required. The Division conducted a power analysis with a lower standard deviation and determined that Astra could probably show a significant difference with 60 patients per arm (.5 mg arm, 1.0 mg arm, and placebo). Astra replied that they cannot do this but they are very interested in conducting the studies. The Division offered that if Astra will add the third (placebo) arm, we would consider allowing 30 patients per arm for a total of 90 patients. Astra expressed concern about recruiting 90 patients due to a variety of factors, including blood draws, and were concerned that if they end up with several study sites with only one patient they will not be able to show a statistically significant difference. The Division replied that we would accept urinary free cortisols instead of blood draws, or any other reasonable mean for collecting the data. The Division emphasized that we are intent on obtaining information on optimal dosing and that the pediatric working group felt strongly about dose ranging. With regard to statistical significance, we will put the data in perspective based on other data that are available. Astra suggested that they enroll 20 patients per arm. The Division replied that this suggestion needed to be discussed internally, but reminded Astra that this product would probably be the first inhaled nebulized corticosteroid

suspension on the market and is very likely to be used in young patients. Information on safety and reasonable doses is therefore essential.

With regard to the doses, Astra wants to study .25 mg (low dose), 1.0 mg (high dose) and placebo (active control). The Division agreed to consider .25 and 1.0.

With regard to the duration of the study, the Division wants the study to last for 12 weeks. Astra pointed out that if the NDA is approved during the study it will be difficult to recruit patients because parents will be able to get prescriptions for the product without having to put their children on a study. Astra also stated that there are data in the NDA which show that there are separation of the groups at six weeks. The Division replied that we are looking for a safety signal, not just separation of efficacy. The Division also pointed out that with the drastic reduction in the number of subjects enrolled, the total number of dosing days will be very low. Astra suggested that they could pull patients from the existing safety trials to increase the numbers. The Division replied that in order to meet the exclusivity requirements, the data cannot be in the NDA which has already been submitted.

Astra indicated that they are potentially in a position where they would agree to a study that they will not be able to conduct. Astra questioned if they initiate the study and show after a certain period of time that they could only enroll "X" patients, would they be able to stop enrollment and go forward with the study (i.e., further amend the written request). The Division replied that while it is possible to amend the written request at that time, we would have to give the change a great deal of thought.

With regard to timing of the submission of the study reports, the Division agreed that December 2001 is acceptable.

The Division reminded Astra that to obtain the additional pediatric exclusivity the study results do not have to be positive, they just have to provide the data we requested. However, the study results would impact on what language is included in the labeling. [redacted] the point of the written request is to obtain safety information. The Division also reminded Astra about the pediatric rule which allows us to require studies of sponsors, however we prefer to use the written request route.

[redacted]

/S/

Gretchen Trout, Project Manager

cc: NDA 20929
Div. File
HFD-570/Purucker
HFD-570/Anthracite
HFD-570/Meyer
HFD-570/Chowdhury
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Rd accepted by: Purucker/12-28-99
No comments: Anthracite
Meyer

MINUTES

APPEARS THIS WAY
ON ORIGINAL

INDUSTRY TELECONFERENCE MINUTES

AstraZeneca
NDA 20-929
Pulmicort Respules (budesonide)
July 27, 1999

FDA REPRESENTATIVES

Bob Meyer, Acting Division Director
Mary Purucker, Medical Reviewer
Gretchen Trout, Project Manager

SPONSOR REPRESENTATIVES

Frank Casty, Global Medical Leader
Eric Couture, Director Regulatory Affairs
Mike Elia, Director, Regulatory Affairs
Robert Monaghan, Regulatory Project Manager

BACKGROUND: The Division issued a formal Written Request for pediatric studies on budesonide on December 14, 1998. On June 16, 1999, Astra submitted a request to amend the Written Request. The Division requested this teleconference in order to gain a greater understanding of the issues.

Astra explained that the issue is primarily logistical. Astra feels that a study of the size requested could take years to complete, and that there aren't enough patients available in the age range specified to study. Astra requested comments from the Division on this issue.

The Division indicated that we are not offering a counter-proposal at this teleconference, however we wanted to discuss the lack of an attempt to collect efficacy data in Astra's revised proposal. The division explained that safety data without the perspective of efficacy data to establish a correct dose are not particularly helpful. We also need to know that any dose that we might recommend for this population is the lowest effective dose. The Division's primary concern is to get information on this age group into the label, developing an indication for this age groups is secondary. Astra agreed that this kind of data would be helpful, however the number of patients requested in the Agency's letter is not practical. Astra questioned if they could [redacted] The Division stated that [redacted] and we may make some assumptions based on adult data. The main issue it to gain comfort that the dosing is reasonable in SAR (and any [redacted] does not answer the question for Pulmicort).

The Division suggested that Astra consider ways of defining the population in order to make it more inclusive, and the Division will continue to consider Astra's request to amend the written request. Astra's proposal to submit the complete study reports by June 30, 2001 may well be acceptable.

/s/

Gretchen Trout, Project Manager

cc: NDA 20-929
Div. File
HFD-570/Purucker
HFD-570/Meyer
HFD-570/Trout

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Rd accepted by: Meyer/8-6-99
MINUTES

MESSAGE CONFIRMATION

04/23/99 08:37
ID=PULMONARY DIV FDA

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
04/23	01'39"	610 722 7784	CALLING	.05	OK	0000

04/23/99 08:34 PULMONARY DIV FDA → 916107227784 NO.747 D01

Memorandum of Telephone Facsimile Correspondence

Date: April 23, 1999

To: Michael Elia
Director, Regulatory Liaison

Fax: 610-722-7784

From: Gretchen Trout
Project Manager

Subject: NDA 20-929
March 25, 1999 meeting

Reference is made to the teleconference held between representatives of your company and this Division on March 25, 1999. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1058.

Memorandum of Telephone Facsimile Correspondence

Date: April 23, 1999

To: Michael Elia
Director, Regulatory Liaison

Fax: 610-722-7784

From: Gretchen Trout /S/
Project Manager

Subject: NDA 20-929
March 25, 1999 meeting

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Thank you.

Mike - I am not faxing the attachments since they were your overheads. If you want me to fax them so that you have an exact replica of what will be in our file - let me know.

IMTS #4095

INDUSTRY MEETING MINUTES

Astra
NDA 20-929
Pulmicort Respules (budesonide inhalation suspension)
March 25, 1999

FDA REPRESENTATIVES

Craig Bertha, Chemistry Reviewer
Chong-Ho Kim, Chemistry Reviewer
Robert Meyer, Medical Team Leader (via telephone)
Guirag Poochikian, Chemistry Team Leader
Gretchen Trout, Project Manager

SPONSOR REPRESENTATIVES

Diane Alleva, Director – Product Operations
Bertil Andersson, Project Director – Astra Draco
Barbara Blandin, Regulatory Project Manager
Elliott Berger, VP – Regulatory Affairs
Eric Couture, Director- Regulatory Liaison
Michael Crawford, Director – Manufacturing
Mario Cruz-Rivera, Action Team Leader
Michael Elia, Director –Regulatory Liaison
Ron Peeples, Director – Pharmaceutical Operations
Ziggy Waraszkiewicz, Director –Analytical Development

BACKGROUND: Reference is made to the submissions dated January 26, and March 8 and 16, 1999. The purpose of the meeting is to discuss the issue of budesonide adhering to the wall of the [redacted] container (see January 26, 1999, submission), and to discuss Astra's proposed responses to the Division's February 11, 1999, approvable letter.

I. Issue of [redacted]

Astra provided a brief background (see attachment 1) on what they did to address the issue of [redacted]

Astra then posed the question "Does the Agency concur with our (Astra) proposal to switch the product to the new respule?" The Division informed Astra that on the surface, based on Astra's findings, they are moving in a reasonable direction. However, the decision will be data driven. The Division will review the stability data when they are submitted.

Astra's second question was whether the FDA agreed that the stability data from the first three commercial batches are the only data requirements needed to support approval for the new respule. The Division first encouraged Astra to submit the [redacted] stability data as soon as possible. The Division also stated that the test procedure should be in place before approval, not after. Astra replied that the method will be available and will be used for validation and stability batches. The Division stated that Astra should do the stability study based on the approved stability protocol, and reminded Astra that the mass median diameter (MMD) is not agreed upon yet. Astra wanted to verify that the data from the first three commercial batches would not be rate limiting. The Division agreed that this would be post approval. Astra informed the Division that they will validate the new [redacted] between now and June. They will run the first two validation batches in June, and in late July/early August they will run the other four (for a total of three batches for each strength).

II. Questions from the Division's February 11, 1999, approvable letter.

Astra presented data, and/or responses to the questions from the letter point by point.

Question 1. Astra stated that they will include methods for all tests. The Division pointed out that MMD for particle size has not been agreed on. Astra replied that this will be revised as agreements are made.

Question 2. Astra presented a graph representing the data they collected. The number of datapoints appear smaller than the "n" due to overlap. The graph indicates 18 months of data from Westboro and 24 months from Sweden. The clinical batches were manufactured in Sweden. The particle size distribution for the Swedish batches is very narrow, the Westboro data covered the range of particle size distribution allowed for the active drug. The specification for the bulk drug substance is [redacted]. Referring to the March 8, 1999, submission, the Division pointed out that batch #1990806903 (Table 1) is an outlier and if they exclude this batch the data from the other batches fit close to our proposals. Similarly batch TK 56 (Table 5) is an outlier. If they exclude these batches the data suggests a range of [redacted] The Division stated that we will not accep[redacted] as an upper limit. The purpose of the specification is to control the process, not to ensure that every batch passes. The Division suggested an upper limit of [redacted] or [redacted] Astra agreed to discuss a range of [redacted] with their specification group.

Question 3.a. Astra provided the requested information.

Question 3.b. The Division clarified what the intent of this question is: the Division has had past experiences when an applicant received material which appeared to be identical and yet later found [redacted] The applicant had to reanalyze the material and found that the [redacted] was of a different grade. This is why the Division would like testing instituted for each shipment to ensure that the applicant is receiving the material which they expected. Astra stated that this explanation will help them address the question.

Question 3.c. Astra provided additional information, explaining that the [redacted] The Division stated that we are looking for periodic testing of the components by Astra to verify that the composition is the same.

Question 4. Astra reminded the Division that the [redacted] are no longer used since they will [redacted] the respules. The Division informed Astra that we want to know the composition of the [redacted] The best way to get this information is if the supplier provides a DMF. Astra explained that this supplier is reluctant to submit a DMF, however they will explore this further with the supplier.

Question 5. Astra showed data that they collected. The Division responded that we will review these data.

Question 6.a. Astra will supply the requested test method.

Question 6.b. Based on the data shown by Astra, the Division stated they are going in the right direction, however we will have to review the data.

Question 7. Astra explained that from the table "modified" refers to the respule with a [redacted] 'new" refers to the respule with a [redacted] (which is the one they have decided to pursue), and "old" refers to the previous respule. The data from the studies will be available in July.

Question 8.a. and b. Astra presented a sample of a respule with [redacted] The Division stated that it looks reasonable, however suggested that they use [redacted] in place of [redacted] etc. The reason for this is that, for example, [redacted] could refer to [redacted] Astra agreed to consider this.

Question 9. This was the first issue addressed in this meeting.

Question 10. Astra acknowledged their commitment.

III. New foil labeling.

Astra brought samples of the new proposed foil labeling (see attachment 2).

The Division pointed out that a strip of respules will be used in less then one week, therefore the statement [redacted] allows too much time. The Division prefers that Astra include [redacted] Astra agreed to discuss this internally and fax a proposal to the Division. The Division agreed to look at the proposal in a short time frame.

IV. Discussion of timing of submission.

The Division informed Astra that the response will not be considered complete until all the data are submitted. However, Astra can submit what responses they have now and if time allows, the Division will start reviewing it.

V. [redacted]

Astra made a brief presentation on a recently identified impurity (see attachment 3). Astra explained that they did not detect the impurity before because it was [redacted] They have submitted a briefing package to the Division and they do have pharm/tox data available.

CONCLUSIONS:

The new respule designed by Astra appears to have addressed the issue of adherence of the budesonide to the walls of the respule, however the Division will have to review the data.

Astra has prepared responses to almost all of the Division's questions from the February 11, 1998, approvable letter, except for where they are waiting for data. The Division will not consider the response to the action letter complete, until all data are submitted.

/S/

Gretchen Trout, Project Manager

cc: NDA 20929
Div. File
HFD-570/Kim
HFD-570/Poochikian
HFD-570/Meyer
HFD-570/Trout
HFD-570/Bertha

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Rd accepted by: Meyer/4-5-99
Kim/4-22-99
Poochikian/4-22-99

MINUTES/CORRESPONDENCE

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MESSAGE CONFIRMATION

06/26/98 13:42
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06/26/98 13:40 PULMONARY DIV FDA → 915088368390 NO.560 P01

Memorandum of Telephone Facsimile Correspondence

Date: June 26, 1998

To: Roberta Tucker
Director, Regulatory Affairs

Fax: 508-836-8390

From: Gretchen Trout
Project Manager

Subject: NDA 20-929
Pulmicort Respules
June 22, 1998 teleconference

Reference is made to the telecon held between representatives of your company and this Division on June 22, 1998. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the telecon. If you have any questions or comments regarding the minutes, please call me at 301-827-1058.

Memorandum of Telephone Facsimile Correspondence

Date: June 26, 1998

To: Roberta Tucker
Director, Regulatory Affairs

Fax: 508-836-8390

From: Gretchen Trout
Project Manager

Subject: NDA 20-929
Pulmicort Respules
June 22, 1998 teleconference

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Thank you.

IMTS # 2958

MEMORANDUM OF TELECON

DATE: June 22, 1998

NDA: 20-929

PRODUCT: Pulmicort Respules (budesonide inhalation suspension)

PARTICIPANTS:

FDA:	Shan Chu	Medical Reviewer
	Chong-Ho Kim	Chemistry Reviewer
	Guirag Poochikian	Chemistry Team Leader
	Gretchen Trout	Project Manager
ASTRA:	Mike Crawford	Director of Operations
	Murad Hussain	Regulatory Affairs
	Cheryl Larrivee-Elkins	Manager, Formulation Dev.
	Roberta Tucker	Director, Regulatory Affairs
ASTRA DRACO:	Bertyl Andersson	Project Management

BACKGROUND: During a May 7, 1998, teleconference between Astra and the Division (to discuss comments from the Division's April 15, 1998, information request letter) Astra agreed to explore labeling alternatives on the —— respules in order to ——— Astra submitted a proposal on June 12, 1998, for ——— . This teleconference was held to discuss Astra's proposal.

The Division informed Astra that the following information needs to be included on the respules: ——— d ——— The Division suggested that Astra put the additional information on the back of the respule, or they could extend the top flap portion and engrave information on the flap.

Astra's concerns are 1) that it will be confusing to put the ——— on the respule since the ——— the respule being stored in the foil pouch. Once the respules are removed from the pouch they are only good for —— 2). In order to ———

Astra stated that the Division's suggestion to extend the flap would effect all of their packaging equipment since the boxes, foil pouches, etc. have all been designed based on the respules being the current size. Astra stated that they consider the foil pouch to be the immediate container which is why they planned on including the requested information on the foil pouch and not on the respules. Astra questioned if they could use just the [redacted] on the respules and then include the [redacted] on the foil overwrap. Astra also suggested that they could put some of the information on the side flap. The Division had concerns with information being on the side flap because the individual respules can be separated from the side flap and the consumer may not then have necessary information.

CONCLUSION: Astra and the Division could not reach an agreement on this issue. The Division feels strongly that [redacted] Astra feels that with their current equipment this is not possible.

The Division agreed to discuss this internally with Office level input then let Astra know what the Office's decision is. Astra questioned if this issue is not resolved by July 15, 1998, could they submit the rest of their response to the May 20, 1998, approvable letter. The Division informed Astra that without this issue being resolved the response would not be complete and therefore would not start the PDUFA review clock. The Division agreed to move on this as quickly as possible.

/S/

Gretchen Trout
Project Manager

cc: NDA 20-929
Div. File
HFD-870/Kim
HFD-570/Poochikian
HFD-570/Chu
HFD-570/Meyer
HFD-570/Trout

drafted: GST/June 24, 1998/n:\staff\troutg\20929.tel

rd initial by: Chu/6-25-98
Kim/6-25-98
Poochikian/6-25-98

TELECONFERENCE

1 Page(s) Withheld

MEMORANDUM OF TELECON

DATE: May 7, 1998

APPLICATION NUMBER: NDA 20-929

PRODCUT: Pulmicort Respules (budesonide nebulizing suspension)

PARTICIPANTS:

ASTRA USA:

Michael Crawford	
Murad Hussain	Regulatory Affairs
Cheryl Larrivee-Elkins	Manager, Formulation Development
Larry Paglia	Senior Director, Quality Assurance CMC
Roberta Tucker	Director, Regulatory Affairs

ASTRA DRACO:

Bertyl Andersson

FDA:	Chong-Ho Kim	Chemistry Reviewer
	Alan Schroeder	Chemistry Reviewer/Acting Team Leader
	Gretchen Trout	Project Manager

BACKGROUND: The Division issued a CMC IR letter to Astra on April 15, 1998. Astra subsequently requested a teleconference to discuss some of the comments from the letter (see attached facsimile from Astra dated April 23, 1998, which outlines their specific questions).

With regard to comment 5.b., the Division referred to data submitted in volume 1.6 (of the original NDA submission) pages 139-196 which supports the specification proposed by the Division. The Division explained that Astra's MMD does not reflect their data, and we do not usually set specifications on accelerated data. Under ICH guidelines, if they fail on accelerated data then they should go to an intermediate 30°C condition. Astra's supportive shelf-life stability data on the [redacted] product at [redacted] would pass the specifications that the Division proposed. Astra agreed to look at their data again.

SUMMARY: The specifications for particle size distribution of the micronized drug substance are consistent with all of Astra's shelf-life stability data. Data at the intermediate storage condition (30°C) should be collected over [redacted] if drug

product fails under accelerated conditions. Astra will re-evaluate their data.

With regard to comment 11., the Division explained that previously Astra only compared [redacted] which does not tell us whether the [redacted] used in the secondary packaging materials are equivalent. The Division referred Astra to our comment 10. from the April 15, 1998, letter and explained that addressing comment 10. will help them to respond to comment 11. The Division further explained that stability data does not address the issues of [redacted] and the potential for [redacted], [redacted] through the packaging. Stability methods are not sensitive enough and are not developed to assay specific [redacted] We recommend that Astra obtain information from their suppliers on potential [redacted] and develop appropriate [redacted] methods. We encourage suppliers to establish DMFs which will allow us to be aware of changes as DMFs are updated.

SUMMARY: Astra needs to address the issue of [redacted] and the possibility of [redacted]

With regard to comment 14., the Division referred Astra to volume 1.7, page 307, their stability protocol is different from what is in the drug product specification sheet. The main issue is that the test and specification for [redacted] is missing from the stability protocol. Astra replied that they understood.

SUMMARY: Missing parameters from the stability protocol will be included.

With regard to comment 18., the Division strongly encouraged Astra not to use [redacted] on the [redacted] respule container. The Division reminded Astra that we have never previously approved an [redacted] nebule with [redacted] The Division recommended [redacted] but informed Astra that if they choose to use the [redacted] they will need to address comments 9. and 10. for [redacted] Astra would need to address potential [redacted]

[redacted]

Astra questioned what would be the minimum amount of information that the Division would require on the respule. The Division replied that the [redacted] (this is a preliminary response and may need further discussion within the division). Astra explained that they feel confusion would arise from having the [redacted] on the respules, because once the foil pouch is open, the respules have to be used within [redacted] Astra then questioned if the Division would consider [redacted] The Division replied that we would have many of the same concerns because of the [redacted] Astra asked if they could put together a proposal for how to address the issue and submit it to the Division for feedback. The Division agreed. Astra also verified that if they decide against using [redacted] that they would not then have to answer comments 9. and 10. for [redacted] only. The Division confirmed this was correct, however they still need to respond to comments 9. and 10. for other [redacted] packaging components.

SUMMARY: The Division expressed serious concerns with regard to the use of [redacted] and strongly recommended that information be [redacted] Astra will put together a proposal for how to address these concerns and submit it to the Division for feedback.

ADDITIONAL DISCUSSION

The Division had a question with regard to the package insert. Astra has a statement in the DOSAGE AND ADMINISTRATION section of the package insert which states that ultrasonic nebulizers should not be used for the administration of Pulmicort Respules. The Division questioned why ultrasonic nebulizers are not suitable. Astra referred the Division to section 6 of the original NDA submission (volume 1.25) under "overview of nebulizers." Astra specifically recommends jet nebulizers for this product.

The Division also questioned Astra about their statement that the respules should be stored upright. The Division pointed out that once the respules have been removed from the foil packaging there is no way to store them upright so Astra should think about using different wording. Astra agreed.

Astra stated they also had a question about comment 17. from the letter about subfreezing temperatures. The Division explained that patients do not always follow directions, and/or the product could be stored incorrectly during shipping, so it is important to know what would happen to the product if it was stored at subfreezing temperatures.

/S/

Gretchen Trout
Project Manager

ATTACHMENT

MEMORANDUM OF TELECON

DATE: April, 1998

NDA: 20-929

PRODCUT: Pulmicort Respules (budesonide nebulizing suspension)

PARTICIPANTS:

FDA:	Brad Gillespie	Clinical Pharmacology and Biopharmaceutics Reviewer
	Gretchen Trout	Project Manager
Astra:	Dennis Bucceri	Regulatory Affairs

Ms. Trout informed Mr. Bucceri that Dr. Gillespie had finished his review of the clinical pharmacology and biopharmaceutics section of the NDA, and he had two comments to provide to Astra. The first comment is just for their information and does not require a response, the second comment requires a response.

Dr. Gillespie informed Mr. Bucceri that for study 03-3043, the quality control samples were not ideal because the low level control was below the lower limit of quantification. Astra could best validate the assay by choosing 2 or three samples evenly distributed along the assay range of quantitation. This comment was for Astra's future reference.

Also for study 03-3042, on page 59 of volume 1.17, Astra provided a table listing the formulations used in the study. Several entries were marked "not existing." Dr. Gillespie asked for clarification on what Astra means by "not existing," could they not find the information, or is the information literally non-existent? Mr. Bucceri agreed to look into this and get back to Dr. Gillespie.

/S/

Gretchen Trout
Project Manager

cc: NDA 20-929
Div. File
HFD-570/Gillespie
HFD-870/Mei-Ling Chen
HFD-570/Trout

drafted: GST/April 7, 1998/n:\staff\troutg\20929.3tel

rd initial by: Gillespie/4-10-98

TELECONFERENCE

MEMORANDUM OF TELECON

DATE: March 30, 1998

APPLICATION NUMBER: 20-929

DRUG PRODUCT: Pulmicort Respules (budesonide nebulizing suspension)

PARTICIPANTS:

FDA: John Jenkins — Division Director
Bob Meyer — Medical Team Leader
Gretchen Trout — Project Manager

Astra USA: Dennis Bucceri
Roberta Tucker
Ross Rocklin
Karen Walton-Bowen
Tony Helstosky

Astra Draco: Anders Ullman
Cecilia Seidegard
Christer Hultquist
Bertil Andersson

BACKGROUND: The Division requested this teleconference with Astra to discuss issues with regard to the Advisory Committee meeting scheduled for April 20, 1998, at which this product would be discussed.

The Division identified two main issues to discuss with Astra.

1. Based on the chemists' review of the NDA, which has almost been completed, and discussion at a team meeting, the Division has determined that there are some serious chemistry, manufacturing, and control (CMC) deficiencies which will need to be addressed before this application can be approved. The Division intends to send an information request (IR) letter to Astra with the CMC deficiencies in 1-2 weeks. Given the nature of the deficiencies the Division feels that it would be very difficult for Astra to respond to the deficiencies prior to the user fee due date of May 20, 1998, therefore the IR letter would be followed by an approvable (AE) or not-approval (NA) letter on, or before, May 20, 1998.

2. For the April 20, 1998, Advisory Committee meeting, there are no pediatricians on the committee as voting members who are pulmonologists or allergists. A pediatric endocrinologist is available, as a voting member, to provide expertise on systemic safety issues, however all of the pediatric pulmonologists or allergists were either conflicted (had

participated in trials supporting this application) or had scheduling problems. The Division expressed serious concern with presenting this product, for which Astra has requested an indication for use only in [redacted] to 8 year old patients, to an Advisory Committee without adequate representation by pediatric pulmonologists or allergists.

With regard to issue #2, the Division presented two options: the Agency can continue to try to recruit pediatric pulmonologists or allergists who can attend as guests, but can not vote on the issues, or the advisory committee meeting can be postponed until we can obtain better representation. Since this application will not be approved on the first cycle, and we will have another six months available when Astra responds fully to the action letter, the Division prefers postponing the meeting until Astra has responded to the action letter. This has been discussed with Dr. Bilstad who agrees that it is preferable at this time to postpone the meeting.

While the Division cannot tell Astra at this time whether the letter will be NA or AE, because the reviews have not been completed, the Division did inform Astra that one of the major deficiencies identified by the chemists is the [redacted] vials. [redacted] In the past the Division has not approved [redacted]

Astra agreed to discuss the Division's proposal with regard to postponing the Advisory Committee meeting and notify the Division of their decision.

Follow-Up March 31, 1998

Dennis Bucceri telephoned John Jenkins on March 31, 1998, and notified Dr. Jenkins that Astra has agreed with the cancellation of the Advisory Committee meeting at this time. Astra will send out a press release with regard to the cancellation.

Following the conversation between Mr. Bucceri and Dr. Jenkins, Astra sent via facsimile a draft copy of their press release. Bob Meyer and Gretchen Trout telephoned Mr. Bucceri to provide comments on the draft press release (see attachment 1, with comments indicated).

Astra submitted a revised press release via facsimile later in the day on March 31, 1998 (see attachment 2).

Follow-Up on April 1, 1998

Gretchen Trout telephoned Dennis Bucceri and informed him that Dr. Meyer did not have any comments on the revised press release.

/S/

Gretchen Trout
Project Manager

cc: Orig. NDA 20-929
Div. File
HFD-570/Meyer
HFD-570/Jenkins
HFD-570/Kim
HFD-570/Poochikian
HFD-570/Trout

drafted: GST/April 1, 1998/n:\staff\troutg\20929.2tel

rd initial by: Meyer/4-1-98
Jenkins/4-2-98

TELECONFERENCE

FAX

ASTRA®
Astra USA

FROM	DATE
Dennis Bucceri	3/31/98
DEPARTMENT	FAX NO.
Regulatory Affairs	(508) 836-8390
TO	FAX NO.
Gretchen Trout	(301) 827-1271
SUBJECT	PAGES
Press Release	1(1)

Dear Gretchen

During my conversation with Dr. Jenkins this morning, I explained that we needed to have a press release to explain the postponement of the April 20, 1998 PADAC meeting. He asked that I fax a draft of the press release for review, please find attached.

We would appreciate comments as soon as possible.

Attachment 1

MAILING ADDRESS:
Astra USA, Inc.
P.O. Box 4500
Westborough, MA 01581-4500

OFFICE:
50 Otis Street
Westborough, MA

TEL:
508-366-1100

FAX:
508-366-7406
TELEX:
6810105-Cable/Astrapharm

1 Page(s) Withheld

FAX

ASTRA®
Astra USA

FROM Dennis Buccari	DATE ~~02/13/98~~ 3/5/98
DEPARTMENT Regulatory Affairs	FAX NO. 508-836-8390
TO Gretchen Trout	FAX NO. 301 827 1271
cc:	
SUBJECT Press Release	PAGES

Gretchen,
Here is the revised release that incorporates your comments. Please get back to me if you have comments. We'll probably release it later in the day on Wednesday.

Thanks
Dennis

Attachment 2

1 Page(s) Withheld

MEMORANDUM OF TELECON

DATE: January 16, 1998

NDA: 20-929

PRODCUT: Pulmicort Respules (budesonide nebulizing suspension)

PARTICIPANTS:

FDA:	Gretchen Trout	Project Manager
Astra:	Murad Husain	Regulatory Affairs
	Roberta Tucker	Regulatory Affairs

BACKGROUND: The Division sent a facsimile to Astra on January 16, 1998, requesting justification for Astra conducting study No. 97058-1 in dogs aged 5 to 6 weeks for the proposed pediatric population of [redacted] of age. Ms. Tucker and Mr. Husain called to discuss the request.

Astra pointed out that this issue had been discussed previously numerous times, and in fact Astra had sent in several submissions with regard to this same issue, therefore they do not understand why the request is being repeated. Astra also pointed out that they are now conducting a study in younger dogs, as had been requested by the Division. After discussing the issue with Dr. Tripathi, I informed Astra that the current study will not be available until almost the end of the review cycle for this NDA and therefore is not particularly helpful, and reminded Astra that their previous justification was that the study could not be done in younger animals, however they are now doing the study in younger animals so their justification is not valid. I explained that what Dr. Tripathi was looking for, for example, is information in the literature that [redacted]

Astra responded that the Division was aware that the final study report would not be available until April prior to Astra beginning the study, however the Division had not indicated that this would be too late. Astra also stated that they are doing what had been requested by the Division, even though they do not believe the study will be acceptable. Astra stated that they had talked to several consultants and no one could provide concrete evidence that [redacted]
This was all addressed in the previous submissions.

I informed Astra that I would share their arguments with the review team and we would discuss the issue further internally. I agreed to arrange another teleconference if necessary.

/S/

Gretchen Trout
Project Manager

cc: NDA 20-929
Div. File
HFD-570/Tripathi
HFD-570/Sun
HFD-570/Himmel
HFD-570/Trout

drafted: GST/January 20, 1998/n:\staff\troutg\20-929.tel

TELECONFERENCE

PRE-NDA TOXICOLOGY MEETING MINUTES

Date: December 6, 1996

Product: budesonide nebulizing suspension IND: 44,535
Rhinocort Aqua (budesonide) Nasal Spray NDA: 20-746

Attendees

Astra USA:	Dennis Bucceri	Vice President Regulatory Affairs
	Murad Husain	Associate Director Regulatory Affairs
	Paul Alessandro	Regulatory Affairs
	Roberta Tucker	Regulatory Affairs
	Ross Rocklin	Medical
Astra Draco:	P. Brennan	Regulatory Affairs
	C. Engelbrecht	Toxicology
	B. Andersson	Project Management
Astra AB:	A. Ryerfeldt	Toxicology
	H. Marchner	Toxicology
FDA:	Ray Anthracite	Medical Reviewer
	Lindsay Cobbs	Project Manager
	Peter Honig	Medical Team Leader
	Bob Meyer	Medical Team Leader
	Tunde Otulana	Medical Reviewer
	Luqi Pei	Pharmacology Reviewer
	Hilary Sheevers	Pharmacology Team Leader
	Joseph Sun	Pharmacology Team Leader
	Satish Tripathi	Pharmacology Reviewer
	Gretchen Trout	Project Manager

BACKGROUND: Astra requested a meeting with the Division of Pulmonary Drug Products to discuss their proposed toxicology program for budesonide nebulizing suspension (BNS) and Rhinocort Aqua. Astra submitted a meeting package for each product, both dated November 1, 1996.

The meeting began with introductions, and Astra made a short presentation (see overheads attached).

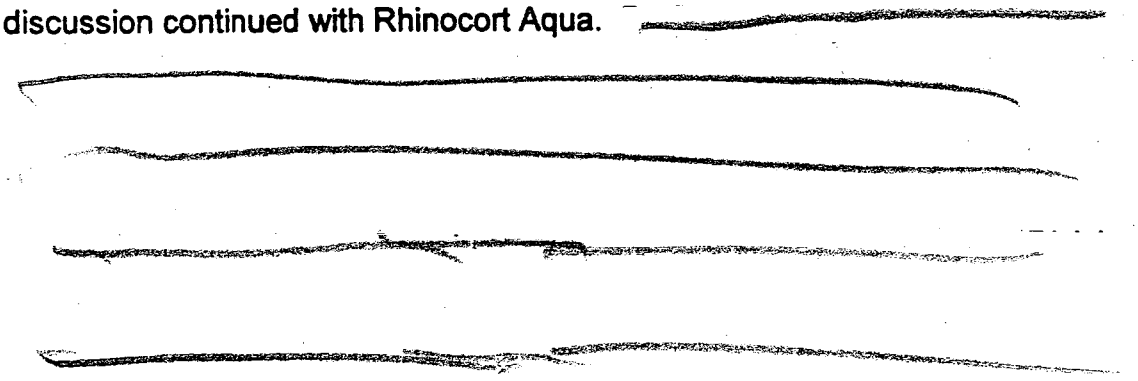
The discussion began with budesonide nebulizing suspension (IND 44,535). Dr. Tripathi presented an overhead (see attached). In addition to the comments from his overhead, Dr. Tripathi informed Astra that a [redacted] month study in dogs is not needed for the BNS NDA. Based on Dr. Tripathi's comment #2 from his overhead that 6 week old dogs were not young enough, Astra explained that they have a number of logistical

problems with conducting studies on dogs younger then 6 weeks. Astra explained that none of the contractors that they contacted could conduct this study on dog even as young as 6 weeks, so Astra will have to conduct the study in-house. Astra explained that the kennels which house the dogs are several miles from the inhalation facility, therefore the dogs have to be transported back and forth. Astra pointed out that 4 week old pups have not been weaned, and therefore the pups will have to be shuttled back and forth between the research facility, and the kennels where the mothers are. Not only is this logistically difficult, Astra expressed concern that the stress on the pups could lead to some deaths. Astra also stated that antibody transfer during nursing is quite high, and they are concerned that this could have an effect on the study results. Dr. Sun agreed to consider Astra's arguments and to get back to them with a decision on what age would be acceptable, however he still encouraged Astra to use animals as young as possible. Dr. Sun also pointed out that Astra could be having difficulty with the study design because they are doing nose-only inhalation. Astra replied that nose-only is standard for dogs because dogs are obligate nose-breathers. Dr. Sun reminded Astra that the purpose of this study is to see the toxicity profile between the normal animals and the immature young animals, and the Division wants to see systemic and local effects.

The next issue was the delivered dose of polysorbate. Dr. Sun pointed out to Astra that based on the numbers presented in the overhead "Inhaled Doses in Toxicity Studies Related to Clinically Delivered Doses", the pre-clinical dose proposed by Astra only gives them a twofold dose, the Division wants a tenfold dose. Calculation of the dose should be based on the lower respiratory areas. Astra replied that they did not know if they could raise the dose. Dr. Sheevers informed Astra that if they cannot reach a tenfold dose they should explain why it is not feasible, and they should be very specific and show data if possible. Astra questioned if testing the excipient alone at tenfold was acceptable. The Division replied that it was.

With regard to the timeline for the submission of the study reports, Dr. Sun informed Astra that the final report for the six month chronic study must be submitted by the 60 day filing date of the application, or the application will not be fileable. However, the 1 month rat study and the 3 month dog study must be included in the NDA at the time it is submitted.

The discussion continued with Rhinocort Aqua.



SUMMARY

For BNS:

- The final report for the 6 month chronic study must be submitted by the 60 day filing data of the NDA.
- The 1 month and 3 month study reports must be included with the NDA at the time of submission.
- A [redacted] month study in young dogs is not required.
- A tenfold dose of the excipients should be studied for the safety profile.
- The Division will consider Astra's arguments with regard to the age of the pups to use in the 3 month dog study.

For Rhinocort Aqua:

- [redacted]
- [redacted]
- [redacted]

/S/

Gretchen Trout
Project Manager

cc: orig. IND 44,535, Div. File
orig. NDA 20-746, Div. File
HFD-570/Sun
HFD-570/Pei
HFD-570/Tripathi
HFD-570/Sheevers
HFD-570/Anthracite
HFD-570/Otulana
HFD-570/Meyer
HFD-570/Honig
HFD-570/Cobbs
HFD-570/Trout

rd initial by: Pei/12-11-96
Sun/12-18-96
Tripathi/12-12-96
Sheevers/12-19-96

drafted: Gtrout/Dec. 11, 1996/n:\ind\44535\pm\96-12-06

Meeting Minutes (meeting ID 539)

ATTACHMENTS

12 Page(s) Withheld

PRE-NDA CMC MEETING MINUTES

Date: November 20, 1996

Product: budesonide nebulizing suspension

IND: 44,535

Attendees

Astra USA:	Dennis Bucceri	Vice President Regulatory Affairs
	Murad Husain	Associate Director Regulatory Affairs
	Paul Alessandro	Regulatory Affairs
	Joseph Anisko	Quality Assurance
	Brian Graeff	Quality Assurance
	Larry Paglia	Quality Assurance
	Cheryl Larrivee-Elkins	Pharmaceutical Development
	William Hartnett	Operations
	Victor Keslake	Quality Assurance
Astra Draco:	Sedney Hugosson	Pharm./Analytical R&D
	Ann-Kristin Karlsson	Pharm./Analytical R&D
	Claes Ahlneck	Pharm./Analytical R&D
	Ove Molin	Quality Assurance (APL)
	Peter Akerman	Production (APL)
FDA:	John Jenkins	Director, Division of Pulmonary Drug Products
	Bob Meyer	Medical Team Leader
	Guirag Poochikian	Chemistry Team Leader
	Dale Koble	Chemistry Reviewer
	Linda Ng	Chemistry Reviewer
	Lindsay Cobbs	Project Manager
	Gretchen Trout	Project Manager

BACKGROUND: Astra requested a meeting with the Division of Pulmonary Drug Products to discuss their CMC program for budesonide nebulizing suspension (BNS). Astra intends to submit an NDA for this product in June of 1997. Astra submitted a meeting package dated October 30, 1996.

The meeting began with introductions, and Astra made a short presentation (see overheads attached). The following are clarifications that were made during the presentation.

- With regard to the primary packaging for BNS, the ampules are [redacted]
- The budesonide content is an average of three units.

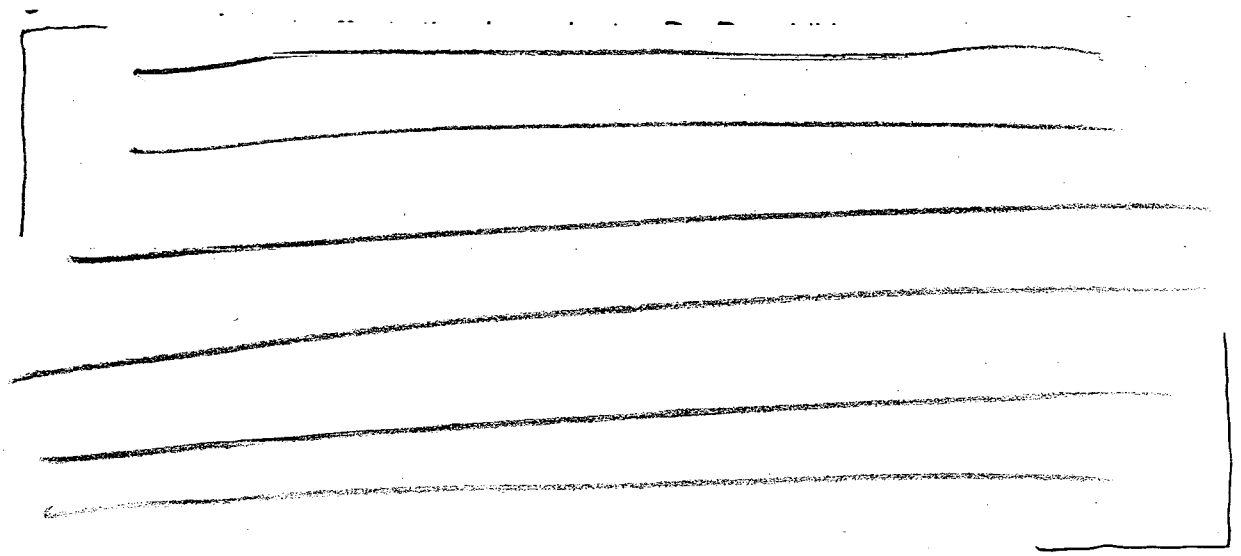
- The content uniformity was expressed around target fill because [redacted]
- The fill volume is an average of 5 respules in a strip.
- When Astra [redacted]

After Astra's presentation, Dr. Koble informed Astra of the Division's issues with the drug substance. The following were Dr. Koble's comments.

- Some of the DMF's are deficient, and letters have already been issued to the DMF holders.
- Based on Pulmicort Turbuhaler, the particle size specification needs to be tightened, and the particle size by microscopy needs to have an upper limit for large particles. (Dr. Koble acknowledged that BNS is a different product from Pulmicort so the comments may not be exactly the same, but these are issues that Astra should keep in mind).
- Many specifications need to be tightened for related substances.
- There should be specifications for [redacted], and the Division will consider a reduced program.
- The Division has concerns about the microbiological quality. The specification for the drug substance will have to be consistent with what is decided for the drug product.

Dr. Koble questioned Astra about the three stability studies on [redacted] substance, why was it not balanced between suppliers. Astra explained that there are 4 batches, 3 and 1 are matrixed from the 9 batches. For the lowest rank - 3 are on stability, 1 from Astra substance and the other [redacted] substance. Dr. Poochikian questioned if it was feasible to introduce another batch of Astra chemical to be used in the drug product. If Astra has already started stability, the Division would have to look and see that they are comparable. Dr. Koble reminded Astra that with Rhinocort they ran into some stability problems. Dr. Koble questioned if all the contact surfaces in Sweden and the USA are the same. Astra replied that they are, and they will have 1 batch of each strength from Astra Sweden. Dr. Poochikian pointed out that since Astra is only [redacted] if there is a problem there will be no way to know if the problem is because of the drug substance or something else. Dr. Poochikian informed Astra that this was an issue for them to consider.

Dr. Ng then discussed issues relating to the drug product. Dr. Ng mentioned that the product is labeled sterile, [redacted]



Dr. Ng made the following points with regard to the drug product.

- There are some concerns with the excipient polysorbate, however this will be discussed at the meeting with the toxicologists in December.
- With regard to specifications, Dr. Ng indicated that she could not comment at this time because Astra has not submitted any data. However, comments will be provided for the attributes tested.
- With regard to attributes, for particle size the Division prefers to see a distribution profile rather than a single time point.
- For droplet size, the Division wants to know the distribution of the spray droplets from the nebulizer under *in vitro* conditions.
- For osmolarity, there should be a test for release.
- For the container, appropriate DMF references should be made.
- Dr. Ng questioned if Astra will test for water loss from the closed container. Astra agreed that they could do that.
- Express assay on per container basis is recommended (see discussion on overfill).
- Photostability studies should be submitted as per ICH.
- Data should be submitted to support stability - physical, chemical and microbiological, for the , manufacutring fill time.
- Astra should test for nto the container; e.g.

Dr. Ng questioned Astra about one of their overheads where they mentioned
" Astra explained that they

Astra does this to see whether there is bility,

it is a physical test not an actual dose.

Dr. Ng informed Astra that for their stability studies, since this product is aqueous based, high humidity might not be relevant, however Astra should refer to the ICH guidelines. Dr. Poochikian added that the ICH guidelines do not discuss long-term data, only accelerated data, however the Agency recommends not more then 40% humidity. Astra questioned if the Division would want to see these data even on the foiled units. Dr. Poochikian replied that the data is definitely needed for the unfoiled units, for the foiled units the Division will discuss internally and get back to Astra with an answer.

Dr. Ng informed Astra that for the storage temperature Astra should look at [redacted] in addition to the 25° [redacted] that they proposed. Dr. Poochikian explained that the Division requests [redacted] case there is a problem at [redacted] if everything is acceptable at 40°, then Astra will not need to generate data at [redacted]

In addition to the Division's comments, Astra requested feedback from the Division on Astra's [redacted]

[redacted] Dr. Poochikian informed Astra that the Division would discuss this internally and get back to Astra with a response. Dr. Poochikian informed Astra that based on the [redacted] how Astra expresses content uniformity might be effected. [redacted] Astra presented an overhead illustrating distribution, and verified that this [redacted] was also true of the clinical batches.

Dr. Poochikian encouraged Astra to develop a method, and set specifications for, [redacted] in addition to their drug substance particles. The [redacted] could come from the [redacted] closure system, etc.

With regard to the [redacted] the difference between the [redacted] machines is the [redacted] However the machines use the [redacted] Astra was told that they need to describe in the NDA the similarities and/or differences between the [redacted] machines.

In addition, the following points were clarified by Astra.

- Astra will conduct a study where they remove the respules from the foil package, put into paper envelopes and store in a controlled dark room. The purpose of the study is to simulate patient use. The instructions tell consumers to use the respules within [redacted] after removing from the foil, and to [redacted]

- There will be a [redacted] printed on each respule unit on the tab.

With regard to labeling, the Division informed Astra that for these types of preparations, the drug should be expressed as an amount, [redacted]. Dr. Jenkins questioned if Astra included instructions to [redacted] Astra replied that there were such instructions. Dr. Jenkins questioned also if Astra had conducted any *in vitro* testing with the nebulizer when the product hadn't been [redacted] to determine if it effects the amount of drug delivered. The directions will [redacted]. Dr. Poochikian stated that it might be appropriate for Astra to see how much residual drug is left behind after nebulization. Astra replied that they have data on that and will include it in the NDA.

Astra was reminded to be aware in their studies for [redacted] of the [redacted]

With regard to microbiology, in the NDA Astra was told to justify the [redacted] storage time. Astra needs to document and supply validation data.

/S/

Gretchen Trout
Project Manager

cc: orig. IND 44,535
Div. File
HFD-570/Jenkins
HFD-570/Meyer
HFD-570/Poochikian
HFD-570/Koble
HFD-570/Ng
HFD-570/Cobbs
HFD-570/Trout

rd initial by: Koble/12-3-96
Ng/12-4-96
Poochikian/12-6-96
Meyer/12-6-96
Jenkins/12-9-96

Meeting Minutes (meeting ID 407)

ATTACHMENTS

23 Page(s) Withheld

4 Page(s) Withheld

PRE-NDA MEETING MINUTES

Date: September 16, 1996

Product: budesonide nebulizing suspension

IND: 44,535

Attendees

Astra USA:	Michael J. Fox	Sr. Vice President Clinical Development
	Mario Cruz-Rivera	Clinical Scientist
	Ross Rocklin	Sr. Director Clinical Research
	Alistair Wheller	Sr. Director Clinical Operations
	Dennis Bucceri	Vice President Regulatory Affairs
	Murad Husain	Associate Director Regulatory Affairs
	Roberta Tucker	Director Regulatory Affairs
	P.K. Tandon	Sr. Director Biostatistics
	Karen Walton-Bowen	Biostatistics Group leader
Astra Draco:	Staffan Edsbacker	Associate Director Clinical Development
	Goran Erikson	Director Clinical Development
	Kurt Nikander	Clinical Research Manager
	Ake Ryrfeldt	Sr. Scientific Advisor, Pre-clinical
	Cecilia Seidegard	Vice President Regulatory Affairs
	Bertil Andersoon	Project Manager
FDA:	John Jenkins	Director, Division of Pulmonary Drug Products
	Bob Meyer	Medical Team Leader
	Steve Wilson	Biometrics Team Leader
	Hilary Sheevers	Pharmacology Team Leader
	Joe Sun	Pharmacology Team Leader
	Dale Conner	Clinical Pharmacology Team Leader
	Tunde Otulana	Medical Reviewer
	Alexandra Worobec	Medical Reviewer
	Satish Tripathi	Pharmacology Reviewer
	Barbara Bono	Biometrics Reviewer
	Brad Gillespie	Clinical Pharmacology Reviewer
	Gretchen Strange	Project Manager

BACKGROUND: Astra submitted a pre-NDA meeting request and package dated July 18, 1996 to discuss budesonide nebulizing solution.

The meeting began with introductions, and Ms. Strange stated that CMC issues would not be discussed at this meeting. Per an earlier conversation with Ms. Tucker of Astra, a separate CMC package will be submitted for a CMC meeting.

Astra presented overheads giving a brief background (see attached).

Dr. Tripathi presented an overhead (see attached - "Pharmacology-Toxicology Issues") outlining additional studies which may be required. Dr. Tripathi pointed out two pharmacology-toxicology issues (see attached - "Pharmacology-Toxicology issues"): (1) Polysorbate-80 (Sorbitan monooleate), an inactive ingredient in the drug product, has not been approved via inhalation route. If Polysorbate-80 is to be present in the final drug product, chronic toxicity testing (6 months) of this inactive ingredient should be done in animals. Since ASTRA has an approved NDA (20,233) in which sorbitan trioleate has been used, a bridging from trioleate to monooleate may be adequate. (2) Since the proposed patient population for this NDA is pediatric (children from —— to 8 years age), safety of the drug should be assessed in young immature animals by conducting a one-month inhalation toxicity study in a rodent species and a three-month inhalation toxicity study in a non-rodent species. Astra responded that the data they have available is a study in 1 week old rats, for 3 months, subcutaneous. Additionally they have data from studies in 4-6 week old rodents, which Astra stated correlates to puberty in humans. Astra is also working on a model with 14 day old rats. Astra stated that they would consider the issues raised by the FDA and submit a report of what they have currently available, and what they will have available in the short-term. Astra and FDA agreed that this was appropriate. The FDA also encouraged Astra for the rat study to use animals as young as possible, however the FDA will look at whatever data Astra submits.

The FDA then addressed Astra's questions from the July 18, 1996 meeting package. The questions and responses were as follows.

> Astra question 1: This document identifies and summarizes the studies Astra is relying on to establish the safety and effectiveness of budesonide nebulizing suspension in children with asthma under the age of eight years. Are the data acceptable for an NDA submission?

Response: Astra and the Division discussed the reliability of the primary endpoints and the handling of dropouts in the planned analyses. The FDA and Astra statisticians agreed to further discuss these issues in a teleconference. In addition, the FDA expressed concerns regarding the standardization of peakflow measures across devices and time. Astra was asked to address these issues in the NDA.

Astra question 2: Given the clinical need for a nebulizable glucocorticosteroid for asthmatic infants and very young children, will the FDA grant a priority review?

FDA response: Astra was informed that the FDA could not tell them at this point that the application would receive a priority review, that determination will be made when the NDA is submitted. However, based on the information already provided by Astra, the application will likely qualify for a priority review. Astra was reminded that if the application is granted a priority review, it is crucial that the application be complete when submitted as there will be very limited time to make requests for information after submission. The FDA encouraged Astra to submit the final clinical study reports and the study database to the IND as soon as they are finalized, so that the Division can begin the reviews and can identify sites for clinical audits.

Astra question(issue) 3: The LC-Jet Plus™ nebulizer connected to the Pari Master compressor is the system being used in the U.S. pivotal clinical studies. Other nebulizer/compressor systems, some of which are available in the U.S. market, have been used in the non-U.S. supportive clinical studies. Extensive *in vitro* work has been performed assessing drug mass output delivery and particle size distribution of budesonide nebulizing suspension in various nebulizer/compressor systems available in the U.S. market.

FDA response: The FDA questioned what claim Astra wants to make in the package insert. Astra presented an overhead of a

cont."). Dr. Otulana informed Astra that typically the Division does not include data by itself in the package insert, particularly in the section. Generally the Division includes data that has direct clinical impact. Dr. Otulana displayed an overhead taken from the DNAse labeling which he recommended Astra use as a model. Astra responded with another overhead (see attached) indicating that they have more detailed *in vitro* and *in vivo* data. Astra stated that they have a bridge between *in vivo* and *ex vivo*. Dr. Jenkins informed Astra that content of the package insert is a review issue, and that the data which will have the most support to be included in the package insert will be from the controlled trials.

Astra question(issue) 4: After the U.S. clinical program was initiated, Dr. M. Scheinbaum of the Pilot Division contacted Astra on March 2, 1994 to suggest that ACTH infusion tests be performed instead of one-hour ACTH stimulation tests. Astra conferred with three consultants, two institutional review boards and the manufacturer of regarding the utility and feasibility of performing the requested test. Based on the information obtained, it was concluded that the one-hour cortisol assessments would provide

adequate data to define any possible effect of budesonide nebulizing suspension on adrenal function in the study population. Therefore, the requested [redacted] infusion test was not performed.

FDA response: The Division agreed that the one-hour ACTH test was acceptable.

Additional items which were discussed:

- The age range Astra will request as an indication for this product will be [redacted] 8 years.
- Astra hopes to submit the application around June of 1997.
- Astra was informed that it is likely that this application will go to a PADAC meeting.

In conclusion Ms. Strange stated the action items which were agreed to at this meeting:

- Astra will submit a summary of studies completed and ongoing to address the pharmacology issues;
- a telecon will be scheduled to discuss statistical issues; and
- Astra will submit a CMC package and request a meeting as soon as possible.

/S/

Gretchen Strange
Project Manager

cc: orig. IND 44,535
Div. File
HFD-570/Jenkins
HFD-570/Meyer
HFD-570/Wilson
HFD-570/Sheevers
HFD-570/Sun
HFD-570/Conner
HFD-570/Otulana
HFD-570/Worobec
HFD-570/Bono
HFD-570/Gillespie
HFD-570/Strange

rd initial by: Bono/9-26-96
Wilson/10-24-96
Conner/9-26-96
Tripathi/9-26-96
Sun/9-26-96
Meyer/10-1-96
Otulana/9-30-96
Jenkins/10-28-96

Meeting Minutes (meeting ID 164)

ATTACHMENTS

23 Page(s) Withheld